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RIVM letter report 2019-0191
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Colophon

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Synopsis

Potential health risks of nanomaterials in food: a methodology to identify signals and prioritise risks

Thanks to nanotechnology, an abundance of new products and nanomaterials for food can be developed. Nano-iron, for example, could be added to foods to fight anaemia and nano-packaging methods can be developed to improve the shelf life of products.

Manufacturers are responsible for public safety and must meet legislation and regulations. But the current legislation and regulations may not be sufficiently up-to-date to identify any health risks nanotechnology may entail. Policymakers could therefore press for changes in the legislation to enable this. There may also be cause for further assessment. RIVM has developed a method that clarifies the developments (known as signals) relating to nanomaterials in food which policymakers first have to assess for possible health risks. They can then take measures based on the outcomes.

Along with the method, RIVM has elaborated six of these signals. They concern the exposure of people to nanoplastic particles via food and drinking water, nano-silver, nano-encapsulation methods for food, the use of nanoparticles to add iron to foods and the use of the needle-shaped nano-hydroxyapatite in infant formula. Finally, researchers also investigated whether exposure to multiple poorly soluble particles at the same time causes a greater health effect. RIVM makes recommendations in this respect and suggests follow-up actions.

The new methodology is based on the existing method for new or emerging risks of chemical substances. This method has been adapted for assessing the possible health risks of nanomaterials in food. The method collects information about products and materials that contain nanomaterials and are used in food. Experts subsequently assess the risks relating to characteristics and nano-characteristics of the substance in question.

Keywords: nanoparticles, risk assessment, health risk, strategy, microplastics, nano-iron, nanosilver, nano-encapsulation methods, nano-hydroxyapatite, poorly soluble low toxic (PSLT) particles

Publiekssamenvatting

Mogelijke gezondheidsrisico’s van nanomaterialen in voedsel: een methode om risico’s te signaleren en te prioriteren

Nanotechnologie maakt het mogelijk om voor voedsel veel nieuwe producten en nanomaterialen te ontwikkelen. Zo zou nano-ijzer aan voedingsmiddelen kunnen worden toegevoegd om bloedarmoede tegen te gaan. Nano-verpakkingsmethoden kunnen worden ontwikkeld voor betere houdbaarheid van het product.

Producenten zijn verantwoordelijk voor de veiligheid en moeten voldoen aan de wet- en regelgeving. Maar het kan zijn dat de huidige wet- en regelgeving onvoldoende up-to-date is om eventuele gezondheidsrisico’s van nanotechnologie te herkennen. Beleidsmakers kunnen er dan op aansturen de wetgeving aan te passen. Ook kan er aanleiding zijn voor verder onderzoek. Het RIVM heeft een methode ontwikkeld die duidelijk maakt welke ontwikkelingen (signalen genoemd) van nanomaterialen in voedsel beleidsmakers als eerste moeten beoordelen op mogelijke gezondheidsrisico’s. Op basis van de uitkomst kunnen zij maatregelen nemen.

Het RIVM heeft met de methode zes van deze signalen uitgewerkt. Het gaat om de blootstelling van mensen aan nanoplastic deeltjes via voedsel en drinkwater, nanodeeltjes om ijzer aan voedingsmiddelen toe te voegen, nano-zilver, nano-verpakkingsmethoden voor voedsel, en naaldvormig nano-hydroxyapatiet in zuigelingenvoeding. Ten slotte is ook onderzocht of blootstelling aan meerdere slecht oplosbare deeltjes tegelijk een groter gezondheidseffect veroorzaken. Het RIVM doet hiervoor aanbevelingen en reikt vervolgacties aan.

Als basis voor de methodiek is de bestaande methode voor risico's van nieuwe chemische stoffen aangepast op mogelijke gezondheidsrisico's van nanomaterialen in voedsel. De methodiek verzamelt informatie over producten en materialen voor voeding waarin nanomaterialen zijn verwerkt. Daarna beoordelen experts eventuele risico’s van de (nano)eigenschappen van een stof.

Kernwoorden: nanodeeltjes, risicobeoordeling, gezondheidsrisico, strategie, microplastics, nano-ijzer, nano-zilver, nano-verpakkingsmethoden, nano-hydroxyapatiet, PSLT deeltjes

Contents

1 Introduction

The field of nanotechnology in food is dynamic: innovative scientific developments, possible future applications, as well as concrete new products are often observed. Although producers are first responsible for the marketing of safe products, the safety of some new products may not be adequately covered by current regulations. Unsafe products, developments, and materials may go unnoticed due to progressing scientific insights and new technological possibilities such as related to nanotechnology. Identification and prioritisation of such products, developments, and materials for their potential health risks would be helpful to facilitate scientific-based decision making. Therefore, the aim of the present study is to build and apply a systematic methodology in the field of nanotechnology in food, in order to facilitate decision making by the Netherlands Food and Consumer Product Safety Authority (NVWA) on:

1) the need for further research in view of public health;
2) enforcement (whether inspection or action is required); and/or
3) advise to policy makers on the need to develop new, or adapt existing regulations, or to develop policy to address potential risks (together with other stakeholders).

The methodology should be systematic, transparent and applicable for possible health risks of nanomaterials in food already on the market as well as those of possible future applications. The methodology should start with collecting information and identification of signals and a brief description of each signal to provide a clear starting point. It should also indicate whether current legislation is adequate to assess safe use of nanomaterials in food, or if legislation is adequate to identify potential health risks and/or provides tools for enforcement. Finally, the methodology should be able to connect similar information, provide an indication of the strength of the signal, and present a manner to prioritise the signals. The signals with highest priority should be explored in more detail and recommendations on the need and direction for further action can be given.

In the development of this methodology, the existing methodology for New or Emerging Risks of Chemicals (NERCs) was used as a starting point [1, 2], as well as the 'risk potentials' which were developed for nanomaterials within the NANoREG project [3]. For NERCs, as a general approach for early warning methodology, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) [4] and RIVM [1, 2], developed five steps as described in Figure 1. These steps were used as basis for the development of the present methodology.

Figure 1. Components and steps involved in an early warning system as developed for New or Emerging Risks of Chemicals (NERCs) [5].

Dekkers et al. (2016) proposed a set of aspects of exposure, (toxico)kinetic behaviour and hazard assessment that are most likely to be influenced by nano-specific properties of the material [3]. These aspects are exposure potential, dissolution, nanomaterial transformation, accumulation, genotoxicity and immunotoxicity [3]. Together with other relevant information obtained from literature overviews on nano-specific behaviour and expert knowledge, these aspects are used in the methodology to highlight nano-specific behaviour that may be relevant for potential health risks.

Chapter 2 of this report describes the developed methodology, which is illustrated in a process flowchart. The different steps of the flowchart are further described in the chapter, starting with collection of information relating to nanomaterials in food (Section 2.1) and the identification of relevant signals (Section 2.2). A signal is summarised according to a predefined format (Section 2.3). Signal prioritisation is performed on the basis of scoring by multiple experts, based on a list of questions addressing nano-specific health risk related characteristics (Section 2.4). Section 2.5 describes whether existing legal frameworks enable risk management of potential risks. Next, Section 2.6 indicates other issues that should be considered in decision making and follow-up actions.

Chapter 3 illustrates the application of the methodology on a systemic literature and information search performed from January 2017 up to June 2019. It reports on the collection of information regarding nanomaterials in food and identification of relevant signals (Section 3.1), including a short description of the individual signals (Section 3.2).

The scoring of the selected signals and subsequent prioritisation is performed in Chapter 4.

Based on their scores five signals are prioritised and considered in more detail in Chapter 5. On request of the NVWA a signal on Poorly Soluble and Low acute Toxicity (PSLT) particles[1] was added to this selection. Chapter 6 provides overall considerations on the prioritised signals, and discussions and conclusions on the methodology including recommendations.

[1] Poorly Soluble and Low acute Toxicity (PSLT) particles are a group of granular particles that are poorly soluble under normal physiological circumstances and have low acute toxicity (see Section 5.1.6).

2 Methodology

The elaborated methodology consists of the following main steps identified (these are illustrated as a flowchart in Figure 2):

1) **Information collection**: information from nanomaterials in food from several sources.
2) **Signal identification by expert judgement**: Signals with respect to nanomaterials in food are distinguished from signals in other areas such as nanomaterials in cosmetics or non-food consumer products by expert judgement.
3) **Signal description**: The signal is briefly described for a set of standard fields, i.e. physicochemical properties, hazard characteristics, (toxico)kinetics and exposure. Here, when no or limited information is available, there is a higher level of uncertainty.
4) **Signal assessment and scoring**: Using several risk descriptors per field, each signal is assessed by several experts using a set of key questions for physicochemical properties, hazard, (toxico)kinetics and exposure that cover the aspects considered most relevant for health risk assessment of nanomaterials. Each answer yields a score that is used to rank the different signals.
5) **Applicability legal frameworks to enable risk management of potential risks**: The applicability of the various food related legal frameworks is considered for each signal. This provides insight if 1) the products, materials or development in the signal is, or will be, assessed by a legal framework, and 2) whether the relevant legal frameworks are adequate for this assessment.
6) **Prioritisation and considerations for follow-up**: The scoring/ranking, information on similar signals, and the assessment with regard to legal frameworks are used to come to the overall prioritisation and further exploration of signals.

The methodology strives to provide a systematic approach to signal identification, assessment and prioritisation. However, it should be noted that the methodology still does not ensure that every signal with respect to nanomaterials in food is identified, and subsequently prioritised.

In the following sections step 1 to 6 of the methodology are described in more detail.

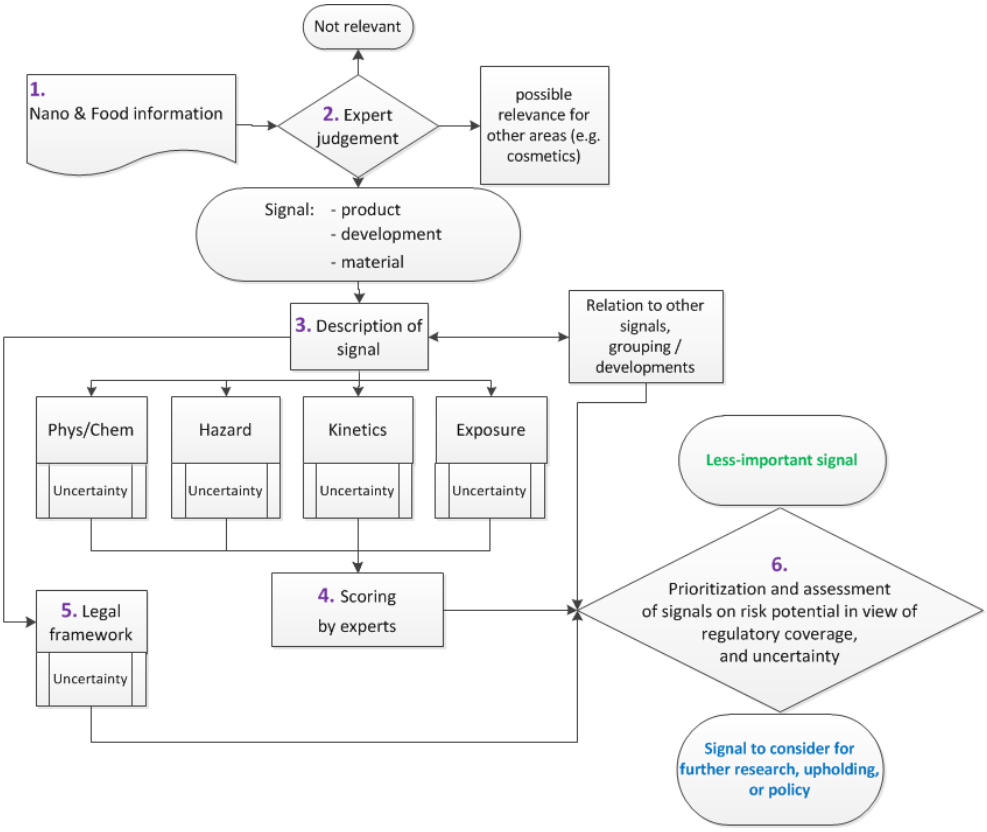

Figure 2. Graphical presentation of the methodology described in this report to systematically identify, describe and prioritise signals relevant for the field of nanomaterials and food. The numbers refer to the main steps indicated in the text of Chapter 2 (A bigger flowchart without this numbering is included in Appendix 4).

2.1 Information collection

Information on nanomaterials in food is collected from several sources, e.g. news items, scientific literature, reports, or other communications. The **information** includes developments in nanomaterials in food, specific products as well as materials. To this end, scientific literature was examined by a monthly search performed by the library of the RIVM. Details on this literature search are provided in Appendix 1. In addition to scientific literature, also 'grey' literature was searched on internet, i.e. research produced outside the traditional academic publishing sources by research institutes, universities, non-governmental organisations (NGOs) (see Appendix 1 for details). Also additional information from the RIVM Nano-Working Group, individual RIVM nano-experts, and the European Food Safety Authority (EFSA) Nano Network was used to extract signals.

2.2 Signal identification by expert judgement

The relevance of the collected information is determined by expert judgement. The expert judgement has to confirm that the information is relevant from the perspective of nanomaterials in food. A **signal** is a product, development or material which has the potency to result in a health risk. Exclusion of signals is based on low probability of resulting in a health risk. A product, development or material falling outside the

scope of nano-materials in food may be relevant for other areas such as cosmetics, or non-food consumer products. These signals can be regarded as input in the execution of the existing methodology for New or Emerging Risks of Chemicals (NERCs).

2.3 Signal description

Signals may relate to products, in which nanomaterials are used. In most cases, specific physicochemical properties, or considerations with respect to hazard, kinetics or exposure may be described or known for the nanomaterial of the signal. Further, current or future use can be estimated based on product description. Signals can also relate to developments, which can include a broader group of nanomaterials and/or applications and do not necessarily describe a product use or a specific material. For signals on developments, the information will be more general and therefore will have a higher level of uncertainty.

Each signal is systematically described according to the following items (indicated in bold in the listing below; see Section 3.2 for examples of the systematic descriptions):

- choosing whether an signal concerns a **Product, Development, or Material**;
- a **Short description of the content** of the signal;
- a **Physicochemical description on material and quality assessment considerations** providing the available information on, e.g. particle size, aggregation/agglomeration, surface area, dissolution (rate), density, reactivity, including information of the quality of the physicochemical analysis;
- **Hazard considerations** with information on e.g. target organs, type of effects, effect levels. In case of a toxicity study, information on the design of the study can be included, such as study duration, species, number of animals;
- **Exposure considerations** including e.g. a description of the exposure in the toxicity study, or a description of information on the current or expected product use;
- **Kinetic considerations** with information on (toxico)kinetics, e.g. absorption, accumulation, distribution, target tissues, metabolism, excretion;
- **Consideration on applicability of legal framework(s) in which** coverage by and adequacy of the legal framework is described (see Section 2.5); and
- the **Relation to other signals**, relevant information on e.g. the number of scientific publications which might be combined in the signal, or any link or overlap with other, similar signals.

Of the abovementioned items, those on considerations with regard to physicochemical properties, hazard, kinetics and exposure are used for signal assessment and scoring.

2.4 Signal assessment and scoring

To create a robust and systematic methodology to evaluate the signals, a scoring system was developed based on a set of key questions (Table 1), as explained below. In line with the risk assessment paradigm, the questions relate to information on physicochemical properties, hazard,

(toxico)kinetics and exposure. Expert judgement is needed to answer the questions, i.e. to allocate a score.

Each of the questions can be answered by yes, no or unknown, corresponding to a score of 3, 0, or 1, respectively. Scoring is performed in a conservative way: the questions refer to specific information that may not be available or described in the signal, and therefore, an *indication* (in contrast to clear evidence) for a specific physicochemical property, hazard, (toxico)kinetic behaviour or exposure is sufficient to attribute the maximum score of 3. When no information is available, information on that property is unknown and a score of 1 is applied. *Unknown may also be interpreted as 'maybe'*, in case the indications are too weak to attribute the maximum score.

For relevant comparison of different signals, the signals need to be considered per group (product, material or development). Thus, when comparing the signals, products should be compared to other products, materials to other materials, and developments to other developments. Signals describing products or materials are in general more specific and include information on kinetics and toxicity. In the contrary, developments are likely to have a higher number of 'unknowns', due to the more general description.
With regard to the different descriptors, for instance both indications for high toxicity or high exposure (as well as unknown toxicity or unknown exposure) can lead to high scoring, but will have a different justification for the scoring. This should be taken into account when further exploring the signals in case they are prioritised.

2.4.1 *Physico-chemical properties*

The questions relating to physicochemical properties are based on available information on relationships between these properties and hazard as, for example, outlined in Dekkers et al. [3] and Oomen et al. [6], and on the criteria of the NanoRiskCat tool as described by Hansen et al. [7]. A low dissolution or degradation rate can be an indication of persistency. High reactivity, either due to the material and/or to the surface area, and release of ions or molecules, may enhance the induction of toxic effects. High Aspect Ratio Nanoparticles (HARN)[2] may result in 'frustrated phagocytosis': phagocytes that are not able to completely engulf the particle, which after inhalation may lead to mesotheolioma, a specific form of cancer also known from exposure to asbestos [8, 9]. Although it is unknown to which extent frustrated phagocytosis also occurs after oral exposure, phagocytes that may be unable to deal with such thin and long particles are considered a potential hazard. Also particle size, both primary and aggregate size are of importance as this greatly affects the cellular uptake (bioavailability) and subsequent effects such as generation of reactive oxygen species.

2.4.2 *Hazard*

Hazard-related questions mainly related to known information on the chemicals themselves and to toxicodynamics-related elements important

[2] A High Aspect Ratio Nanoparticles (HARN) is a material that has a diameter <100 nm and a length many times greater than its diameter (aspect ratio greater than 5:1) [8].

for risk assessment of nanomaterials, as defined by Dekkers et al. [3]. Indications for risk potential may at first arise when the chemical itself is regarded as a substance of high concern for human health according to the Dutch national ZZS-list ('Zeer Zorgwekkende Stoffen'). Further, important hazards relating to nano-specific concerns and used for prioritisation are mutagenicity, carcinogenicity and immunotoxicity. Remaining toxicity endpoints are covered collectively in the final scoring question.

2.4.3 *Kinetics*

Two (toxico)kinetic parameters that have major impact on the exposure and hazard of nanomaterials are absorption from the gut and accumulation in organs, which were included in the scoring system. The brain and reproductive organs are considered important target tissues. Although they are normally protected by barriers, they may be penetrated by nanomaterials. Further, size and surface properties of the material influence the (toxico)kinetic behaviour, including distribution in an organism, which should be taken into consideration in the risk assessment of nanomaterials [10]. Differences in kinetic profile can result in different toxicodynamics.

2.4.4 *Exposure*

Scoring related to exposure focused on the use of the products concerned, i.e. a wide population, sensitive groups such as elderly people or young children, and the frequency of product use. Further, also the release of the nanomaterial from the product is taken into account to assess the risk potential of the signal.

Table 1. Scoring system with key questions to assess a selected signal for prioritisation on risk potential for human health.

Descriptor	Question	Answer[a] *(score)*		
		Yes *(3)*	**No** *(0)*	**?** *(1)*
Physico-chemical properties[b] *(max 12 pts)*	Indication of low or no dissolution or degradation rate in physiologically relevant media?			
	Indication of reactivity? E.g. due to surface area, type of chemical, surface treatment.			
	Indication of release of toxic ions or molecules?			
	Indication that the nanomaterial is persistent and rigid, i.e. a High Aspect Ratio Nanoparticle (HARN)[c] ?			
Hazard *(max 12 pts)*	Is the chemical itself a substance of very high concern, relating to human health hazard[d] ?			
	Indication of mutagenicity/carcinogenicity (of the material)?			
	Indication of immunotoxicity (of the material)?			
	Indication of other toxicity (of the material)?			
Kinetics *(max 12 pts)*	Indication of absorption?			
	Indication of distribution to brain or reproductive organs?			
	Indication of accumulation in any tissue?			
	Indication of change in kinetic profile compared to non-nano situation?			
Exposure [e] *(max 12 pts)*	Products used or likely to be used much or in many products and/or by wide population?			
	Is exposure of sensitive subgroups anticipated? (e.g. babies or elderly people)			
	Is exposure likely to occur frequently (more than a few incidental times)?			
	Is there potential for nanomaterial exposure likely, based on the product use description?			
	Total marks	…	…	…
		x 3	**x 0**	**x 1**
	Sub-score	…	**0**	…
	Total score	…		

[a] An indication for a specific physicochemical property, hazard, (toxico)kinetic behaviour or exposure is sufficient to attribute the maximum score of 3. Unknown (=?) can also be interpreted as 'maybe', in case the indications are weak.
[b] Take into account that outer layers may not be stable and therefore consider changes in surface properties.
[c] HARN = a material that has a diameter <100 nm and a length many times greater than its diameter (aspect ratio greater than 3 or 5:1), as defined by ECHA (2017) [11].
[d] Reference to ZZS list:http://www.rivm.nl/rvs/Stoffenlijsten/Zeer_Zorgwekkende_Stoffen, only substances on this list that relate to human health hazards are considered.
[e] Restricted to exposure of consumers.

