Tentative Translation

A Comprehensive Study for Ensuring Food Safety
The Cabinet Office Food Safety Commission (FY 2009)

A Basic Survey Report on Safety Assessment Information on the Use of Nanotechnology in the Food Sector

Toray Research Center

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Contents

Overview

This survey was conducted with an aim to give the present status of the use of nanotechnology in Japan's food sector, collect the latest literature and reports, etc. produced by international organizations/foreign countries, and organize/analyze the scientific insights contributing to safety assessment in the case of ingesting food products involving nanotechnology.

<Field survey in Japan>

Field surveys were carried out by means of questionnaire and interview. The subjects of this survey were food businesses (food manufacturers, food equipment manufacturers, and a part of cooperative associations) and food container/packaging industries. Out of the valid responses (237) to the questionnaire, about 20% used nanotechnology and a little more than 10% had development plans. As for the purpose of products using nanotechnology, 60% chose health food. And regarding what effects companies using nanotechnology expected, around a little more than 40%, the largest of the responses, chose absorption efficiency enhancement. The number of firms that chose more than one of solubility, transparency or stability enhancement, all of which have to do with quality improvement, was more than those that chose absorption efficiency enhancement.

<Reports of foreign countries>

Among those surveyed were reports on food nanotechnology use produced by international organizations/foreign countries, including the following reports on nanotechnology in the food sector:

Name of organization	Title of the document	Publication year
FAO/WHO (Expert Meeting on the Application of Nanotechnologies in the Food and Agriculture Sectors)	FAO/WHO Expert Meeting on the Application of Nanotechnologies in the Food and Agriculture Sectors : Potential Food Safety Implications	2009
IRGC (International Risk Governance Council)	Risk Governance of Nanotechnology Applications in Food and Cosmetics	2008
Woodrow Wilson International Center for Scholars (WWICS) Project on Emerging Nanotechnologies (PEN) (WWICS/PEN)	Nanotechnology in Agriculture and Food Production	2006
	Assuring the safety of nanomaterials in food packaging : The regulatory process and key issues	2008
Institute of Medicine (IOM)	Nanotechnology in Food Products	2009
EU/European Commission /Nanoforum /European Nanotechnology Gateway	Nanotechnology in Agriculture and Food	2006

Name of organization	Title of the document	Publication year
EU/European Food Safety Authority (EFSA)/Scientific Panel on food additives, flavorings, processing aids and materials in contact with food	Inability to assess the safety of a silver hydrosol added for nutritional purposes as a source of silver in food supplements and the bioavailability of silver from this source based on the supporting dossier	2008
EU/EFSA/Scientific Committee	The Potential Risks Arising from Nanoscience and Nanotechnologies on Food and Feed Safety	2009
EU/Observatory NANO	Nanotechnology in Agrifood.	2009
EU/European Parliament	Novel foods, MEPs set new rules	2009
UK/Advisory Committee on Novel Foods and Processes (ACNFP)	NANOPARTICLES IN FOODS	2005
UK/British Food Standards Agency (FSA)	A review of potential implications of nanotechnologies for regulations and risk assessment in relation to food. (August 2008)	2008
	Nanotechnology	2009
UK/HOUSE OF LORDS Science and Technology Committee	Nanotechnologies and Food	2010.1
Royal Society of Chemistry(RSC)	RSC Nanoscience & Nanotechnology Nanotechnologies in Food (summary only)	2010.5 (Scheduled for publication)
Germany/Federal Institute for Risk Assessment (BfR)	The data to evaluate the application of nanotechnology in food and food commodities is still insufficient	2008
France/Food Safety Agency (AFSSA)	Nanotechnologies et nanoparticules dans l'alimentation humaine et animale	2009
Ireland/Food Safety Authority of Ireland (FSAI)	The Relevance for Food Safety of Application of Nanotechnology in the Food and Feed Industries	2008
The Netherlands/Institute of Food Safety, Wageningen University and Research Center (RIKILT)/National Institute for Public Health and the Environment (RIVM)	Health impact of nanotechnologies in food production (September 2007)	2007
Switzerland/Swiss Centre for Technology Assessment(TA-SWISS)	Dinner is served! Nanotechnology in the kitchen and in the shopping basket, Abridged version of the TA-SWISS study "Nanotechnology in the food sector"	2009

Experts of FAO/WHO agreed that an agreement would be required on clear and internationally harmonized definitions concerning nanotechnology applications to the food sector and on a method of categorizing nano-structured materials that would be helpful to risk managers. At the global level, they also noted that it was necessary to identify and address potential gaps in the procedures for formulating food standards applied by the Codex Alimentarius Commission.

Meanwhile, food nanotechnology has become a topic of hot debate in Europe, particularly in UK recently, leading to the publication of several reports. What these reports have in

common is that under the assumption that nanotechnology provides benefits and possibilities in the food sector (including agriculture), considering the deficiency of techniques and information for risk assessment, they pressed for promoting the development of related techniques. They also made it clear that the definition of nano-substances in the food sector is not conclusive.

<Literature study>

We collected and analyzed 200 major documents on safety assessment of nanotechnology use in the food sector, and prepared a summary. In the area of food nanotechnology, it became apparent that not so many studies were available on the safety effects of nano-scaling organic as well as inorganic materials. Also, limited studies reviewed the change of absorbability and safety effects of food nano-substances.

<Summary>

The experts review board of this survey considered these studies and categorized the present food products in Japan that use nanotechnology.

The board presented the following three directions which any future safety assessment of nanotechnology food products should follow.

- ♦ Assessment on the basis of the classification of nanotechnology-using food products within the scope of application
- ♦ Confirmation of the scope of application of existing assessment methods (What are the subjects to which the existing safety assessment methods for food products and industrial nanomaterials can be applied, and what are those for which new safety assessment methods need to be introduced?).
- ♦ Review and development of “safety assessment methods for nanotechnology-using food products.”

In addition, in assessing the materials based on classification, the following activities were noted for consideration for the time being.

- Defining the scope for classification (including the definition and identification of nanotechnology food products for which safety assessment is not considered necessary at present.)
- Determination and concrete definition of classification items.
- Confirmation of and data accumulation on the safety effects of changes in absorption, ingestion, reactivity, etc. involved with nano-scaling.
- Selection and justification of classification items that need data collection and safety assessment
- Consideration of the possibility of food products deviating from the classification tables.

When considering above issues, it will be required to identify the available data and deficient data at present (confirm the knowledge gap). In this survey, we sorted out the available and unavailable data on safety assessment, but for efforts and management based on the classification, further reviews will be needed in line with the classification items.

Main text

1. Purpose/content of the survey

1-1 Purpose

We conducted a field survey on the use of nanotechnology in the food sector in Japan and collected the latest literature and reports, etc. produced by international organizations/foreign countries for the purpose of organizing/analyzing the scientific insights contributing to safety assessment in the case of ingesting food products involving nanotechnology.

1-2 Content of the survey

The following work and surveys were undertaken. The results of our sorting out and analyses are discussed in Chapter 2 and beyond.

(1) The experts review board

A review session consisting of experts in food engineering, food nanotechnology, toxicology and epidemiology, etc. (hereinafter they will be called as the experts review board; the member composition is shown in Table 1-1.) was held to review the content of the survey and methods of sorting-out/analysis, etc.

Table 1-1 The experts review board

	Name	Affiliation
	Atsuo Kishimoto	Head of Sustainability Governance Group, Research Institute of Science for Safety and Sustainability of National Institute of Advanced Industrial Science and Technology
	Kiyotaka Sato	Professor at the Food Science and Biofunctions Division in the Graduate School of Biosphere Sciences, Department of Biofunctional Science and Technology, Hiroshima University, Japan
	Shigeru Sugiyama	Head of the Nano-bioengineering unit, Food Engineering Division, National Food Research Institute, National Agriculture and Food Research Organization
	Ryuichi Hasegawa	Head of the Division of Medical Safety Science, National Institute of Health Sciences
	Akihiko Hirose	Director of Risk Assessment Division, Biological Safety Research Center, National Institute of Health Sciences
○	Shoji Fukushima	Head of Japan Bioassay Research Center, Japan Industrial Safety & Health Association
	Akemi Morita	Leader of the Nutritional Epidemiology Program, National Institute of Health and Nutrition

(In the order of the Japanese syllabary; ○ denotes Chairman)

(2) Field survey

① Questionnaires were administered to companies conducting research and development of food products and apparatuses/containers/packages that use nanotechnology.

② Field surveys were conducted of those companies selling nanotechnology-related food products in Japan.

(3) Collecting literature, producing Japanese excerpts, sorting out and analysis

We collected 200 pieces of literature on the safety of using food nanotechnology and produced an excerpt of 1,000 characters for each of the literature pieces. In addition, we collected 30 pieces of foreign reports, etc., and produced an excerpt of around 2,000 characters from each report. We also produced complete translations of five of these foreign reports which we found of particular importance. These were meant as unpublicized internal information materials for this survey due to their copyrights.

Then we sorted out and analyzed the literature and foreign reports thus collected in terms of ① substance property, ② identification/analyzing method, ③ exposure route, ④ metabolism, etc., ⑤ toxicity test, ⑥ epidemiological survey, ⑦ safety for food use, and ⑧ domestic/foreign regulations.

2. Use of nanotechnology in the food sector

2-1 Nanotechnology in the food sector

Although it is relatively recently that nanotechnology came to be used in the food sector, the research and development activities are gaining momentum these years.

The main objectives of using nanotechnology in the food sector include improvement of the texture of food raw materials, nano-capsulization of food raw materials and additives, creation of new taste and flavor, control of flavor release, enhancement of the bioavailability of nutrients, etc. With regard to food packaging, development of new materials is being pursued, which have better mechanical, barrier and antimicrobial properties.

The publicized and planned application and use of nanotechnology in the food sector can be categorized as follows (Chaudhry et al., 2008):

- Fabricate/prepare food ingredients so that nano-structure is formulated.
- Use nano-sized, nano-capsulized or artificially manufactured nano-particle additives in food products.
- Incorporate artificial nanomaterials in packaging materials, etc. in order to develop “actively-” or “intelligently-” improved materials for food containers/packages.
- Use devices and materials that use nanotechnology (e.g., nano-filtration, water treatment, nano-sensors for food safety and traceability).

2-2 Scope of the survey

The scope of this survey was determined as follows via the experts review board:

(1) Definition of “nano” : The size of “nano-raw materials” (including “nanoparticles”) that were examined in this survey (“A Basic Survey Report on Safety Assessment Information on the Use of Nanotechnology in the food sector”) was determined in principle as submicron (less than 1,000 nm). However, considering the possibility of nano-raw materials agglomerating, we also paid attention to those with a size of 1 to several μm. (In our field survey, we collected information widely, including those with a size of 1 to several μm.)

(2) The subject of this survey included those nano-raw materials incorporated in food products intentionally. (In this document, “nano-raw material” is also mentioned as “nanomaterial” or “nano-substance” as appropriate.)

(3) We excluded some food products manufactured (processed/analyzed, etc.) using nanotechnology from the subjects of this survey because they had no intentionally incorporated nano-raw materials.

(4) We also excluded from the subjects of this survey those nano-substances that had come to exist in food products by some no-intentional/passive means such as through environmental exposure.

(5) We included in this survey the nano-substances of which we have eating experience.

(6) We also included in this survey those nano-substances of which we do not have eating experience, provided that animal experiment information on oral intake is available through literature study.

(7) As for packages/containers, we included those using nano-raw materials.
However, we excluded from this survey the package/container products that do not contain nano-raw materials even if some nano-raw materials were used in the manufacturing process.

(8) We excluded from this survey the appliances such as kitchen gadgets.

3. The current status of the use of food nanotechnology in Japan

We conducted a survey on the current status of use, etc. of food products and apparatuses/containers/packages (including those under research and development as well as imports from abroad) that use nanotechnology by means of questionnaires (hereinafter called questionnaire surveys) and field researches.

3-1 Utilization of food nanotechnology in Japanese firms

We prepared questionnaires each consisting of more than 30 questions from the perspective of the following items (i) to (iii), and then administered them to companies and organizations (numbering around 500) that were engaged in the research, development and manufacturing of food products and apparatuses/packages using nanotechnology, whose responses were later collected, analyzed and summarized in our survey report.

(i) Overview of the product (intended use, expected effectiveness, state of distribution, representation and advertisement, etc. of nanotechnology products)
(ii) Type, size, quantity, work procedures, etc. of the nano-substances used in manufacturing processes of food products and apparatuses/packages
(iii) Status of research and development (status of research/development, etc. of nano-substances available for food products and apparatuses/packages)

3-1-1 The questionnaire survey

(1) Purpose of the survey

Though it is said that “nanotechnology” has come to be used not only in industrial sector but in food sector as well, and is expected to be used/utilized further in future, information on the status is quite scarce. This survey was conducted for the purpose of gaining an understanding of the current status of nanotechnology use in the food sector of Japan.

(2) Subject of the questionnaire survey

We chose 900 food businesses (food manufacturers, food equipment manufacturers, and a part of cooperative associations) and food container/packaging industries as the subjects of this survey.

(3) Method of the questionnaire survey

The survey was undertaken by way of sending out self-administered questionnaire survey slips (with 33 questions in total; attached in the documents of Appendix I). The questions were divided into two parts: Part 1 to which everyone responded and Part 2 to which they responded to the extent possible. We also sent electronic file versions of the survey slips individually to those who were interested, and then the responses were

collected electronically.

(4) Period of the questionnaire survey

November 4 to 25, 2009[1]

(5) Result of the responses

a. The number of questionnaires sent: 900

b. The number of responses received: 238 (valid responses: 237)

c. Collect rate (b/a): 26.4% (26.3%)

3-1-2 Summary of the result of the questionnaire survey

This section summarizes the result of this questionnaire survey as follows[2] (see Appendix I for details of the aggregate results):

(1) Attributes of the respondent companies

① Description of the respondent companies' business (Survey slip Part 1-1.1 description of the business)

The business of the respondent companies is shown in Figure 3-1.

	Multiple choice (N = 237)	*Number of responses*
1)	Manufacturing/processing and packaging of processed food	123
2)	Manufacturing/processing of processed food (raw) materials	106
3)	Manufacturing of functional food materials	54
4)	Manufacturing of food container/packaging (materials)	22
5)	Manufacturing of food processing machinery	16
6)	Others	32

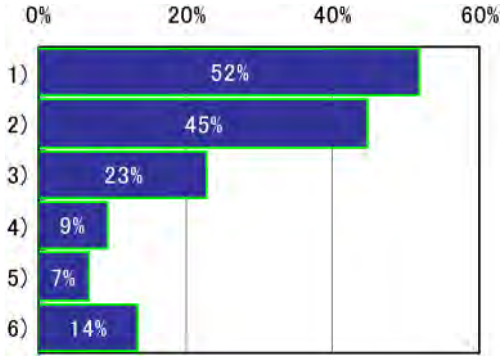


Figure 3-1 Business of the respondent companies

② Payrolls of the respondent companies (Survey slip Part 1-1.2 Payrolls)

Figure 3-2 shows the distribution of payrolls of the respondent companies. About a third of the respondent companies had not more than 100 employees.

[1] Responses delivered after the deadline of survey slips were also called into account.

[2] The percent expressions in the text are rounded to one place of decimal and therefore may not add up to 100%.

	Single choice (N = 237)	*Number of responses*
1)	Not more than 50	59
2)	51–100	24
3)	101–300	63
4)	301–1000	53
5)	1001–3000	21
6)	3001 –5000	9
7)	Not less than 5001	8

* It is unknown whether the payrolls include part-timers.

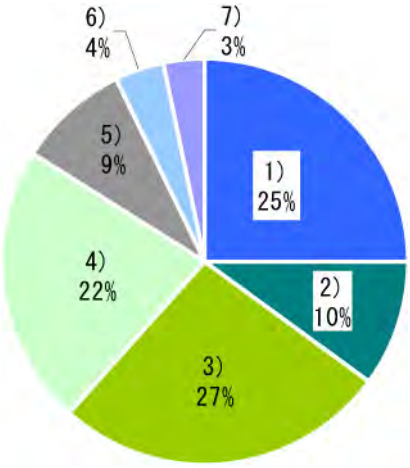


Figure 3-2　Payrolls of the respondent companies

③ Payrolls engaged in research and development (hereinafter "R&D") (Survey slip Part 2-6.2 R&D payrolls)

The distribution of R&D payrolls of the respondent companies is shown in Figure 3-3. Companies without R&D payrolls accounted for a quarter.

	Single choice (N = 204)	*Number of responses*
1)	None	50
2)	Not more than 50	118
3)	51–100	19
4)	101–300	12
5)	Not less than 301	5

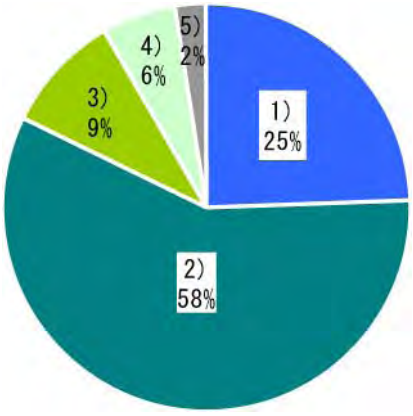


Figure 3-3　R&D payrolls of the respondent companies

(2) Use of nanotechnology in the food sector

① Outlook of nanotechnology use (respondents' opinion) (Survey slip Part 1-2.1 Outlook of nanotechnology use)

As for the outlook of nanotechnology use, in response to the question "Do you think the use will increase in your industry in future?", affirmative responses [3] "1) Definitely" and "2) Yes" accounted for 60%, whereas "5) Not at all" was none. However, the response "3) Yes and no" accounted for about a third, which seemed to include those

[3] The questions were intended to ask for each respondent's opinion and accordingly the responses are not unified views of the companies concerned. (The questionnaires were administered to those who "were the representative officers or who understood each company's overall manufacturing processes and R&D activities, and were in a position to review the future directions of their efforts.") These responses may be regarded as general views of those at the heart of the food sector.

cases where the respondents hadn't paid particular attention to nanotechnology and where the respondents took a cautious stance on nanotechnology.

Single choice (N = 237)	*Number of responses*
1) Definitely	26
2) Yes	121
3) Yes and no	80
4) No	9
5) Not at all	0
No response	1

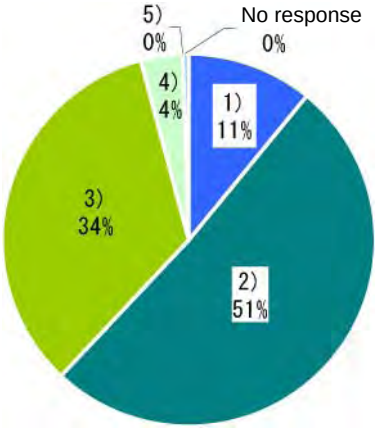


Figure 3-4 Outlook of nanotechnology use in the food sector

② Noteworthy nanotechnology use (respondents' opinion) (Survey slip Part 1-2.2 Noteworthy nanotechnology-related technologies)

As for noteworthy nanotechnology use, many of the responses chose "1) Food raw materials" and "2) Food manufacturing/processing" (around a little less than 50% and 40%, respectively)[3]. Meanwhile, "7) Nothing in particular" accounted for as much as a quarter.