2.5 Applicability of legal frameworks to enable risk management of potential risks

Dependent on the specific (foreseen) uses(s) of the nanomaterial in a product, development or material, specific legislation(s) will be applicable. The various legislations in the field of food differ with regard to the level of detail by which provisions for nanomaterials are elaborated. Dependent on the legislation involved, a substance is the subject of health risk assessment during, for instance, an authorisation procedure. With regard to the prioritisation of risk potential, it is important to know which legal framework applies, and to what extent it enables risk management of potential risks.

In addition to regulation, EFSA published in 2018 a **guidance** document to assist risk assessment of nanomaterials for human and animal health that covers the application areas within EFSA's remit, e.g. Novel foods, food contact materials, food/feed additives and pesticides [12]. This "Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain (Part 1, human and animal health)" (referred to as '2018 EFSA Guidance on nanomaterials' throughout this report) concerns nanomaterials according to the criteria for an engineered nanomaterial as outlined in the Novel Foods Regulation (EU) No. 2015/2283 [13], but can also apply to materials consisting of particles with size range above 100 nm, if they could retain properties characteristic of the nanoscale [12].

Table 2 below summarizes potentially relevant legislations with regard to nanomaterials and food. This includes their relation with nanomaterials, and the practise of risk assessment or authorisation, when present. More details on the respective legislations can be found in Appendix 4.

Table 2. Summary of potentially relevant legislations with regard to nanomaterials and food. More details are provided in Appendix 4.

Legislation/product	**Novel Food** (see 9.2.1)
Short definition	Food not consumed "significantly" prior to May 15th 1997. Also vitamins, minerals and other substances with changed composition or structure, way they are metabolised, or when containing a nanomaterial or consist thereof.
Regulation	Novel foods Regulation (Reg. (EU) No. 2015/2283). Labelling according to FIC Regulation.
Takes nano specifically into account	Yes. Contains a definition for an 'engineered nanomaterial'.
Product/substance specific assessment	Yes. By EFSA NDA-Panel.

Legislation/product	**Functional food** (see 9.2.2)
Short definition	Foods with an added component, in order to improve the nutritional value or to exert a certain beneficial health effect, sometimes with a health claim. Also foods with an increased amount of an existing component (normally Fortified foods) with a health claim are Functional foods.
Regulation	Dutch Commodities Act. Claims according to Regulation on nutrition and health claims made on foods (Reg. (EC) No. 1924/2006). Labelling according to FIC Regulation. Regulation on the addition of vitamins and minerals and of certain other substances to foods (Reg. (EC) No. 1925/2006), and the Decree on addition of micronutrients to foods under the Dutch Commodities Act ("Warenwetbesluit Toevoeging micro-voedingsstoffen aan levensmiddelen") also applies on the added substances to Functional foods.
Takes nano specifically into account	No.
Product/substance specific assessment	No.

Legislation/product	**Fortified food** (see 9.2.3)
Short definition	Foods with added nutrients already present in the product.
Regulation	Regulation on the addition of vitamins and minerals and of certain other substances to foods (Reg. (EC) No. 1925/2006), and the Decree on addition of micronutrients to foods under the Dutch Commodities Act ("Warenwetbesluit Toevoeging micro-voedingsstoffen aan levensmiddelen"). Labelling according to FIC Regulation.
Takes nano specifically into account	No.
Product/substance specific assessment	No.

Legislation/product	**Food supplements** (see 9.2.4)
Short definition	Food and drink which are intended as an addition to the regular diet, a concentrated source of one or more micronutrients or other substances with a nutritional or physiological effect, and consumed in small, measured amounts.
Regulation	Directive No. 2002/46/EG concerning food supplements is nationally implemented in the in the Decree Food supplements under the Dutch Commodities Act ("Warenwetbesluit

Legislation/product	**Food supplements** (see 9.2.4)
	voedingssupplementen"). In addition, Regulation on the addition of vitamins and minerals and of certain other substances to foods (Reg. (EC) No. 1925/2006), and the Decree on addition of micronutrients to foods under the Dutch Commodities Act ("Warenwetbesluit Toevoeging micro-voedingsstoffen aan levensmiddelen"). Labelling according to FIC Regulation.
Takes nano specifically into account	No.
Product/substance specific assessment	No.

Legislation/Product	**Herbal supplements** (see 9.2.5)
Short definition	Food supplements containing herbs.
Regulation	Herbal Preparations Decree under the Dutch Commodities Act ("Warenwetbesluit Kruidenpreparaten"). Herbal supplements which are also Novel foods or Food supplements should meet the legal requirements to these respective products as well.
Takes nano specifically into account	No.
Product/substance specific assessment	No.

Legislation/product	**Food additive** (see 9.2.6)
Short definition	Substance added to food to fulfil a certain technological function, such as preserving, stabilising, colouring of sweetening.
Regulation	Regulation on food additives (Reg. (EC) No. 1333/2008). Labelling according to FIC Regulation.
Takes nano specifically into account	Yes.
Product/substance specific assessment	Yes. By EFSA FAF-Panel (previously by ANS-Panel).

Legislation/product	**Food Contact Material** (see 9.2.7)
Short definition	Materials and articles intended to come into contact with food.
Regulation	Regulation on materials and articles intended to come into contact with food (Reg. (EU) No. 1935/2004). Regulation on plastic materials and articles intended to come into contact with food (Reg. (EU) No. 10/2011) contains a Union list of approved substances that may be intentionally used in the manufacture of plastic layers in plastic materials and articles. In the Netherlands, the legislation on FCMs contains an additional restrictive (positive) list of substances authorised for use in plastics and on other materials.
Takes nano specifically into account	Yes.
Product/substance specific assessment	Yes. By EFSA CEF-Panel.

Legislation/product	**Plant Protection Products** (see 9.2.8)
Short definition	Substances which protect crops and plants from undesired organisms, or regulate plants growth.
Regulation	Plant Protection Products Regulation (Reg. (EC) No. 1107/2009)
Takes nano specifically	Yes (active ingredients), Possibly (formulations).

Legislation/product	**Plant Protection Products** (see 9.2.8)
into account	
Product/substance specific assessment	Yes. Active ingredients by EFSA, Formulation by national competent authority (Ctgb in the Netherlands).

Legislation/product	**Biocides / Biocidal Products** (see 9.2.9)
Short definition	Chemical substance or microorganism intended to destroy, deter, render harmless, or exert a controlling effect on any harmful organism.
Regulation	Biocidal Product Regulation (Reg. (EC) No. 528/2012).
Takes nano specifically into account	Yes.
Product/substance specific assessment	Yes. Active ingredients by ECHA, Formulation by national competent authority (Ctgb in the Netherlands). ECHA ad hoc working group for the Assessment of Residue Transfer to food (ARTfood) assesses biocidal residue transfer to food.

2.6 Prioritisation and considerations for follow-up

The scoring system (Table 1) is used to enable prioritisation between different signals in a systematic manner. Prioritisation is performed by ranking the different signals. Subsequently, a signal with relative high score that might be considered relevant can be further explored in view of regulatory coverage, (un)certainty, and whether the strength of the signal is increased by the identification of similar signals (i.e. the relation to other signals). With regard to legislation, uncertainty about regulations covering a product, development or material, or missing attention for nanomaterials in a certain legislation, add to the prioritisation.

A **prioritised signal** can be considered for follow up actions in different manners: by 1) further research on the signal in view of public health, which could reduce uncertainty on certain aspects, 2) enforcement, i.e. inspection or action, and/or 3) adapting or development of new regulation, or development of policy to cover potential risks (together with other stakeholders).

In the present methodology on nanomaterials in a food context, products, developments and materials were distinguished and prioritised separately, as they are different entities that cannot be directly compared, though materials often are or will be used in products. For example, developments are likely to consist of several general signals, whereas a signal on a product (or material) is likely much more specific with regard to the descriptors and key questions in Table 1, affecting the scoring result.

3 Identified signals

3.1 Identification of signals

The systematic literature search performed from January 2017 up to June 2019 resulted in a list containing 349 scientific publications and 77 grey literature and news items (Table 3), thus on average of about twelve scientific papers and two and a half additional items per month.

Table 3. Number of scientific publications and grey literature or news items resulting from the systemic literature search per month (sometimes two months are taken together).

2017	Scientific Publ.	'Grey' lit./ news	2018	Scientific Publ.	'Grey' lit./ news	2019	Scientific Publ.	'Grey' lit./ news
Jan	*23*	*1*	**Jan**	*5*	*4*	**Jan**	*11*	*4*
Feb			**Feb**			**Feb**	*20*	*0*
Mar	*8*	*0*	**Mar**	*15*	*3*	**Mar**		
Apr	*14*	*0*	**Apr**	*7*	*3*	**Apr**	*16*	*2*
May	*12*	*5*	**May**	*8*	*4*	**May**	*16*	*13*
Jun	*17*	*3*	**Jun**	*13*	*6*	**Jun**	*16*	*3*
Jul	*19*	*5*	**Jul**	*20*	*1*	**Jul**	*-*	*-*
Aug			**Aug**			**Aug**	*-*	*-*
Sept	*6*	*3*	**Sept**	*18*	*1*	**Sept**	*-*	*-*
Oct	*7*	*4*	**Oct**	*17*	*2*	**Oct**	*-*	*-*
Nov	*8*	*2*	**Nov**	*12*	*3*	**Nov**	*-*	*-*
Dec	*19*	*2*	**Dec**	*22*	*3*	**Dec**	*-*	*-*
Total	*133*	*25*	**Total**	*137*	*30*	**Total**	*79*	*22*

During the process of expert judgment, information non-relevant (see Figure 2) was excluded, for example, a scientific paper on encapsulation of vegetable oils as source of omega-3 fatty acids for fortified or functional food [14]. Though this paper mentioned once the word 'nano' in the abstract (and therefore was picked up by the literature search), its content was directed at microstructures. As another example, a news item on replacement of microbeads with the nanomaterial silicon dioxide was deemed 'not relevant' as it did not concern food, however, it has possible relevance for other areas (e.g. cosmetics) (see Figure 2). Information was combined when possible, with regard to their content. For example many scientific papers on nano-encapsulation systems in food were combined into one item.

A pre-selection of signals was made based on the information collection and expert judgement, in which also the number of information items was taken into account. From the pre-selection, a limited selection of nine signals was identified, which is presented in Table 4. Pre-selected signals not taken further taken into account included 'Uptake by plants', 'Cadmium selenide (CdSe) quantum dots', 'Nanoclay', 'Nanoselenium', 'Nanomagnesium oxide', and 'phage-engineering'. Information specifically on titanium dioxide (E 171) and silicon dioxide (E 551) was not selected as a signal, as there is already an alert for this material,

and several actions are currently ongoing [15-21].The nine signals which were selected (Table 4), are further described below.

Table 4. Nine signals selected by expert judgement for further systematic description and prioritisation (scoring).

Section	Signal	Source and reference(s)
3.2.1	**Effect of nanoparticles on gut microbiome**	Scientific publications: Jiang et al. (2018), Pinget et al. (2019), and Siemer et al. (2018) [22-24]
3.2.2	**Nanoparticles for iron fortification of foods**	Scientific publications: Fernandez-Mennendez et al. (2018), Shen et al. (2017), and von Moos et al. (2017) [25-27]
3.2.3	**Exposure to micro- and nanoplastic particles via food and drinking water**	Multiple scientific publications [28-32]
3.2.4	**Antibacterial Food Contact Materials**	Multiple scientific publications [33-41]
3.2.5	**Nano-cellulose**	Multiple scientific publications [42-46]
3.2.6	**Nanosilver**	Multiple scientific publications [33, 41, 46-49]
3.2.7	**Zinc nanoparticles**	Multiple scientific publications [50-57]
3.2.8	**Nano-encapsulation systems in food**	Multiple scientific publications [39, 58-83]
3.2.9	**Needle-like nano-hydroxyapatite in infant formulae**	NGO report [84], and Schoepf et al. (2017) [85]

3.2 Description of selected signals

According to the items from Chapter 2, the identified signals are further systematically described below. Where applicable, notes with regard to uncertainty are made.

3.2.1 *Effect of nanoparticles on gut microbiome*

Item	Description
Product, Development, or Material	Development
Short description of the content	The microbiome is the collection of micro-organisms, mainly bacteria, present on the barriers separating its host from the outside world. Lately, the microbiome, especially the gut microbiome, receives a lot of scientific attention. The gut microbiome is about 1.5 kg in weight and sometimes even considered as an additional, external organ with high metabolic activity. The activity and role of the gut microbiome has been related to various diseases, including Inflammatory Bowel Disease (IBD) (e.g. Crohn's disease). Some nanoparticles were reported to affect the microbiome. Therefore, exposure of the gut microbiome to nanoparticles has in some publications been associated with the occurrence of specific diseases

Item	Description
	[22-24]. On the other hand, nanoparticles could also be employed to improve the gut microbiome and contribute to an improved health too [22, 24].
Phys-chem description on material and quality assessment considerations	Siemer et al. (2018) studied and characterized the formation of complexes between 30 types of nanoparticles (many of which silicates) and 10 types of bacterial species, including probiotic as well as pathogenic bacteria, *in vitro* [24]. A second experimental study was performed by Pinget et al. (2019), who exposed groups of mice (n=10) for 4 weeks to food grade TiO_2 via the drinking water (back-calculated doses of 0, 2, 10 or 50 mg/kg bw/day) to study the effect of on the gut microbiome [23]. TiO_2 was characterized by Dynamic Light Scattering (DLS), Nanoparticle Tracking Analysis (NTA) and Scanning Electron Microscopy (SEM).
Hazard considerations	Dependent on the type and concentration of nanoparticles and the composition of the microbiome, nanoparticles could affect the microbial population with both negative as well as positive health effects [22, 24]. According to Siemer et al. (2018), depending on the type of nanoparticle, binding of nanoparticles with specific bacteria is possible [24]. The formation of complexes led to altered interaction with the immune system, possibly because the complex is recognized less effectively. This could both lead to increased as well as decreased inflammatory reactions. Siemer et al. (2018) suggest that, nano-particles could help to shape the microbiome, which could in principle be exploited to improve health [24]. In the experiment with mice by Pinget et al. (2019), though the effect on types of bacteria was shown to be minimal, their activity was altered by the two highest TiO_2 doses, shown as plasma values of metabolites of bacterial origin [23]. Also specific gene expression was altered, histological changes (crypt length), cytotoxic T-cells, and inflammatory cytokines were noted, and the number of macrophages increased. Such effects can be related to IBD [23].
Exposure considerations	For interaction between nanoparticles and the gut microbiome, nanoparticles need to reach the lower parts of the small intestine and especially the colon. The concentration of nanoparticles in the gut needs to be high enough to cause effects. The lower doses of TiO_2 used in the study by Pinget et al. (2019) are not that far from physiologically relevant [23], as realistic worst-case intake of TiO_2 is about 1 mg/kg bw/day for humans [20]. For humans, life-long exposure to nanoparticles should be taken into account.
Kinetic	Nanoparticles often have a low oral bioavailability. In that

Item	Description
considerations	case, the levels of insoluble particles are not expected to decrease considerably during transfer through the gastrointestinal tract and interaction with the microbiome is plausible.
Consideration on applicability of legal framework(s)	Effects on the role of the microbiome are currently not taken into account in any legal framework. The 2018 EFSA Guidance on nanomaterials, however, pays attention to effects on the microbiome [12]. According to this guidance, in view of the potential long-term exposure from food, potential effects of nanomaterials on the gut microbiome should also be considered especially in case a nanomaterial has antimicrobial effects [12].
Relation to other signals	Several scientific papers on this subject were published. Application of various nanoparticles could potentially affect the gut microbiome, and therefore this signal is automatically related to other signals (especially those concerning antimicrobial effects), e.g. nanosilver, zinc nanoparticles, etc.

3.2.2 *Nanoparticles for iron fortification of foods*

Item	Description
Product, Development, or Material	Material
Short description of the content	Iron deficiency is a health problem, especially for women. Fortification of foods with iron is a successful method to overcome iron deficiency. However, current practices have downsides. Conventionally, $FeSO_4$ (the 'golden standard') is used for iron fortification, however, this has negative effects with regard to taste. Also iron-EDTA is being applied, but it has a low bioavailability. Other iron substances are $FePO_4$ and iron oxides, though also their application is hampered by low bioavailability, and low solubility in aqueous solutions (such as food). Nanoformulations of iron could be used as a remedy for iron deficiency. Several methods for this have been described in scientific literature: Iron phosphate nanoparticles for food fortification combine good sensory properties with high bioavailability. In an *in vivo* study by von Moos et al. (2017) rats were exposed for 90 days to 35 or 350 mg/kg diet $FePO_4$ nanoparticles in 3 different particle sizes, or to conventional $FeSO_4$ [27]. Histopathology did not reveal toxic effects; no difference between iron accumulation and iron status (blood levels) between the 2 groups of smallest $FePO_4$ nanoparticles and $FeSO_4$ were found. In an *in vitro* study, effects on metabolic activity and membrane integrity were observed in different intestinal cells showing only negative effects for

Item	Description
	the largest $FePO_4$ particle size group (actually larger than nano-size). No significant effects for the other two $FePO_4$ nanoparticles groups or $FeSO_4$ were found. Shen et al. (2017) tested a hybrid nanomaterial of elemental Fe nanoparticles bound with fibrils made of beta-lactoglobulin from whey [26]. This yields a stable and soluble Fe source with high bioavailability. In the *in vivo* study iron deficient rats were exposed to 10 or 20 mg material/kg diet, or to $FeSO_4$ (the 'golden standard'). There were no significant differences in blood levels or iron accumulation in organs between the same doses of Fe nano-fibrils and $FeSO_4$. Fernández-Menéndez et al. (2018) investigated tartrate-modified nano-dispersion of oxo-hydroxide iron nanoparticles as a substance to be added to infant formulae in order to increase iron uptake [25]. This nanoform is capable of a delayed release of the iron. For the experiment, it was enriched with a stable Fe isotope. Two-week old rats were exposed ad libitum for two weeks to formula milk containing iron-nanoparticles (16 µg Fe/g milk powder), or $FeSO_4$ (16 µg Fe/g milk powder), or maternal feeding as a control. Milk powder was formulated in ultrapure water. Absorption of the iron from iron-nanoparticles was increased as expected. Despite the iron absorption from the iron nanoparticles showed no statistically differences comparing with iron absorption from $FeSO_4$ (at the same dose), it can be seen from the results that the Fe isotope used for formula milk fortification has been incorporated more efficiently [25].
Phys-chem description on material and quality assessment considerations	In the study by von Moos et al. (2017), the nanomaterials were characterized by X-ray diffraction and Transmission Electron Microscopy (TEM); the $FePO_4$ particles were near-spherical and in the size range 5-10 nm, 10-40 nm or 50-200 nm [27]. Shen et al. (2017) deployed several analytical techniques (TEM, X-ray Photoelectron Spectroscopy (XPS), Small-Angle Neutron Scattering (SANS), Energy Dispersive X-Ray Analysis (EDX)) for characterisation of the material; the iron nanoparticles with a diameter of 5-20 nm were attached to the fibrils (as analysed by TEM) [26]. Fernández-Menéndez et al. (2018) characterized the iron nanoparticles by TEM, X-ray Powder Diffraction (XRD), DLS, and Energy Dispersive Spectroscopy (EDS). According to TEM analysis, the iron nanoparticles had a diameter of 3.2 nm ± 0.7 nm [25].
Hazard considerations	Iron overload could lead to related toxic effects (iron poisoning). As iron (Fe) is a micronutrient and limited intake has negative effects on health, risk-benefit considerations could play a role in the safety assessment.

Item	Description
	With regard to the study by Shen et al. (2017), the authors state "although these initial results suggest a lack of toxicity, specifically designed long-term toxicity studies are needed to confirm these findings" [26]. For the application form, it should also be noted that people might be allergic to beta-lactoglobulin from whey. Because of the delayed release in the study by Fernández-Menéndez et al. (2018) the initial observations indicate superior safety of iron nanoparticles compared to soluble forms of iron, according to the authors [25].
Exposure considerations	Possible future applications can be in Functional foods, fortified with iron (e.g. meat-replacing products) or as food supplements. Up to date no concrete applications of $FePO_4$ nanoparticles or hybrid nanomaterial of Fe nanoparticles bound with fibrils made of beta-lactoglobulin are known. Because of possible health benefits, future applications of Fe nano-delivery strategies in food and/or in medicine seem obvious.
Kinetic considerations	It is not certain whether any different (toxico)kinetics of $FePO_4$ nanoparticles, Fe nano-fibrils, tartrate-modified nano-dispersion or oxo-hydroxide iron nanoparticles compared to $FeSO_4$ could possibly lead to a different distribution profile, accumulation of nanoparticles in certain organs and/or to iron overload.
Consideration on applicability of legal framework(s)	$FePO_4$ nanoparticles or hybrid nanomaterial of Fe nanoparticles bound with fibrils made of beta-lactoglobulin or tartrate-modified nano-dispersion of oxo-hydroxide iron nanoparticles would fit the definition of engineered nanomaterial according to the Novel Foods Regulation (EU) 2015/2283 [13], and safety assessment of such nanoparticles in products is therefore expected to occur. In this case, when this is nano-sized, according to the FIC Regulation it should be labelled as "[nano]" (when >50% of the particles are nano-sized). $FePO_4$ (ferric phosphate) is not on the list of minerals allowed to be added to Functional foods, fortified foods or food supplements according to Regulation (EC) No. 1925/2006 [86], on the addition of minerals to foods (and the Decree on addition of micronutrients to foods under the Dutch Commodities Act ("Warenwetbesluit Toevoeging micro-voedingsstoffen aan levensmiddelen" [87])). However, one can imagine other Fe-minerals which are on the list, such as ferric diphosphate, may be used as (partly) nano-sized [88]. Nanoparticles are not considered in Regulation (EC) No. 1925/2006, therefore the addition of some Fe salts containing nano-sized particles may go unnoticed.
Relation to other signals	Several scientific papers on this subject were published.

3.2.3 *Exposure to micro- and nanoplastic particles via food and drinking water*

Item	Description
Product, Development, or Material	Material
Short description of the content	Considerations on the exposure to and potential health risk of micro- and nanoplastic via food and drinking water, which can be present via contamination from degraded plastic. The interest in human health risks due to exposure to micro- and nanoplastics is growing and the number of publications on this topic grows rapidly.
Phys-chem description on material and quality assessment considerations	Microplastics are generally characterised as water-insoluble, solid polymer particles that are ≤ 5 mm in size. Micro- and nanoplastics are diverse in size, polymer type composition and shape. The lower size detection limit in many studies ranges between 5 and 500 µm [30], indicating that nanoplastics can yet not be measured reliably. The analytical determination of especially nano-sized plastic particles, including its physicochemical properties, is technically challenging and under development. Polyethylene (PE) and polypropylene (PP) have densities below 1 g/cm^3 and are buoyant in water, whereas polyvinyl chloride (PVC) and polyethylene terephthalate (PET) have densities between 1.3-1.7 g/cm^3. Presence of microfilms on particles may increase the density.
Hazard considerations	The plastic particles are poorly soluble and thus persistent [30]. Furthermore, the particles may sorb substances such as for hydrophobic chemicals and metals and provide a structure for microbes to grow on [29, 30]. Chemical toxicity could occur due to leaching of plastic associated chemicals (additives used in plastic as well as ad- or absorbed toxins). In addition, hazard may occur related to exposure to microbial pathogens. Limited data from animal studies suggest that microplastics may accumulate and cause particle toxicity by inducing an immune response [30, 89, 90].
Exposure considerations	Microplastics have been determined in honey, salt, sugar, beer, marine species and water [32]. Nevertheless, it is impossible to assess human exposure to micro- and nanoplastics through food consumption due to the lack of validated methods and standardisation [32]. Koelmans et al. (2019) reviewed the presence of microplastics in freshwater and drinking water [30]. Microplastics are frequently present in these waters and number concentrations spanned ten orders of magnitude ($1x10^{-2}$ – 10^8 per m^3). The overall order in detected polymers was PE ≈ PP > polystyrene (PS) > PVC > PET. Fragments, fibres, film, foam and pellets were the most frequently reported shapes. As indicated, more high quality data is needed to better understand human exposure.

Item	Description
	There is especially a need to quantify the presence of very small microplastics and nanoplastics in food and water matrices to allow exposure estimation. Cox et al. (2019) estimate that the annual microplastics consumption ranges from 39,000 to 52,000 particles depending on age and sex [28]. This increases with an additional 90,000 microplastics annually when only bottled sources are used rather than tap water. Furthermore, these estimates increase to 74,000 and 121,000 when inhalation is considered. The authors indicate that these estimates are subject to large amounts of variation, and that, given methodological and data limitations, these values are likely underestimates. The authors did not take the size of the plastic particles into account. They indicate that uptake in the gut is dependent on the size of the particles, and that limitations in the size classes of the plastic particles present in consumed items render it unclear to assess to what extent these plastic particles pose a risk to human health.
Kinetic considerations	It is unknown to which extent absorption of micro- and nanoplastics occurs in humans.
Consideration on applicability of legal framework(s)	Micro- and nanoplastics are contaminants in food, feed and water.
Relation to other signals	Multiple scientific papers on this subject were published.

3.2.4 *Antibacterial Food Contact Materials*

Item	Description
Product, Development, or Material	Development
Short description of the content	Nanomaterials can play a role because of antibacterial (or anti-microbial) properties in food contact material (FCM). Many publications appear on the application of nanomaterials in food packaging. Nanoparticles with antimicrobial properties can act as active components when added to a polymer, leading to a prolonged protective function of food packaging material. In addition to the application in food packaging, also metal surfaces of objects with contact to food can be treated with nanomaterials. For instance Oh et al. (2019) report the modification of aluminium surfaces with a combination of nano-silica and hydrocarbons [40]. Migration from food packaging and other FCMs is a concern because of potential toxicity in the human body, and the environment. As antibacterial activity remains after migration, this could also lead to bacterial resistance. For this reason, as waste, these nanoparticles could hamper circular economy.
Phys-chem description on material and quality assessment considerations	Most nano-applications in food packaging involve silver nanoparticles or nanoclay, however also metal-oxide nanoparticles (i.e. TiO_2, ZnO, SiO_2, Al-oxides, and CuO) can be used. Often they are encapsulated by polymers.
Hazard considerations	The level of toxicity is dependent on the type of nanoparticle, and not for all nanoparticles very well established.
Exposure considerations	If the nanoparticles need to be released for the antibacterial function, this means also migration to the contained food can take place, which eventually will result in human exposure. However, nanoparticles could also have a function within the packaging. Migration studies have demonstrated that only a negligible amount of nanomaterial migrates from packaging into food simulants or foods, suggesting that consumer exposure to these nanomaterials and its associated health risks would be low [35].
Kinetic considerations	None specifically for the use in FCM; when exposure to nanoparticles migrated from FCM takes place, the general kinetic considerations with regard to nanoparticles apply, dependent on the type of nanoparticle
Consideration on applicability of legal framework(s)	Most oxide-based nanocomposites are being developed and are not yet commercialised. In literature advantageous characteristics of these nanocomposites have been demonstrated. Often it seems difficult to determine migration of nanomaterials from packaging. Until

Item	Description
	satisfactory answers are provided on the level of nanomaterial migrating from packaging into actual foods, in which form (nanoparticles or ions) and about the level of toxicity, safety concerns will remain (for which guidance is available from EFSA [12]). This currently seems to prevent the widespread commercialisation of this application.
Relation to other signals	Multiple scientific papers on this subject were published. There is a relation with some of the specific materials, i.e. with the signals on nanosilver and zinc nanoparticles.

3.2.5 *Nano-cellulose*

Item	Description
Product, Development, or Material	Material
Short description of the content	Nanocellulose is a material for which a series of products and applications have been indicated. Various applications of cellulose nanomaterials are foreseen and are possibly already in use because commercial production of the material has started. Within the food and feed area, potential applications include reinforced plastic food packaging and replacement of synthetic polymers [42]. For example, Hayden et al. (2019) developed transparent nanopaper with UV-blocking functionality using cellulose nanoparticles as a biobased alternative for plastic [43]. Composite materials of nanocellulose and e.g. Ag, CuO or ZnO nanoparticles are proposed as antimicrobial food packaging material [42, 45, 46]. In addition, the high viscosity at low nanocellulose concentrations makes nanocellulose very interesting as a non-caloric stabilizer and gellant, whereas it can also function as suspension stabilizers and carrier/encapsulation material [44]. Cellulose nanomaterials are often seen as green, biocompatible and biodegradable materials that can be obtained from renewable sources. It may be useful as a barrier in grease-proof type of papers and for example mentioned as possible alternative to per- and polyfluoroalkyl substances (PFAS) containing food contact paper and board. Many different forms and applications of nanocellulose in the food/feed area are foreseen. Nanocellulose is mostly considered to be benign, though limited toxicity studies are available. It may form the basis of biobased and biodegradable alternatives to plastic or PFAS containing food contact paper and board.
Phys-chem description on material and quality assessment	Nanocellulose may be cellulose nanocrystal (CNC or NCC), cellulose nanofibers (CNF), cellulose nanowhiskers (CNWs) or bacterial nanocellulose, which refers to nano-structured cellulose produced by bacteria [91]. CNF have a typical fibril width of 5–20 nm and a wide of several µm and consist of

Item	Description
considerations	mixtures of amorphous and crystalline cellulose chains [44]. CNC consist of crystalline nanoparticles. Materials can be prepared from any cellulose source material, but woodpulp is normally used. Also nanocellulose foams are being studied. Many different forms of nanocellulose have been described, as developed with different processes and potentially chemically modified. Also chemical modification and combination with other substances or nanomaterials is possible [42]. Nanocellulose displays a high concentration of hydroxyl groups at the surface where reactions can take place.
Hazard considerations	A review by Endes et al. (2016) concludes that there are limited studies on nanocellulose available [91]. Especially *in vivo* oral toxicity studies seem to be lacking. Most studies show an overall benign nature of nanocellulose, whereas others stress the potential for adverse effects [91]. In 2018 the EFSA ANS-Panel published a scientific opinion on the re-evaluation of the safety of microcrystalline (plant-based) cellulose and chemically modified celluloses [92]. The particle size of the different forms of cellulose particles evaluated by EFSA is described as 'not less than 5 µm (not more than 10% of particles of less than 5 µm)'. It concludes that the celluloses are not absorbed and are excreted intact in the faeces. They could be fermented during their passage through the large intestine by strains of bacteria found in the human colon. Specific toxicity data were not always available for all the celluloses evaluated in the EFSA opinion and for all endpoints. Given their structural, physicochemical and biological similarities, the ANS-Panel considered it possible to read-across between all the celluloses. The acute toxicity of celluloses was low and there was no genotoxic concern, the no observed adverse effect level (NOAEL) values reported ranged up to 9,000 mg/kg bw/day. The ANS-Panel noted that the data provided by industry indicated that the majority of particles of individual modified celluloses were in the range of 10–100 µm. In addition, based on the known ability of cellulose particles to swell in water, the presence of nanoscale material after ingestion is considered highly unlikely.
Exposure considerations	Little is known about the actual use and exposure to nanocellulose. In 2015 a pilot plant for the production of nanocellulose was opened in Mumbai[3]. According to Endes et al. (2016), the commercial production of CNCs and NFC has been launched and world production is expected to increase [91]. Khan et al. (2018) indicates that nanocellulose represents an attractive material for many applications, also

[3] See https://en.wikipedia.org/wiki/Nanocellulose

Item	Description
	due to the low cost and renewable source [44].
Kinetic considerations	Reducing the particle size of cellulose to the nano-range may result in intestinal uptake of such particles. Persistence of particulate nanocellulose in the gastrointestinal tract can be expected as microcellulose is not degraded in the gastrointestinal tract of humans (including activity by bacteria in the colon), and excreted intact. In rat, nanocellulose can be degraded by bacteria present in the colon to some extent.
Consideration on applicability of legal framework(s)	Nanocellulose applications in the food-feed area would most likely require specific sectorial assessment (e.g. food additives) or would be seen as a Novel food. Hence, it can be assumed that an application of nanocellulose would require a safety assessment by EFSA.
Relation to other signals	Multiple scientific papers on this subject were published. Many different applications of nanocellulose have been proposed, including as part of antibacterial food contact materials and as nanocarrier/encapsulating material that are described as separate signals.

3.2.6 *Nanosilver*

Item	Description
Product, Development, or Material	Material
Short description of the content	Nanosilver contains a broad spectrum of antibacterial activities, which makes the nanoparticle interesting for the application in various domains of nano-food. These include e.g. use in food contact materials, during food processing, or the (potential) use in feed. Although the use in the food and feed domain in the EU is restricted, many applications are described in literature, and are sometimes current practice in other parts of the world such as in South Korea, Japan or the US. In the EU, silver in its elemental form is authorised as a food additive (E 174) in the EU in spirit drinks, specific confectionary, and decorations, coatings and fillings as a colourant. It is however unclear if E 174 contains nanoparticles [93]. The use in plastic FCM, however, is not allowed (apart from certain silver zeolites). In addition to many publications on the use of nanosilver as FCM in food containers, nanosilver can also be used in life-stock in order to increase meat production by fighting pathogens, [47], or in wine-making as a replacement of SiO_2, to prevent contamination by unwanted microorganisms [49]. A suspension with nanosilver particles (colloidal silver), also

Item	Description
	referred to as silver water, can be purchased via internet websites[4].
Phys-chem description on material and quality assessment considerations	Mainly the use of silver-nanoparticles is reported, but also nanosilver combined with other materials such as polyethylene glycol (PEG) or reduced glutathione (GSH) [49], or cellulose-nanofibrils are proposed [46].
Hazard considerations	There is a lack of data with regard to toxicity studies on silver nanoparticles. The EFSA ANS-Panel re-evaluated the safety of silver as a food additive (E 174). The ANS-Panel concluded that the information available was insufficient to assess the safety of silver as food additive: "The major issues included chemical identification and characterization of silver E 174 (e.g. quantity of nanoparticles and release of ionic silver) and the absence of specifications of the material used in the available toxicity studies". An aspect on which even less data are available so far, is the effect of nanosilver on the gastrointestinal flora, considering the antibacterial properties of silver.
Exposure considerations	With regard to the safety of FCMs, migration is important. In a Korean study, Choi et al (2018) tested the migration of silver from baby bottles, and its dependence on the food simulant contained and bottle material it was incorporated in [48]. Release from cutting boards was studied by Addo Ntim et al. (2019) [33].
Kinetic considerations	There are no kinetic considerations described within the publications. It is known that silver nanoparticles are systematically available (bioavailability 2-20%), and distribute to tissues, especially the liver [93].
Consideration on applicability of legal framework(s)	In the EU, silver or nanosilver is not on the Union list of approved substances according to Regulation (EU) No. 10/2011 and therefore not authorized for use in plastic FCMs [94]. The presence of certain silver zeolites is authorized in plastic food containers and rubber seals. Colloidal silver is not allowed according to Regulation No. 1925/2006 to be added as mineral to food. As the safety of colloidal silver could not be concluded upon by EFSA [95], colloidal silver is not allowed as food supplement (nor as Functional or enriched food). Colloidal silver is not authorised as a Novel food, nor as medicinal product, either. Nevertheless, such products can still be purchased online (though in some cases is described very vaguely how the product should be used).

[4] See for instance: https://www.nanomineralen.nl/nano-zilver/, https://www.puurcolloidaal.nl/product/colloidaal-zilver/ and www.colloidaalzilver.eu/nano/zilverwater.

Item	Description
Relation to other signals	Multiple scientific papers on this subject were published. The signal is closely related to the signal on antibacterial FCMs and effects on gut microbiome.

3.2.7 *Zinc nanoparticles*

Item	Description
Product, Development, or Material	Material
Short description of the content	Different potential applications of zinc oxide (ZnO) or phosphate-based zinc nanoparticles have been mentioned in a series of publications. These applications are related to the antimicrobial activity of these nanoparticles or the ability to absorb UV light. The use of ZnO nanoparticles in food contact material is to some extent allowed in the EU, based on the absence of migration of these particles. Zinc ions migrate to some extent. Several studies suggest that ZnO nanoparticles dissolve completely in conditions of the gastrointestinal tract. In this case, for hazard assessment, read-across to zinc-ions can be applied. A potential increase in intake due to new uses of Zn nanoparticles should be considered so that the upper limit of zinc intake is not exceeded.
Phys-chem description on material and quality assessment considerations	Mainly the use of ZnO-nanoparticles has been proposed, and in some cases phosphate-based zinc nanoparticles. Coated and uncoated ZnO nanoparticles have been described, mostly as granular material but also needle-shape is possible [53].
Hazard considerations	Wang et al. (2017) found that oral exposure to 250 mg/kg nanozinc oxides for 7 weeks reduced the body weight, increased serum glutamic-pyruvic transaminase activity, and increased the zinc concentrations of the serum, liver, and kidney while it did not affect the relative organ weight, intestinal microbiota, and other mineral concentrations (Fe, Cu, and Mn) in the kidney, liver, and thigh muscle [54]. Oral administration with 250 mg/kg soluble zinc sulphate showed more severe and acute toxicity [54]. Rats treated with various phosphate-based zinc particles showed higher Zn liver and kidney concentrations compared to controls [51]. Also changes in bacterial population in rat faeces were observed.
Exposure considerations	The use of zinc oxide nanoparticles as a transparent ultraviolet light absorber in unplasticised polymers is allowed at up to 2% by weight (see considerations on legal framework). Application of ZnO nanoparticles in food packaging due to their antimicrobial properties is proposed in scientific literature [52, 57]. Such particles may also be released from cans treated with ZnO. ZnO seems to be used

Item	Description
	in cans as ‘‘fine-particle-sized’’ or ‘‘finely divided precipitated ZnO’’, but no comprehensive characterization of the ZnO particles or nanoparticles is available [52]. Due to their antibacterial activity, ZnO nanoparticles and phosphate-based zinc particles have also been investigated for utilization in veterinary medicine [51]. ZnO nanoparticles in combination with other substances with an antibacterial activity such as the protein nisin have been investigated to reduce the microbial activity after addition to food (e.g. minced meat) [39]. Also the use of Zn nanoparticles has been mentioned as supplements of animal diets [47], and as a dietary source of zinc, e.g. for use as a Functional food [55, 56].
Kinetic considerations	According to Sohal et al. (2018), commercially available ZnO nanoparticles dissolved completely in gastric conditions and remained completely dissolved in the intestinal phase [96]. Complete dissolution of ZnO nanoparticles in simulated gastrointestinal tract conditions was also observed by Moreno-Olivas (2019) [52]. After 13 weeks of oral exposure to 130-540 mg/kg ZnO nanoparticles, Zn concentrations in the liver and kidney were significantly increased compared with the vehicle control [50]. Zn in spleen and brain were minimally increased.
Consideration on applicability of legal framework(s)	Zinc is an essential trace element, with a requirement of up to 12.7 mg/d for women and 16.3 mg/d for men [97]. Zinc ascorbate is therefore allowed as food supplement, taking in account that the upper level of zinc should not be exceeded [98]. ZnO nanoparticles are allowed to be used as food contact material; EFSA concluded that ZnO nanoparticles used as a transparent ultraviolet light absorber in unplasticised polymers at up to 2% by weight, do not migrate into food [99]. The migration for zinc ions complies with the specific migration limit (a note that the dietary exposure should not exceed the upper level of 25 mg/person has been added). According to EFSA ZnO “is a safe source of zinc for all animal species and no concerns for consumer safety are expected from the use of zinc oxide in animal nutrition, considering the maximum contents for total zinc in feeding set by EU legislation” [100]. Limited information on particle size is available, indicating that 50-63% of the particles were smaller than 63 µm. Though certain zinc salts are allowed according to Regulation No. 1925/2006 to be added as mineral to food, nanozinc is not authorised as a Novel food. Nevertheless, suspensions with nanozinc particles can be purchased online[5].

[5] See for instance: https://unlimitedhealth.nl/nl/the-health-factory-nano-zinc-200-ml, or https://www.nanomineralen.nl/nano-zink-koper/

Item	Description
Relation to other signals	Multiple scientific papers on this subject were published.