Multiple choice (N = 237)	*Number of responses*
1) Food raw materials (structure, emulsion, etc.)	109
2) Food manufacturing/processing (micromachining and tiny bubbles, etc.)	94
3) Food function (nano-order capsule, etc.)	78
4) Container/packaging materials	34
5) Measurement (nano-sensor, etc.)	18
6) Others	7
7) Nothing in particular	55
No response	57

* Others: Use of food products related to coating materials, sterilization/disinfection and oxidization/reduction, and enhancement of functionality/absorption, etc.

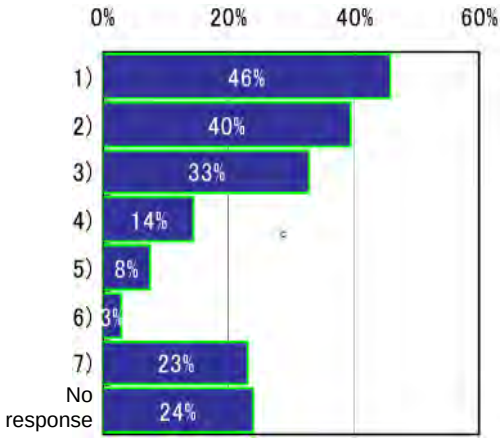


Figure 3-5 Noteworthy nanotechnology uses

③ Status/area of nanotechnology use (Survey slip Part 1-3.1 Use or nonuse of nanotechnology)

As for the status of nanotechnology use, 20% mentioned their use, while a little more than 10% mentioned their development plans. Looking at the scale of payrolls of 78 companies that chose "1) Using (nanotechnology)" or "2) Not using (with development plan)," it was shown that the scale was not necessarily large. Regarding the area of use, food raw materials dominated the responses.

	Single choice (N = 237)	*Number of responses*
1)	Using	48
2)	Not using (with development plan)	30
3)	Not using (without development plan)	158
No response		1

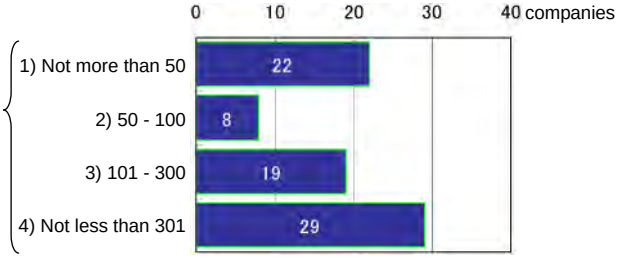


Figure 3-6 Status of nanotechnology use (Left)/distribution of the payrolls of companies using/developing nanotechnology (Right)

	Multiple choice (N = 48)	*Number of responses*
1)	Food raw materials (structure, emulsion, etc.)	28
2)	Food manufacturing/processing (micromachining and tiny bubbles, etc.)	17
3)	Food function (nano-order capsule, etc.)	5
4)	Container/packaging materials	4
5)	Measurement (nano-sensor, etc.)	0
6)	Others	5

* Others: Nano-bubble water, cosmetics, food additives and food additive preparation, food processing machines.

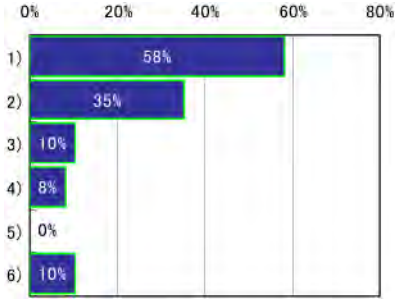


Figure 3-7 Objectives of nanotechnology use

(3) Responses from nanotechnology using companies

① Nano-substances used and the average size (Survey slip Part 1-4.2 The nano-substances used and the average size)

Responses received on the nano-substances used and the average size are summarized in Table 3-1. It shows that the nano-substances used vary widely in both the type and size.

Table 3-1 The nano-substances used and the average size

Total number of responses (N = 62)	*Number of responses*
1) Not more than 10 nm [Primary particle] polysaccharide (1); cyclodextrin and clathrate (CoQ10 α-lipoic acid, EPA, DHA, etc.) (1); platinum colloid (1); clay (1); montmorillonite (1); [Aggregate] lactobacillus (inactivated) (1); [No mention of substance] (1)	7
2) 10–100 nm [Primary particle] emulsion (3); carotenoid (2); polymer-glycoprotein (1); casein micelles in milk (1); lipid (oily substance) (2); fat and oil, liped-soluble vitamin, flavour (1); nano-bubble water (1); silica (1); CoQ10 (1); polyphenol (1) [Aggregate] dairy content (1); gold colloid (1); skin care cream (1); emulsion (fat and oil) (1) [Unclear whether primary particle or aggregate] CoQ10 (1); [No mention of substance] (1)	20
2) and 3) 10–500 nm; 2), 3) and 4)10–900 nm [Primary particle] oxygen nano-bubble, Ozone nano-bubble, air nano-bubble, hydrogen nano-bubble (2); [Aggregate] bilberry extract (1); [Unclear whether primary particle or aggregate] health food raw materials, cosmetic materials (1)	4

Total number of responses (N = 62)	*Number of responses*
3) 100–500 nm [Primary particle] cyclodextrin clathrate (1); mineral (1); fish oil emulsion (1); [Aggregate] calcium preparations (1); curcumine (1); [Unclear whether primary particle or aggregate] emulsion (2); clay, etc. (1)	8
4) 500–900 nm [Primary particle] calcium (1); [Aggregate] water and gas (1); [No mention of substance] (1)	3
5) Around 1000 nm (1 μm) [Primary particle] colloidal iron (1); aroma chemical emulsion (1); [Unclear whether primary particle or aggregate] pigment emulsion, milk fat emulsion (1)	4
6) Around several μm [Primary particle] potassium (1); spices (1); plant (1); rice powder (1); oil pigment emulsion(1); [Aggregate] pharmaceutical products, Chinese medical materials (1); calcium carbonate (1); [Unclear whether primary particle or aggregate] Vitamin C (1); various types of emulsion (1); edible dye emulsion (1); [No mention of substance] (2)	12
(No responses on the size) Film (1); oily pigment emulsion (1); [No mention of substance] (2)	4

② Purpose of the use of nano-substances/nanotechnology products (Survey slip Part 1-4.3 Purpose of the use)

As for the purpose of the use of nano-substances/nanotechnology products, 60% chose "1) Health food."

Meanwhile, 49 responses chose either or both of "1) Health food" or "2) Food products other than health food." Of a total of 62 nano-substances, 80% was used for food products.

Multiple choice (N = 62)		*Number of responses*
1) Health food	Either of these 49	37
2) Food products other than health food	Either of these 49	32
3) Food container/packages		6
4) Apparatuses other than food container/packages		1
5) Nanoparticle formation		3
6) Others		9
No response		3

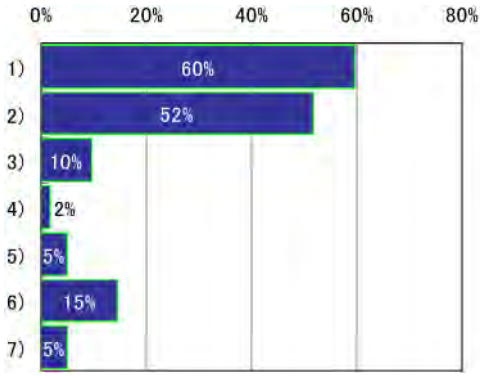


Figure 3-8 Purpose of the use of nano-substance/nanotechnology products

③ Expected effectiveness of nano-substances (Survey slip Part 2-6.4 Effectiveness expected of nano-substances)

As for the expected effectiveness of nano-substances the companies were using, about a little more than 40% of the responses, which was the largest share, chose "1) Absorption efficiency enhancement." As described in the preceding section, it seemed to have something to do with the fact that health food was the dominant purpose of use. Next came "6) Stability enhancement." Out of these choices, by putting together the three which were related to quality improvement of products, i.e., ("4) Solubility

enhancement," "5) Transparency enhancement," "6) Stability enhancement") into one choice where the responses chose at least one of the subchoices, we obtained the number of total responses as 29, which was even more than "1) Absorption efficiency enhancement." This fact appears to indicate the aspect where food nanotechnology is utilized in the technological development for improving food quality.

	Multiple choice (N = 48)		*Number of responses*
1)	Absorption efficiency enhancement		21
2)	Taste enhancement		14
3)	Reactivity enhancement		6
4)	Solubility enhancement	Responses that chose at least one of these (29)	17
5)	Transparency enhancement		10
6)	Stability enhancement		19
7)	Detection by food containers		1
8)	Sterilization, antibacterial, freshness preservation by container/packaging materials		4
9)	Others		6

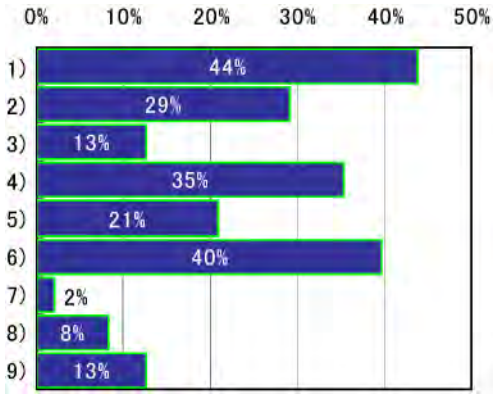


Figure 3-9 Expected effectiveness of nano-substances

(4) Opinions on the treatment of nanotechnology (Survey slip Part 1-2.3 Nanofication of substances of which respondents have eating experience)

① Substances in nano-order size of which respondents have a long eating experience as such (respondents' opinion)

As to how the substances (including food raw materials, additives, etc.) in nano-order size of which respondents have a long eating experience (e.g., dextrin, homogenized milk, etc.) should be treated, the following responses[3] were obtained. More than half of the responses chose "unnecessary" in terms of regulation, indication and safety assessment for substances in nano-order size of which respondents have a long eating experience as such.

Figure 3-10 Opinions on "substances in nano-order size of which respondents have a long eating experience as such"

② Substances of which respondents have a long eating experience processed in nano-order size

As for substances of which respondents have a long eating experience processed in nano-order size, more than 70% of responses chose "necessary" for safety assessment.

Choices selected (N=237)	Necessary Responses (ratio)	Unnecessary Responses (ratio)	No choice /no idea (ratio)
1) Some regulation is (necessary/unnecessary)	100(42%)	115(49%)	22(9%)
2) Some labeling obligation is (necessary/unnecessary)	109(46%)	107(45%)	21(9%)
3) Scientific safety assessment before launching into market is (necessary/unnecessary)	168(71%)	51(22%)	18(8%)

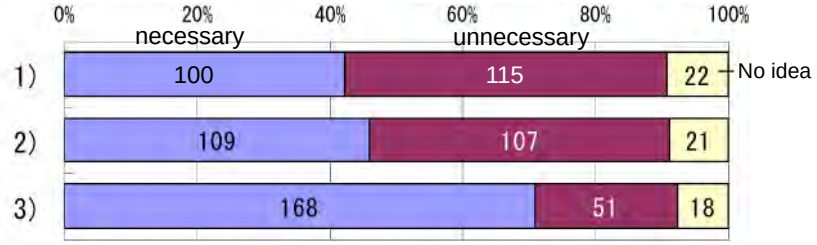


Figure 3-11 Opinions on "substances of which respondents have a long eating experience, processed in nano-order size anew"

(5) Opinions on the use and regulations of nanotechnology in the food sector (respondents' opinion) (Survey slip Part 1-2.4 Opinions on the use and regulations of nanotechnology)

Shown below is a summary of free-answered opinions of the companies that mentioned using nanotechnology or having development plans[3] (we supplemented parts of the texts). We obtained many valuable views including their insights.

① Opinions mainly related to regulation

• Safety assessment should be carried out in a proper manner regardless of past results. Regarding "substances of which respondents have a long eating experience, processed in nano-order size anew," some form of regulation or labeling obligation may be applied if the resulting merits are strong.

• Raw materials developed by nano-sizing in pursuit of new functions will be regarded as new raw materials and need some form of regulation.

• Regulations on substances of which we have enough eating experience and the safety has been established will deliver a blow against existing industries. Meanwhile, malicious food products should never be left uncontrolled and a degree of regulation is needed for new products.

• Regulation is needed as it is critical to make sure that no food raw materials, as chemical substances, have undergone any changes in their chemical structure.

• In the case of food products, dissolved substances have higher bio-activity than nano-sized substances. However, regulations will be necessary in principle because the substances that are inherently insoluble may have physical interactions.

• While a degree of regulation makes a difference, it should not be strict but should clarify the corporate responsibility.

• Labeling is necessary.
• Labeling of the properties on the products causes no problems, but it is not desirable or necessary to impose any labeling obligation or regulations on nano-sized products.
• On the assumption that food products are not free of any risk, regulation on the food products of which we have a long eating experience should be avoided as such regulation will lead to deterioration of domestic competitiveness and isolation of Japan's food industry from the rest of the world.
• We should see to it that stricter regulations applied only in Japan will not impair its international competitiveness.
• Regulations are not desirable.

② Opinions mainly related to safety assessment
• Influence of enhanced oral absorption need to be understood.
• When nanotechnology is applied to food products, it could change the speed of systemic absorption and reactivity. Therefore, some kind of prior assessment might be necessary.
• Caution will be needed in nanoscaling poorly-water soluble substances to enhance intestinal absorption.
• Since nano-sized food products are capable of being taken in by living organisms relatively more easily, their heavy metal and toxic contents need to be checked carefully.
• As for applicability of nanotechnology to food products, we have high expectations for it considering the past achievements of existing technologies contributing to functional upgrades. However, we believe that due consideration needs to be given to ensuring safety.
• As those food ingredients which are usually taken in small amounts and could have harmful influences when taken in excessive amounts may well change their bioavailability, including absorption through nano-order sizing, some special safety assessment might be necessary in some cases.
• Efforts are needed to avoid any resistance against launching into market by harmful rumors (reduction of consumer benefit) as in the case of "genetic modification." Also for that purpose, scientific safety assessment should be conducted appropriately.
• Unlike those in aerosol form, nano-substances contained in solids and liquids might have a moderate effect on human organism. In the case of food products, especially in the evaluation of acute/chronic toxicity, any regulation system will depend on not only our eating experiences but also their accumulation in human body.
• We believe no regulation is needed for nano-order sized food products at present, but research/investigation should be conducted on the bioavailability and safety of nano-sized food products immediately and the results should be made available to related companies.
• It can be suggested that those nano-substances soluble in living organisms should be

discussed separately from insoluble nano-substances. Compared with industrial materials, safety information on the nano-substances that are supposed to be taken into the body should be publicized/shared more immediately.

• We found it uncomfortable that the substances that are not regarded harmful in their wet state are suddenly considered harmful when dried in terms only of the particulate form (particle size). However, since this tendency can be seen abroad, we believe it's very important for Japan to lead the way in suggesting the right direction for it.

• If any regulation is to be introduced at all, safety assessment methods should be established first.

• Although it's beside the question to argue that some substance is safe without any scientific basis, it is like witch-hunting to emphasize the danger with no distinction among substances, and scientific discussions are needed on the basis of the properties of substance. Abstract discussions only on the size are questionable.

3-2 Details of substance utilization

On the basis of the results of questionnaire survey, we conducted field surveys on 11 companies selling nanotechnology-related food products in Japan. The survey items were formulated in the review session in consideration of the questionnaires and were approved by the review session.

3-2-1 The field survey

(1) Subject of the survey

Based on the responses of the questionnaire, we conducted field surveys on the 11 companies that mentioned using nanotechnology. (We actually visited 10 of them for the survey.) Table 3-2 below shows the use of nanotechnology in the subject companies.

Table 3-2 Use of nanotechnology in the companies where the field surveys were conducted

Use of nanotechnology	Number of companies visited
Carotenoid (food products)	3
Carotenoids, polyphenols (food products)	1
Minerals, carotenoids, fats/lipids (food products)	1
Fats/lipids (food products)	1
Minerals (food products)	1
Clathrates (sugar) (food products), coenzyme clathrates (food products)	2
Clays (packages)	1
High-pressure emulsification machines	1

(2) Period of the field survey

December 8, 2009–January 13, 2010

3-2-2 Results of the field survey

Information and opinions obtained in the field survey can be summarized as follows:

(1) Widespread use of nanotechnology in future

- In our questionnaire on the widespread use of nanotechnology in future (Survey slip Part 1-2.1 Outlook of nanotechnology use), 2 companies chose “1. Definitely,” 7 chose “2. Yes” and one chose “3. Yes and no.”
- Many firms seem to be rather hesitant to use nanotechnology on a wider scale considering the sensitive matter of public acceptance as seen in Europe, which is now cautious about it (main reason for choosing “Yes” rather than “Definitely”).
- Europe is reluctant but willing to pursue nanotechnology in light of its merits. Europe regards nano-scaling technology as beneficial to consumers.
- For food dyes, it is critical to improve the colorfastness, and cost reduction is prioritized over (costly) technologies in the food sector.
- We believe nanotechnology will lead to cost and waste reduction.
- Food manufacturers around the world are using low-technologies. Nanotechnology itself doesn’t appear to appeal to the consumers of food products.
- We began to turn our attention (not only to food applications but also) to industrial applications as well.

(2) Ensuring safety of nano-substances

- We conduct a variety of toxic tests of nano-substances and publish the results in scientific articles.
- We do not publish articles, but conduct toxic tests voluntarily.
- We manage nano-scaled substances as food additives in the positive lists including emulsions. We consider nano-substances as ordinary substances.
- We do not pay special attention to ensuring the safety of nano-substances as they have been derived from ordinary food products.
- From the perspective of safety, we need to examine our corporate policy toward nanotechnology. We are planning to implement animal tests shortly (absorption effects, excessive intake. etc.) (now under research/development).
- We use those products with established standards (through international debates) as nano-substances.

(3) Opinions on ensuring safety and regulations

① Categorization and regulations of nanotechnology use in the food sector

- Clear definitions of industrial nanotechnology and food nanotechnology should be made (for industrial products, edibility [related to nanotechnology as a processing

technology], application/medical goods, etc.).

- New substances (i.e., those originally not meant for eating and substances for which we have no prior eating experience such as inorganic substances) will need regulation.
- Nanomaterials are so different from each other that if they are regulated, it is desirable to categorize and prioritize them according to their respective chemical properties rather than regulating them in an entirety.
- Safety information may as well be disclosed. The information should be considered on the basis of categorization in terms of nanoparticle contents, time of exposure, amount of intake, extent of nano-scaling, size, factors, etc.
- Needless to say, it will cause some damage to the industry to regulate the products that are ensured of safety to a certain extent. However, new unruly substances should not be left unregulated.

② Nano-substances in the food sector and ensuring their safety

- Safety needs to be ensured not only for nano-substances (in the food sector).
- Safety assessment is needed just the same for substances that were made available for assessment recently.
- Medium- and small-sized companies might, for lack of funding, have no choice but only to follow the assessment already made. For instance, many of the companies engaged in emulsification for a long time do not even measure the size. As the scale of the companies decreases, there are greater chances of unavailability of detailed data such as particle size distribution in a most of such companies
- We believe safety confirmation should be done in house as far as possible. We should make researches to find the basis of judgment ourselves and if necessary, consider applying voluntary restraints as a (responsible) food company (regardless of the existence of regulations).
- Irrespective of laws, it is our stance as well as the responsibility of a company involved in the food community to publish adequate data.
- We are already conducting voluntary toxic tests and absorption tests. Therefore, if clear-cut regulations are to be established and required tests are to be imposed, of course, we are willing to address them.
- ADI (Acceptable Daily Intake) may be adopted for the criterion of judgment.
- Examination of the safety of packaging materials seems to be running late in every parts of the world.
- (From a standpoint of an equipment maker) In principle, it will be an issue for food manufacturers to address.

③ Request to the government/disclosure of information, etc.

- We ask the government to disclose the related information and learn the lessons of GMO. Based on the disclosed information, we hope to emphasize the safety of our

in-house products accurately.

- We hope that the government discloses the related information on this issue in a felicitous way (to the public).
- A longer time of grey area will affect the industry. We ask the government to set the time schedule adequately.
- Health foods are different from ordinary food products. In addition, (compared with drugs and medicines) the lethal dosage is also different between them. These points are not regulated appropriately in Japan, and we hope to see the situation corrected.
- We ask for the government not to simply follow the developments abroad, especially the trend of regulations in Europe and the United States.

4. The current status of the use of nanotechnology in the food sector abroad

We collected and analyzed 30 pieces of information on risk managing measures concerning the use of nanotechnology in the food sector, including the reports of foreign countries (the United States, European Union (EU), United Kingdom, Ireland, Australia/New Zealand, France, Germany, etc.), survey researches/current regulations and attention-calling information (hereinafter referred to as reports, etc.) in our efforts to collect, sort-out and analyze literature, etc. (overseas information).

A list of these 30 pieces of reports, etc. is shown in Appendix II.

In choosing the reports, etc., we picked up the latest publications of the following documents.

- Reports/documents on nanotechnology produced by international organizations and food regulating authorities of the respective governments.
- Reports/documents on nanotechnology in the food sector produced by international organizations and the respective governments.

4-1 International organizations

As for reports, etc. on the use of nanotechnology in the food sector, we could obtain the documents issued by Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) and International Risk Governance Council (IRGC) (Table 4-1).

Table 4-1 Reports, etc. of international organizations

International organization, etc.	Publishing body	Title of document	Publication year
FAO/WHO	Expert Meeting on the Application of Nanotechnologies in the Food and Agriculture Sectors	FAO/WHO Expert Meeting on the Application of Nanotechnologies in the Food and Agriculture Sectors : Potential Food Safety Implications	2009
IRGC	IRGC	Risk Governance of Nanotechnology Applications in Food and Cosmetics	2008

In this section, we summarized the report issued by FAO/WHO in 2009 as follows:

"Expert Meeting on the Application of Nanotechnologies in the Food and Agriculture Sectors: Potential Food Safety Implications," issued by the FAO/WHO Expert Meeting on the Application of Nanotechnologies in the Food and Agriculture Sectors in December 2009, is a report summarizing the results of discussions of the Meeting on the use of nanotechnology in food production/processing, potential risks to human health, and the basic elements for transparent and constructive dialogues on nanotechnology among stakeholders, which were held among 17 experts majoring in the related areas of food technology, toxicology and communication in the FAO Headquarters from June 1st to 5th, 2009.

The Expert Meeting agreed that based on the recognition that nanotechnology would provide a host of opportunities to various sections of the food sector and bring in potential benefits for farmers, food industries and consumers, they had to agree on clear and internationally harmonized definitions when applying nanotechnology to the food sector and to develop a system of classifying nano-structures that will be of help to risk managers. At the global level, the Meeting also noted that it was necessary to identify and address potential gaps in the procedures for formulating food standards applied by the Codex Alimentarius Commission. Regarding the assessment of risks to human health, they suggested that we should promote researches that would lead to a new risk assessment strategy for the use of nanotechnology in food products, etc. In addition, FAO/WHO proposed to the member states to encourage the general public to participate in the discussions on the use of nano-science and nanotechnology in the food and agriculture sectors as well as to provide the resources required for instruction, training and capacity building to involve stakeholders in the efforts. They also emphasized the significance of communication and partnership with other inter-governmental organizations.

What these reports have in common is that under the assumption that nanotechnology provides benefits and possibilities in the food sector (including agriculture), considering the deficiency of techniques and information for risk assessment, they pressed for the promotion of the development of related techniques.

4-2 The United States

Available reports, etc. on the use of nanotechnology in the food sector included the documents issued by Food and Drug Administration (FDA), Woodrow Wilson International Center for Scholars Project on Emerging Nanotechnologies (WWICS/PEN), Institute of Medicine (IOM) and US Environmental Protection Agency (EPA) (Table 4-2).

Table 4-2 Reports, etc. of US

Name of organization	Title of document	Publication year
Food and Drug Administration (FDA)	Nanotechnology : A report of the U. S. FDA Nanotechnology Task Force	2007
	FDA Nanotechnology public meeting (Briefing paper at the meeting (multiple documents))	2008
	Nanotechnology in Agriculture and Food Production	2006
Woodrow Wilson International Center for Scholars (WWICS) Project on Emerging	Assuring the safety of nanomaterials in food packaging : The regulatory process and key issues	2008

Name of organization	Title of document	Publication year
Nanotechnologies (PEN) (WWICS/PEN)	A Hard Pill to Swallow : Barriers to Effective FDA Regulation of Nanotechnology-Based Dietary Supplements	2009
Institute of Medicine (IOM)	Nanotechnology in Food Products	2009
Environmental Protection Agency (EPA)	U.S. Environmental Protection Agency Nanotechnology White Paper	2007

US Food and Drug Administration (FDA) formed a Special Committee on Nanotechnology (the Special Committee) in 2006 and released a report analyzing the scientific programs and its regulatory authority with an aim of directing attention to the use of nanotechnology in medication, medical devices, biologics and supplements. This report, entitled "Nanotechnology: A report of the US FDA Nanotechnology Task Force," presents the current status, challenges and recommendations on the scientific details of nanotechnology and scientific/regulatory issues involved with FDA. The principal recommendations can be summarized in two points: enhancement of technological insights for monitoring/managing nanotechnology-using products and informing stakeholders of the information required to support the market launch of products using nano-scaled substances (products under the control of FDA).

Enhancement of technological insights was proposed to be pursued specifically by ① evaluation of harmful biological interactions involving particular particles, ② clarification of the relationship between the surface area/electric charge and the toxicity of nano-substances, ③ collection of scientific information by all means, including requests for data on specific products, ④ nurturing of experts within FDA, ⑤ formulation of a system for data accumulation, ⑥ re-examination of the adequacy of the current toxicity assessment system, ⑦ promotion of establishment and standardization of characteristic evaluation of nanoparticles.

Additionally, they addressed such regulatory policy issues as ability of FDA to identify FDA-regulated products, including nano-scaled substances, scope of FDA's authority over the assessment of safety and effectiveness, permission indication/indication obligation and national environmental policy acts, and drafted specific recommendations on each of the issues.

Another point of this report deserving special mention is that it dared not to clarify the definition of nanotechnology expressed in particle size, etc. The Special Committee hasn't adopted the definitions of "nano-scaled substances," "nanotechnology" or related terms for the purpose of establishing the scope of work. "Nanotechnology," "nano-scaled substance" and the related terms or concepts may have certain meanings under certain circumstances; under other circumstances, the definitions could be too narrow or too wide. Therefore, the Special Committee says, "We do not recommend adopting certain formalistic and fixed definitions of those terms for regulatory purposes at present." This clearly shows the outlook and view that the use of nanotechnology in the food sector is very likely to evolve in such a wide range of areas that a set of determinate definitions may not be applicable.

Woodrow Wilson International Center for Scholars (WWICS) of US is a think tank founded by the US Congress in 1968 in honor of Thomas Woodrow Wilson, the 28th President of the United States. This think tank implements the Project on Emerging Nanotechnologies (PEN), under which it is pursuing active collection and transmission of information on the use of nanotechnology. It has also published several reports concentrating on the food sector.

"A Hard Pill to Swallow: Barriers to Effective FDA Regulation of Nanotechnology-Based Dietary Supplements," published in 2009, examined the question of whether FDA has prepared itself to address new regulations on health supplements using artificial nanoparticles. This report says that since the competence of FDA that regulates the safety of health supplements using nano-substances is extremely constrained for lack of information and resource and in terms of its regulatory authority in some parts of crucial areas, enhancement of authorities, information capacity and resources of FDA are needed to resolve these drawbacks. It concludes that until these drawbacks are resolved, consumers taking in those health supplements that contain artificial nano-substances will be placed at additional and even greater unpredictable risks.

This report of FDA was published (in 2007) almost earlier than any of those similar reports by international organizations and other countries, including Europe. Since then, no formal reports have ever been released summarizing the views of FDA (As of March 2010, a public meeting was held once in 2008 as shown in Table 4-2.), and a new announcement of policies, etc. of the U.S. is awaited.

4-3 Europe

Available reports, etc. on the use of nanotechnology in the European food sector included the documents issued by the related organizations of EU (including European Food Safety Authority (EFSA)), United Kingdom, Germany, France, Ireland, the Netherlands, etc. (Table 4-3)

Table 4-3 Reports, etc. of European countries

Country/ region	Name of organization	Title of document	Publication year
EU	European Commission /Nanoforum /European Nanotechnology Gateway	Nanotechnology in Agriculture and Food	2006
	European Food Safety Authority (EFSA)/Scientific Panel on food additives, flavorings, processing aids and materials in contact with food	Inability to assess the safety of a silver hydrosol added for nutritional purposes as a source of silver in food supplements and the bioavailability of silver from this source based on the supporting dossier	2008

Country/ region	Name of organization	Title of document	Publication year
	EFSA/Scientific Committee	The Potential Risks Arising from Nanoscience and Nanotechnologies on Food and Feed Safety	2009
	Observatory NANO	Nanotechnology in Agrifood.	2009
	European Parliament	Novel foods, MEPs set new rules	2009
United Kingdom	Advisory Committee on Novel Foods and Processes (ACNFP)	NANOPARTICLES IN FOODS	2005
	Department for Environment, Food and Rural Affairs (DEFRA)	Environmentally beneficial nanotechnologies :barriers and opportunities	2007
		EMERGNANO A review of completed and near completed environment, health and safety research on nanomaterials and nanotechnology	2009
	British Food Standards Agency (FSA)	A review of potential implications of nanotechnologies for regulations and risk assessment in relation to food. (August 2008)	2008
		Nanotechnology	2009
	HOUSE OF LORDS Science and Technology Committee	Nanotechnologies and Food	2010.1
	Royal Society of Chemistry (RSC)	RSC Nanoscience & Nanotechnology Nanotechnologies in Food (Summary only)	2010.5 (Scheduled for publication)
Germany	Federal Institute for Risk Assessment (BfR)	The data to evaluate the application of nanotechnology in food and food commodities is still insufficient	2008
France	Food Safety Agency of France (AFSSA)	Nanotechnologies et nanoparticules dans l' alimentation humaine et animale	2009
Ireland	Food Safety Authority of Ireland (FSAI)	The Relevance for Food Safety of Application of Nanotechnology in the Food and Feed Industries	2008
The Netherlands	Institute of Food Safety, Wageningen University and Research Center (RIKILT)/National Institute for Public Health and the Environment (RIVM)	Health impact of nanotechnologies in food production (September 2007)	2007
	National Institute for Public Health and the Environment (RIVM)	Nanotechnology in perspective. Risks to man and the environment	2009
Switzerland	Swiss Centre for Technology Assessment (TA-SWISS)	Dinner is served! Nanotechnology in the kitchen and in the shopping basket, Abridged version of the TA-SWISS study "Nanotechnology in the food sector "	2009

EU/EFSA Scientific Committee released "The Potential Risks Arising from Nanoscience and Nanotechnologies on Food and Feed Safety" in February 2009. This document also noted

a variety of potential applications of nanotechnology in the food sector, saying that this technology is most promising in the area of food packaging in the short term. Additionally, summarizing the study cases of drug kinetics and toxicity assessment of artificial nano-raw materials, this report stated that very few study cases of oral toxicity using nano-raw materials, for instance, had been released and most of them were on insoluble metals or their oxides.

Main recommendations of the Scientific Committee were to develop the methodology for detecting artificial nano-raw materials contained in food products, animal feedstuff and living tissue; to investigate the use of artificial nano-raw materials in the food/feedstuff sector; to assess the exposure of consumers and livestock; and to create a database of various types of artificial nano-raw materials.

Among European countries, the United Kingdom was most proactive in issuing reports, etc. through various governmental agencies. "Nanotechnologies and Food," published by the HOUSE OF LORDS Science and Technology Committee in January 2010, summarized the concerns and recommendations related to the use of nanotechnology in the food sector on the basis of the information and opinions collected from a wide range of experts, government officials, representatives of the food/beverage industry, consumer groups and NGOs through the public meeting held by the House of Lords in 2009, seminars and door-to-door surveys.

This report suggests unifying the names of nano-sized structures and calling them nanomaterials. This term, it says, indicates the use of nano-scaled substances that do not occur naturally in food products or natural foodstuff deliberately manipulated on the nano-scale, and the definition doesn't include the nano-substances occurring naturally or produced by conventional manufacturing processes.

The recommendation proposed by the House of Lords consists of no less than 32 items, including nanotechnology in the food sector (promotion of commercialization), health and safety (filling the knowledge gap), subjects of regulation (making the definitions fall within the scope of laws, etc.), REACH (Regulation 1907/2006/EC of the European Parliament and of the Council concerning the Registration, Evaluation, Authorization and Restriction of Chemicals)[4], enhancement of regulations and implementing effective communication.

Meanwhile, in anticipation of future needs for risk assessment, British Food Standards Agency (FSA) and the food industry both recommended providing a database of nanomaterials under development. They noted that effective public communication and transparency are essential for consumers to make decisions based on the information on the use of nanotechnology in the food sector.

According to a report by the French Food Safety Agency (AFSSA) released in March 2009, unlike the conventional substances concerned, few treatises are available on the oral toxicokinetics (absorption, distribution, metabolism and excretion) and oral toxicity of nanoparticles, and while they seem to depend on chemical composition, size, surface reaction, etc., risk assessment needs to be considered on a case-by-case basis. Moreover, says the

[4] (EC) No 1907/2006 (Registration, Evaluation, Authorisation and Restriction of Chemicals)

report, without accurate identification of hazards, measuring tools or knowledge about the use of potential food, we have limitations on assessing consumers' exposure and health risk involved with nanoparticles at present. And it concludes that under these circumstances, progress of researches should be ensured, and until the data especially applicable to digestion/absorption are obtained, an alert must be issued on the use of nanotechnology or nanoparticles in food products and feedstuff.

AFSSA concludes that it believes a systematic reporting scheme on these substances and products used in food products is needed in the rulemaking process, and a licensing system should be pursued for market launching. France is expected to proceed with regulation on nanotechnology[5] more aggressively than other EU member states.

4-4 Others

Food Standards Australia New Zealand (FSANZ) provides an article on its webpage titled "Small Particles, Nanotechnology and Food," which describes the relationship between nanotechnology and food products, how nanotechnology is used in food products, etc. and the regulations on the food products using nanotechnology. FSANZ monitors the research and development activities concerning nanotechnology and food safety conducted in each country on implementation basis, adjusting the framework for regulation as needed.

4-5 Existing foreign/domestic regulations, etc.

As summarized in the previous section, various food regulatory agencies in the world have released documents presenting the views and reports, etc. on the availability/usability of nanotechnology in the food sector.

In the United States, FDA formed a Special Committee on Nanotechnology (the Special Committee) in 2006 for the purpose of deciding on a regulatory approach for realizing products that use the nano-scaled substances prescribed by FDA in an innovative, safe and effective manner. As described in Section 4-2, recommendation of the Special Committee was formulated in 2007, and a public meeting was held in 2008 in order to collect comments and data to support the realization of the recommendations.

In Europe, several analyses were conducted on the legal gap between the current laws on food products and the use of nanotechnology, which concluded that although the existing basic fundamental framework for risk assessment can be applied to the use of nanotechnology in food products and feedstuff, the current evaluation methods for toxicity and exposure dose should be improved before application. In 2009, the Scientific Panel of EFSA announced its scientific views especially on artificial nanoparticles and supported the conclusion. The Scientific Panel noted two parts where some uncertainty poses a challenge to risk assessment, i.e., (1) difficulty in characterizing, detecting and measuring artificial nanoparticles and (2)

[5] AIST-TOKYO Nanotechnology Information, version 2009.3.19

scarcity of information available on the aspect of toxicology. Accordingly, it recommended assessing the risks for an individual artificial nanoparticle until a detailed risk assessment process has been developed. The gap analyses suggested that the possibility of using nanotechnology in food products and feedstuff would be covered by respective approval processes such as the General Food Law (EC 178/2002), which is the framework for existing regulations or regulations on newly developed food products. Europe takes a far more cautious stance to nanotechnology compared with the United States, and deliberations on regulation are well underway. Among the European countries, as shown in Table 4-3, France is expected to pursue regulation on nanotechnology in advance of other EU members.

The current food products standard code of Australia and New Zealand (FS CODE) doesn't provide for any special standards for regulating nano-substances, and as a framework for regulation, it deals with nano-substances as a subject of regulation for food additives, conducting risk assessment and reviews as necessary.

5. Results of literature study on the survey of nanotechnology use in the food sector

We searched through the literature and commercial databases cited in the reports, etc. of international organizations and others (JSTPlus, JMedPlus, STNTOXCENTER, MEDLINE) and picked up the pieces of literature that would contribute to safety assessment of nanotechnology use in the food products sector, out of which, under the approval of the review meeting, we collected 200 pieces to publish in the survey report. Then we analyzed the literature collected and extracted the information on the property, identification/analyzing method, exposure route, absorption/distribution/metabolism/excretion, etc., toxicity test and epidemiological survey (influence on humans), etc. of nano-substances.

We created a list of literature pieces collected (Appendix III).

5-1 Safety information of nanotechnology food products using organic materials

5-1-1 Property of substance

Organic materials used for the nanotechnology products that are now under consideration in terms of safety regarding absorption/distribution/metabolism/excretion, toxicity test, etc. include the following:

- Various functional substances such as vitamin E, coenzyme Q10 (hereinafter called CoQ10), β-glucan, β-cryptoxanthin, astaxanthin, and curcumin
- Food raw materials such as red yeast rice and middle bone of the fish
- Polystyrene, poly-lactic acid, chitosan, latex, etc. for the capsule base material to convey the object substances to the body

Many of these had been nano-scaled in order to enhance absorbability. The particle size was in the range of around 100 nm for the functional substances and around 500 nm to several μm for the food raw materials.

As for the state of particles, the functional substances were often in the form of nano-emulsions and the food raw materials were in powder form.