3.2.8 *Nano-encapsulation systems in food*

Item	Description
Product, Development, or Material	Development
Short description of the content	Numerous scientific publications, including many reviews, on the application of nano-encapsulation techniques are appearing. Such techniques are applied to a great variety of nanomaterials. Usually naturally occurring (bio-based) molecules such as food-grade ingredients are used to encapsulate, emulsify or contain substances with altered properties as a result. The various nanomaterials applied for encapsulation can generally be divided into carbohydrates, lipids, proteins and hybrid materials. The group of substances reported to be contained by nano-encapsulation techniques is as diverse, and includes anti-microbial agents (including bacteriocins, antimicrobial proteins and plant-derived antimicrobials), anti-oxidants, colorants, essential oils, fatty acids, flavours, minerals, nutraceuticals, (fish) oils, phenolic compounds such as flavonoids or curcumin, probiotics, and vitamins. Such substances are encapsulated in order to improve food quality, e.g. by improving the stability, preventing degradation or improving solubility of specific ingredients, or to increase optical transparency. Apart from developments in food quality, encapsulation techniques can also be used to further improve the nutritional value of food, e.g. by improving oral delivery, controlled release, epithelium permeability and bioavailability. For instance, the water solubility of vitamin D can be improved by nano-emulsions resulting in increased bioavailability, and lipid nanocarriers can be used to increase the uptake of lipophilic compounds such as carotenoids, tocopherols (including Vitamin E), omega-3 fatty acids or phytosterols. Encapsulation could for example be used for controlled release and targeted delivery. Improved food quality and nutritional value could positively affect human health.
Phys-chem description material and quality assessment considerations	The nano-encapsulation structures are generally produced from food-grade ingredients that are considered to be safe (i.e. naturally occurring molecules, substances with a Generally Regarded AS Safe (GRAS) status in the US, or registered as food additive). These include carbohydrates, lipids, and proteins (and combinations thereof). Many of these are already listed/registered as food additives. Carbohydrates can originate from plants, animals, bacteria or algae. Plant-based delivery systems include e.g. pectin, Arabic gum, guar gum, (malto)dextrins, starch and

Item	Description
	cellulose. Animal-based carbohydrate materials include chitosan, algae-based examples are alginate and carrageenan, and microbial based are dextran and xanthan gum. Lipids used can be polar or non-polar, which causes significant differences in their solubility and functional properties. Phospholipids are an example of polar lipids, triacylglycerol and cholesterol of non-polar lipids. Lipids can be applied as solid lipid nanoparticles, nanostructured lipid carriers and liposomes. Proteins that are frequently used in the food industry are obtained from plant or animal sources. The types of proteins which are applied is very diverse, for instance: beta-lactoglobulin, bovine serum albumin, casein, collagen, gelatin, gliadin, milk proteins, nisin, pea protein, silk fibroin, soy proteins or zein. In addition, hydrolysates and composites of different substances can be used too, such as pea protein isolate with canola oil, maltodextrin with gelatin, or arabic gum with gelatin. An example of frequently encapsulated substances are antimicrobials, for example nisin, pediocin, lactoferrin, lysozyme, bificin C6165, plant extracts (e.g. garlic extract) and essential oils (terpenes and terpenoids, aromatic and aliphatic constituents), or phytochemicals (thymol from thyme, curcumin). Several of the encapsulated substances are known food additives themselves (e.g. lecithin, nisin).
Hazard considerations	There is not much information available on hazards related to nano-encapsulation, as the focus of the studies is mostly on technological possibilities and benefits. Altered kinetics may cause undesired and uncharacterized effects. The nano-encapsulation enabled slow degradation or release, which may result in potential adverse effects because of higher bioavailability and other altered kinetics, and may also affect the intestinal microflora (microbiome).
Exposure considerations	Nano-encapsulation could be applied in food, Functional foods, food supplements, but also in food contact materials. Attention should be paid to ingredients that are normally degraded in the gastrointestinal tract, as encapsulation may lower, delay or even prevent degradation there. For example, antimicrobials that are not degraded in the gastrointestinal tract because of encapsulation may result in increased systemic exposure. On the other hand, as the compounds are less susceptible to degradation, a high concentration in a product may not be needed in order to reach a certain level in the body or product (i.e. for antimicrobial properties). In other words, the reason that some food-grade ingredients are considered to be safe may be that they are degraded in the gastrointestinal tract. Encapsulation may prevent or slow down this degradation, which may result in exposure, uptake (and potential adverse

Item	Description
	effects) that normally do not occur.
Kinetic considerations	Nano-encapsulation may lead to increased bioavailability and altered kinetics, or the prevention or slowing down of degradation of the ingredient in the gastrointestinal tract. Further information on the kinetic behavior of such products is limited, although it is acknowledged that knowing the fate and behaviour of nanoparticles in food and in the body is important for safety assessment. The 2018 EFSA Guidance on nanomaterials pays attention to encapsulation techniques, mentioning the possibilities and importance of altered kinetics [12].
Consideration on applicability of legal framework(s)	Different legal frameworks may be applicable dependent on the type of material used for encapsulation, as well as on the substance contained and its foreseen use and function. The application could be regarded as a Novel food depending on the encapsulation material and whether this qualifies the criteria in the Novel Foods Regulation. In this case, when this is nano-sized, according to the FIC Regulation it should be labelled as "[nano]" (when >50% of the particles are nano-sized). Novel foods need to be authorised by EFSA. However, it remains unclear whether these nano-encapsulations are excluded from the nano-definition used in the Novel Foods Regulation to which the FIC Regulation directs, or not, as it is dependent on the interpretation on the definition of "engineered nanomaterial". Nano-encapsulations could be prepared with compounds already present in food for decades (i.e. 'consumed "significantly" prior to May 15th 1997'), which would exclude them from the Functional foods definition. Nevertheless, the contained substance and its function could make the nano-encapsulation a Functional food. For instance an encapsulated nutrient with improved intake or bioavailability, a food additive (e.g. an encapsulated food preservative), or a food supplement (e.g. a nano-emulsion of specific nutraceuticals). In case of a Functional food, e.g. containing specific minerals, or intended as infant food, or for medical use this could mean it has to comply to specific legislations. Frameworks can be very different with respect to the level of authorisation practices: a food additive has to be authorised by EFSA, a food supplement containing nutraceuticals (other than vitamins and minerals) needs to be safe, according to the Dutch Commodities Act, which is less stringent (see section 2.5).
Relation to other signals	As an indication of the size of this development, it is important to realise there are numerous scientific publications on this topic. The present signal is based on a limited selection of about 25 scientific publications, which is less than a quarter of the articles on this precise subject a year (during the last years according to a search in Scopus on just the string 'nano-encapsulation AND food'). There is a

Item	Description
	relation with the signal about antibacterial FCMs, as these could be applied as a nano-encapsulate.

3.2.9 *Needle-like nano-hydroxyapatite in infant formulae*

Item	Description
Product, Development, or Material	Product
Short description of the content	Among other nanoparticles, needle shaped nano-hydroxyapatite has been detected in several US infant formulae. The dissolution of such particles in acidic environments was tested: after 2 hours, 60% of a representative amount dissolved in pH 5 or pH 1.6 fluids, mimicking different stomach environments, while under neutral pH (pH 7) conditions only 6% dissolved. Needle-shaped particles dissolved better than spherical nano-hydroxyapatite particles. The authors speculate that needle-shaped nano-hydroxyapatite was added because of the increased dissolution and the resulting higher bioavailability of calcium and phosphate compared to regular calcium phosphate. Remarkably, the use of needle-shaped nano-hydroxyapatite particles has been banned by the Scientific Committee on Consumer Safety (SCCS) for the use in oral cosmetic products such as toothpaste and mouthwash [101].
Phys-chem description material and quality assessment considerations	Analysis of the nanomaterials in samples was performed by TEM, SEM and EDS techniques.
Hazard considerations	The SCCS has banned the use of needle shaped nano-hydroxyapatite in oral cosmetic products in an opinion, as such particles may become systemic available [101]. It is uncertain whether the particles are able to be absorbed in the gastrointestinal tract, and if so, what the consequences for health would be (if any). According to the SCCS there is insufficient evidence to conclude that nano-hydroxyapatite is safe. The use of this form of hydroxyapatite may be beneficial for infants, as it may increase the bioavailability of calcium and phosphate. Additional information would be needed to allow for science-based risk-benefit considerations. This would only be relevant if needle-shaped hydroxyapatite is applied in Dutch/EU infant formulae.
Exposure considerations	It is unclear if needle-shaped nano-hydroxyapatite is present in EU infant formulae, and thus whether exposure is possible. Infants can be regarded as a sensitive population,

Item	Description
	also because the stomach pH can be relatively high resulting in less dissolution of the particles.
Kinetic considerations	It is uncertain whether the particles are (all) dissolved in the stomach, especially for young children. It is also uncertain what the fate of the particles would be if the particles are able to be absorbed in the gastrointestinal tract.
Consideration on applicability of legal framework(s)	Hydroxyapatite is not explicitly mentioned as being allowed (or not) to be used in infant formulae according to Regulation (EU) No. 609/2013, as this regulations allows different forms of calcium salts, including salts of orthophosphoric acid [102]. However, "calciumhydroxyapatite" seems to be a synonym for E 341(iii) – tricalciumphosphate (a calcium salt of orthophosphoric acid) in Regulation (EU) No. 231/2012 [102], deciding on the specifications of the food additives allowed in Regulation (EC) No. 1333/2008 [103]. Regulation (EU) No. 1129/2011 allows the use of E 341 in certain food products and medical food products for infants [104]. It depends on the interpretation of these definitions whether hydroxyapatite is allowed in infant formulae in the EU, and whether it can be potentially present in a nano-sized form, including its needle-shaped form.
Relation to other signals	None

4 Scoring and prioritisation

4.1 Scoring

Seven experts individually scored the identified signals described in Chapter 3 according the descriptors and questions in Table 1. The summarized results are shown in Table 5 (See Appendix 3 for the table with the individual scoring data). For all signals, the descriptor 'Exposure' has the highest contribution to the total score. The level of contribution of the other descriptors differs between the signals. As mentioned earlier, for relevant comparison of signals they need to be compared within each group of products, materials or developments. Signals describing products or materials are in general more specific and therefore likely to receive a lower number of 'unknown' answers to the questions due to the more specific description and thus a relatively higher score than signals describing developments.
There is only one signal identified within the group 'products': Needle-like nano-hydroxyapatite in infant formulae, with a total score of 159 (Table 5). This signal scored high on the descriptor 'Physicochemical properties' (in addition to 'Exposure') because of concern regarding persistency and rigidity because needle-like nano-hydroxyapatite is a HARN. The variation in total scores for the three identified signals under 'Developments' was small, ranging from 147 to 164 (Table 5). The highest total score of 164 in this group was for 'Nano-encapsulation systems in food', mainly due to a high score of the descriptor 'Kinetics' (in addition to 'Exposure'). The variation in range of total scores for 'Materials' was larger: 125 to 205 (Table 5).
The signals 'Exposure to micro- and nanoplastic particles via food and drinking water' (205), 'Nanosilver' (187), and 'Nanoparticles for iron fortification of foods' (179) accounted for the highest scores within this group. 'Exposure to micro- and nanoplastic particles via food and drinking water' received the highest score with all descriptors contributing about equally to the total score (in addition to 'Exposure'). This signal received the highest scores due to concerns on dissolution/degradation, and immunotoxicity (Table 5). The signals 'Nanosilver' and 'Nanoparticles for iron fortification of foods' scored high because of the descriptor 'Kinetics' (in addition to 'Exposure').

As can be seen from the table in Appendix 3, although different experts noted different scores, the resulting trend between signals usually seems similar. The different experts had their own system of scoring, resulting in systematically higher or lower values compared to the other experts. However, the order of ranking of the signals is generally the same.

4.2 Prioritising signals

In order to prioritise the signals based on the former scoring, the highest scoring signal per group has been selected (for the group 'product' there was only one). These three signals were supplemented with the second and third highest scoring signals from the group Materials. These prioritised signals were further explored in Chapter 5, sometimes by including additional information to obtain a broader perspective.

*Table 5. Total scoring of the different signals per descriptor and key questions according to Table 1, by 7 different experts. The signals are categorised in 'product', 'development' and 'material' groups. The summed scores per subject and the total sum of the expert scores are indicated in bold. The maximum score per cell (non-bold) is 21 (7*3). A table with the individual scoring per expert can be found in Appendix 3.*

Signal	**Physicochemical properties (Pchem)**				**Hazard**				**Kinetics**				**Exposure**				**Total Score**				
	Dissolution/ degradation	Reactivity	Toxic ions/ molecules	HARN	CMR	Mutagenicity/ carcinogenicit	Immunotoxicit y	Other toxicity	Absorption	Distribution brain and	Accumulation	Other kinetic profile	Widely used	Sensitive subpopulation	Frequent use	Likely exposure	**Pchem**	**Hazard**	**Kinetics**	**Exposure**	**Total (sum of expert**
Product																					
nano-hydroxyapatite in infant formulae	13	10	2	17	1	8	7	7	9	7	6	9	8	19	17	19	**42**	**23**	**31**	**63**	**159**
Development																					
effect of NPs on gut microbiome	9	11	6	3	3	8	9	10	6	3	6	11	19	19	19	17	**29**	**30**	**26**	**74**	**159**
antibacterial food contact materials	11	9	10	1	4	6	7	6	7	6	7	9	21	13	17	13	**31**	**23**	**29**	**64**	**147**
nano-encapsulation systems in food	8	5	5	2	4	4	8	9	19	6	7	19	19	15	17	17	**20**	**25**	**51**	**68**	**164**
Material																					
NPs for iron fortification foods	7	4	11	2	2	2	11	11	19	5	9	14	21	21	19	21	**24**	**26**	**47**	**82**	**179**
Exposure to micro-/nanoplastics	19	4	15	6	4	4	19	10	9	6	15	12	21	21	21	19	**44**	**37**	**42**	**82**	**205**
nano-cellulose	17	5	1	3	0	2	4	5	4	2	4	6	21	15	19	17	**26**	**11**	**16**	**72**	**125**
nanosilver	8	9	21	2	3	5	11	15	17	10	15	11	15	15	15	15	**40**	**34**	**53**	**60**	**187**
zinc particles	7	6	12	3	2	4	5	16	14	5	11	8	15	13	14	13	**28**	**27**	**38**	**55**	**148**

5 Assessment of prioritised signals

On request by the NVWA, the five signals that were prioritised on their scores in Chapter 4, were supplemented with another signal on Poorly Soluble and Low acute Toxicity (PSLT) particles. The prioritised signals were further explored with respect to their prioritisation and regulatory coverage, and discussed in order to come to recommendations. The additional signal, which was selected in advance, it is explored whether exposure, toxicity and risk assessment of different PSLT particles should be considered as a mixture or whether separate assessment of such particles would suffice. For technical details on the five prioritised signals, please refer to the respective sections in Chapter 3.

5.1 Assessment of selected signals

5.1.1 *Nanoparticles for iron fortification of foods*

Iron fortification of foods is an approach to prevent iron deficiency through the diet. Conventionally, iron sulphate ($FeSO_4$) is used, but this gives unpleasant taste effects and causes oxidation in the products by which it is contained. Iron-ethylenediaminetetraacetic acid (EDTA) is also used for fortifications, but displays low bioavailability. Other options include fortification with iron phosphate ($FePO_4$) or iron oxides, but both have a low solubility (which also makes it difficult for use in food) and bioavailability. To counteract such disadvantages, nanoparticles for iron fortification were developed, combining suitable sensory properties with high bioavailability [25-27].

Prioritisation

The signal 'Nanoparticles for iron fortification of foods' (Section 3.2.2) scored high because of the descriptor 'Kinetics' (in addition to 'Exposure'). Distribution and accumulation of nano-iron can be different from that of non-nano-iron, which can result in altered toxicity [105, 106]. To establish differences in kinetics between nano- and non-nano-iron, it should be assessed if the nano-iron particles dissolve quickly in the gastrointestinal tract, as this would render it likely that the iron would behave similar to soluble iron forms. If the nano-iron particles do not quickly dissolve in the gastrointestinal tract, further assessment is needed.

In order to gain better insight into the possible risks of nano-iron particles for humans, it will be necessary to study in particular the distribution throughout the body and possible accumulation in certain organs, after long-term exposure. The potential risk from lifelong exposure in humans may not be covered by subchronic toxicity studies in rats.

Regulatory coverage

The iron nanoparticles being developed as mentioned in the signal (Section 3.2.2), are clearly nano-sized and intentionally produced. Therefore, these could fit in the definition of an engineered nanomaterial according to the Novel Foods Regulation, and risk assessment of such nanoparticles in products should be performed according to the 2018

EFSA Guidance on nanomaterials [12]. According to this guidance, the dissolution (degradation) of the material in the gastro-intestinal tract should be assessed. Nanomaterials that quickly degrade can be expected not to show nanorelated behaviours.
If iron particles in a food product are indeed nano-sized, "[nano]" should be put on the label after the ingredient consisting the nanoparticles according to the FIC Regulation (when >50% of the particles are nano-sized). It is possible that a material containing nano-iron particles is not recognised as a Novel food, for example because of the interpretation of the term 'engineered nanomaterial'. With particles of iron salts that are allowed in food supplements or fortified food, functional foods could be developed (partly) in nano-size as well. Also the use of such nanoparticles in fortified foods or in food supplements, may go unnoticed, as there is no authorisation procedure and Regulation (EU) No. 1925/2006 does not take nano-properties into account [86].

Discussion
The union list of Novel foods (see Section 9.2.1) does mention two powdered iron salts, i.e. ferric sodium EDTA and ferrous ammonium phosphate. However, the information provides no insight whether these consist of or contain nano-sized particles or not. Given the possibilities of nano-sized iron particles an application of nano-iron is obvious. Furthermore, a Fe fortification product with ferric pyrophosphate that contains at least a fraction of nano-sized iron particles [107], has recently been approved by the US-FDA[6], indicating that such products may also become available on the EU market in the near future. Applications seem especially likely for e.g. preventing anemia or, enriching vegetarian meat substitutes, because meat is naturally an important dietary source of iron. If the iron for fortification consists solely of nanomaterials and is developed for its increased bioavailability, it is expected to fall under the Novel Foods Regulation. This means that EFSA needs to assess the safety before market introduction. However, if a fraction of the particles is nano-sized, it is less clear whether the Novel Foods Regulation applies. Other Regulations, such as on the addition of vitamins and minerals and of certain other substances to foods, does not consider nano-sized particles. There is no regulation with specific specification for nutrients, in contrast to food additives. Hence, some of these products may go unnoticed.
It should be noted that a risk-benefit assessment could additionally be a part of the overall assessment because a low iron status can result in an adverse health effects as well.
Bottled water with iron nanoparticles is sold online[7] and it is not clear whether the risks (and benefit) have been assessed properly. In principle, the Novel Foods Regulation should apply, but because these products are sold solely via web shops, often with an non-specific description of the product and its use, registration and assessment may not have occurred.

[6] See: https://www.newhope.com/supply-news-amp-analysis/sunactive-iron-achieves-unlimited-gras-status-foods-and-beverages
[7] See for instance: https://www.nanomineralen.nl/nano-ijzer/, https://unlimitedhealth.nl/nl/nano-mineraalwater-ijzer-1000-ml?gclid=EAIaIQobChMI-7Pc4-mR5QIVAuJ3Ch0e-g-bEAAYASAAEgJSyPD_BwE, or https://www.vitaminadviceshop.nl/nl/396312/nano-ijzer-200-ml/

5.1.2 *Exposure to micro- and nanoplastic particles via food and drinking water*

Concerns consists about the potential health risk of exposure to micro- and nanoplastic via food and drinking water. Micro- and nanoplastic particles are mainly present from contamination by degraded plastic.

Prioritisation

'Exposure to micro- and nanoplastic particles via food and drinking water' (Section 3.2.3) gained the highest score of all signals and all descriptors contributed about equally to the total score (in addition to 'Exposure'). The signal also gained the highest scores due to concerns on dissolution/degradation, and immunotoxicity (Table 5).

The presence of microplastics has been detected in various food and drinking water. Meanwhile, microplastics have been detected in human stool too [108]. The concerns with regard to dissolution/degradation (Table 5) arise from the fact that plastic particles are poorly soluble and persistent. With regard to immunotoxicity, According to the signal, a limited number of studies suggest that microplastics may accumulate and cause immunotoxicity, i.e. particle toxicity by inducing an immune response [30, 89, 90]. Furthermore, there is concern because the particles may adsorb other substances and provide a structure for microbial growth [29, 30]. A recent study, including a 28-day feeding study with mice, found only limited uptake of particles in the gastro-intestinal tract, and did not show histologically detectable lesions and inflammatory responses [109]. However, considering the persistent nature of micro- and nanoplastics, effects after long-term chronic exposure are more likely to occur than after 28-days.