Table 5-1 summarizes the property data of the substances described in the literature collected. We chose eight items for the property data of substances: chemical composition, state of agglomeration, crystal structure, particle size/distribution, purity (including impurity information), form, surface area and surface charge.

Table 5-1 Mention/no-mention of the respective property data of substances in the literature collected (Organic substances)

Nano-substance	Chemical composition	State of agglomeration	Crystal structure	Particle size/ distribution	Purity (incl. impurity information)	Form	Surface area	Surface charge
CoQ10	○	○	○	○	—	—	—	○
β-cryptoxanthin	○	○	—	○	—	—	—	—
β-glucan	○	○	—	○	○	—	—	—
Astaxanthin	○	○	—	○	—	—	—	—
Curcumin	○	○	—	○	○	—	—	—
Vitamin B_{12}	○	—	—	○	○	—	—	—
Vitamin E	○	—	—	○	—	—	—	—
Vitamin K	○	○	—	○	—	—	—	—
Sesame lignan glycoside	○	—	—	○	○	○	—	—
Middle bone of salmon	○	—	—	○	○	○	—	—
Edible vegetable powder	○	○	—	○	—	—	○	—
Red yeast rice	○	○	—	○	—	—	—	—
Chitosan	○	○	—	○	—	○	—	○
Polyvinyl chloride	○	—	—	○	—	○	—	—
Polystyrene	○	○	—	○	—	○	○	○
Poly-lactic acid, glycolic acid	○	○	—	○	—	○	—	○
Poly(propyleneimine) Dendrimer	○	○	—	○	○	○	—	○
Polymethyl methacrylate	○	○	—	○	○	○	—	—
Latex	○	○	—	○	—	○	—	—
Emulsified wax	○	○	—	○	—	—	—	○

(○: Mention of the data —: No mention of the data)

5-1-2 Identification/analyzing method

The studies measured the concentration of nano-scaled substances in the blood and the respective tissues, as well as conducted the identification of chemical properties of the substances, but not the size .

5-1-3 Exposure route

The studies conducted oral administration to humans and rats/mice, intravenous administration to rats/mice and dermal administration to hamsters in considering the safety of organic substances.

5-1-4 Absorption/distribution/metabolism/excretion, etc.

It was reported that nano-scaled CoQ10 (particle size: 30–100 nm),vitamin E (particle size: around 50 nm), astaxanthin (particle size: 110 nm), and β-cryptoxanthin (particle size: 100 nm) showed higher absorption than conventional forms (many of these were macrosized) from the results of oral administration tests to humans and rats. Enhancement of absorbability through nano-scaling varies in the range of several percent to 10-fold (Ankola et al. 2007; Schulz et al.,2006; Nishimura et al., 2009; Wajda et al., 2007; Takaishi et al., 2007; Ogawa et al., 2007; Back et al., 2005).

For the purpose of examining the change in absorbability of nano-scaled food raw materials (Sesame lignan glycoside was also included as it is not a single substance.), sesame lignan glycoside (particle size: 200 nm) and middle bone of salmon (particle size: 1900 nm) were orally administered to rats to examine the distribution in the respective organs. Sesame lignan glycoside was found to be distributed in larger quantity in the form of nano-scaled groups, showing particularly higher concentration in the liver and small intestine (Chia-Ding et al., 2009). For middle bone powder of salmon, as the effect of nano-scaled powder was judged by the quantity of calcium, the distributed quantity of nano-scaled powder itself was unknown (Akino et al., 2009).

Poly-lactic acid and chitosan are among those used for the capsule base material to convey the object substances to the body. As for the absorbability of poly-lactic acid-glycolic acid copolymer particles with diameter of 100 nm, 500 nm, 1 μm and 10 μm in the intestinal tract of rats, those particles with diameter of 100 nm showed 15 to 250-fold higher absorbability than larger particles. A histologic evaluation also showed that while 100-nm particles were dispersed over the whole area of the submucosal layer, larger particles were localized mainly in the epithelial layer of tissues (Desai et al., 1996).

In an oral administration of polystyrene nanoparticles (with diameter between 50 nm and 3 μm) to rats, smaller sizes showed higher absorbability in the gastrointestinal tract, and absorption was further enhanced by modifying the surface with tomato lectin (Hussain et al.,1997). In another oral administration of polymethyl methacrylate nanoparticles (with diameter 130 ± 30 nm) to rats, they were absorbed from gastrointestinal tract and distributed in the body with *in vivo* concentration, particularly higher in the blood and muscles (Araujo et al., 1999 b). In other oral administration tests to rats using polymethyl methacrylate nanoparticles (particle size: 130 nm), the seemingly low-molecular-weight part was absorbed from the gastrointestinal tract and transferred to bile and urine. Excretion rate from bile and urine was so high that 95% was eliminated from the body in 2 days (Nefzger et al., 1984).

Table 5-2 summarizes the information on how the absorbability of organic materials change by nano-scaling. The data were extracted from those literature documents dealing with oral administration tests.

Additionally, we summarized the data collected so far in terms of absorption,

distribution/accumulation, and metabolism/excretion of respective nano-substances in Table 5-3.

Table 5-2 Change in absorbability of nano-scaled organic materials

Nano-substance	Change in absorbability by nano-scaling	Literature
Vitamin E	As a result of administration tests to 24 test subjects, the bioavailability of nano-prepared vitamin E (particle size: 30–60 nm) was 10-fold higher than the conventional capsule.	Wajda et al., 2007
CoQ10	As a result of administration tests to 24 test subjects, the bioavailability of nano-prepared CoQ10 (particle size: 30–60 nm) was 5-fold higher than the conventional capsule.	Wajda et al., 2007
	As a result of oral administration tests to rats, it showed 3.7–4.7-fold higher absorbability than the control group dissolved in olive oil.	Nishimura et al., 2009
	As a result of oral administration tests to rats using carboxymethyl cellulose suspension, commercial preparation and developed nanoparticles, absorbability were 45%, 75% and 79%, respectively.	Ankola et al., 2007
Sesame lignan glycoside	As a result of examining the distribution in tissues using SD rats, the nano-scaled groups showed higher distributed quantities than non-nano-scaled groups in most of the tissues. They were particularly high in the liver and small intestine. The nano-scaled groups also showed a 2-fold higher concentration in liver at 3 hours after administration.	Chia-Ding et al., 2009
Astaxanthin	As a result of oral administration of astaxanthin oleaginous solution, emulsion preparation (particle size: 250 nm), nanoparticulated astaxanthin (particle size: 110 nm) to rats, the concentration of emulsified liquid with particle size of 110 nm in the blood was 2-fold the oleaginous solution.	Ogawa et al., 2007
β-cryptoxanthin	In oral administration tests to humans (using emulsified preparation of average particle size 1 μm), the maximum concentration of the emulsified preparation of β-cryptoxanthin in the blood serum was 2-fold higher than commercially available juice.	Takaishi et al., 2007
Poly-lactic acid, glycolic acid	As a result of the examination of absorption in the gastrointestinal tract using *in situ* intestine loop models formulated in the duodenum and ileum by ventrotomy of rats, the absorption efficiency of particles with diameter 100 nm was 15–250-fold higher than that of larger particles (500 nm, 1 μm and10 μm).	Desai et al., 1996
Polystyrene	As a result of an oral administration of polystyrene micro-spheres with diameter in the range of 50 nm–3 μm to rats, the absorbability in the gastrointestinal tract were: 34% for the 50-nm group, 26% for the 100-nm group, 9% for the 300-nm group, 14% for the 500-nm group, 5% for the 1-μm group and 0% for the 3-μm group (measured from the amount of polystyrene).	Jani et al., 1990

(Data extracted from documents dealing with oral administration tests)

Table 5-3 Mention/no-mention of the data on the absorption, distribution/accumulation, and metabolism/excretion of substances in the literature collected (Organic substances)

Nano-substance	Absorption	Distribution/ accumulation	Metabolism/ excretion
CoQ10	○	—	—
β-cryptoxanthin	○	—	—
β-glucan	—	—	—
Astaxanthin	○	—	—
Curcumin	—	—	—
Vitamin B_{12}	—	—	—
Vitamin E	○	—	—
Vitamin K	○	—	—
Sesame lignan glycoside	○	◎	—
Middle bone of salmon	—	◎	○
Edible vegetable powder	—	—	—
Red yeast rice	—	—	—
Chitosan	—	—	—
Polyvinyl chloride	○	—	—
Polystyrene	○	◎	—
Poly-lactic acid, glycolic acid	○	—	—
Poly(propyleneimine) Dendrimer	—	—	○
Polymethyl methacrylate	○	◎	○
Latex	—	○	—
Emulsified wax	—	○	—

(○: Mention of the data —: No mention of the data)
* For distribution/accumulation, ○: Mention of the data from a single organ,
◎: Mention of the data from multiple organs

5-1-5 Toxicity studies

Organic materials whose toxicity test results were reported include food raw materials such as β-glucan, red yeast rice and edible vegetable powder, as well as chitosan as a capsule base material, on which genotoxicity tests and repeated dose tests were conducted.

However, the number of reports dealing with the toxicity tests of nanotechnology food products is very few. What's behind this is surmised to lie in the fact that there are many cases where toxicity tests, even if they have actually been conducted, are rarely published under the basic assumption that food products must be safe right from the start, and there are only a few cases where toxicity tests are conducted or the results are published in treatises even when they have been conducted because the substances that have long been taken in with food products are considered safe substances.

β-glucan (particle size: 90 nm) showed no change in toxicity in a repeated dose test over 4 weeks, a reverse mutation test or a chromosome aberration test (Odagiri et al., 2006 a;

Odagiri et al., 2006 b). As for chitosan, an *in vivo* acute toxicity test using rats (limit tests, OECD 2001) showed that the LD_{50} values of chitosan nanoparticles were not less than 2000 mg/kg body weight (Yoksan et al., 2008). Red yeast rice (particle size: 259.3 nm) didn't show toxicity even in subacute toxicity tests using rats, and the No-Observed-Adverse-Effect-Level (NOAEL) was 1,000 mg/kg body weight/day for both sexes of NRMR mice (Yu Chiun-Chieh et al., 2008). Edible vegetable powder (particle size: 955 nm) showed no harm in terms of general toxicity in oral administration tests to rats (Kim, Dong-Heui et al., 2009).

5-1-6 Epidemiological survey (influence on humans)

β-glucan (particle size: 90 nm) was also used in repeated dose tests on normal subjects and in oral tests on patients with cancer.

A test meal containing 15 mg of β-glucan (lentinan) was given to normal subjects (adequate intake of this substance is 15 mg/day) once a day over 2 weeks, and after 2 weeks, the frequency was increased to three times per day over additional 4 weeks in a repeated dose test over a total of 6 weeks to confirm the safety. As a result, some of the subjects noticed symptoms (headache, backache and stomachache) and showed urine occult blood, but these had no causal relations with the β-glucan test meals nor were the extents of particular clinical significance. Besides, other examination findings didn't show any events of special mention either, verifying the safety of the test meals in this repeated intake (Odagiri et al., 2006 c).

In a dose test on patients with cancer, test meals were given to 315 patients with cancer once a day for 12 successive weeks as much as possible. General state, nutritional state, white blood cell count, side effects of anticancer agent and adverse events were assessed before administration, after 4 weeks, 8 weeks and 12 weeks. As a result, 10 cases showed events such as diarrhea, headache, etc. whose causal relations with test meals couldn't be denied; all the symptoms, however, disappeared or were alleviated during the observation period. The incidence rate of incidental consequences was as low as 3.2%, leading to the evaluation that the test meal was highly safe so that no safety problems were expected if the patients took the meal on their own judgment (Oka et al., 2006).

In a double-blind, placebo-controlled trial using CoQ10 (particle size: 190 nm), 900 mg/day of CoQ10 tablets or placebo tablets were given for 4 successive weeks. As a result of physical examination, hematologic test, biochemical examination of blood and urine analysis, etc. on the first day, after 2 weeks, after 4 weeks and at 2 weeks after the end of intake in order to evaluate the safety, no change was observed that was attributable to the intake of CoQ10 and the safety was verified (Nukui et al., 2007).

5-1-7 Influence on the safety of food products

Toxicity tests were conducted on some of the food raw materials but no reports of

toxicity tests were available on many of the organic materials. In addition, only a very few studies were available on the safety influence of nano-scaling food products. Nano-scaling is expected to enhance absorption, but the available literature was also limited in terms of evaluated absorption change and safety tests (oral toxicity in particular).

Data are lacking on the safety influence of absorption change, and the causal relations between safety and various changes in properties by nano-scaling in terms of particle size, surface area, surface modification, etc.

5-2 Safety information of nanotechnology food products using inorganic materials

5-2-1 Property of substance

The inorganic substances which were used as orally administered nano-substances in the safety studies include gold, silver, copper, platinum, iridium, selenium, titanium oxide, zinc oxide, ferric pyrophosphate, pearl powder and fullerene, etc. The particle sizes were mostly below 100 nm.

Among these, few nano-substances mentioned with safety information were silica, ferric pyrophosphate, platinum and pearl powder. Gold, fullerene and Layered Double Hydroxide (LDH) were studied for their absorption property and safety as drug carriers. Other data are safety assessment data based on oral administration in the process of industrial application of materials.

Table 5-4 shows the property data of substances mentioned in the literature collected. We chose eight items from the property data of substances: chemical composition, state of agglomeration, crystal structure, particle size/distribution, purity (including impurity information), form, surface area and surface charge.

Table 5-4 Mention/no-mention of the respective property data of substances in the literature collected (Inorganic substances)

Nano-substance	Chemical composition	State of agglomeration	Crystal structure	Particle size/ distribution	Purity (incl. impurity information)	Form	Surface area	Surface charge
Zinc	○	○	—	○	○	○	—	—
Aluminum	○	○	—	○	—	○	—	○
Iridium	○	○	—	○	—	○	—	○
Carbon nanotube	○	○	○	○	○	○	—	—
Carbon Black	○	○	—	○	—	○	○	○
Gold	○	○	—	○	○	○	—	○
Silver	○	○	—	○	○	○	—	○

Nano-substance	Chemical composition	State of agglomeration	Crystal structure	Particle size/ distribution	Purity (incl. impurity information)	Form	Surface area	Surface charge
Cobalt-chromium alloy	○	—	—	○	○	○	—	—
Zinc oxide	○	—	—	○	○	○	—	—
Titanium oxide	○	○	○	○	○	○	○	○
Ferric oxide	○	○	—	○	—	○	—	○
Molybdenum oxide	○	○	—	○	—	○	—	○
Silica	○	○	○	○	○	○	—	○
Selenium	○	○	—	○	○	—	—	—
Copper	○	○	—	○	○	○	○	○
Platinum	○	○	—	—	—	—	—	—
Ferric pyrophosphate	○	○	○	○	○	○	○	○
Fullerene	○	○	—	○	○	○	○	—
Montmorillonite	○	○	—	○	○	—	—	—
Quantum dot	○	○	—	—	—	○	—	—

(○: Mention of the data —: No mention of the data)

5-2-2 Identification/analyzing method

The studies measured the chemical composition, particle size, form, surface area (BET analysis), etc. of the administered nano-substances. The purity analyses used fluorescence emission method, etc. and particle size/form identification used transmission electron microscope (TEM), scanning electron microscope (SEM) and optical microscopes.

5-2-3 Exposure route

Considering the safety of inorganic materials, oral administration to humans, rats, mice and birds; intraperitoneal administration to mice; abdominal cavity administration to dogs; intravenous administration to rabbits, rats and mice; endotracheal administration to rats and mice; and inhalation exposure of rats and mice were conducted.

* As this survey addressed the use in the food sector, we mainly collected the literature dealing with oral administration.

5-2-4 Absorption/distribution/metabolism/excretion, etc.

Available data on absorption/distribution/metabolism/excretion after oral administration were very scarce, and more information is needed to understand the mechanism of absorption/distribution/metabolism/excretion. Based on this limited amount of data, it

seems that smaller sizes of particles generally enhance absorption, and the nanoparticles absorbed from the gastrointestinal tract are distributed in various organs. However, it is known that absorption is significantly influenced by not only the particle size but also the surface modification of nanoparticles as well.

As the substances intended for use in food products are expected to fulfill certain functions in the body, development efforts are under way to enhance the absorption.

As for iron, by nano-scaling ferric pyrophosphate, the absorption enhanced by two-fold when compared with microparticles, which was comparable to the level of ferric sulfate as a medical product (Nanbu, 2003; Mark A. Roe et al., 2009; Christine Hotz et al., 2008; Angeles-Agdeppa I et al., 2008). Pearl powder, which is used as a health supplement in China, shows better calcium absorbing/retaining ability in nano-particulate form than microparticles (H.S. Chen et al., 2008). As for platinum nanoparticles, the result of examination showed they are not absorbed when orally administered to rats (Ishida et al., 2007).

The following data were obtained on gold and fullerene considered for use as drug carriers (nano-carriers).

In an oral administration test of gold nanoparticles using mice, the smaller particles showed higher distributed concentration in the blood and various organs (Hillyer et al., 2001). Fullerene orally administered to rats was excreted to feces without being absorbed (for the sake of reference, intravenously administered fullerene was transferred from blood to liver, and disappeared from the main organs, but moved to skeletal muscles and skin hair as well as to the brain.) (Yamago et al., 1995).

Others are safety assessment data based on oral administration in the process of industrial application of materials.

Silver nanoparticles orally administered to rats accumulated not only in the stomach, liver, kidney, and lung but also in the brain in a small quantity as well (Kim, Y.S. et al., 2008). In an oral administration test of titanium oxide nanoparticles on humans, the smaller particles (in a comparison between 160-nm and 380-nm particles) showed higher absorbability (Bockmann et al., 2000). In an oral administration test on rats, the particles accumulated in the colonoscope, liver, small intestine tissues, peritoneal tissues and lung, but they didn’t accumulate in the heart or kidney (Jani et al.,1994), while in another oral administration to mice, they were distributed in the liver, spleen and kidney (Wang, J. et al., 2007). In an oral administration of zinc oxide nanoparticles to mice, they accumulated in the bone, kidney and pancreas (Wang, B. et al., 2008). In another oral administration of copper nanoparticles to mice, the data shows a considerable accumulation in the liver, kidney and blood (Chen, Z. et al., 2007). Though we couldn’t obtain any oral test data of carbon nanotubes, in an intravenous administration to mice, these didn’t accumulate in the liver or kidney, but were immediately eliminated from the body (Singh et al., 2006).

We summarized the data of the respective nano-substances within the scope of this survey in terms of absorption, distribution/accumulation, and metabolism/excretion of

respective nano-substances in Table 5-5.