Regulatory coverage

There are legal limits for *the release*, i.e migration of the constituents from plastic food contact materials into food, i.e. in Regulation (EU) No. 10/2011 on plastic materials and products? intended to come into contact with food [94], and also in Commission Regulation (EC) No. 282/2008 on recycled plastic materials and articles intended to come into contact with foods [110]. In contrast, there are no legal limits for *the amount* of micro- or nanoplastics in certain foods.

With regard to drinking water, the Drinking Water Directive is being revised including its monitoring parameters. Likely, the revised Drinking Water Directive will include a monitoring obligation for the presence of microplastics in the water bodies used for the drinking water production as part of the hazard assessment [111, 112]. Recently, also research needs for microplastics in drinking water have been postulated by the WHO [113].

With regard to food, EFSA took a first step in 2016 towards a future assessment of the potential risks from micro- and nanoplastics in food, especially seafood. This has been done in the form of a comprehensive literature review on presence of micro- and nanoplastics in food (with particular focus on seafood) including an overview of scientific developments, identifying data and knowledge gaps and recommending future research priorities to address them [114]. Science Advice for Policy by European Academies (SAPEA) recently published an overview on the current knowledge on potential risks of micro- and nanoplastics [115]. They concluded that the best available evidence suggests that microplastics and nanoplastics do not pose a widespread risk to humans

or the environment, except in some locations. However, evidence is limited, and the situation could change if pollution continues at the current rate [115].

Discussion

The interest in human health risks due to exposure to micro- and nanoplastics is growing resulting in an increasing number of publications on this topic. It is unknown to which extent absorption of micro- and nanoplastics occurs in humans. Microplastics have been determined in honey, salt, sugar, beer, marine species and water, including drinking water [30, 32, 116]. Nevertheless, it is impossible to assess human exposure to micro- and nanoplastics through food consumption due to the lack of validated and standardises analytical methods [32]. There is a need to quantify the presence of very small microplastics and nanoplastics in food and water matrices to allow for exposure estimation. Although analytically challenging, it can be expected that only very small particles are taken up by the human body after (oral) exposure. In addition, there is insufficient data with regard to toxicity of nanoplastic and risk assessment should include an assessment of possible accumulation of nanoplastic particles over time. It is highly recommended to follow the developments in this field and to develop further scientific knowledge on the presence, exposure and toxicity (including toxicokinetics) of micro- and nanoplastics in food.

5.1.3 *Nanosilver*

According to the literature, nanosilver displays a broad spectrum of antibacterial activities, which makes it interesting for application in food contact materials such as in food packaging or during food processing, or other (potential) uses in food and feed. Some of such applications seem to be current practice in other parts of the world, such as in South Korea or in the US. In the EU, however, nanosilver is not allowed in plastic food contact materials, and only elemental silver (which could potentially consist partly of nanoparticles) has only a limited use as food additive. Another issue which deserves attention is the use of nano-sized colloidal silver, e.g. in bottled mineral water. This is sold online for 'detoxification' purposes, whereas the risks, nor the benefits, have not been assessed properly.

Prioritisation

The signal 'Nanosilver' (Section 3.2.6) scored high because of the descriptor 'Kinetics' (in addition to 'Exposure'). It is known that silver nanoparticles can be absorbed after oral exposure and reach the systemic circulation (bioavailability 2-20%), and distribute to tissues, especially the liver [93].

Apart from potential systemic toxicity, considering the antibacterial properties of silver, the effect of nanosilver on the gastrointestinal flora (microbiome), is of concern, as well as is its possible role in antimicrobial resistance. For such reasons, SCENIHR and the German Federal Institute for Risk Assessment (BfR) reported critically on the application of nanosilver [117, 118].

Regulatory coverage

Although the use of nanosilver in the food and feed domain is restricted in the EU, silver in its elemental form is authorised as a food additive (E 174) in liquers, external coatings of confectionary, decoration of chocolates [103]. It is unclear to which exact extent E 174 contains nanoparticles [93], but this could possibly be considerable. There appear to be differences between pristine and E 174 contained in food stuffs, the latter containing a smaller number of nanoparticles [119]. However, the formation of silver nanoparticles from silver ions *in vivo* has been demonstrated [120]. During the re-evaluation of E 174, the EFSA concluded that the information available was insufficient to assess the safety of silver as food additive. The major issues include chemical identification and characterization of E 174 and the absence of specifications of the material used in the available toxicity studies [93]. In 2018, a call for scientific and technical data on E 174 has been published [121] and EFSA will continue the safety assessment of E 171 once these data are made available.

The use of silver in plastic food contact material is not allowed in the EU (apart from certain silver zeolites). Silver, or nanosilver, is not on the Union list of approved substances according to Regulation (EU) No. 10/2011 and therefore not authorized for use in plastic FCMs [94]. The presence of certain silver zeolites is authorized in plastic food containers and rubber seals.

Colloidal silver, e.g. in bottled mineral water is not allowed according to Regulation No. 1925/2006 to be added as mineral to food. As the safety of colloidal silver could not be concluded upon by EFSA [95], colloidal silver is not allowed as food supplement (nor as Functional or enriched food). In addition, colloidal silver is not authorised as a Novel food, or as medicinal product, either. Nevertheless, such products can still be purchased online, marketed as a dietary supplement and alternative medicine cure-all.

It should be noted that nanosilver can also be used as biocide, in two product types related to food: Disinfectants cleaners in domestic kitchens (PT04), and drinking water disinfection (PT05). There are currently no such PT04 applications authorized in the Netherlands. Some PT05 applications have been authorized in electrodes to fight Legionella bacteria[8].

Discussion

Multiple scientific papers on nanosilver in relation to food were published. Naturally, the signal is closely related to the signal 'Antibacterial food contact materials' (which was not prioritised). Most areas seem to be well regulatory covered, i.e. with regard to food contact materials, and the use in food. However, as nanosilver is allowed in food contact materials outside the EU, it could be checked whether such products can enter the EU market. Therefore, it is recommended to monitor the presence of nanosilver in food contact materials. Another issue which deserves attention is the use of nano-

[8] See: https://toelatingen.ctgb.nl/nl/authorisations

sized colloidal silver, e.g. in bottled mineral water, which is sold online for 'detoxification' purposes, whereas the risks, nor the benefits, have not been assessed properly[9].

5.1.4 *Nano-encapsulation systems in food*

There are many publications about nano-encapsulations and (mainly) about their technical functionality. Nano-encapsulation systems can be used for improved bioavailability, controlled release or targeted delivery of the encapsulated substance. Nano-encapsulation systems may also provide benefits such as increased bioavailability and increased stability of the encapsulated substance by protection against environmental conditions from outside, within the product or in the gastrointestinal tract. Many different food-grade substances are indicated or have been used in nano-delivery systems. This is a good starting point for the development of safe products, but further information is needed to fully assess the safety of materials or products.

Prioritisation

The highest total score of 164 within the group Developments was reached by 'Nano-encapsulation systems in food' (Section 3.2.8), for which, in addition to 'Exposure', the descriptor 'Kinetics' contributes subsequently to the total score (Table 5).

Safety issues may arise due to a different (toxico)kinetics of the encapsulated substance compared to the non-nano-form, resulting for instance in a different distribution profile or increased bioavailability. This may lead to higher internal concentrations. In case of materials that are normally degraded in the gastrointestinal tract, encapsulation may lead to absence or a reduction of this degradation and should be considered in the risk assessment.

Regulatory coverage

Nano-encapsulation can be used for various products falling under different legal frameworks. The regulations as well as the attention for nanoparticles herein differ greatly between frameworks. On one hand, for products falling under the scope of Novel foods, Food contact materials, Food additives or Plant Protection Products, implications of any significant alteration (increase) in bioavailability leading to potential harmful effects should be considered according to the 2018 EFSA Guidance on nanomaterials [12]. On the other hand, application of nano-encapsulation in food or herbal supplements, which are less regulated, may be unnoticed. The safety assessment should consider the following three different forms: the active ingredient per se, the encapsulating material, and the encapsulate/nanocarrier as a whole.

Discussion

The large number of publications in this area suggests that considerable effort is put in this development, and products and materials are likely to find their way to the market. The 2018 EFSA Guidance on nanomaterials addresses potential safety issues, at least in certain

[9] See for instance: https://www.nanomineralen.nl/nano-zilver/, https://www.puurcolloidaal.nl/product/colloidaal-zilver/ and www.colloidaalzilver.eu/nano/zilverwater.

regulatory areas. However, potential safety issues in other fields, such as food or herbal supplements, may be missed. Therefore, it is recommended to follow developments in this field. In addition, it is recommended to develop further scientific knowledge on the likelihood of a different (toxico)kinetic profile and related hazards for nano-encapsulated substances related to food.

5.1.5 *Needle-like nano-hydroxyapatite in infant formulae*

In several US infant formulae needle shaped nano-hydroxyapatite has been detected. It was speculated that it was added because of the increased dissolution and resulting higher bioavailability of calcium and phosphate, compared to regular calcium phosphate. The use of needle-shaped nano-hydroxyapatite particles has been banned by the SCCS for the use in oral cosmetic products such as toothpaste and mouthwash [101].

Prioritisation

This signal 'Needle-like nano-hydroxyapatite in infant formulae' (Section 3.2.9) was prioritised as an illustration of the group products, as only one signal was identified in this group. Its total score of 159 (Table 5) does, however, not seem very high, although it cannot be compared to the total scores of other products. As with other signals, it scored high on the descriptor 'Exposure'. For this signal, this also includes the sensitive subpopulation of infants involved. However, it is unclear whether needle-shaped nano-hydroxyapatite is present in EU infant formulae.

The signal also scored high on the descriptor 'Physicochemical properties' because of concern with regard to persistency and rigidity (i.e. being HARN); needle-like nano-hydroxyapatite indeed fits within the HARN definition [85].

Regulatory coverage

Hydroxyapatite is not mentioned in the union list of substances that may be added to infant formulae in the EU according to Regulation (EU) No. 609/2013 [122]. As 'calcium hydroxyapatite' seems to be a synonym for tricalciumphosphate (food additive E 341(iii)), which is allowed in certain products for infants according to Regulation (EU) No. 231/2012 [102], it is unclear if nano-hydroxyapatite in food is covered by this. Regulations on infant formulae do not mention 'nano' specifically. As nutrients do not have regulated specifications, changes of allowed substances to a nanoform may go unnoticed. Nano-sized phosphate particles was addressed in the recent re-evaluation of phosphates (including E 341(iii)) by the EFSA FAF-Panel [123]. The FAF-Panel noted that based on the data, it is conceivable that a small proportion of these particles may be in the nano-range. They recommend revising the current specifications of phosphates (in Regulation (EU) No. 231/2012). This revision should include characterisation of particle size distribution, which should be obtained according to analytical methodology in compliance with the 2018 EFSA Guidance on nanomaterials [12]. Differences in crystalline structures (e.g. needle-like or spherical) have not been addressed by the FAF-Panel, however, when the methodology of the 2018 EFSA Guidance on nanomaterials is to be followed, such differences should be reported [12].

Discussion
Nano-hydroxyapatite may act as a more bioavailable form of calcium and/or phosphate, and may have a benefit. At the same time, there are concerns related to the shape of the material, and there is uncertainty if the nanomaterial is fully dissolved before absorption. Because of these concerns and the policy to be highly protective for infants, it is recommended to analyse Dutch/EU infant formulae on the presence of needle-shaped nano-hydroxyapatite (or request producers to provide this information) as it is unclear whether needle-shaped nano-hydroxyapatite is present in EU infant formulae. As a start, the feasibility of detection methods of these needle-shaped nano-hydroxyapatite nanoparticles could be assessed. Next, Dutch/EU infant formulae can be analysed. Finally, if this nano-hydroxyapatite is present in Dutch/EU infant formulae, additional information on increased bioavailability and uptake and of potential hazards of nano-hydroxyapatite would be needed to allow for risk-benefit considerations.

In addition to particle size distribution characteristics as recommended by EFSA, different crystalline structures should be addressed in the specifications of E 314 (iii) in order to clarify whether nano-hydroxyapatite (including the needle-shaped form) are covered by this food additive.
Apart from the possible presence of needle-like nano-hydroxyapatite in Dutch infant formulae, also additional assessment of the presence of this nanomaterial in other calcium-enriched products, such as calcium-fortified milk, could be considered.

5.1.6 *Poorly Soluble and Low acute Toxicity (PSLT) particles*
The sixth signal was not prioritised according to the present methodology, however, selected in advance on request by the NVWA. With no clear starting information, the signal is explored in a different format as compared to the other prioritised signals.
Poorly Soluble and Low acute Toxicity (PSLT) particles as a group received a lot of attention lately, e.g. by Borm et al. (2019) [124, 125]. The aim of this signal is to assess the available scientific information whether co-exposure to different PSLT particles could result in an additive effect and whether this should be taken into account in risk assessment.

What are PSLT particles?
Granular particles that are poorly soluble under normal physiological circumstances and have low acute toxicity, are considered to be part of the group PSLT. There is no clear definition or description on the meaning of 'PSLT', 'Poorly Soluble' and 'Low acute Toxicity'. For this reason, Borm & Driscoll (2019) argued for a better definition of the concept PSLT [124]. Also the terms granular biodurable particles (GBP) or Poorly Soluble Particles (PSP) have been suggested [126, 127].

In the present description of PSLT, low *acute* toxicity rather than low toxicity is used. This is because these particles may show low toxicity based on available information which is mostly on acute (*in vitro*) toxicity, but long term effects cannot be excluded. For this reason, such particles are sometimes referred to as the more general term Poorly Soluble Particles (PSP). Due to the poor solubility, the particles are

persistent in the gastrointestinal tract and within cells. When taken up by cells, the particles tend to accumulate over time upon repeated exposure. This accumulation in tissues increases the likelihood for long-term effects. Effects that have been related to PSLT particles include chronic inflammation and carcinogenicity in rats (Braakhuis et al., accepted for publication), which cannot be considered as 'acute' or 'low' toxicity.
As examples, TiO_2, CeO_2 and Au particles are considered to be PSLT particles, whereas ZnO and CuO are not, due to their higher dissolution rate.

It should be noted that there are different forms of a specific PSLT materials (e.g. for TiO_2 or CeO_2). These forms differ in physicochemical properties such as size distribution, crystal structure, shape and surface properties (coatings, functionalization). These differences can affect the behavior of the nanomaterial in many ways, including its solubility/dissolution rate, the exposure, toxicokinetic behaviour and hazard of the material. These different forms should thus be regarded as different materials for which the issue of co-exposure, additive effect and risk assessment can be applicable.

Why is co-exposure and additive effect of importance?
Due to the above-described potential for accumulation, the widespread use and presence of PSLT particles in a.o. food and consumer products will result in co-exposure to different of these (nano)particles. When such PSLT materials act in the same manner, this may bring about an additive effect. The present signal focuses on whether such an additive effect can be expected and should be taken into consideration in risk assessment of PSLT particles, rather than assessing each particle separately. The latter is presently common practice.

When can an additive effect be expected?
In order to have an additive effect of different PSLT particles, it would be expected that these particles 1) end up at the same site(s), and 2) have the same mechanism of action that lead to the same endpoint(s), after co-exposure.
In general, when a mixture consists of chemicals with the same or a very similar mechanism of action (and the same target site) dose additivity, i.e. summing of the (potency) adjusted exposure, is to be expected and should be taken into account when assessing the potential health risk of such a mixture. Synergisms or antagonisms are defined in relation to this additivity assumption as upwards or downwards deviations, respectively.

It should be noted that also other types of interaction between substances exist that do not work via interaction at the mechanism of action [128]. These are presently not considered, although a few possibilities are mentioned under 'other effects'.

Distribution to the same target sites
In order to have an additive effect, different nanomaterials should distribute to the same target site at a cellular or even intracellular level. This is because the different steps towards effects in the postulated mechanism of action (see next section on mechanism of action) mostly

occur on an intracellular level: Reactive Oxygen Species (ROS) production, oxidative stress, release of inflammatory mediators and inflammation, the entry in the nucleus, DNA damage.

Nanomaterials will be taken up to a large extent by macrophages, cells that are designed to ingest and digest foreign material [129-132]. For example, Liu et al. (2019) showed by X-ray micro-computed tomography (micro-CT) the accumulation of granular material in Kupffer cells (macrophages in the liver) and spleen macrophages following intravenous injection [133]. Similarly, Graham et al. (2019) found densely packed nanosized CeO_2 particles in engorged Kupffer cells in the liver [134]. Macrophage uptake of nanoparticles is highly influenced by particle size and surface properties, e.g. surface charge, hydrophobicity/hydrophilicity, surface modification, shape and protein binding to the particles [129, 135-138]. Nevertheless, in all cases some nanoparticles end up in macrophages. In addition, other cells than macrophages that are not specialized for phagocytosis are able to internalize nanoparticles, though to a different extent [138].

Within cells, the nanoparticles appear to accumulate in lysosomes [139]. Lysosomes are subcellular organelles present in many cell types, including macrophages, that play a role in plasma membrane repair, autophagy (degradation and recycling of cellular components) and pathogen degradation. They contain hydrolytic enzymes that can break down many kinds of biomolecules. The pH in the lumen of the lysosomes is 4.5–5.0. However, PSLT nanoparticles are less prone to degradation under lysosomal conditions.

In conclusion, it seems likely that different PSLT particles are taken up by macrophages at the site of exposure, i.e. the gastrointestinal tract, and once they become systemically available in secondary tissues. Differences in the extent of uptake by macrophages can occur between particles. In macrophages as well as in other cell types, the particles will preferentially be present in lysosomes. Hence, upon co-exposure, different PSLT are expected to be present in the same site(s) and remain there for longer periods of time.

Mechanism of action
In scientific literature, hardly any study is available that investigates the toxicity after single and co-exposure to different PSLT nanoparticles. Tsugita et al. (2017) found a stronger inflammatory response in mouse bone marrow-derived macrophages after co-exposure to SiO_2 and TiO_2 nanoparticles as compared to single exposure to these nanoparticles [140]. SiO_2 appeared to be localized mainly in lysosomes whereas, surprisingly, TiO_2 nanoparticles did not. The mechanism of the synergistic effect is poorly understood.

Braakhuis et al. (accepted for publication) investigated the mechanism of action of TiO_2 after inhalation and oral exposure and concluded that the effects could be related to PSLT whereas also additional effects due to its reactive surface may be of relevance [15]. After inhalation, PSLT particles in general are known to induce pulmonary toxicity and lung cancer in rats under conditions of impaired clearance from the lung (also referred to as lung overload). Furthermore, Braakhuis et al. (accepted

for publication) also postulated an adverse outcome pathway (AOP) related to potential carcinogenicity of TiO_2 after oral exposure [15]. This scheme can be taken as a basis to assess whether different PSLT particles act via the same mechanism. Note, also other adverse effects than carcinogenicity may be triggered by inflammation.

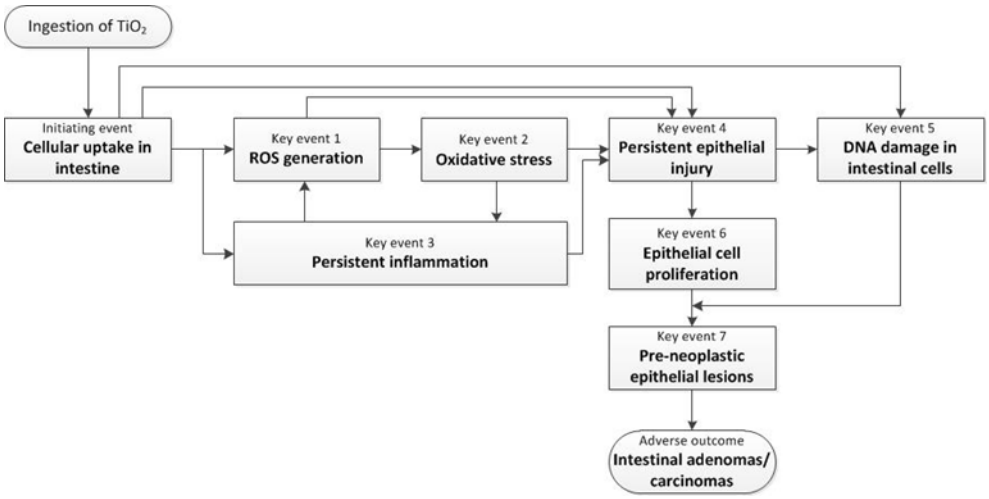

Figure 3. Postulated adverse outcome pathway (AOP) of TiO2 related to potential intestinal carcinogenicity after oral exposure [15]. Note, also other adverse effects than carcinogenicity may be triggered by inflammation.

ROS generation and oxidative stress are often observed in mechanistic studies with poorly soluble nanoparticles [141, 142]. Besides raising ROS production, nanoparticles such as TiO_2 can be cytotoxic, for example by reducing the mitochondrial membrane potential and eliciting a cascade of cytotoxic events [143]. According to Rathore et al. (2019), some nanoparticles may cause destabilization of lysosomes and permeabilisation of lysosomal membranes [131]. A fraction of lysosomal membrane permeabilisation can induce apoptotic cell death and ROS generation, whereas larger permeabilisation leads to cell death. Also accumulation of components in lysosomes may result in adverse effect [131]. Normally, cytoplasmic components are digested through a lysosomal-dependent pathway. However, if this process aiming at maintaining cellular homeostasis does not function well, accumulation in the lysosome or an autophagosome can occur, which can lead to a number of diseases related to inflammation.

In conclusion, nanomaterials in general seem to be able to induce ROS production, oxidative stress, inflammation and release of inflammatory mediators. Effects on the lysosomal membrane may be related to these effects. Different PSLT particles are taken up by macrophages and can accumulate in time due to their poor dissolution. Based on these observations, some kind of additivity of the effect of PSLT nanoparticles upon co-exposure seems plausible. However, hardly any studies are available to see if such additive effects actually occur. The absence of studies that compare mixtures of PSLT particles to single exposure can be regarded as a major information gap.

Other effects
In addition to additive effects related to interaction via the mechanism of action, also other interactions leading to increased effects are possible. For example, for different crystal structures of TiO_2, rutile and anatase, it has been noted that the combination can lead to an increased ROS generation because of surface interactions between the two different forms ('hyper-ROS'), as observed by Xia et al. (2013) and Buchalska et al. (2015) in abiotic (non-living) conditions [144, 145]. One could hypothesize such synergistic interaction to occur at a cellular level, and potentially also between other different PSLTs, depending on the energy of electron transfer.

Furthermore, simultaneous exposure to different nanoparticles may lead to a greater degree of agglomeration of the particles, which may have consequences for the absorption.

Nanoparticles are known for their ability to absorb other substances, both organic and inorganic compounds [146]. When the nanoparticles including their adsorbed substances are absorbed, this is called the 'Troyan horse effect'. This can also be viewed at as a different kind of mixture effect.

TiO_2 is known to photocatalyse in the presence of ultraviolet light, i.e. it absorbs light and transfers this energy. Hence, the combination of TiO_2 with the abiotic factor light may also lead to a greater oxidative stress that may trigger cell death [146]. This effect may also be exploited for its antibacterial activity.

Conclusion
Although a very limited number of actual studies investigate co-exposure to different nanomaterials, there is substantial evidence that additive effects of different PSLT particles are plausible. It is likely that the PSLT particles distribute to the same cells and trigger one or more aspects of the same mechanism of action, leading to the same adverse effect(s).

Although it can be assumed that PSLT particles distribute to the same organs and cells, the extent of uptake by these cells is affected by properties such as size, surface characteristics and shape. In addition, it is likely that between PSLT particles differences exist in properties that determine to which extent steps in the mechanism of action are triggered. Hence, an additive effect due to co-exposure of PSLT particles seems plausible, although it is unknown whether this effect is less than additive, additive or even synergistic. This is probably highly particle dependent. Yet, toxicity studies and risk evaluations are generally performed for a single substance/material. Given that exposure will be to a mixture, including different PSLT particles, this is a major information gap and further research on this topic is highly recommended.

6 Discussion and conclusions

In this study, we aimed to build a systematic and transparent methodology for the identification, assessment and prioritisation of potential risks of nanomaterials in food. The developed methodology results in risk-based, prioritised signals and suggestions for subsequent actions. The methodology was applied for the period January 2017 up to June 2019. Signals were selected, assessed, prioritised, and explored in some more detail. In section 6.1, several aspects of the methodology itself are discussed and recommendations for the use and further development of the methodology are presented. In section 6.2 conclusions and recommendations for the prioritised signals is provided.

6.1 Aspects of the methodology

The methodology consisted of information collecting and subsequent signal identification by expert judgement. Identified signals were systematically described and scored by experts using a list of key questions for certain descriptors. The score was the basis for prioritisation in which also the applicability of a regulatory framework to enable risk management of potential risks was taken into account. Some aspects of the methodology are discussed below.

Type of signal

We made a distinction between signals on materials, products, or developments, which were considered differently with respect to their scores. While signals about materials and products often contain specific information on physicochemical, (toxico)kinetic and hazard properties, information on developments is usually more general and describes less specific information. The information on developments will usually result in lower expert scores. It also turned out that for one of the signals ('Effect of nanoparticles on gut microbiome') the questions with regard to Kinetics were difficult to answer, as these turned out to be less applicable to the subject. Therefore, it is recommended to analyse different types of signals separately to enable a better comparison of the signals in relation to their priority, or at least take into account these systematically lower or higher scores.

Scoring and prioritisation

For now, the scores are the basis for prioritisation. One should look further to the detailed scoring per descriptor ('Physicochemical properties', 'Hazard', 'Kinetics', 'Exposure'), or specific questions (Table 5), to understand what might be key considerations behind any outcome.

Because the scoring of the signals is assigned by experts, this raises the question if personal expertise, opinions and knowledge related to a signal influence the scoring. For example, an expert on iron nanoparticles may have more knowledge on the material than may be described in the signal itself, or the expert may have a different opinion on the relevance of the outcome. Hence, the scoring will be subjective to a certain extent. Therefore, a more robust scoring can be performed by

selecting a larger pool of experts, including experts from different backgrounds and fields with regard to knowledge on nanomaterials.

The scoring system was used to enable prioritisation in a standardised way. Key questions considered of importance for risk assessment of nanomaterials were developed and can be answered during the scoring using the description of the signal. These questions were based on proposals for efficient risk assessment strategies for nanomaterials, e.g. by Dekkers et al. (2016) [3], and Hansen et al. (2014) [7], but evaluation of the suitability of these questions and further fine-tuning is recommended (as is illustrated by the example mentioned above). This could, for example, be performed by asking another group of experts with diverse backgrounds in human health hazard and risk assessment of nanomaterials to evaluate the questions.

Uncertainty
The signals are often accompanied by uncertainty due to lack of information, which an important aspect and needs to be reflected upon in the prioritisation of the signals. In the currently developed scoring system, uncertainty is taken into account. by assigning a score of 1 when a certain aspect of the information is unknown. It therefore adds to the overall expert score to a limited extend. In addition, just an indication for a specific property according to the questions under the scoring system is sufficient to allocate a score of 3, because of the conservative scoring. Indications, regardless their uncertainties on the evidence, add to the relevance for signal follow-up and therefore uncertainty is part of the current methodology.
Uncertainty is, however, not further specified or quantified in the total score. For further development of the scoring system, additional quantification of uncertainty might be developed. For example, a separate score for uncertainty per question under the scoring system may be considered and, for instance, an allocation of a percentage per score item to uncertainty. This may enable a better interpretation of relevance of the score for follow-up. Alternatively, an even higher score than 3 (e.g. 5) could be introduced in case of sufficient scientific evidence related to a key questions.

Combining information and overlap
During signal selection, information (e.g. single scientific papers) was combined. By combining, information can usually processed a more efficient manner. Combining also contributes to the strength of the signal. For further development of the methodology, the weight of information behind a combined signal needs to be considered in the scoring of signals. This may reflect higher importance and could be used in order to given a higher priority to a signal.

Several of the selected signals show overlap or are related to each other: the signal ‘Effect of nanoparticles on gut microbiome’ is related to the signal ‘Antibacterial food contact materials’, ‘Nanosilver’ and ‘Zinc nanoparticles’. Furthermore, nanocellulose is related with nano-encapsulation systems and antibacterial food contact materials. In addition to combining signals, eventual overlap between separate signals should be taken into account as well. Gathering of all signals in a database would allow searches when the number of signals becomes

larger (on type of materials, developments etc.) and comparison to signals of other horizon scanning initiatives.

When combining signals, it is assumed that the nanomaterials concerned are comparable in terms of physicochemical properties, (toxico)kinetic behaviour, toxicity and exposure. However, general knowledge on nanomaterials has demonstrated that specific differences in physicochemical properties of a nanomaterial, e.g. size, shape, crystal structure and surface functionalities, can largely influence the (toxico)kinetic behaviour and toxicity of a material [12]. Therefore, when signals are combined, implicit assumptions are made on similarity, hence introducing additional uncertainty. Knowledge on the impact of different characteristics of a material on its behaviour is increasing, for example whether to use certain characteristics to enable grouping and read-across approaches for nanomaterials in legal frameworks [6, 147]. Read-across can be defined as the use of information on one or more nanomaterials to fill a knowledge gap on another one with substantiated and sound scientific justification. In 2017, ECHA published a guidance on grouping and read-across of nanomaterials to assist users in complying with their obligations under the REACH legislation [8]. This information will help the general approach to justify grouping, but further development is needed for practical application of grouping and read-across. In addition, further development is needed to address the uncertainty due to different nanoforms that people are exposed to, in comparison to the material used in hazard studies, or the different nanoforms used in signals that are grouped, as is also indicated by the assessment of the signal on PSLTs (Section 5.1.6).

Legislation

As indicated in Section 2.5, particular legislation applicable in the field of nanomaterials in food can depend on factors such as its novelty, functionality and use of the nanomaterial and product. Sometimes the applicability of a legal framework is unambiguous and clear. A material or product designed as a plant protection product such as a spray designed to improve crop production has to meet criteria laid down by the Plant Protection Products Regulation. However, the applicability of a specific legislation can be debatable, as often is the case with (new) developments in which the materials or the purposes are not specifically described. In addition, it could also depend on marketing decisions, e.g. whether to register a product as a functional food, food supplement or place it on the market as a medicine, or as PPP, biocide or food additive (i.e. preservative). For prioritisation of the signals, it is important to know which legislation is or could be applicable or relevant, and if/how they enable risk management of potential risks. However, for reasons discussed above, assigning the applicable legislation appeared in some cases to be a difficult task due to possible overlap in legislations and ambiguity. Defining which legislation applies could therefore be a follow-up action for a signal as well.

Some of the legislation include authorisation procedures involving expert panels (e.g. on Food additives, or Plant Protection Products), while other legislation leave the responsibility very much to the producer or importer or (web)shop (i.e. certain food supplements, herbal supplements, or other products containing nanomaterials).

Conclusion
The field of nanotechnology in food is dynamic. From a risk management point of view, it is important to stay up to date of the nanotechnology developments and identify potential risks in order to prevent human health risks relating to the innovations. The methodology as developed provides a tool that enables collecting information and identification of signals, and their assessment and prioritisation in a systematic, transparent and simple way. The tool can be useful for the Office for risk assessment & research of The Netherlands food and consumer product safety authority (BuRO-NVWA), but also for other governmental institutes.

6.2 Overall considerations on the prioritised signals

All prioritised signals in Chapter 5 scored highest on 'Exposure'. Possibly, because the questions concerned can be easily answered positively, as an indication of potential exposure is enough to allocate the highest score. The descriptors 'Physicochemical properties' (for 'Needle-like nano-hydroxyapatite in infant formulae' and 'Exposure to micro- and nanoplastic particles via food and drinking water') or 'Kinetics' (for 'Nano-encapsulation systems in food', 'Nanosilver' and 'Nanoparticles for iron fortification of foods') contributed highest after 'Exposure'.

Below an overview of the conclusions and recommendations on the prioritised signals is provided.

Table 6. Overview of conclusions on the prioritised signals, and the respective recommendations (in bold). Further details are available in Chapter 3 and 5.

Prioritised signal	Conclusion / recommendation
Nanoparticles for iron fortification of foods (see also 5.1.1)	Based on scientific developments and an iron product containing nano-sized iron particles that is recently allowed on the market in the US as nutrient supplement/fortificant, applications with nano-sized iron particles are anticipated on the EU market. The hazards of such applications should be considered, whereas also the possible benefits should be taken into consideration. It depends on the application which legal framework would apply and how much information for risk assessment should be provided. As nano-iron particles could be considered novel foods, authorisation including risk assessment in this framework is foreseen. However, certain nano-iron salts consisting (partly) of nano-sized particles may also enter the market unnoticed in functional foods, fortified foods or food supplements. Legal limits for added minerals do not take nano-specific aspects into account. **It is therefore recommended to follow the field on application of nano-sized iron particles in specific products, and perform analysis whether application occurs. Having better specifications for nutrients to be used in functional foods, fortified foods or food supplements and infant formulae would also**

Prioritised signal	Conclusion / recommendation
	helpful to reduce possible risk of nano-sized nutrient particles.
Exposure to micro- and nanoplastic particles via food and drinking water (see also 5.1.2)	Micro- and nanoplastics have been determined in all kinds of food products indicating that oral exposure occurs. Micro- and nanoplastics can be seen as a contaminant, with no clear problem owner. The techniques to detect these particles are rapidly evolving, allowing a better intake estimate of especially the smaller sized particles in the near future. To assess the possible risk of this intake, knowledge on the toxicokinetic behaviour and hazards of micro- and nanoplastics is needed. **It is recommended to follow the developments in this field and consider contributing to research to increase the knowledge on the human health risks of the oral exposure to micro- and nanoplastics.**
Nanosilver (see also 5.1.3)	Application of nanosilver in food contact materials is often described in literature due to its antibacterial properties, though this is currently not allowed within the EU. In addition, elemental silver that is used as a food colorant (E 174) may contain nano-sized particles. Within the EU, producers are currently invited to provide scientific and technical data on the size distribution of the food additive. Based on this, further steps can be taken. For both types of applications, the current legislation is considered to suffice and further steps are likely to be taken where relevant. **It is recommended to further follow up nano-sized colloidal silver that is sold online for e.g. 'detoxification' purposes, as it does not clearly fall under a specific legislation.**
Nano-encapsulation systems in food (see also 5.1.4)	Nano-encapsulation using food-grade ingredients seems to be a considerable and growing field resulting in improved bioavailability, controlled release and/or increased stability of the encapsulated ingredients. For these nano-encapsulation systems, it is often not clear if nano-specific aspects are considered in the risk assessment, such as increased bioavailability and the potential of a different distribution profile if the encapsulated product does not quickly disintegrate in the gastrointestinal tract. **It is recommended to develop further scientific knowledge on nano-encapsulation systems in order to assess whether and when such applications could lead to a health risk.**
Needle-like nano-hydroxyapatite in infant formulae (see also 5.1.5)	Needle-shaped nano-hydroxyapatite has been detected in infant formulae in the US, possibly to increase the bioavailability of calcium and phosphate. As the calcium hydroxyapatite seems to be a synonym for

Prioritised signal	Conclusion / recommendation
	tricalciumphosphate, which is allowed in certain products for infants as food additive, it is unclear if such particles are present on the Dutch market. **Analysis of infant formulae on the presence of these particles is therefore recommended, whereas also other calcium-enriched products may be included.**
Poorly Soluble and Low acute Toxicity (PSLT) particles (see also 5.1.6)	Simultaneous exposure to different PSLT particles is likely to occur. As is seems likely that the absorbed particles 1) distribute to some extent to the same tissues and cells, and 2) trigger to some extent the same key events leading to an adverse outcome, an additive effect of PSLT particles seems plausible. As hardly any studies are available on the toxicity after co-exposure to different nanoparticles, this is a major information gap. **Further research on the toxicity as a result of co-exposure to PSLTs is recommended.**

As can be seen in Table 6, assessing if the nano-specific aspects in risk assessment will be adequately covered by the current legal frameworks is difficult when the exact type of application is unknown. A nanomaterial may enter the market in different ways. For example, nano-sized iron may be recognized as novel food or food additive with the respective authorisation procedure, but could also be used in functional foods, to fortify foods or in food supplements. The definition of an engineered nanomaterial under the Novel Food Regulation leaves room for interpretation. If a product is a functional food, fortified food or food supplement and not considered a novel food at the same time, the nano-aspect may go unnoticed. A product could also be marketed in different manners, e.g. a nanoformulation with flavonoid containing liposomes with increased bioavailability as a food supplement, herbal supplement or medicinal product. In addition, especially for products that are only available online, some do not seem to be marketed in accordance with the current food regulations.

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9 Appendices

9.1 Appendix 1: Details literature and information search

Scientific literature was examined by a monthly search by the library of the RIVM in Scopus and Pubmed. The search terms used were:

- 'nanomaterials' AND 'food',
- 'nanoparticles' AND 'food',
- 'nanotechnology' AND 'food',
- 'nanofood',
- 'novel foods' AND 'nano',
- 'fortification' AND 'nano',
- 'food supplements' AND 'nano',
- 'dietary supplement' AND 'nano',
- 'vitamin' AND 'nano',
- 'nano emulsion' AND 'food',
- 'risk nano food',
- 'safety assessment nano food',
- 'infant formula' AND 'nano',
- 'nanoclay' AND 'migration' AND 'food contact materials',
- 'nanosilver' AND 'food' AND 'microbiome',
- 'nanozinc' AND 'food contact materials' AND 'microbiome',
- 'nano-iron' AND 'fortified foods', and
- 'review' (optional in combination with other search terms).

In addition to scientific literature, also 'grey' literature was searched, i.e. research produced outside the traditional academic publishing sources. This was done on internet by the search terms 'nano & food' in addition to the name of a certain organisation (i.e. research institutes, universities, non-governmental organisations (NGOs)) from the listing below, which are considered relevant within this field:

- ANSES (Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail) www.anses.fr/en
- APVMA (Australian pesticides and Veterinary Medicines Authority) www.apvma.gov.au/
- BfR (Bundesinstitut für Risikobewertung) www.bfr.bund.de/de/start.html
- Danish Environmental Protection Agency www.eng.mst.dk/
- ECHA (European Chemical Agency) www.echa.europa.eu/nl/home
- EFSA (European Food safety Authority) www.efsa.europa.eu/
- ETH Zürich (Swiss Federal Institute of Technology) www.ethz.ch/en.html
- Fraunhofer Institute www.fraunhofer.de/en.html
- Friends of the Earth www.foe.org
- FSANZ (Food Standards Australia New Zealand) www.foodstandards.gov.au
- Greenpeace www.greenpeace.org
- Health Canada www.hc-sc.gc.ca/index-eng.php
- INRA (Institut National de la Recherche Agronomique) www.inra.fr/en
- Public Health England www.gov.uk/government/organisations/public-health-england

- JRC (Joint Research Centre) www.ec.europa.eu/jrc/en
- University of Massachusetts www.massachusetts.edu/
- US FDA (Food and Drug Administration) https://www.fda.gov/
- Wageningen Food Safety Research (formerly known as RIKILT) https://www.wur.nl/nl/Onderzoek-Resultaten/Onderzoeksinstituten/food-safety-research.htm
- WUR (Wageningen University) www.wur.nl

In addition to the systematic scientific and grey literature search mentioned above, also information from de RIVM Nano-Working Group, individual RIVM nano-experts, and the EFSA nano working group (WG).

9.2 Appendix 2: Legal frameworks

9.2.1 *Novel foods*

Novel foods are 'new' foods, or ingredients, derived from new sources or produced according to new methods, which have not been on the European market earlier than May 15th 1997. In 2015, the new Novel Foods Regulation (EU) No. 2015/2283 was published [13], which came into force in 2018. Under this Regulation, a license for the use of 'engineered nanomaterials' should be granted by EFSA, before they can be used in food. Within EFSA, the Panel on Dietetic products, Nutrition and Allergies (NDA-Panel) evaluates the safety of Novel foods. It takes (engineered) nanomaterials into account, which are defined as:

"Engineered nanomaterial' means any intentionally produced material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale.
Properties that are characteristic of the nanoscale include: (i) those related to the large specific surface area of the materials considered; and/or (ii) specific physico-chemical properties that are different from those of the non-nanoform of the same material" [13].