Table 5-5 Mention/no-mention of the data on the absorption/distribution/metabolism/ excretion of substances in the literature collected (Inorganic substances)

Nano-substance	Absorption	Distribution	Metabolism/excretion
Zinc	—	—	—
Aluminum	—	—	—
Iridium	—	◎	○
Carbon nanotube	—	◎	○
Carbon black	—	—	—
Gold	○	◎	—
Silver	—	◎	—
Cobalt chrome	—	—	—
Zinc oxide	—	◎	—
Cerium oxide	—	—	—
Titanium oxide	○	◎	—
Ferric oxide	—	—	—
Copper oxide	—	—	—
Molybdenum oxide	—	—	—
Silica	—	◎	—
Selenium	—	◎	—
Copper	—	◎	—
Platinum	—	—	—
Ferric pyrophosphate	○	—	—
Fullerene	○	◎	○
Magnetite	—	—	—
Montmorillonite	—	—	—
Quantum dot	—	—	—

(○: Mention of the data —: No mention of the data)
* For distribution/accumulation, ○: Mention of the data from a single organ,
◎: Mention of the data from multiple organs

5-2-5 Toxicity studies

The information we obtained on the toxicity tests of inorganic materials consists mainly of safety assessment data for industrial nanomaterials, which include the results of various toxicity tests conducted using montmorillonite, silica, silver, copper, gold, platinum, zinc, selenium, titanium oxide, zinc oxide, molybdenum oxide, ferric oxide, carbon nanotube, fullerene, etc.

The toxicity test results of silica and ferric pyrophosphate that are envisaged to be applied to food products are as follows.

As for silica, when human bronchoalveolar cancer cells were exposed to silica nanoparticles with diameters of 15 nm and 46 nm at a dose of 10–100 μg/ml for 48 hours, the cell viability decreased in proportion to the dosage. Both the silica particles showed higher cytotoxicity than crystalline silica, but in this range of dosage, the cytotoxicity of 15-nm and 46-nm silica nanoparticles had no significant difference. As a result of measuring the time-sensitivity and oxidative stress response of the cytotoxicity using 15-nm silica nanoparticles, the cell viability showed a significant decrease as functions of both the nanoparticle dosage (10–100 μg/ml) and exposure time (24–72 h) (Lin,W. et al., 2006).

As for ferric pyrophosphate, its influence on rats' gastric mucosa was examined. In the dosage groups of ferric sulfate and sodium ferrous citrate, though some showed ulcers, all of the individual rats administered with nano-scaled ferric pyrophosphate showed no aberration in the gastric mucosa. Its acute toxicity in LD_{50} value was not less than 650 mg iron/kg and showed no aberration in terms of mutagenicity, either (Nanbu, 2004).

5-2-6 Epidemiological survey (influence on humans)

Safety tests were conducted on humans using platinum nanoparticles. In these tests, adults with lipid metabolism abnormality (10 males and 25 females) were administered with platinum nanoparticles with dosages of 18 μg and 36 μg per day for 2 weeks of repeated administration to evaluate the safety of excessive intake. As a result of examinations based on subjective symptom, physical examination, hematologic examination and urine examination, no adverse events that were caused by the test foods during and after the test period were observed (Hattori et al., 2008).

5-2-7 Influence on the safety of food products

Only a very few studies were available on the safety influence of nano-scaling food products. In addition, nano-scaling is expected to enhance absorption, but the available literature was also very scarce that both evaluated absorption change and dealt with safety tests (oral toxicity in particular).

Data are lacking on the safety influence of absorption change, and on the causal relations between safety and various changes of properties by nano-scaling in terms of particle size, surface area, surface modification, etc.

5-3 Safety information of food containers/packaging using nanotechnology

Although few safety data were obtained on the nano-substances transferred from food container/packages to food products, one report examined the possibility of transfer of artificial nanoparticles from packaging materials to food products by a physicochemical method. The report showed that when polymer matrix with a relatively low dynamic viscosity

that doesn't react with artificial nanoparticles and very small artificial nanoparticles with a diameter of 2 nm were used in packaging materials, the artificial nanoparticles had the possibility of being transferred from the packaging material to food products. This observation is considered to be applicable to the case of nanocomposites comprising silver and polyolefins (LDPE, HDPE, and PP). Meanwhile, in the case of larger artificial nanoparticles and polymer matrix with a relatively high dynamic viscosity, such as polystyrene and polyethylene terephthalate, a large amount of transfer wasn't considered likely (Simon et al., 2008).

CSL of UK conducted a study on the transfer of artificial nanoparticles from the two types of food contact materials composed of nanocomposites (Biopolymer Nanocomposite Films for Use in Food Packaging Applications (2007–2010)). According to the study, no clay minerals were detected in the beer bottles filled with PET (polyethylene terephthalate) and nanocomposites. Also in another test using food containers composed of polypropylene/silver nanocomposite, the transferred amount of silver was at a very low level (below detection limit). These experimental data conformed very well with physicochemical observations.

5-4 Other information on the safety of food nanotechnology

Enhancement of absorption by surface modification

- As a result of examining the bodily intake of polymethyl methacrylate (coated with nonionic surfactant) in an intravenous administration to rats, while at a surfactant concentration of not more than 0.1%, it showed the same behavior as uncoated nanoparticles, at 0.1%; however, the concentration of polymethyl methacrylate suddenly increased in the liver (75% → 13%), and the concentration apparently increased in the blood and other organs as well (Araujo et al., 1999 a).
- It became apparent that surface modification with polyethylene glycol (PEG) minimizes non-specific adsorption of protein to the surface of nanoparticles (cause of agglomeration), and reduces the intake in the liver. 20-nm particles were taken into reticuloendothelial cells at the lowest rate and excreted from the body last, whereas these were easily taken into tumors and exuded from tumor vessels at a high rate, giving expectations as a drug carrier (Zhang et al., 2009).
- Polystyrene (coated with PEG) could pass through the mucus barrier even in the form of large nanoparticles (200–500 nm) (Lai et al., 2007).
- Dextran (with surface modification with vitamin B_{12}) was capable of delivering insulin to blood plasma via oral administration in the form of both dextran nanoparticles alone and insulin carrier, while a combination of vitamin B_{12} and low cross-bridge/poly-disperse dextran nanoparticles was able to release insulin in the blood as a high-efficiency, long-lasting insulin carrier (C Kishore et al., 2007).
- Surface modification with vitamin B_{12} provided the function of conveying nanoparticles from the apical surface to the basal surface of cells (Russell-Jones et al., 1999).

- As a result of oral administration of a combination of latex particles (500 nm), invasin and maltose binding protein (MBP), 13% of the administered combination of MBP-invasin-nanoparticles were transferred to the cardiovascular region within 24 hours of administration, while only 2% of them were transferred to the region when they had been incubated under coexistence with porcine mucin as an invasin inhibitor in advance and when MBP alone was combined with the nanoparticles (Hussain et al., 1998).
- As a result of oral administration to rats of polystyrene nanoparticles (500 nm), the intestinal absorption increased by 50-fold. The surface of these nanoparticles had been modified using tomato lectin, a bio-adhesive molecule (Hussain et al., 1997).

Information on the intestinal absorption mechanism of nanoparticles

- In general, the smaller size of particles show higher absorption in gastrointestinal tract. Intake of particles into the gastrointestinal tract occurs mainly in Peyer's patch, where lymph supply and mononuclear phagocytic cells exist in large amounts. Then the particles are transferred to the mesentery network, particularly to mesenteric lymph nodes and the sinusoidal region of liver via venous circulation, where they are ingested via phagocytosis by Kupffer cells and epithelial cells (Jani et al., 1990).
- From an evaluation of ingestion under an oral administration to rats, 60% of the intestinal intake was attributable to Peyer's patch (Hillery et al., 1994).
- The main path of nanocapsule absorption lies in M cells and the neighboring intestinal cells in Peyer’s patch (Damge et al., 2000).
- As a result of examining whether particulate ingestion can occur in an animal where M (microfold) cells contained in Peyer's patch had been completely eliminated, it was confirmed that the intake of particles was occurring in other paths of Peyer's patch of the small intestine (Smyth et al., 2008).
- The intake via Peyer's patch increased by nano-scaling, and the particles accumulated in the spleen and liver by the activities of macrophages.
- It is considered important to make the nanoparticles intended for delivering drugs small enough (not larger than 100 nm) to extend the duration of the *in vivo* distribution phase and the plasma half-life as well as to avoid non-selective intake by reticuloendothelial macrophages. However, since particles not larger than 5 nm are eliminated by renal clearance, the particle size needs to be larger. Most nanoparticles are taken into the spleen and liver by macrophages; so their circulation half-life is generally short. In particular, particles with hydrophobic surface tend to be localized in the spleen and liver. Some recent studies show that nanoparticles accumulate in the kidney, heart, brain, etc. as well. By adequately applying surface modification, etc., the life of nanoparticles can be extended and made to decrease gradually. In general, particles with size of 20–50 nm are expected to exist in plasma longer than those with size not less than 100 nm (Choi Soo-Jin et al., 2008).
- In a study on β-glucan (lentinan), β-glucan particles were labeled and their intake into

Peyer's patch was examined. β-glucan usually exists with the molecules not in a dispersed state but in huge agglomerated forms of molecules (about 130 μm in size), which are not absorbed from small intestines, etc. even when they are orally administered as they are. Two types of this material, i.e., β-glucan particulated into microparticles with a size of about 1/2000 (90 nm) and the conventional type of β-glucan, were administered to mice, and the absorption in the small intestine was examined (identified by gold colloid label). It was observed that the conventional type of β-glucan didn't exist on the surface of intestinal Peyer's patch at all, but the particulated β-glucan existed on the surface of Peyer's patch, and additionally, examination by an electron microscope showed that β-glucan had been taken into the epidermal cells (Suga, 2003).

- As a result of administering micelle form of vitamin K to rats with ligated bile ducts, the concentration of vitamin K in plasma didn't increase, but the concentration (in plasma) increased when bile was administered at the same time. From this observation, it was suggested that bile should be present for vitamin K to be absorbed, free bile was involved in the absorption of micelle form of vitamin K in the alimentary tract, and intake of the micelles via pinocytosis was not significant (van Hasselt et al., 2009).

6. Summary

6-1 The current status of the use of nanotechnology in the food sector in Japan

We obtained the following opinions, etc. by questionnaires to the major food-related companies and door-to-door surveys of the companies using nanotechnology.

- Nanomaterials have already been used in some food products.
- As “nano-scaling” is usually not the aim of food products (transparency and stabilization are often the objectives), the awareness of dealing with nanotechnology food products is at a low level.
- The definition of “nano” is ambiguous.
- We are concerned that the products of companies properly conducting safety assessment and those unreliable goods simply using the word “nano” are lumped all together by the word “nano-food products.”
- Major companies will not get in a bind even if they are obligated to conduct safety assessment. (They have been taking the data from the very start.) On the contrary, we hope dubious products to be regulated out of the market in an appropriate manner.
- In the case of food products, dissolved substances have higher bio-activity than nano-sized substances. However, safety assessment will be necessary in principle because the substances that are inherently insoluble may have physical interactions.
- Safety assessment should be carried out to a satisfactory extent before launching nano-substances into market. Substances used for sterilization and virucidal disinfection must undergo a thorough adequacy verification process and they should be promoted through revision of regulatory measures
- Safety assessment and labeling obligation are needed for the substances not used in conventional food products.
- We believe that no regulation is needed for nano-order sized food products at present, but research/investigation should be conducted on the bioavailability and safety of nano-sized food products immediately and the results should be made available to related companies.
- Regulations on all the substances (mandating safety assessment, etc.) for which we have enough eating experience will deliver a blow against the existing food industries.
- While a degree of regulation makes a difference, it should not be strict, but should clarify the corporate responsibility.
- As there is no regulation at present, some form of arrangements will be needed.
- We’d like to see the regulatory policies decided early.
- We hope that the regulations of this country won’t be engulfed in foreign regulations.
- We should see to it that stricter regulations applied only to Japan will not impair its international competitiveness.
- If any regulation needs to be introduced at all, safety assessment methods should be

established first.

6-2 The current status of the use of nanotechnology in the food sector abroad

6-2-1 Definition of “nanotechnology-using food product”

The views of each country and international organization on the definition of nanotechnology products are summarized as follows：

<Scope of application>

- The application scope of nano-substance has not been defined in the food sector.
- It is ambiguous whether natural nanomaterials are included or not.

<Size>

- In many cases, the definition of industrial nanomaterials is quoted (for substances with at least one dimension less than 100 nm).
- The size range is not provided in the policy measures (U.S. FDA).
- “Food products containing constituents not more than 300 nm” should be distinguished from the perspective of safety assessment (based on the data in which particles not more than 300 nm are taken into the cell) (Friends of the Earth Australia).
- On the basis of the concept that the novelty of a nanomaterial lies in the property of substance (in the new function, in particular) and not in the size, all substances below 1000 nm should be the subject of review as “nanomaterials” (the United Kingdom).

We chose the “food products (or containers/packages, etc. for food products) containing nanomaterials that are ultimately ingested by consumers” for the subject of this survey. Though the containers/packages using nanomaterials with concerns over the transfer to food products were included in the subject of this survey, the nanotechnologies used in manufacturing process such as nano-filtration and nano-bubble wash as well as non-intentional tramp materials from environmental sources were excluded. As for the range of the size, we regarded a wide range of food products containing substances with at least one dimension less than 100 nm as nanotechnology-using food products and collected the related information.

6-2-2 Categorization of “nanotechnology-using food products”

In the reports of international organizations, etc., they often adopted the categorization by type of raw materials used such as “inorganic or organic materials” and by type of application such as “food (processing), supplement or container/packaging.”

The report entitled “Expert Meeting on the Application of Nanotechnologies in the Food and Agriculture Sectors: Potential Food Safety Implications”, issued by the FAO/WHO Expert Meeting on the Application of Nanotechnologies in the Food and Agriculture

Sectors in December 2009, and the EFSA report both referred to Chaudhry et al., 2008 for the use of nanotechnology in food products, and presented the following five items for consideration.

- Manufacturing/processing resulting in nano-structuring the food constituents
- Use of nano-sized or nanocapsuled additives for food products
- Application of artificial nanomaterials to coating and container/packaging materials (development of innovative food-contacting materials and nano-sensors aimed for "Smart Package")
- Use of nanomaterials in nano-filtration for eliminating undesired substances from food products
- Application of artificial nanomaterials to pesticides, animal drugs and other agrichemicals for the purpose of improving food producing systems (indirect application to the food sector)

Meanwhile, they classified nanomaterials into the three categories of inorganic (transition metals like silver and iron: alkaline-earth metals like calcium and magnesium; nonmetals like selenium and silicate; titanium dioxide), surface functionalization (the second-generation materials, functionalized to provide the functions of oxygen absorption, antimicrobial activity and antiseptic action such as nano-clay) and organic (mainly used as food additives and supplements such as vitamin, antioxidant substance, dyes, flavors, etc.).

The EFSA report "The Potential Risks Arising from Nanoscience and Nanotechnologies on Food and Feed Safety" released in February 2009 dealt mainly with artificial nanomaterials, whereas among "natural" nano-raw materials like micelles, it addressed only those materials used for the purpose of intentionally retaining the properties of nano-substances, including, for instance, the purpose of capsulizing bioactive substances and excluded those "natural" nano-constituents in the form of emulsion (homogenized milk, mayonnaise, etc.).

As for the use of nanotechnology in the food/feedstuff sector, as with FAO/WHO, it quoted the treatise by Chaudhry et al. and classified them into the following five categories:

- Food contacting raw materials (materials interacting with food or the ambient environment; coating process for nano-structuring the surface, etc.)
- Manufacturing/processing resulting in nano-structuring the food/feedstuff constituents
- Food/feedstuff with nano-sized constituents added (additives such as artificial color, flavor, preservatives; nanocapsules, etc.)
- Bio-sensors for monitoring the status of food products in storage/transport (including packaging materials with display function)
- Indirect application of nano-sized agrichemicals (fertilizer, pesticide, etc.), animal drugs, etc. to the food sector

The report of House of Lords Science and Technology Committee (Nanotechnologies and Food), released in January 2010, describes the current status of nanotechnology use in the food sector for the four categories of food product/supplement, food additive, food contacting material and agriculture.

6-2-3 Challenges facing the use of nanotechnology in the food sector

In the reports of the respective international organizations, etc., the following issues were cited as the challenges facing the safety assessment of nanotechnology-using food products.

<Definition/scope>

- The definitions are ambiguous.
- Since the properties of nanomaterials often depend on the surface properties, the definitions not only by size but also by surface area should be added as well.
- In assessing the food exposure, distinction between natural and artificial nanoparticles becomes an issue.
- Unintentional incorporation of nanomaterials into food products through environmental release needs to be considered.
- It also needs to be considered that nanomaterials which are not envisaged to be applied to food products at present have the possibility of being used in such applications in future.

<Regulation/risk assessment>

- Although food products and food contacting materials using nanomaterials are already sold in the market, safety assessments are conducted only on substance basis, and no regulations that control the particle size are provided.
- The current safety assessment approaches are applicable, but another issue is very likely to take place involved with the properties of artificial nanomaterials.
- Assessment methods (experimental selection, etc.) have not been established yet.
- It is difficult to measure “the status of being nano-sized.” (“Substance” is measured at present.)

<Scientific data>

- As one of the risks of artificial nanomaterials, interaction with protein, etc. is now an issue of concern (Nano-carriers are capable of taking in and transporting other substances than the intended ones.).
- The safety assessments conducted so far on nanomaterials have been focused mainly on the efforts concerning exposure of laborers associated with the manufacture and handling of nanomaterials, and regarding the safety assessment, only a very little information is available that takes into account oral ingestion. Besides, the nanomaterials under review are mostly inorganic materials.
- Few data are available regarding organic materials.

- It has been suggested that the properties of nanomaterials have a high probability of influencing ADME (absorption, distribution, metabolism, excretion). While some reports noted that the smaller particles are more likely to be absorbed from the alimentary tract and are also more distributed in respective organs, the related data are very limited.
- Natural nanomaterials are assumed to pose no risk. Some artificial nanomaterials such as cyclodextrin have long been used safely.
- As for a variety of nanomaterials already used in the medical drug industry, including liposome and nanoemulsion, showing no toxicity even in cases of non-oral administration, these have been approved and used.

6-3 Results of literature study on the safety assessment of nanotechnology use in the food sector

We classified the collected data into those on organic and inorganic materials, and then conducted analysis/sorting out from the perspective of the safety of nanotechnology-using food products. Table 6-1 shows a summary on the mention/no-mention of the data on physical property and absorption/distribution/metabolism in the literature collected.

<Organic materials>

- Many of the organic materials are tested on the assumption that they will be ingested as food products.
- In many of the reports dealing with the change in absorption rate, the purpose of developing nano-scaled food products is described as to enhance absorption. Meanwhile, enhancement of transparency, solubility, reactivity and stability are among the purposes of nanotechnology use in the food sector, but it seems absorption is not necessarily examined in these cases.
- While the degree of absorptive enhancement by nano-scaling is difficult to compare in a simple way due to the fact that test methods are not unified, the reports varied in the range of several % to 10-fold.
- The reports on absorption/distribution/metabolism/excretion are refined in relation to the purpose of delivering drugs. However, no reports were available on the tests conducted on every aspect of absorption, distribution, metabolism and excretion for the substances considered for ingestion as food products.
- Though reports were available on the toxicity test of nano-scaled food products, the number was very small. Food products are supposed to be safe from the very start of things, and in many cases, no toxicity test was conducted. Or, even when the test was conducted, the results weren’t reported in treatises.
- No reports that assessed the influence of nano-scaling on safety were available.

<Inorganic materials>

- Inorganic materials include not only food additives and materials on which safety

assessment has been conducted for so-called health food, but also those materials on which oral toxicity tests have been conducted as a part of safety assessment for industrial nanomaterials.

- While the tests on absorption, distribution, metabolism and excretion were conducted on only a few substances, studies on absorption and body distribution were dominant for industrial materials.
- Materials developed for food applications are expected to enhance absorption, and tests were conducted on the change of absorption rate associated with nano-scaling.
- Conventional toxicity tests were conducted on materials developed for food applications.
- Only a few studies examined the causal relationship between nano-scaling and toxicity. A study of the influence of silica particle size on the living body was among them.

<Absorbability>

- Many studies examined the influence of a variety of surface modifications on absorption rate. Behavior of nanoparticles depends on the types of surface modifications.
- Studies that used polystyrene and latex to survey the particle-absorbing mechanism of intestinal tract were available. Intake from the small intestine is often through Peyer's patch, but it was observed that other paths also played a role in this activity.
- Most nanoparticles are taken into the spleen and liver by macrophages. In addition, it was reported that particles with hydrophobic surface tend to be localized in the spleen and liver.

Table 6-1 Mention/no-mention of the data on the physical property and absorption/distribution/metabolism of substances in the literature collected

	Nano-substance	Mention/no-mention of physico chemical data								Mention/no-mention of the data on absorption/distribution /metabolism		
		Chemical composition	State of agglomeration	Crystal structure	Particle size/distribution	Purity (incl. impurity information)	Form	Surface area	Surface charge	Absorption	Distribution/accumulation	Metabolism/excretion
Organic materials	CoQ10	○	○	○	○	—	—	—	○	○	-	-
	β-cryptoxanthin	○	○	—	○	—	—	—	—	○	-	-
	β-glucan	○	○	—	○	○	—	—	—	-	-	-
	Astaxanthin	○	○	—	○	—	—	—	—	○	-	-
	Curcumin	○	○	—	○	○	—	—	—	-	-	-
	Vitamin B_{12}	○	—	—	○	○	—	—	—	-	-	-
	Vitamin E	○	—	—	○	—	—	—	—	○	-	-
	Vitamin K	○	○	—	○	—	—	—	—	○	-	-
	Sesame lignan glycoside	○	—	—	○	○	○	—	—	○	◎	-
	Middle bone of salmon	○	—	—	○	○	○	—	—	-	◎	○
	Edible vegetable powder	○	○	—	○	—	—	○	—	-	-	-

	Nano-substance	Mention/no-mention of physico chemical data								Mention/no-mention of the data on absorption/distribution /metabolism		
		Chemical composition	State of agglomeration	Crystal structure	Particle size/distribution	Purity (incl. impurity information)	Form	Surface area	Surface charge	Absorption	Distribution/accumulation	Metabolism/excretion
Organic materials	Red yeast rice	○	○	—	○	—	—	—	—	-	-	-
	Chitosan	○	○	—	○	—	○	-	○	-	-	-
	Polyvinyl chloride	○	—	—	○	—	○	—	—	○	-	-
	Polystyrene	○	○	—	○	—	○	○	○	○	◎	-
	Poly-lactic acid, glycolic acid	○	○	—	○	—	○	—	○	○	-	-
	Poly(propyleneimine) Dendrimer	○	○	—	○	○	○	—	○	-	-	○
	Polymethyl methacrylate	○	○	—	○	○	○	—	—	○	◎	○
	Latex	○	○	—	○	—	○	—	—	-	○	
	Emulsified wax	○	○	—	○	—	—	—	○	-	○	-
Inorganic materials	Zinc	○	○	—	○	○	○	—	—	-	-	-
	Aluminum	○	○	—	○	—	○	—	○	-	-	-
	Iridium	○	○	—	○	—	○	—	○	-	◎	○
	Carbon nanotube	○	○	○	○	○	○	—	—	-	◎	○
	Carbon black	○	○	—	○	—	○	○	○	-	-	-
	Gold	○	○	—	○	○	○	—	○	○	◎	-
	Silver	○	○	—	○	○	○	—	○○	-	◎	-
	Cobalt-chromium alloy	○	—	—	○	○	○	—	—	-	-	-
	Zinc oxide	○	—	—	○	○	○	—	—	-	◎	-
	Titanium oxide	○	○	○	○	○	○	○	○	○	◎	-
	Ferric oxide	○	○	—	○	—	○	—	○	-	-	-
	Molybdenum oxide	○	○	—	○	—	○	—	○	-	-	-
	Silica	○	○	○	○	○	○	—	○	-	◎	-
	Selenium	○	○	—	○	○	—	—	—	-	◎	-
	Copper	○	○	—	○	○	○	○	○	-	◎	-
	Platinum	○	○	—	—	—	—	—	—	-	-	-
	Ferric pyrophosphate	○	○	○	○	○	○	○	○	○	-	-
	Fullerene	○	○	—	○	○	○	○	—	○	◎	○
	Montmorillonite	○	○	—	○	○	—	—	—	-	-	-
	Quantum dot	○	○	—	—	—	○	—	—	-	-	-

(○: Mention of the data —: No mention of the data)
* For distribution/accumulation, ○: Mention of the data from a single organ,
◎: Mention of the data from multiple organs

6-4 Discussion

On the basis of the above data, and considering the status of the use and development of nanomaterials in Japan obtained in this survey, the nanotechnology food products of Japan may be summarized as follows:

Table 6-2 Categorization of nanotechnology-using food products

• Range of the particle size:
1 nm – 100 nm – 5 μm

Major categories	Middle categories (main raw materials)	Subcategories (assorted in consideration of safety assessments)	Product groups	Typical substances
Substances ordinarily existent in food products in nano to micron size			Ordinary food products	Water, food products (intracellular substances derived from animal/plant cells or microorganism), micelles in raw milk, etc.
Manufactured nanomaterials (intentionally created and intentionally used)	<Food products> Organic	Products expected to undergo a little change in absorption compared with the unprocessed state	Traditional processed food products, raw materials, etc.	Micelles of homogenized milk, various emulsions, green powdered tea, etc.
		Products likely to show an increase in absorption quantity compared with the unprocessed state (Note 1)	Food materials	Cyclodextrin, etc.
			Health food, etc. (Note 2,3)	Vitamin E, β-carotene, fish oil (EPA, DHA), CoQ10, β-glucan, astaxanthin, β- cryptoxanthin, etc.
	<Food products> Inorganic	Products with a distribution history as food products and additives, that are nano-scaled	Food ingredient	Calcium, selenium, iron, etc.
			Additives	Magnesium silicate, montmorillonite, etc.
			Health food, etc. (Note 2,3)	Silica, gold, silver, platinum, titanium oxide, zinc oxide, iridium, etc.
		Nano-substances without a history of use as food products and additives	With possibility of being used in future	(e.g.) Carbon nanotube (e.g.) Fullerene
	<Packaging materials> Organic	Products with a history of use as food resources	With possibility of being used in future	None at present
		Products with a little or no history of use as food raw materials		None at present
	<Packaging materials> Inorganic	Products with a history of use as food raw materials	Beverage containers	Silica, titanium oxide, nanoclay, etc.
		Products with a little or no history of use as food raw materials	With possibility of being used in future	(e.g.) Carbon nanotube (e.g.) Fullerene

* This survey didn't deal with the nanomaterials unintentionally incorporated into food products. The nanomaterials unintentionally incorporated into food products may be classified into environment-derived (nanomaterials released into the environment have a possibility of accumulating in food products via aquatic/terrestrial organisms), agriculture-derived (nanomaterials contained in agrichemicals have a possibility of remaining in/transferring to food products) and livestock-derived (nanomaterials contained in feedstuff and animal drugs have a possibility of remaining in/transferring to animals for food). The transfer from food contacting materials (container/packaging, processing equipment) to food products may be considered unintentional, but we included the related materials in the Table in consideration of "intentional use of them for food contacting materials."

* Based on the results of our literature study, considering the purposes of nano-scaling being divided between organic materials "for enhancing absorption" and inorganic materials "for functions such as transparency, etc." as well as the differences found in safety assessments, we subdivided them into "Organic," "Inorganic" and "Packaging" materials in line with the respective current status.

Note 1) Absorption quantity: includes both enhancement of absorption rate itself by nano-scaling and increase in exposure by intentional production.

Note 2) Health food: Food that is taken with the expectation of some health enhancing function.

Note 3) Health food, etc. includes the substances on the list of food additives despite the fact that they are already under research/development or sold in the market as health food.

According to the reports of respective international organizations and governmental agencies, the directions of safety assessments can be summarized as follows:

- The conventional framework can be applied as a framework for safety assessment (for hazard identification/characterization, exposure assessment, risk characterization, etc.).
- Europe shows a direction toward assessing safety of food products manufactured using nanotechnology in a similar manner as “novel food.” (European Parliament)
- Though no guiding principles have been provided yet, some guidance may be expected on what kind of tests and data are required to show the safety of nanotechnology-using food products. (FDA, U.S.)
- The size ranges are not to be specified in the safety assessment of nanotechnology. (FDA, U.S.)
- An approach on a case-by-case basis is desirable. (EFSA, UK)
- Based on the idea that the novelty of nanomaterials lies not in the size but in the property of substances (new functions, in particular), all materials below 1000 nm should be reviewed as “nanomaterials.” (UK)
- While natural nanomaterials should be excluded from regulation, intentionally selected or processed natural materials should be regulated. (UK)
- Nanomaterials should be regulated not under an independent “nano-food act” but under the framework of existing frameworks. (Switzerland)
- The conventional safety assessment data are inadequate for the safety assessment of nanomaterials use in food products, and these materials should be reassessed from the perspective of health. (Germany)
- A licensing system should be established before market launch of the nanomaterials in food and related products. At present, safety of the ingested nanoparticles can’t be assessed. In particular, until enough data are available on digestion and absorption, we should send out a warning regarding the nanotechnology use in the food sector. (France)
- The nanoparticles incorporated in food products and food containers/packages should be labeled as such. (Ireland)
- It is requested that the sale of nanotechnology-using food products should be prohibited until an arrangement to manage the safety of nanotechnology has been provided. (Friends of the Earth Australia)

Under the recognition of these international developments, the experts review board of this survey discussed the direction of risk assessment of the nanotechnology-using products in Japan.

Table 6-3 shows a combination of the concepts (range of the substances/sizes) of nanotechnology-using food products in Japan (Table 6-2), and the information on the “mention/no-mention of the data on the toxicity of nanomaterials” and “mention/no-mention of the data on absorbability after oral administration of nanomaterials” from the safety assessment information obtained from the literature in this survey.

The organic materials were nano-scaled for the main purpose of enhancing the absorption rate of food products and ingredients that have traditionally been taken. In addition, toxicity tests weren't conducted on many of the organic materials. What's behind this is presumed to lie in the fact that toxicity tests haven't been conducted, or even if they have actually been conducted, the results are rarely published in treatises under the basic assumption that food products must be safe right from the start. As for the physicochemical property data, though the particle size was measured, the measurements were only on the concentration in the blood or respective organs after administration of nano-scaled substances, and only a few data were available on the properties of administered nano-substances.

Regarding inorganic substances, oral toxicity tests have often been conducted as a part of safety assessment for industrial nanomaterials, but the reported number is far from many. We couldn't obtain any information on packaging materials.

Table 6-3(1/3) Classification of nanotechnology-using food products and the current status of the safety assessment (Food products)

- Range of the particle size: 1 nm ~ 100 nm ~ 5 μm
- Oral ingestion

Major categories	Middle categories	Subcategories	Product groups	Typical substances	Mention/no-mention of the data on the toxicity of nanomaterials	Mention/no-mention of the data on the absorbability after oral administration of nano-substances
Substances ordinarily existent in food products in nano to micron size			Ordinary food products	Water, food products (intracellular substances derived from animal/plant cells or microorganism), micelles in raw milk, etc.		
Manufactured nanomaterials (intentionally created and intentionally used)	<Food products> Organic	Products expected to undergo a little change in absorption compared with the unprocessed state	Traditional processed food products, raw materials, etc.	Micelles of homogenized milk, various emulsions, green powdered tea, etc.		
		Products likely to show an increase in absorption quantity compared with the unprocessed state (Note 1)	Food materials	Cyclodextrin	(Safety assessment of food additives by JECFA) (Note 4)	DATA GAP
				Others		
			Health food, etc. (Note 2,3)	Vitamin E	DATA GAP	Blood concentration (humans)
				Vitamin K		
				β-carotene		DATA GAP
				Fish oil (EPA, DHA)		
				Curcumin		
				Astaxanthin		Blood concentration (rats)
				β-cryptoxanthin		Blood concentration (humans)
				CoQ10		Blood concentration (humans), blood concentration (rats)
				Sesame lignan glycoside		Body distribution (rats)
				Bone powder		Blood concentration, body distribution (rats)
				β-glucan	*in vivo* (human & rats) studies (p.o.), *in vitro* assays	
				Red yeast rice	*in vivo* rat study (p. o.), *in vitro* assays	DATA GAP
				Edible vegetable powder	*in vivo* mouse study (p.o.)	

Table 6-3(2/3) Classification of nanotechnology-using food products and the current status of the safety assessment (Food packaging materials)

Major categories	Middle categories	Subcategories	Product groups	Typical substances	Mention/no-mention of the data on the toxicity of nanomaterials	Mention/no-mention of the data on the absorbability after oral administration of nano-substances
				Chitosan	*in vivo* rat study (p. o.), *in vitro* assays	
				Others	DATA GAP	
Manufactured nanomaterials (intentionally created and intentionally used)	<Food products> Inorganic	Products with a distribution history as food products and additives, which are nano-scaled	Food ingredient	Calcium		
				Selenium	*in vivo* (human & rats) studies (p.o.)	body distribution (mice, birds)
				Iron		
				Others	DATA GAP	
			Additives	Magnesium silicate		
				Montmorillonite	*in vivo* bird study (p.o.)	
				Others	DATA GAP	DATA GAP
			Health food, etc. (Note 2,3)	Silica	*in vivo* mouse study (p.o., i.v.), *in vitro* assays	
				Gold	*in vivo* rat study (i.v.)	Body distribution (mice)
				Silver	*in vivo* rat study (p. o.), *in vitro* assays	Body distribution (rats)
				Platinum	*in vivo* rat study (human)	Body distribution (rats)
				Titanium oxide	*in vivo* rat study (i.v.), *in vivo* mouse study(p.o.), *in vitro* assays	Blood concentration (humans), body distribution (rats), body distribution (mice)
				Zinc oxide	*in vivo* mouse study (p.o.)	Body distribution (mice)
				Iridium	DATA GAP	Body distribution (rats)
				Others		

Table 6-3(3/3) Classification of nanotechnology-using food products and the current status of the safety assessment (Food packaging materials)

Major categories	Middle categories	Subcategories	Product groups	Typical substances	Mention/no-mention of the data on the toxicity of nanomaterials	Mention/no-mention of the data on the absorbability after oral administration of nano-substances
		Nano-substances without a history of use as food products and additives	With possibility of being used in future	(e.g.) Carbon nanotube	Mesothelium administration test/intranasal test/oral test/endotracheal administration test/intraperitoneal administration test with mice, subcutaneous administration test with rats	DATA GAP
				(e.g.) Fullerene p.o.: per os, I,V.: intravenous drip	*in vivo* mouse study (p.o.), *in vitro* assays	Body distribution (rats)
Manufactured nanomaterials (intentionally created)	<Packaging materials> Organic	Products with a history of use as food resources	With possibility of being used in future	None at present	DATA GAP	
		Products with a little or no history of use as food raw materials	With possibility of being used in future	None at present		
	<Packaging materials> Inorganic	Products with a history of use as food raw materials	Beverage containers	Silica, titanium oxide, nanoclay, etc.		
		Products with a little or no history of use as food raw materials	With possibility of being used in future	(e.g.) Carbon nanotube (e.g.) Fullerene		

p.o. :per os , i.v.: intravenous drop

Note 1) Absorption quantity: includes both enhancement of absorption rate itself by nano-scaling and increase of exposure by intentional production.

Note 2) Health food: Food that is taken with the expectation of some health enhancing function.

Note 3) Health food, etc.: includes the substances on the list of food additives despite the fact that they are already under research/development or sold in the market as health food.

Note 4) Safety assessment of food additives by JECFA: JECFA conducted a safety assessment of β-cyclodextrin as a food additive (JECFA, 1995 TRS 859-JECFA44/28), and FAO/WHO Expert Meeting on the Application of Nanotechnologies in the Food and Agriculture Sectors, 2009 chose this material as a subject of case study for a nano-carrier meeting the definition of manufactured nanomaterials. Safety assessments were also conducted on α-cyclodextrin (JECFA, 2001 TRS 928-JECFA 63/16) and γ-cyclodextrin (JECFA, 1999 TRS 896-JECFA 53/26) as food additives by JECFA.

Based on the above, the direction of our efforts in Japan on future safety assessment of nanotechnology-using food products is to be dictated by the following activities:

- ♦ Assessment on the basis of the classification of nanotechnology-using food products within the scope of application
- ♦ Confirmation of the scope of application of existing assessment methods (What are the subjects to which the existing safety assessment methods for food products and industrial nanomaterials can be applied, and what are those for which new safety assessment methods need to be introduced?).
- ♦ Review and development of “safety assessment methods for nanotechnology-using food products”

In addition, in assessing the materials based on classification, the following activities were noted for consideration for the time being.

- Defining the scope for classification (definition and identification of nanotechnology food products for which safety assessment is not considered necessary at present.)
- Determination and concrete definition of classification items
- Confirmation of and data accumulation on the safety effects of changes in absorption, ingestion, reactivity, etc. involved with nano-scaling.
- Selection and justification of classification items that need data collection and safety assessment
- Consideration of the possibility of food products deviating from the classification tables.

When considering the above issues, it is necessary to nail down the existing and deficient data at present (confirm the knowledge gap). In this survey, we sorted out the available and unavailable data on safety assessment, but for efforts and management based on the classification, further reviews will be needed in line with the classification items.