For consistency and coherence purposes in the area of food law the definition of "engineered nanomaterial" is copied from the definition in the Regulation on the provision of food information to consumers (Regulation (EU) No. 1169/2011), also known as the Food Information to Consumers (FIC) Regulation [148]. According to this legislation with regard to labelling, "engineered nanomaterials" should be clearly mentioned in the ingredients (followed by "[nano]") when >50% of the particles are nano-sized. The definition of "an engineered nanomaterial" can leave room for different interpretations as no cut-off value for the fraction of particles smaller than 100 nm is provided. Furthermore, "intentionally produced" and "properties that are characteristic of the nanoscale" may also be interpreted differently. Hence, recognition as Novel foods may not always occur. A union list of authorised Novel foods

with updates is published[10]. It does currently not mention to contain any nanomaterials.

The Novel Foods Regulation itself is not clear whether micelles, emulsions and liposomes (so called 'soft' nanomaterials) are included in the nano-definition used in the FIC Regulation, or not, as it is also dependent on the interpretation on the definition of "engineered nanomaterial". Nevertheless, it only considers food that was not consumed "significantly" prior to May 15th 1997 as novel. This excludes emulsions such as mayonnaise or milk, strictly containing soft nanomaterials, from the definition. Though many soft nanomaterials are larger than "dimensions of the order of 100 nm or less", they still can "retain properties that are characteristic of the nano-scale". The EFSA Nano Network, in its meeting of July 2015, recognised the further need for consideration of 'soft' formulations designed to deliver nutrients/ supplements in food and health-food products at the nano-scale [149]. The reason for this is related to (toxico)kinetics as some of the nano-scale delivery systems have been described to significantly enhance the uptake and bioavailability of the encapsulated substances. Therefore, for these nano-scale delivery systems, according to the 2018 EFSA Guidance on nanomaterials, implications of any significant alteration (increase) in bioavailability to potential harmful effects must be considered [12]. Especially when a nanocarrier is not disintegrated in the gastrointestinal tract, the safety assessment should consider the active ingredient, the encapsulating material, and the encapsulate/nanocarrier as a whole [12].

Food additives and flavours are excluded from the Novel foods definition, as they have their own legislation: Regulation (EC) No. 1333/2008 and No. 1334/2003, respectively [103, 150]. Novel foods can be functional foods too (see Section 9.2.2).

The Novel Foods Regulation also indicates that when vitamins, minerals and other substances change significantly in composition or structure, the way they are metabolised, or when these vitamins, minerals and other substances contain a nanomaterial or consist thereof, they should be regarded as novel foods [13].

In order to get a novel food on the market, it needed an authorisation or notification at national level, in addition to its Authorisation at the EU level by EFSA. In the Netherlands, this task was performed by the "Bureau Nieuwe Voedingsmiddelen" (BNV) of the Medical Evaluation Board (CGB-MEB). From January 2018, the authorisation and notification is completely coordinated by EFSA. Any broad future application of nanomaterials as novel foods by industry will depend on the inclusion of soft nanomaterials in the FIC Regulation, i.e. whether soft nanomaterials in food products are regarded as 'engineered nanomaterial'. Up to then, the uncertainty with respect to regulatory coverage for nano-applications in Novel foods is considered to persist, because of a lack of clarity with regard to the definition. The potential applications of soft nanomaterials in the field of nanomaterials and food

[10] https://ec.europa.eu/food/safety/novel_food/authorisations_en

are numerous, as is also reflected by the enormous amount of publications with respect to this topic (See Section 3.2.8).

9.2.2 *Functional foods*

Though there is no uniform definition of a Functional food, these are considered foods with an additional component in order to improve the nutritional value or to exert a certain beneficial health effect. Examples of Functional foods are bread with added dietary fiber, or margarine with phytosterols. They should be distinguished from fortified foods with added nutrients already present in the product, such as milk with extra calcium or butter with extra vitamin E. According to the definition of the British Nutrition Foundation, Functional foods:

"d*eliver additional or enhanced benefits over and above their basic nutritional value. The term 'Functional foods' can be viewed as encompassing a very broad range of products. Some Functional foods are generated around a particular functional ingredient, for example foods containing probiotics, prebiotics, or plant stanols and sterols. Other Functional foods or drinks can be foods fortified with a nutrient that would not usually be present to any great extent (e.g. folic acid fortified bread or breakfast cereals). Functional foods and drinks may provide benefits in health terms, but should not be seen as an alternative to a varied and balanced diet and a healthy lifestyle*" [151].

Functional foods should have an added health effect, which can be distinguished from the normal effect of the food concerned. There is no specific regulation for Functional foods, however, any claim of the effect on improving nutritional value and/or health should be in accordance with the Regulation on nutrition and health claims made on foods (Regulation (EC) No. 1924/2006 [152]), and labelling according to the FIC Regulation ((EC) No. 1169/2011 [148]). The safety of Functional foods is to be guaranteed under the Dutch Commodities Act, which, however, does not specifically consider nano-applications. Regulation (EC) No. 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods [86], and the Decree on addition of micronutrients to foods under the Dutch Commodities Act ("Warenwetbesluit Toevoeging micro-voedingsstoffen aan levensmiddelen" [87]) also applies on the added substances to Functional foods. Both legislations do not take nano into account specifically. Note that Functional foods can be Novel foods too (Section 9.2.1).

There are some specific EU regulations with regard to food for specific groups, e.g. food for infants and young children, and food for special medical purposes[11]. Such products are regarded as fortified food (see Section 9.2.5). Whenever a fortified food is accompanied by a health claim, it would still be a Functional food. Foods with a medical claim (i.e. to prevent, treat or cure a disease) are by definition products under the Medicines act. As Functional foods can have such effects as well, some are to be regarded as borderline products (between food and medicine).

[11] See: https://ec.europa.eu/food/safety/labelling_nutrition/special_groups_food/medical_en

9.2.3 *Fortified foods*

Fortified foods are foods with added nutrients already present in the product such as milk with extra calcium or butter with extra vitamin E. Regulation (EC) No. 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods [86], and the Decree on addition of micronutrients to foods under the Dutch Commodities Act ("Warenwetbesluit Toevoeging micro-voedingsstoffen aan levensmiddelen" [87]) concerning the maximum amount of specific micronutrients allowed in fortified food. As mentioned earlier, these regulations do not specifically take nanomaterials into account. With regard to labelling, however, any nano-sized additions need to be mentioned according to the FIC Regulation ((EC) No. 1169/2011 [148]). At least in the Netherlands, fortified foods may be marketed without prior authorisation, as long as they are safe, only contain the approved vitamins and minerals, regarding recommended daily intake levels according to the regulations. However, if a vitamin, mineral or other substance contains or consists of 'engineered nanomaterials', these should also be regarded as Novel food (Section 9.2.1), and should go through evaluation by EFSA. Given the uncertainty on the interpretation of the term 'engineered nanomaterial', it is unclear to which extent the Novel Foods Regulation is applied in practice.

9.2.4 *Food supplements*

According to Dutch Legislation, Food supplements are food and drink which are: 1) intended as an addition to the regular diet, 2) are a concentrated source of one or more micronutrients or other substances with a nutritional or physiological effect, and 3) are consumed in small, measured amounts. These include pills, powders, drops, capsules or beverages intended as an addition to daily nutrition contain vitamins, minerals, or bioactive ingredients ("nutraceuticals"). The Directive No. 2002/46/EG concerning food supplements [153], is nationally implemented in the in the Decree Food supplements under the Dutch Commodities Act ("Warenwetbesluit voedingssupplementen" [154]), however, these only concern food supplements containing minerals and vitamins and no other nutrients or substances.

There are additional (national) regulations concerning the maximum amount of specific micronutrients allowed in a food supplement. These are the Regulation (EC) No. 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods [86], and the Decree on addition of micronutrients to foods under the Dutch Commodities Act ("Warenwetbesluit Toevoeging micro-voedingsstoffen aan levensmiddelen" [87]). As mentioned earlier, these regulations do not specifically take nanomaterials into account. With regard to labelling, however, any nano-sized additions need to be mentioned according to the FIC Regulation ((EC) No. 1169/2011 [148]). At least in the Netherlands, food supplements may be marketed without prior authorisation, as long as they are safe, only contain the approved vitamins and minerals, regarding recommended daily intake levels according to the regulations. However, if a vitamin, mineral or other substance contains or consists of 'engineered nanomaterials', these should also be regarded as Novel food (Section 9.2.1), and should go through evaluation by EFSA. Given the uncertainty on the interpretation

of the term 'engineered nanomaterial', it is unclear to which extent the Novel Foods Regulation is applied in practice.

As no specific recommended daily intake levels are set for other bioactive ingredients than vitamins and minerals, food supplements containing "nutraceuticals" just need to comply to the Dutch Commodities Act, and need to be safe. Health claims are allowed according to labelling (a.o. according to Regulation (EC) No. 1924/2006 [152], see also Section 9.2.2 on Functional foods). As there are no specific requirements (nor authorisation procedure), nano-specific aspects such as an increased bioavailability or a potentially altered toxicokinetic profile due to the nano-size or nanoformulation, are not taken into account. Still, if those bioactive ingredients contain or consist of engineered nanomaterials, these should also be regarded as Novel food, and should go through evaluation by EFSA (see Section 9.2.1).

9.2.5 *Herbal supplements*

Food supplements containing herbs (herbal supplements, herbal preparations or 'botanicals') are often used because of their (supposed) health benefits. All herbal preparations must meet the safety requirements laid down in the Herbal Preparations Decree under the Dutch Commodities Act ("Warenwetbesluit Kruidenpreparaten" [155]). However, there is no pre-market assessment of the safety and composition of herbal preparations. Such assessments are only performed if there are indications that a product that is on the market may pose a public health risk. Herbal supplements which are also Novel foods (Section 9.2.1) or food supplements (Section 9.2.4), should meet the legal requirements to these respective groups as well. It is often difficult to assess the risks of herbal preparations, because there is little information available concerning the composition of the herbal preparation. An overview of national and EU legislation with regard to herbal supplements is available [156].

There is overlap between herbal supplements and several classes of pharmaceuticals (e.g. traditional herbal medicines), as well as food supplements. One can envision that nano-encapsulations strategies could be used e.g in order to improve bioavailability of herbs. A herbal extract though (i.e. the bioactive ingredient(s) of a herb) falls outside the scope of Herbal Preparations Decree under the Dutch Commodities Act, as they are defined as food supplements (see Section 9.2.4).

It is unknown whether there are nano-herbal preparations on the market, as they are not registered. In addition to the General Food Law (Regulation (EC) No. 178/2002), aimed at securing food safety, the Herbal Preparations Decree only lists herbs that are allowed to be used (or in what extend), but there are no requirements with respect to production methods, encapsulation materials, or information on the label [157].

9.2.6 *Food additives*

Food additives are substances added to food to fulfil a certain technological function, such as preserving, stabilising, colouring of sweetening. Food additives are regulated in the EU according Regulation (EC) No. 1333/2008 on food additives [103], and need to be authorised.

The EFSA Panel on Food Additives and Flavourings (FAF), since 2018 the successor of the EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS), evaluates the safety of chemical substances added to food and the subsequent consumer exposure. The Panel's work concerns substances to be evaluated by EFSA before their use can be authorised in the EU, and the re-evaluation of current food additives. The nano-character is taken into consideration by the ANS-Panel. It is possible that the information on to particle size and size distribution could lead to nano-labelling according to the FIC Regulation. For instance, synthetic amorphous silica (SAS), widely used as food additive E 551 and a nanostructured material consisting of aggregates and agglomerates of primary particles in the nano-range (<100 nm) should be regarded as nanomaterial because of the nano-size of its primary particles. However, RIVM noticed there appears to be ambiguity in the interpretation as E 551 as nanomaterial, as this food additive is still not being labelled as "[nano]" on the ingredient listings of new products [158].

A programme has been set-up for the re-evaluation of food additives permitted before 20 January 2009, which must go through a new risk assessment by EFSA [159]. There is often a lack of information with regard to particle size and size distribution data of food additives which are be re-evaluated. Actions are ongoing to request this information, but this takes time.E 171 (titanium dioxide) was re-evaluated in 2016 [160], and it was noted that there are no legal limits for the particle size in the EU specifications (Commission Regulation (EU) No. 231/2012 [102]), and that characterisation of the particle size in the food additive E 171 should be included among the specifications [160]. As a result, recently an amendment of the specifications of E 171 with respect to the inclusion of additional parameters for particle size distribution based on industry data was proposed [161].
The same has been noted for E 172 (iron oxides and hydroxides) [162], silver (E 174) [93], gold (E 175) [163], E 551 [164], and calcium silicate (E 552), magnesium silicate (E 553a) and talc (E 553b) [165]. Hence, also information on size distribution of other food additives may come available.
For the several forms of cellulose (E 460 up to E 469), based on the known ability of (plant-based) cellulose particles to swell in water, the presence of nanoscale material after ingestion is highly unlikely, according to the EFSA ANS-Panel [92].

9.2.7 *Food contact materials*

Food contact materials (FCMs) are all materials and articles intended to come into contact with food, such as packaging and containers, kitchen equipment, cutlery and dishes. Regulation (EU) No. 1935/2004 generally regulates FCMs [166]. Regulation (EU) No. 10/2011 on plastic materials and articles intended to come into contact with food, contains a Union list of approved substances that may be intentionally used in the manufacture of plastic layers in plastic materials and articles [94]. This list contains a few nanomaterials, however, the use is only allowed if the nanoform is explicitly authorised and mentioned in the specifications in Annex I of Regulation (EU) No. 10/2011, as mentioned in Article 9(2) of the regulation [94]. The Union list is a restrictive list of 'monomers and other starting substances', and 'additives' that are allowed for use in

plastics. Other substances used in plastics are either 'polymerisation production aids' (PPAs) or 'aids to polymerisation' (APs) and these groups are subject to national legislation. In addition to plastics, also active and intelligent materials, recycled plastic materials, ceramics, and regenerated cellulose film are covered by specific EU measures [167]. In the Netherlands, the legislation on FCMs contains an additional restrictive (positive) list of substances authorised for use in plastics as PPAs or AP. In contrast to European provisions, according to the Dutch FCM legislation, authorised substances may also be used in nanoform (i.e. without specific listing of the nanoform), provided that the final product still complies with Article 3 of Regulation (EC) No. 1935/2004 stating that migration from FCM should not harm the safety of food [166]. This not only applies to PPAs and AP used in plastics, but to all other FCMs regulated with national positive lists in the Netherlands, like paper and board, coatings, rubbers, metals and alloys, textiles (jute), etc., as taken up in the "Warenwetregeling Verpakkingen en Gebruiksartikelen (WVG)" [168].

The most essential information for risk assessment of chemicals in FCMs is migration. If a nanomaterial does not migrate from the material, there is no exposure to humans and no human health risk. Regulation (EU) No. 10/2011 includes an Annex on testing for specific migration of materials and articles already in contact with food [94]. This contains information on the sample preparation, condition of the testing (e.g. temperature, food simulant to use, type of medium) and analysis method. No specific information on nanomaterials is provided in this Annex.

The following nanomaterials are included in the Union list of approved substances for use in plastic FCM by Regulation (EU) No. 10/2011 based on the absence of migration of the nanoparticles to food (as amended up to 12th amendment / last amendment 10 January 2019 (M12): titanium nitride, nanoparticles (FCM 807); carbon black (FCM 411); silicon dioxide (FCM 504); montmorillonite clay (FCM 1030); zinc oxide, coated (FCM 1046) or uncoated (FCM 1050); methacrylic acid, ethyl acrylate, n-butyl acrylate, methyl methacrylate and butadiene copolymer in nanoform (FCM 1016), and three other different copolymers of at least butadiene, ethyl acrylate, methyl methacrylate and styrene, in nanoform (FCM 859, FCM 998, FCM 1043) [94].

9.2.8 *Plant Protection Products*

The Plant Protection Products Regulation (PPPR), Regulation (EC) No. 1107/2009 [169], concerns the authorisation of PPPs ("pesticides") which protect crops and plants from undesired organisms, or regulate plants growth. The safety of residues on plant products (e.g. on fruit and vegetables for consumers) is also part of this authorisation. The regulation comprises safe use in both professional agriculture as well as in non-professional use at home gardens and greenhouses. In addition, also products used to protect the harvested agricultural products fall within the scope of the PPPR.

The risk assessment evaluation of the active ingredients in PPPs is performed at a EU level under supervision of EFSA. The authorisation of the use of formulations (i.e. the PPP products), including a risk

assessment, is a national task performed by the Competent Authorities of individual member states. Also the consumer safety of the residues on plant and animal products is assessed. If required, MRLs (maximal residue levels) are set according to Regulation (EC) No. 396/2005 under supervision of EFSA [170]. In the Netherlands, the Board for the authorisation of plant protection products and biocides (Ctgb) is the Competent Authority responsible for product authorisation. Authorisation of a PPP by the Ctgb is necessary before a product can be placed on the Dutch market. The safety of products is looked upon thoroughly in a case-specific manner, but, no nano-specific aspects are taken into account at the moment. When a nano-aspect is recognised, it is expected it will be assessed on an ad-hoc basis during the authorisation procedure.

At present there are no known active 'nano' ingredients registered to be used in PPPs. With regard to the formulations, there are few products (all nano-emulsions) which contain a nano-sized co-formulant in order to improve e.g. the solubility of the active ingredient in the spray tank, reducing mixing time upon loading [171]. The 2018 EFSA Guidance on nanomaterials argues that 'unless a valid justification can be provided, each formulation should also be assessed for any change(s) in the properties and behaviour of the nanopesticide' [12].

9.2.9 *Biocides / Biocidal products*

The Biocidal Product Regulation (BPR), Regulation (EC) No. 528/2012, distinguishes a number of product types (PTs) of which few are related to food [172]. The guidance on the BPR has been supplemented with chapters on assessing the intake of residues of biocides via food and provides technical advice on the assessment of health effects and exposure assessment [173]. PT groups for which scenarios have been identified for how food can be come in contact with biocidal products have been identified in the guidance on estimating dietary risk from transfer of biocidal active substances into food [173]. These include PT04 (Disinfectants cleaners in domestic kitchens), PT05 (Drinking water disinfection), PT04 and PT06 (In-can preservatives and disinfectants in dishwashing detergents), PT18 (Insecticides in domestic environments), and PT19 (Repellents and attractants). Products in these PT groups could potentially result in nano-sized residues and oral exposure. For example (residues of) products used for the control of arthropods (in PT18), e.g. for controlling poultry red mite at poultry farms, could end up in e.g. meat or eggs of animals housed in stables where such products are being used.

Under the BPR a union list is established of active substances approved for use in specific PTs following an opinion from ECHA. According to the BPR, the approval of the active substance does not comprise the nanoform of the active substance, unless this is explicitly mentioned (by the applicant). In parallel with the risk assessments of PPPs, the risk assessment of biocides (i.e. the biocidal products) is a national task performed by the Competent Authorities of individual member states. In the Netherlands, like with PPPs, the Ctgb is responsible for this task.

As biocidal products used in the manufacture of FCMs are also in the scope of the BPR, the overlap of these areas, regulations, and agencies

concerned (both ECHA and EFSA) has caused confusion (see the Discussion document on the regulation of the use of biocides in FCMs [172]). Transitional arrangements have been made for such products [172]. Meanwhile, the European Commission is working on the Regulation of the use of biocides in FCMs, including a possible measure for setting limits on biocides in FCMs [172]. When biocides are applied as FCM, they have to comply to both the FCM legislation as well as the BPR. Within the biocide context, their use, however, can also be seen as a 'treated article'. The BPR lays down rules for treated articles (Article 58), which includes FCMs [172]. The placement on the market of treated articles will only be allowed after the appropriate approval of the active substance for the relevant biocidal PT (PT04), and for treated articles manufactured in the EU, the authorisation of the biocidal product itself. Furthermore, the BPR foresees a role for other areas of legislation concerning food and feed to set limits that may restrict the presence of the biocidal substance in food to protect consumer health, including FCMs. The BPR provides the opportunity to submit information on the use in a treated article and data on migration. It has been proposed that substances as those contained within Regulation (EC) No. 1333/2008 on food additives [103], and Regulation (EC) No. 1334/2008 on flavours [150], are specifically excluded from the scope of the BPR (see Article 2(2)(f) and (g)) of Regulation (EC) No. 528/2012 [172].

Possibly, the nano-character of an active ingredient is not registered, as it is the responsibility of the applicant during registration. However, as every biocidal product needs to be authorised by the Competent Authority, the formulation is taken into account in the risk assessment. It is, however, unclear to what extend transfer of residues are taken into account. Also changes in formulation to a nano-formulation may not be picked up, e.g. a change in form, i.e. from one nanoform to another or from a non-nanoform to a nano-form, may not be picked up because the authorisation is based on chemical composition. Mackevica et al. (2016) noticed several (possible) nanomaterials in biocidal products and treated articles on the EU market, including silver, silver-zinc-zeolite, silver copper-zeolite and silicon dioxide, with respect to the PTs mentioned above [174]. At ECHA, there is an ad hoc working group for the Assessment of Residue Transfer to food (ARTfood), which assesses biocidal residue transfer to food, and developed some (draft) guidances in this respect [175]. The OECD recently developed guidance documents to assist the safety evaluation of engineered nanomaterials [176].