End of document

7. References

Author	Title	Bibliographic information	Publication year
Angeles-Agdeppa I, Capanzana MV, Barba CV, Florentino RF, Takanashi K.	Efficacy of iron-fortified rice in reducing anemia among schoolchildren in the Philippines.	Int J Vitam Nutr Res. Mar;78(2) : 74-86.	2008
Ankola D D; Viswanad B; Bhardwaj V; Ramarao P; Kumar M N V Ravi	Development of potent oral nanoparticulate formulation of coenzyme Q10 for treatment of hypertension : can the simple nutritional supplements be used as first line therapeutic agents for prophylaxis/therapy?	Eur J Pharm Biopharm. 2007 Sep;67(2) : 361-369.	2007
Araujo, L., Lobenberg, R. and Kreuter, J.	Influence of the surfactant concentration on the body distribution of nanoparticles.	J. Drug Target 6(5) : 373-385.	1999 a
Araujo, L., Sheppard, M., Lobenberg, R. and Kreuter, J.	Uptake of PMMA nanoparticles from the gastrointestinal tract after oral administration to rats : modification of the body distribution after suspension in surfactant solutions and in oil vehicles.	International Journal of Pharmaceutics 176 (2) : 209-224.	1999 b
Back Evelyn I., Nohr Donatus, Biesalski Hans K. (Univ. Hohenheim, Stuttgart, Deu), Frindt Claudia, Stern Martin (Univ. Children's Hospital Tuebingen, Tuebingen, DEU), Ocenaskova Erika (Fac. Hospital, Hradec Kralove, CZE)	Can changes in hydrophobicity increase the bioavailability of α–tocopherol?	European Journal of Nutrition, Volume 45, Number 1, p.1-6.	2005
Bockmann, J., Lahl, H., Eckert,T., Unterhalt. B.	Blood titanium levels before and after oral administration titanium dioxide.	Pharmazie 55(2), 140-143.	2000
Chalasani Kishore B; Russell-Jones Gregory J; Jain Akhlesh K; Diwan Prakash V; Jain Sanjay K	Effective oral delivery of insulin in animal models using vitamin B_{12}-coated dextran nanoparticles.	Journal of controlled release : official journal of the Controlled Release Society, (2007 Sep 26) Vol. 122, No. 2, pp. 141- 150.	2007
Chaudhry Qasim, Scotter Michael, Blackburn James, Castle Laurence, Watkins Richard (Defra Central Sci. Lab., York UK), Ross Bryony, Aitken Robert (Inst. of Occupational Medicine, Edinburgh, GBR), Boxall Alistair (Univ. York, York, GBR)	Applications and implications of nanotechnologies for the food sector.	Food Addit Contam Pt A Chemistry Analysis Control Expo Risk Assess, 25, 3, 241-258, 2008.03.	2008

Author	Title	Bibliographic information	Publication year
Chen, Z., Meng, H.,Yuan, H., Xing, G., Chen, C., Zhao, F.,Wang,Y., Zhang, C., Zhao,Y.	Identification of target organs of copper nanoparticles with ICP-MS technique.	J. Radioanalytical Nuclear Chem., 272, 599-603.	2007
Chia-Ding Liao, Wei-Lun Hung, Wen-Chien Lu, Kuo-Ching Jan, Daniel Yang-Chih Shih, An-I Yeh, Chi-Tang Ho and Lucy Sun Hwang	Differential Tissue Distribution of Sesaminol Triglucoside and Its Metabolites in Rats Fed with Lignan Glycosides from Sesame Meal with or without Nano/Submicrosizing.	J. Agric. Food Chem., 2010, 58 (1), pp 563–569.	2009
Choi Soo-Jin, Oh Jae-Min, Choy Jin-Ho (Ewha Womans Univ., Seoul, KOR), Choi Soo-Jin (Seoul Women's Univ., Seoul, KOR)	Human-related application and nanotoxicology of inorganic particles : complementary aspects.	J Mater Chem, 18, 6, 615-620.	2008
Christine Hotz, Maribel Porcayo, Germán Onofre, Armando García-Guerra, Terry Elliott, Shirley Jankowski, and Ted Greiner	Efficacy of iron-fortified Ultra Rice in improving the iron status of women in Mexico.	Food and Nutrition Bulletin, vol. 29, no. 2, p140-148.	2008
Damge, C., Aprahamian, M., Humbert, W. and Pinget, M.	Ileal uptake of polyalkylcyanoacrylate nanocapsules in the rat.	J Pharm. Pharmacol. 52(9) : 1049-1056.	2000
Desai, M. P., Labhasetwar, V., Amidon, G. L. and Levy, R. J.	Gastrointestinal uptake of biodegradable microparticles: effect of particle size.	Pharm Res 13 (12) : 1838-1845.	1996
H.S. Chen, J.H. Chang, and J.S.B. Wu	Calcium Bioavailability of Nanonized Pearl Powder for Adults.	Journal of Food Science, Volume 73 Issue 9, Pages H246 - H251.	2008
Hillery,A.M., Jani, P.U., Florence,A.T.	Comparative, quantitative study of lymphoid and non-lymphoid uptake of 60nm polystyrene particles.	J Drug Target, 2,151-2,156.	1994
Hillyer, J. F. and Albrecht, R. M.	Gastrointestinal persorption and tissue distribution of differently sized colloidal gold nanoparticles.	Journal of Pharmaceutical sciences, vol. 90, No.12, December 2001.	2001
Hussain, N. and Florence, A.T.	Utilizing bacterial mechanisms of epithelia1 cell entry : inva-sin-induced oral uptake of latex nanoparticles.	Pharm. Res 15(1) : 153-156.	1998
Hussain, N., Jani, P.U. and Florence, A.T.	Enhanced oral uptake of tomato lectinconjugated nanoparticles in the rat.	Pharm. Res 14(5) : 613-618.	1997
Jani, P., Halbert, G.W., Langridge, J. and Florence, A.T.	Nanoparticle uptake by the rat gastrointestinal mucosa: quantitation and particle size dependency.	J Pharm. Pharmacol. 42(12) : 821-826.	1990
Jani, P. U., McCarthy, D.E., Florence,A.T.	Titanium dioxide (rutile) particle Uptake from the rat GI tract and translocation to systemic organs after oral administration.	International Journal of Pharmaceutics 105, 157- 168.	1994

Author	Title	Bibliographic information	Publication year
Kim, Dong-Heui; Song, Soon-Bong; Qi, Xu-Feng; Kang, Wie-Soo; Jeong, Yeon-Ho; Teng, Yung-Chien; Lee, Seon-Goo; Kim, Soo-Ki; Lee, Kyu-Jae	The Food Safety of Superfine Saengshik Processed by Top-down Technique in Mice.	Molecular & Cellular Toxicology, (MAR 31 2009) Vol. 5, No. 1, pp. 75-82.	2009
Kim, Y. S., Kim, J. S., Cho, H. S., Rha, D. S., Kim, J. M., Park, J. D., Choi, B. S., Lim, R., Chang, H. K., Chung, Y. H., Kwon, I. H., Jeong, J., Han, B. S. and Yu, I. J.	Twenty-eight-day oral toxicity, genotoxicity, and gender-related tissue distribution of silver nanoparticles in Sprague-Dawley rats.	Inhal Toxicol 20 (6) : 575-583.	2008
Lai, S.K., O'Hanlon, D.E., Harrold, S., Man, S.T., Wang, Y .Y ., Cone, R. and Hanes, J.	Rapid transport of large polymeric nanoparticles in fresh undiluted huinan mucus.	Proc.Natl.Acad.Sci US A 104(5) : 1482-1487.	2007
Lin,W., Huang,Y-W., Zhou, X-D, Ma,Y.	*In vitro* toxicity of silica nanoparticles in human lung cancer cells.	Toxicology and Applied Pharmacology 217, 252-259.	2006
Mark A. Roe, Rachel Collings, Jurian Hoogewerff and Susan J. Fairweather-Tait	Relative bioavailability of mi-cronized, dispersible ferric pyrophosphate added to an apple juice drink.	European Journal of Nutrition, Vol.48, p115-119.	2009
Nefzger, M., Kreuter, J., Voges, R., Liehl, E. and Czok, R.	Distribution and elimination of polymethyl methacrylate nanoparticles after peroral administration to rats.	J Pharm Sci 73 (9) : 1309- 1311.	1984
Nishimura Asako, Yanagawa Haruna, Fujikawa Naoko, Shibata Nobuhito (Dep. of Biopharmaceutics, Fac. of Pharmaceutical Sciences, Doshisha Women's Coll. of Liberal Arts), Kiriyama Akiko (Dep. of Pharmacokinetics, Fac. of Pharmaceutical Sciences, Doshisha Women's Coll. of Liberal Arts)	Pharmacokinetic Profiles of Coenzyme Q10 : Absorption of Three Different Oral Formulations in Rat.	J Health Sci , Vol.55, No.4, Page540-548.	2009
Nukui Kazuki, Matsuoka Yuki, Yamagishi Toshihiko, Sato Kiyoshi (Nisshin Pharma Inc., Tokyo, JPN), Miyawaki Hiromi (Miyawaki Orthopedic Clinic, Hokkaido, JPN	Safety Assessment of PureSorb-Q^{TM} 40 in Healthy Subjects and Serum Coenzyme Q10 Level in Excessive Dosing.	J Nutr Sci Vitaminol Vol.53, No.3, Page198-206.	2007
Russell-Jones, G. J., Arthur, L. and Walker, H.	Vitamin B $_{12}$-mediated transport of nanoparticles across Caco-2 cells.	Int J Pharm. 179(2) : 247-255.	1999

Author	Title	Bibliographic information	Publication year
Schulz Christiane, Bernhardt Juergen (BioTeSys GmbH, Esslingen, DEU), Obermueller-Jevic Ute C., Hasselwander Oliver (BASF Aktiengesellschaft, Limburgerhof, DEU), Biesalski Hans K. (Univ. Hohenheim, Stuttgart, DEU)	Comparison of the relative bioavailability of different coenzyme Q10 formulations with a novel solubilizate (Solu™ Q10) .	Int J Food Sci Nutr. 2006 Nov-Dec; 57 (7-8) : 546-555.	2006
Simon, P., Chaudhry, Q. and Bakos, D.	Migration of engineered nanoparticles from polymer packaging to food - a physicochemical view.	Journal of Food and Nutrition Research 47 (3) : 105- 113.	2008
Singh, R., Pantarotto, D., Lacerda, L., Pastorin, G., Klumpp, C., Prato, M., Bianco, A. and Kostarelos, K.	Tissue biodistribution and blood clearance rates of intravenously administered carbon nanotube radiotracers.	Proc. Natl. Acad.Sci U. S A 103(9) : 3357-3362.	2006
Smyth, S.H., Feldhaus, S., Schumacher, U. and Carr, K.E.	Uptake of inert microparticles in normal and immune deficient mice.	Int J Pharm. 346(1-2) : 109- 118.	2008
van Hasselt, P.M., Jailssens, G.E., Slot, T.K., van der Ham, M., Minderhoud, T.C., Talelli, M., Akkermans, L.M., Rijcken, C. J. and van Nostrum, C.F.	The influence of bile acids on the oral bioavailability of vitamin K encapsulated in polymeric micelles.	J. Control Release 133(2) : 161-168	2009
Wajda, R., Zirkel, J. and Schaffer, T.	Increase of bioavailability of coenzyme Q(10) and vitamin E.	J. Med. Food 10(4) : 731-734.	2007
Wang, B., Feng, W. Y., Wang, M., Wang, T. C., Gu, Y. Q., Zhu, M. T., Ouyang, H., Shi, J. W., Zhang, F., Zhao, Y. L., Chai, Z. F., Wang, H. F. and Wang, J.	Acute toxicological impact of nano- and submicro-scaled zinc oxide powder on healthy adult mice.	Journal Of Nanoparticle Research 10 (2) : 263-276.	2008
Wang, J., Zhou, G., Chen, C., Yu, H., Wang, T., Ma, Y., Jia, G., Gao, Y., Li, B., Sun, J., Li, Y., Jiao, F., Zhao, Y. and Chai, Z.	Acute toxicity and biodistribution of different sized titanium dioxide particles in mice after oral administration.	Toxicol Lett 168 (2) : 176-185.	2007
Yamago, S.,Tokuyama, H., Nakamura, E., Kikuchi, K., Kananishi, S., Sueki, K., Nakahara, H., Enomoto, S.,Ambe, F.	*In vivo* biological behavior of a water-miscible fullerene : ^{14}C labeling, absorption, distribution, excretion and acute toxicity.	Chem Biol. 2(6), 385-389.	1995
Yoksan, R. and Chirachanchai, S.	Amphiphilic chitosan nanosphere : studies on formation, toxicity, and guest molecule incorporation.	Bioorg Med Chem 16 (5) : 2687-2696.	2008
Yu Chiun-Chieh; Wang Jyh-Jye; Lee Chun-Lin; Lee Shu-Hui; Pan Tzu-Ming	Safety and mutagenicity evaluation of nanoparticulate red mold rice.	Journal of agricultural and food chemistry, (2008 Nov 26) Vol. 56, No. 22, pp. 11038-11048.	2008

Author	Title	Bibliographic information	Publication year
Zhang, G., Yang, Z., Lu, W., Zhang, R., Huang, Q., Tian, M., Li, L., Liang, D. and Li, C.	Influence of anchoring ligands and particle size on the colloidal stability and *in vivo* biodistribution of polyethylene glycol-coated gold nanoparticles in tumor-xenografted mice.	Biomaterials 30(10) : 1928- 1936.	2009
Shigeru Ishida, Yuichi Tsuda, Kazuhisa Hatayama, Yuko Yamaguchi, Minenobu Okayama, , Masami Hattori (Bozo Research Center Inc., Apt Corp.)	Toxicity test of Apt 231 – Repeated oral toxicity test over 13 weeks using rats	Pharmacogenetics and medical treatment (Jpn Pharmacol Ther), vol.35 no.12, 1227-1240.	2007
Masaaki Oka*1, 2, Isao Makino*1, 3, Tadao Baba*1, 4, Yasuyuki Arakawa *1, 5, Hiroshi Atomi*1, 6, Teruaki Matsui*1, 5, Tetsuya Suga*1, 7, Saburo Nakazawa*1, 8(*1 "The Food and Medicine Study Group on Gastroenterology", Study Group under The Japanese Society of Geneatric Gastroenterogy,*2 Dept. Digestive Surgery and Surgical Oncology, Yamaguchi University Graduate School of Medicine,*3 Hokushinkai Megumino Hospital, *4 Shiga University of Medical Science,*5 Nihon University Itabashi Hospital, *6 Kyorin University Hospital, *7 Pharmaceutical Business Division, Ajinomoto Co. Inc., *8 Yamashita Hospital)	Studies on Safety and Benefits of Particulated Lentinan (β-1,3-glucan)-Containing Food Products for Patients with Cancer – Coordinated National Multicenter Protocol Study -	BIOTHERAPY, 20(6) : 590-606.	2006
Naoki Takaishi, Katsuyuki Mukai (Yunitika), Makoto Shimizu (the University of Tokyo)	Mechanisms for the Intestinal Absorption of Emulsified β-cryptoxanthin	Food Style 21 Vol.11, No.11, Page 35-39.	2007
Masaki Akino, Koji Ebitani, Takuma Imamura (Fisheries Experiment Station of Abashiri, Hokkaido), Tomoyuki Uchiyama, Keiichiro Matsushima (Industrial Experiment Station of Hokkaido), Hiroshi Hara (Hokkaido University Graduate School of Agriculture)	Effects of Salmon Bone Processing Methods on Intestinal Calcium Absorption in Rats	Journal of the Japanese Society for Food Science and Technology, 56, 3, 155-162, 2009.03.15.	2009
Manabu Ogawa, Masao Sato, Keiichi Suzuki (Life Science Systems, Fujifilm Corp.)	Development of Astaxanthin Nano Emulsion with Improved Shelf Life and Enhanced Absorbability	FUJIFILM RESEARCH & DEVELOPMENT, No.52 : 26-29.	2007

Author	Title	Bibliographic information	Publication year
Yasuteru Odagiri*1, Orie Yokoi*1, Hajime Sui*2, Koji Yamakage*2, Tetsuya Suga*3, Tsuyoshi Masuyama*1(*1 Pharmaceutical Research Laboratories, Ajinomoto Co. Inc., *2 Hatano Research Institute, Food and Drug Safety Center, *3 Pharmaceutical Business Division, Ajinomoto Co. Inc.)	Genotoxicity Test- Reverse Mutation Test, Chromosomal Aberration Test and Micronucleus Test Using Particulated Lentinan (β-1,3-glucan)-Containing Food Products	BIOTHERAPY, 20(6) : 557-567.	2006 a
Yasuteru Odagiri, Nobuaki Watari, Tetsuya Suga, Tsuyoshi Masuyama	Repeated Dose Test of Particulated Lentinan (β-1,3-glucan)-Containing Food Products in Drinking Water over 4 Weeks Using Rats	BIOTHERAPY, 20(6) : 568-577.	2006 b
Yasuteru Odagiri *1, Tsuyoshi Masuyama *1, Kazuo Oishi*2, Tetsuya Suga *3, Kuninobu Yasuda*4 (*1 Pharmaceutical Research Laboratories, Ajinomoto Co. Inc., *2 Clinical Development Division, Ajinomoto Co. Inc., *3 Pharmaceutical Business Division, Ajinomoto Co. Inc., *4 Kannnonndai Clinic, Medical Corporation of Yakugawakai)	Safety Assessment of Particulated Lentinan (β-1,3-glucan)-Containing Food Products — Repeated Dose Test on Healthy Adults-	BIOTHERAPY, 20(6) : 578-589.	2006 c
Yasuyo Suga	Anti-tumor Effect of Particulated Mushroom Extract in a Tumor-Bearing Mouse Model	BIOTHERAPY, 17: 267-273.	2003
Hironobu Nanbu (Taiyo Kagaku Co. Ltd.)	“Health Depends on Medicine and Diet”— The current status and future of functional food — absorbability and bioavailability of particulated disperse ferric pyrophosphate	Journal of Chemical Engineering of Japan, vol 68, 9th issue, 481-483.	2004
Hironobu Nanbu (Taiyo Kagaku Co. Ltd.)	Development of Water-Dispersible/Absorbable Iron Supplement Materials	Science & Industry, 77, 5, 240-246, 2003.05.20.	2003
Mikihiko Hattori (Shinagawa Seaside Central Clinic), Minenobu Okayama, Masami Hattori (Apt Corp.), Arimasa Miyamoto (Graduate School of Frontier Sciences, the University of Tokyo)	Studies on Safety and Influence of Repeated Dose of Platinum Nano-Colloids (CPt) for 2 Weeks	Excerpts of the Program, General Meeting of Japanese Society of Anti-Aging Medicine, Vol.8th, p.202 (2008)	2008

Appendix I　Result of Questionnaire

Contents

Appendix I

Survey Slip

Reference materials (Further notes on food nanotechnology)

I. Overview of the questionnaire on the status of nanotechnology use in the food sector

1. Objective of the questionnaire

While “nanotechnology” is said to have come to be used not only in industrial sector but in food sector as well, and is expected to be used/utilized further in future, information on the status is quite scarce.

This survey was conducted for the purpose of gaining an understanding of the current status of nanotechnology use in the food sector of Japan.

2. Subject of the questionnaire

We chose 900 food businesses (food manufacturers, food equipment manufacturers, and a part of cooperative associations) and food container/packaging industries as the subjects of this survey.

3. Method of the questionnaire

The survey was undertaken by way of sending out self-administered questionnaire Survey Slips. We also sent electronic file versions of the Survey Slips individually to those who were interested and then the responses were collected electronically.

4. Period of the questionnaire administration

November 4 to 25, 2009[1]

5. Result of the responses

a. The number of questionnaires sent:	900
b. The number of responses received:	238 (valid responses: 237)
c. Collect rate (b/a):	26.4% (26.3%)

[1] Responses delivered after the deadline of Survey Slips were also called into account.

II. Result of questionnaire

We summarized the results of this survey basically together with the choices of Survey Slips. However, the results of Q4 and Q5 are analyzed in parallel, on the ground that they repeated a range of questions on the nano-substances used.