9.3 Appendix 3: Individual expert scoring

Table A1. Individual and average (plus variance as standard deviation (SD)) expert scoring of the different signals per descriptor and question according to Table 1 (Section 2.4).

Signal **Expert**	**Physicochemical properties (Pchem)**				**Hazard**				**Kinetics**				**Exposure**				**Total Score**				
	Dissolution	Reactivity	Toxic ions/ molecules	HARN	CMR	Mutagenicity/ carcinogenicit	Immunotoxicit y	Other toxicity	Absorption	Distribution brain and	Accumulation	Other kinetic profile	Widely used	Sensitive subpopulation	Frequent use	Likely exposure	Pchem	Hazard	Kinetics	Exposure	Total (sum of expert scores)
Effect of nanoparticles on gut microbiome																					
A	3	1	1	0	0	3	1	1	1	0	1	1	3	3	3	1	5	5	3	10	**23**
B	1	1	1	1	1	1	3	3	1	1	1	1	3	3	3	3	4	8	4	12	**28**
C	1	3	1	0	0	1	1	1	1	0	1	3	3	3	3	3	5	3	5	12	**25**
D	1	1	1	1	1	1	1	3	1	0	0	1	3	3	3	3	4	6	2	12	**24**
E	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	4	4	4	4	**16**
F	1	1	1	0	0	1	1	1	1	1	1	1	3	3	3	3	3	3	4	12	**22**
G	1	3	0	0	0	0	1	0	0	0	1	3	3	3	3	3	4	1	4	12	**21**
Average	1.3	1.6	0.9	0.4	0.4	1.1	1.3	1.4	0.9	0.4	0.9	1.6	2.7	2.7	2.7	2.4	4.1	4.3	3.7	10.6	**22.7**
SD	0.8	1.0	0.4	0.5	0.5	0.9	0.8	1.1	0.4	0.5	0.4	1.0	0.8	0.8	0.8	1.0	0.7	2.3	1.0	3.0	**3.7**
Nanoparticles for iron fortification of foods																					
A	1	1	3	0	0	0	1	1	3	1	3	3	3	3	1	3	5	2	10	10	**27**
B	0	0	3	0	0	0	3	3	3	0	0	3	3	3	3	3	3	6	6	12	**27**
C	0	0	0	0	0	0	1	1	3	1	1	3	3	3	3	3	0	2	8	12	**22**
D	3	0	0	0	0	0	3	3	3	0	0	0	3	3	3	3	3	6	3	12	**24**
E	1	1	1	1	1	1	1	1	1	1	1	1	3	3	3	3	4	4	4	12	**24**
F	1	1	3	0	0	0	1	1	3	1	3	3	3	3	3	3	5	2	10	12	**29**
G	1	1	1	1	1	1	1	1	3	1	1	1	3	3	3	3	4	4	6	12	**26**
Average	1.0	0.6	1.6	0.3	0.3	0.3	1.6	1.6	2.7	0.7	1.3	2.0	3.0	3.0	2.7	3.0	3.4	3.7	6.7	11.7	**25.6**

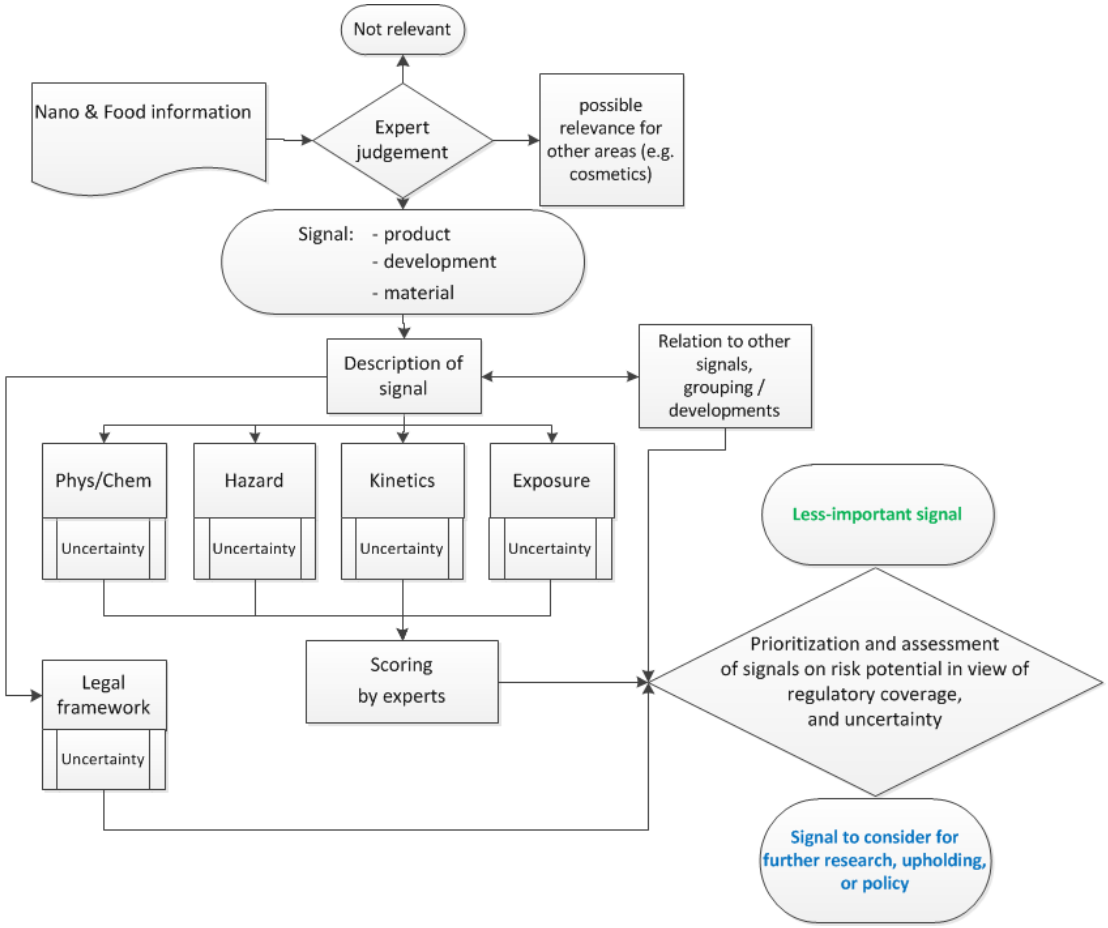
***Signal* Expert**	**Physicochemical properties (Pchem)**				**Hazard**				**Kinetics**				**Exposure**				**Total Score**				
	Dissolution	Reactivity	Toxic ions/ molecules	HARN	CMR	Mutagenicity/ carcinogenicit	Immunotoxicit y	Other toxicity	Absorption	Distribution brain and	Accumulation	Other kinetic profile	Widely used	Sensitive subpopulation	Frequent use	Likely exposure	Pchem	Hazard	Kinetics	Exposure	Total (sum of expert scores)
SD	1.0	0.5	1.4	0.5	0.5	0.5	1.0	1.0	0.8	0.5	1.3	1.3	0.0	0.0	0.8	0.0	1.7	1.8	2.8	0.8	**2.4**
Exposure to micro- and nanoplastic particles via food and drinking water																					
A	3	1	3	0	1	1	3	1	1	1	3	3	3	3	3	3	7	6	8	12	**33**
B	3	0	3	3	0	0	3	3	1	1	1	1	3	3	3	3	9	6	4	12	**31**
C	3	1	3	0	1	1	3	1	1	1	1	3	3	3	3	1	7	6	6	10	**29**
D	3	0	3	0	0	0	3	3	3	1	3	1	3	3	3	3	6	6	8	12	**32**
E	3	1	1	1	1	1	3	1	1	1	3	1	3	3	3	3	6	6	6	12	**30**
F	3	1	1	1	1	1	3	1	1	1	3	3	3	3	3	3	6	6	8	12	**32**
G	1	0	1	1	0	0	1	0	1	0	1	0	3	3	3	3	3	1	2	12	**18**
Average	2.7	0.6	2.1	0.9	0.6	0.6	2.7	1.4	1.3	0.9	2.1	1.7	3.0	3.0	3.0	2.7	6.3	5.3	6.0	11.7	**29.3**
SD	0.8	0.5	1.1	1.1	0.5	0.5	0.8	1.1	0.8	0.4	1.1	1.3	0.0	0.0	0.0	0.8	1.8	1.9	2.3	0.8	**5.2**
Antibacterial Food Contact Materials																					
A	3	1	3	0	0	1	1	1	1	0	1	1	3	1	3	1	7	3	3	8	**21**
B	1	0	1	0	1	1	1	1	1	1	1	1	3	1	1	1	2	4	4	6	**16**
C	1	3	1	0	0	0	1	1	1	1	1	3	3	1	3	1	5	2	6	8	**21**
D	1	1	1	0	1	1	1	1	1	1	1	1	3	3	3	3	3	4	4	12	**23**
E	1	1	1	1	1	1	1	1	1	1	1	1	3	3	3	3	4	4	4	12	**24**
F	3	3	3	0	1	1	1	1	1	1	1	1	3	1	3	1	9	4	4	8	**25**
G	1	0	0	0	0	1	1	0	1	1	1	1	3	3	1	3	1	2	4	10	**17**
Average	1.6	1.3	1.4	0.1	0.6	0.9	1.0	0.9	1.0	0.9	1.0	1.3	3.0	1.9	2.4	1.9	4.4	3.3	4.1	9.1	**21.0**
SD	1.0	1.3	1.1	0.4	0.5	0.4	0.0	0.4	0.0	0.4	0.0	0.8	0.0	1.1	1.0	1.1	2.8	1.0	0.9	2.3	**3.4**

***Signal* Expert**	**Physicochemical properties (Pchem)**				**Hazard**				**Kinetics**				**Exposure**				**Total Score**				
	Dissolution	Reactivity	Toxic ions/ molecules	HARN	CMR	Mutagenicity/ carcinogenicit	Immunotoxicit y	Other toxicity	Absorption	Distribution brain and	Accumulation	Other kinetic profile	Widely used	Sensitive subpopulation	Frequent use	Likely exposure	Pchem	Hazard	Kinetics	Exposure	Total (sum of expert scores)
Nano-cellulose																					
A	3	1	0	0	0	1	1	1	1	0	1	1	3	3	3	3	4	3	3	12	**22**
B	3	0	0	1	0	0	1	1	0	1	0	1	3	1	1	1	4	2	2	6	**14**
C	3	1	0	1	0	0	0	1	1	0	1	1	3	1	3	3	5	1	3	10	**19**
D	3	0	0	1	0	0	0	0	1	1	1	1	3	3	3	3	4	0	4	12	**20**
E	1	1	0	0	0	0	1	1	0	0	1	1	3	3	3	3	2	2	2	12	**18**
F	3	1	0	0	0	1	1	1	1	0	0	1	3	1	3	3	4	3	2	10	**19**
G	1	1	1	0	0	0	0	0	0	0	0	0	3	3	3	1	3	0	0	10	**13**
Average	2.4	0.7	0.1	0.4	0.0	0.3	0.6	0.7	0.6	0.3	0.6	0.9	3.0	2.1	2.7	2.4	3.7	1.6	2.3	10.3	**17.9**
SD	1.0	0.5	0.4	0.5	0.0	0.5	0.5	0.5	0.5	0.5	0.5	0.4	0.0	1.1	0.8	1.0	1.0	1.3	1.3	2.1	**3.2**
Nanosilver																					
A	3	1	3	0	0	1	1	1	1	0	1	1	1	1	1	1	7	3	3	4	**17**
B	0	0	3	0	0	0	3	3	3	3	3	1	3	3	3	3	3	6	10	12	**31**
C	0	3	3	0	0	0	1	3	3	3	3	1	3	1	3	3	6	4	10	10	**30**
D	0	1	3	1	0	1	3	3	3	1	3	3	1	1	1	1	5	7	10	4	**26**
E	1	1	3	1	1	1	1	3	1	1	3	3	3	3	3	3	6	6	8	12	**32**
F	3	3	3	0	1	1	1	1	3	1	1	1	1	3	1	1	9	4	6	6	**25**
G	1	0	3	0	1	1	1	1	3	1	1	1	3	3	3	3	4	4	6	12	**26**
Average	1.1	1.3	3.0	0.3	0.4	0.7	1.6	2.1	2.4	1.4	2.1	1.6	2.1	2.1	2.1	2.1	5.7	4.9	7.6	8.6	**26.7**
SD	1.3	1.3	0.0	0.5	0.5	0.5	1.0	1.1	1.0	1.1	1.1	1.0	1.1	1.1	1.1	1.1	2.0	1.5	2.7	3.8	**5.1**
Zinc particles																					

***Signal* Expert**	**Physicochemical properties (Pchem)**				**Hazard**				**Kinetics**				**Exposure**				**Total Score**				
	Dissolution	Reactivity	Toxic ions/ molecules	HARN	CMR	Mutagenicity/ carcinogenicit	Immunotoxicit y	Other toxicity	Absorption	Distribution brain and	Accumulation	Other kinetic profile	Widely used	Sensitive subpopulation	Frequent use	Likely exposure	Pchem	Hazard	Kinetics	Exposure	Total (sum of expert scores)
A	1	1	3	1	0	1	1	3	1	0	1	1	1	1	3	1	6	5	3	6	**20**
B	0	0	3	1	0	0	1	3	3	1	1	1	3	1	0	3	4	4	6	7	**21**
C	0	1	1	0	0	0	0	1	3	1	1	1	3	3	3	1	2	1	6	10	**19**
D	0	1	1	0	0	0	0	0	0	1	1	0	3	3	3	3	2	0	2	12	**16**
E	3	1	1	1	1	1	1	3	3	1	3	1	3	3	3	3	6	6	8	12	**32**
F	3	1	3	0	1	1	1	3	1	1	1	1	1	1	1	1	7	6	4	4	**21**
G	0	1	0	0	0	1	1	3	3	0	3	3	1	1	1	1	1	5	9	4	**19**
Average	1.0	0.9	1.7	0.4	0.3	0.6	0.7	2.3	2.0	0.7	1.6	1.1	2.1	1.9	2.0	1.9	4.0	3.9	5.4	7.9	**21.1**
SD	1.4	0.4	1.3	0.5	0.5	0.5	0.5	1.3	1.3	0.5	1.0	0.9	1.1	1.1	1.3	1.1	2.4	2.4	2.6	3.5	**5.1**
Nano-encapsulation systems in food																					
A	1	1	1	0	1	0	3	3	3	1	1	3	3	1	3	1	3	7	8	8	**26**
B	1	0	0	0	0	0	0	1	3	1	1	3	3	3	3	3	1	1	8	12	**22**
C	3	0	1	0	1	1	1	1	3	1	1	3	3	1	3	1	4	4	8	8	**24**
D	1	1	1	0	1	1	1	1	3	1	1	3	3	1	3	3	3	4	8	10	**25**
E	1	1	0	1	0	1	1	1	3	1	1	3	3	3	3	3	3	3	8	12	**26**
F	1	1	1	0	1	0	1	1	3	0	1	3	3	3	1	3	3	3	7	10	**23**
G	0	1	1	1	0	1	1	1	1	1	1	1	1	3	1	3	3	3	4	8	**18**
Average	1.1	0.7	0.7	0.3	0.6	0.6	1.1	1.3	2.7	0.9	1.0	2.7	2.7	2.1	2.4	2.4	2.9	3.6	7.3	9.7	**23.4**
SD	0.9	0.5	0.5	0.5	0.5	0.5	0.9	0.8	0.8	0.4	0.0	0.8	0.8	1.1	1.0	1.0	0.9	1.8	1.5	1.8	**2.8**
Needle-like nano-hydroxyapatite in infant formulae																					
A	3	1	0	3	0	1	1	1	1	1	1	1	1	3	3	3	7	3	4	10	**24**
B	1	0	1	1	0	1	1	1	1	1	1	1	1	3	1	3	3	3	4	8	**18**

***Signal* Expert**	**Physicochemical properties (Pchem)**				**Hazard**				**Kinetics**				**Exposure**				**Total Score**				
	Dissolution	Reactivity	Toxic ions/ molecules	HARN	CMR	Mutagenicity/ carcinogenicit	Immunotoxicit y	Other toxicity	Absorption	Distribution brain and	Accumulation	Other kinetic profile	Widely used	Sensitive subpopulation	Frequent use	Likely exposure	Pchem	Hazard	Kinetics	Exposure	Total (sum of expert scores)
C	1	3	0	3	0	0	1	1	3	1	0	1	0	3	3	1	7	2	5	7	**21**
D	3	1	0	3	0	1	1	1	1	1	1	1	1	3	3	3	7	3	4	10	**24**
E	1	3	0	3	1	3	1	1	1	1	1	1	3	3	3	3	7	6	4	12	**29**
F	3	1	0	3	0	1	1	1	1	1	1	1	1	3	3	3	7	3	4	10	**24**
G	1	1	1	1	0	1	1	1	1	1	1	3	1	1	1	3	4	3	6	6	**19**
Average	1.9	1.4	0.3	2.4	0.1	1.1	1.0	1.0	1.3	1.0	0.9	1.3	1.1	2.7	2.4	2.7	6.0	3.3	4.4	9.0	**22.7**
SD	1.1	1.1	0.5	1.0	0.4	0.9	0.0	0.0	0.8	0.0	0.4	0.8	0.9	0.8	1.0	0.8	1.7	1.3	0.8	2.1	**3.7**

9.4 Appendix 4: Flowchart systemic methodology for identification and prioritisation of signals on nanomaterials in food



9.5 Appendix 5: List of abbreviations

ANS-Panel	EFSA Panel on Food Additives and Nutrient Sources added to Food
AOP	Adverse Outcome Pathway
AP	Aids to Polymerisation
ARTfood	ECHA working group for the Assessment of Residue Transfer to food
BNV	Bureau Nieuwe Voedingsmiddelen
BPR	Biocidal Product Regulation
CBG-MEB	Medical Evaluation Board
CEF-Panel	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CMR	Carcinogenic, Mutagenic, Reprotoxic
CNC	Cellulose Nanocrystal
CNF	Cellulose Nanofibers
CNW	Cellulose Nanowhisker
CONTAM-Panel	EFSA Panel on Contaminants in the Food Chain
Ctgb	Board for the authorisation of plant protection products and biocides
DLS	Dynamic Light Scattering
EC	European Commission
EDTA	Ethylenediaminetetraacetic acid
EDX	Energy Dispersive X-Ray Analysis
EFSA	European Food Safety Authority
EU	European Union
FAF-Panel	EFSA Panel on Food Additives and Flavourings
FCM	Food contact materials
FAF-Panel	EFSA Panel on Food Additives and Flavourings
FIC	Food Information to Consumers
GBP	Granular Biodurable Particles
GSH	Reduced glutathione
HARN	High Aspect ratio Nanoparticles
IBD	Inflammatory Bowel Disease
NCC	Cellulose nanocrystal
NDA-Panel	EFSA Panel on dietetic
NERCS	New or Emerging Risks of Chemicals
NOAEL	No Observed Adverse Effect Level
NTA	Nanoparticle Tracking Analysis
NVWA	the Netherlands Food and Consumer Product Safety Authority
OECD	Organisation for Economic Co-operation and Development
PE	Polyethylene
PEG	Polyethylene glycol
PET	Polyethylene terephthalate
PFAS	Per- and polyfluoroalkyl substances
PPA	Polymerisation production aids
PP	Polypropylene
PPP	Plant Protection Product
PPPR	Plant Protection Products Regulation
PS	Polystyrene
PSP	Poorly Soluble Particles
PSLT	Poorly Soluble and Low acute Toxicity
PT	Product Type

PVC	Polyvinyl chloride
ROS	Reactive Oxygen Species
SANS	Small-Angle Neutron Scattering
SAS	Synthetic amorphous silica
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCCS	Scientific Committee on Consumer Safety
SEM	Scanning Electron Microscopy
TEM	Transmission Electron Microsocopy
WVG	Warenwetregeling Verpakkingen en gebruiksartikelen
XPS	X-ray Photoelectron Spectroscopy
XRD	X-ray Powder Diffraction
ZZS	Zeer Zorgwekkende Stoffen

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