1. [Survey Slip Part 1] Overview of the respondent companies

1.1 Description of the business

Q1-1 Choose the number of the item included in your company's business mix from the food industry activities shown below. (Please encircle every item applicable.)

	Multiple choice (N = 237)	Number of responses	Ratio
1)	Manufacturing/processing and packaging of prepared food that consumers directly purchase	123	51.9%
2)	Manufacturing/processing of prepared food (raw) materials that are supplied to companies in 1)	106	44.7%
3)	Manufacturing of functional food materials that are supplied to companies in 1) or 2)	54	22.8%
4)	Manufacturing of food container/packaging (materials)	22	9.3%
5)	Manufacturing of food processing machinery	16	6.8%
6)	Others	32	13.5%

Others: food wholesaling, door-to-door sales, retailing, raw material merchandizing, development of processed products, food packaging machinery manufacturing etc.

1.2 Payrolls

Q1-2 Choose the number of the item applicable on the payrolls of your company (as of the end of September 2009, excluding part-timers). (Please encircle only one number that applies.)

	Single choice (N = 237)	Number of responses	Ratio
1)	Not more than 50	59	24.9%
2)	51–100	24	10.1%
3)	101–300	63	26.6%
4)	301–1000	53	22.4%
5)	1001–3000	21	8.9%
6)	3001–5000	9	3.8%
7)	Not less than 5001	8	3.4%

2. [Survey Slip Part 1] Use of nanotechnology in the food sector (respondents' opinion)

We collected the opinions of those who responded to this questionnaire[2].

2.1 Outlook of nanotechnology use

Q2-1 Do you think the use of nanotechnology will increase (not only in your company but also in your industry) in future food sector? (Please encircle only one number that applies.)

Single choice (N=237)	Number of responses	Ratio
1) Definitely	26	11.0%
2) Yes	121	51.1%
3) Yes and no	80	33.8%
4) No	9	3.8%
5) Not at all	0	0.0%
No response	1	0.4%

2.2 Noteworthy nanotechnology use

Q2-2 Do you see some noteworthy nanotechnology use related to food products? (Please encircle every item applicable.)

Multiple choice (N = 237)	Number of responses	Ratio
1) Food raw materials (structure, emulsion, etc.)	109	46.0%
2) Food manufacturing/processing (micromachining, tiny bubbles, etc.)	94	39.7%
3) Food function (nano-order capsule etc.)	78	32.9%
4) Container/packaging materials	34	14.3%
5) Measurement (nano-sensor, etc.)	18	7.6%
6) Others	7	3.0%
7) Nothing in particular	55	23.2%
No response	57	24.1%

* Others: Use of food products related to coating materials, sterilization/disinfection and oxidization/reduction, and enhancement of functionality/absorption etc.

2.3 Substances of which respondents have a long eating experience processed in nano-order size

[2] The questions were intended to ask for each respondent's opinion and accordingly the responses are not unified views of the companies concerned. (The questionnaires were administered to those who "were the representative officers or who understood each company's overall manufacturing processes and R&D activities and were in a position to review the future directions of their efforts.") These responses may be regarded as general views of those at the heart of the food sector.

Q2-3 How do you think the substances (including food raw materials, additives, etc.) in nano-order size for which respondents have a long eating experience (e.g., dextrin and homogenized milk) should be treated? (Please encircle either necessary or unnecessary in each of the choices.)

Q2-3a "Substances in nano-order size of which respondents have a long eating experience as such"

Single choice (N = 237)		Necessary	Unnecessary	No response/ no idea (Ratio)
		Number of responses (Ratio)	Number of responses (Ratio)	
1)	Some regulation is (necessary/unnecessary)	59 (24.9%)	163 (68.8%)	15 (6.3%)
2)	Some indication obligation is (necessary/unnecessary)	79 (33.3%)	145 (61.2%)	13 (5.5%)
3)	Scientific safety assessment before launching into market is (necessary/unnecessary)	108 (45.6%)	117 (49.4%)	12 (5.1%)

Q2-3b "Substances of which respondents have a long eating experience, processed in nano-order size anew"

Single choice (N = 237)		Necessary	Unnecessary	No response/ no idea (Ratio)
		Number of responses (Ratio)	Number of responses (Ratio)	
1)	Some regulation is (necessary/unnecessary)	100 (42.2%)	115 (48.5%)	22 (9.3%)
2)	Some indication obligation is (necessary/unnecessary)	109 (46.0%)	107 (45.1%)	21 (8.9%)
3)	Scientific safety assessment before launching into market is (necessary/unnecessary)	168 (70.9%)	51 (21.5%)	18 (7.6%)

2.4 Opinions on the use and regulations of nanotechnology

Q2-4 Do you have any opinion about the use or regulation of nanotechnology in the food sector?
(Please write freely.)

Shown below is a summary of free-answered opinions categorized according to the status of use of nanotechnology in each company. We supplemented parts of the texts.

2.4.1 Opinions received from companies that mentioned using nanotechnology in Q3-1

(1) Opinions mainly related to regulation

- Safety assessment should be carried out in a proper manner regardless of past results. Regarding "substances of which respondents have a long eating experience, processed in nano-order size anew," some form of regulation or indication obligation may be applied if the resulting merits are strong.
- Raw materials developed by nano-sizing them in pursuit of new functions will be regarded as new raw materials and need some form of regulation.
- Regulations on substances for which we have enough eating experience and whose safety has been established will deliver a blow against the existing industries. Meanwhile, malicious food products

should never be left uncontrolled and a degree of regulation is needed for new products.

- In the case of food products, dissolved substances have higher bioactivity than nano-sized substances. However, regulations will be necessary in principle because the substances that are inherently insoluble may have physical interactions.
- While a degree of regulation makes a difference, it should not be strict but should clarify the corporate responsibility.
- Indication is necessary.
- Indication of the properties on the products causes no problems, but it is not desirable or necessary to impose any indication obligation or regulations on nano-sized products.
- Regulations are not desirable.

(2) Opinions mainly related to safety assessment

- Influence of enhanced oral absorption need to be understood.
- Since nano-sized food products are capable of being taken in by living organisms relatively more easily, their heavy metal and toxic contents need to be checked carefully.
- It can be suggested that those nano-substances soluble in living organisms should be discussed separately from insoluble nano-substances. Compared with industrial materials, safety information on the nano-substances that are supposed to be taken into the body should be publicized/shared more immediately.
- As for applicability of nanotechnology to food products, we have high expectations for it considering the past achievements of existing technologies contributing to functional upgrades. However, we believe that due consideration needs to be given to ensuring safety.
- Unlike those in aerosol form, nano-substances contained in solids and liquids might have a moderate effect on human organisms. In the case of food products, especially in the evaluation of acute/chronic toxicity, any regulation systems will depend on not only our eating experiences but their accumulation in human body.
- As those food ingredients that are usually taken in in small amounts and can have harmful influences when taken in in excessive amounts may well change their bioavailability, including absorption through nano-order sizing, some special safety assessment could be found necessary in some cases.
- We believe no regulation is required for nano-order sized food products at present, but research/investigation should be conducted on the bioavailability and safety of nano-sized food products immediately and the results should be made available to related companies.
- Although it is beside the question to argue that some substance is safe without any scientific basis, it is like witch-hunting to emphasize the danger with no distinction among substances, and scientific discussions are needed on the basis of the properties of substance. Abstract discussions only on the size are questionable.
- Efforts are required to avoid any resistance against launching into market by harmful rumors (reduction of consumer benefit) as in the case of “genetic modification.” Also for that purpose, scientific safety assessment should be conducted appropriately.

2.4.2 Opinions received from companies that mentioned not using nanotechnology (but having development plans) in Q3-1

(1) Opinions mainly related to regulation

- Regulation is required as it is critical to make sure that no food raw materials, as chemical substances, have undergone any changes in their chemical structure.
- We should see to it that stricter regulations applied only in Japan do not impair its international competitiveness.
- On the assumption that food products are not free of any risk, regulation on the food products for

which we have a long eating experience should be avoided as such regulation will lead to deterioration of domestic competitiveness and isolation of Japan's food industry from the rest of the world.

(2) Opinions mainly related to safety assessment

- If any regulation needs to be introduced at all, safety assessment methods should be established first.
- Caution will be needed in nanoscaling poorly water-soluble substances to enhance intestinal absorption.
- When nanotechnology is applied to food products, it could change the speed of systemic absorption and reactivity. Therefore, some kind of prior assessment might be necessary.
- We found it uncomfortable that the substances that are not regarded harmful in their wet state are suddenly considered harmful when dried in terms only of the particulate form (particle size). However, since this tendency can be seen abroad, we believe it is very important for Japan to lead the way in suggesting the right direction for it.

2.4.3 Opinions received from companies that mentioned not using nanotechnology (and having no development plans either) in Q3-1

(1) Opinions mainly related to regulation

- Nanoparticles are in the size that easily affects the human body not only in the form of food. Therefore, caution is needed to deal with them, and they need to be regulated.
- As for those nanomaterials that have not been used for conventional food products, safety assessment and indication obligation are required.
- There being no regulation at present, some kind of arrangement will be required.
- I answered that no regulation is required for those we have eating experience, but appropriate rules will be needed for those materials that, like supplements, have to be taken in larger amounts continuously than before under the assumption that they are used for ordinary applications.
- Unlike industrial products, it is desirable to treat food products with discretion. To say nothing of scientific safety assessment, commensurate regulation is inevitable in order to restrict the entrance of companies that are pursuing unjustifiable (excessive) profits or whose technical capabilities are questionable.
- Accumulation of knowledge on nanotechnology is poor in the food sector, and a cautious attitude is called for in terms of direct oral intake, which makes the need for regulation understandable. On the other hand, however, more regulations than what is necessary could be an obstacle to prevent the entrance into the food sector, which abounds in companies in poor financial position, leading to poorer accumulation of the knowledge. The government needs to lead the way to set standards for safety assessment, and manage them so that no regulation will be required for companies that have met the standards.
- In cases where safety is not ensured, regulation should be considered over the whole area of related technology.
- Since the properties change completely in the area of nanofication, we should address it with caution.
- At present, safety and sense of security are important evaluation criteria of food products. Therefore, we believe a regulation is required that allows consumers to recognize safety easily.
- Safety and preservability data (confirmation) is necessary, and the predicted results need to be included in the application documents, but regulation should not be too restrictive.
- We hope for a regulation that does not treat the conventional substances and technologies in the frame of "technology."
- We have no idea what deserves to be regulated for lack of information and knowledge.

(2) Opinions mainly related to safety assessment

- A (long-term or short-term) assessment over time is required.
- Safety should be made much of, or should be indicated.
- We believe it important that safety assessment on the use of nanotechnology for food products is fully verified to allow consumers to use them without anxiety.
- It is hoped that safety assessment will be fully conducted before launching into market, appropriateness for sterilization and virucidal disinfection will be thoroughly examined, and a wider use of nanotechnology will be pursued in parallel with regulatory revisions.
- Knowledge of cutaneous absorption seems to be limited, and this causes some concerns. However, we are interested in cutaneous absorption from the standpoint of a user, and in this sense, safety assessment is required.
- Safety should be taken into account in terms of absorption from the skin, etc. other than oral intake.
- As it is unknown how substances that have been treated by physical processes different from ordinary digestion will act in the living organism, considering they will be used for foods, these will need to be checked beforehand.
- As for substances for which we have a long eating experience processed in nano-order size, scientific safety assessment will be required before launching into market, depending on the methods of food processing.
- Nano-order sizing the substances for which we have a long eating experience could change the extent of absorption into the human body, and it needs to be verified how this change will influence the body.
- Even in the case of the substances for which we have eating experience, as nanotechnology processing could make them react with the living organism in a different manner, at least public organizations should conduct safety assessment on them as needed.
- As for the safety of nano-capsuled materials, I am afraid that sudden and unpredictable reactions might take place. Because of their being in nano-size, they might enter the cells directly or have an influence on cellular functions. In the manufacturing process, is it not possible that powder dusts of vegetable allergen nanoparticles could influence the food products in the same plant?
- In the case of fine powders, caution may be required to handle them.
- The substances that can be too fine by nanotechnology may threaten to cause trouble to the body depending on the manner of intake and treatment. In our view, nanotechnology is already causing troubles in Europe.

(3) Other opinions

- Some nanomaterials such as cyclodextrin have already been used for powderizing food flavors, etc.
- Nanotechnology need not be applied to foods forcibly
- We believe foods are essentially traditional and primitive. We see no necessity for the state of the art like nanotechnology for foods in general, but it may find some application in invalid diet and specific health food or in some newly developed area for those who have predisposition of diseases.
- We see no problems concerning submicron-sized materials.
- We hope the authorities concerned will keep us well informed of the international trend.

3. [Survey Slip Part 1] Status of nanotechnology use

3.1 Use or non-use of nanotechnology

Q3-1 Does your company use nanotechnology or nanomaterials (1 nm to several μm) in the manufacturing or research and development of food products? (Please encircle only one number that applies.)

Single choice (N = 237)		Number of responses	Ratio
1)	Using	48	20.3%
2)	Not using (with development plan)	30	12.7%
3)	Not using (without development plan)	158	66.7%
No response		1	0.4%

Q3-1a For respondents who chose "Using," what is the objective of the use? (Please encircle every item applicable.)

Multiple choice (N = 48)		Number of responses	Ratio
1)	Food raw materials (structure, emulsion, etc.)	28	12%
2)	Food manufacturing/processing (micromachining and tiny bubbles, etc.)	17	7%
3)	Food function (nano-order capsule, etc.)	5	2%
4)	Container/packaging materials	4	2%
5)	Measurement (nano-sensor, etc.)	0	0.0%
6)	Others	5	2%

* Others: Nano-bubble water, cosmetics, food additives and food additive preparation, food processing machines.

4. [Survey Slip Part 1] Nano-substances used

4.1 Number of responses received on the nano-substances used (Q4-1 to 5, Q5-1 to 5, Q5-6)

Responses (N = 48)	Number of responses	Ratio
1 Responses on substances (Q4-1 to 5)	34	70%
2 Responses on substances (Q5-1 to 5)	14	29%
Of the above, responses mentioning not less than 3 substances (Q5-6)	8	17%

4.2 Nano-substances used and the average size (Q4-1 to 2, Q5-1 to 2)

Q4-1, Q5-1: What is the nano-substance in the area of nanotechnology for which your company is engaged in the manufacture or research/development?
Q4-2, Q5-2: What is the approximate average size of the nano-substance (primary particle)? (Please encircle only one number that applies.)

Total number of responses (N = 62)		Number of responses
1)	Not more than 10 nm Nano-substance: [Primary particle] polysaccharide (1); cyclodextrin and clathrate (CoQ10 α-lipoic acid, EPA, DHA, etc.) (1); platinum colloid (1); clay (1); montmorillonite (1); [Aggregate] lactobacillus (killed bacteria) (1); [No mention of substance] (1)	7

Total number of responses (N = 62)	Number of responses
2) 10–100 nm Nano-substance: [Primary particle] emulsion (3); carotenoid (2); polymer-glycoprotein (1); casein micelles in milk (1); fat (greasy substance) (2); fat, fat-soluble vitamin types, aroma chemicals (1); nano-bubble water (1); silica (1); coenzyme Q10 (1); polyphenol (1) [Aggregate] dairy content (1); gold colloid (1); skin care cream (1); fat emulsion (1) [Unclear whether primary particle or aggregate] coenzyme Q10 (1); [No mention of substance] (1)	20
2) and 3) 10–500 nm; 2), 3) and 4)10–900 nm Nano-substance: [Primary particle] oxygen nano-bubble, Ozone nano-bubble, air nano-bubble, hydrogen nano-bubble (2); [Aggregate] bilberry extract (1); [Unclear whether primary particle or aggregate] health food raw materials, cosmetic materials (1)	4
3) 100–500 nm Nano-substance: [Primary particle] cyclodextrin clathrate (1); mineral (1); fish oil emulsion (1); [Aggregate] calcium preparations (1); curcumine (1); [Unclear whether primary particle or aggregate] emulsion (2); clay, etc. (1)	8
4) 500-900 nm Nano-substance: [Primary particle] calcium (1); [Aggregate] water and gas (1); [No mention of substance] (1)	3
5) Around 1000 nm (1 μm) Nano-substance: [Primary particle] colloidal iron (1); aroma chemical emulsion (1); [Unclear whether primary particle or aggregate] pigment emulsion, milk fat emulsion (1)	4
6) Around several μm Nano-substance: [Primary particle] potassium (1); spices (1); vegetable extract (1); rice powder (1); oil pigment emulsion(1); [Aggregate] pharmaceutical products, Chinese medical materials (1); calcium carbonate (1); [Unclear whether primary particle or aggregate] Vitamin C (1); various types of emulsion (1); edible dye emulsion (1); [No mention of substance] (2)	12
(No responses on the size) Film (1); oily pigment emulsion (1); [No mention of substance] (2)	4

4.3 Purpose of the use of nanotechnology products

Q4-3 Q5-3: What is the purpose of the use of the nano-substance/nanotechnology using products? (Please encircle every item applicable.)

Multiple choice (N = 62)	Number of responses	Ratio
1) Health food	37	60%
2) Food products other than health food	32	52%
3) Food container/packages	6	10%
4) Apparatuses other than food container/packages	1	2%
5) Nanoparticle formation	3	5%
6) Others	9	15%
No response	3	5%

* Others: Cosmetics (2), microfiltration, intestinal regulation/immunoactivator, cosmetics/medicals, enhancement of food preservation function, growth promotion of living organism (aging)/antiaging of living organism, food products

5. [Survey Slip Part 1] Marketed nanotechnology products

5.1 Procurement of nano-substances

Q4-4 Q5-4: How do you obtain the nano-substances you use? (Please encircle only one number that applies.)

	Single choice (N = 34)	Number of responses	Ratio
1)	Manufacturing in-house	21	16%
2)	Both manufacturing in-house and purchasing	1	3%
3)	Purchasing without manufacturing in-house	12	35%

5.2 Annual production of the products

Q4-5 Q5-5: What is the annual production of the nanotechnology using food products?

Responses (N = 24)	Production amount	Number of responses
As food products	3 to 36,500 tons	4
As nano-substance food raw materials	45 kg to 1 ,200 tons	7
No mention of the material	200 kg to 5,000 tons, 600 to 40,000 kl	13

6. [Survey Slip Part 2] Questionnaire Part 2 (responses made to the extent possible)

6.1 Method of collecting safety information

Q6-1 Considering some review processes on the safety of nanotechnology are to be initiated in Europe and the United States, how do you collect food safety-related information (including nanotechnology) from abroad? (Please encircle every item applicable.)

	Multiple choice (N = 209)	Number of responses	Ratio
1)	Subscription of specialized journals (mail magazines, magazines, newspapers) and news coverages	79	37.8%
2)	Procurement of information released by foreign organizations concerned on a regular basis	17	8.1%
3)	Information exchange among industry groups, etc.	60	28.7%
4)	Database searches on a regular basis	23	11.0%
5)	Not collecting	99	47.4%

6.2 R&D payrolls

Q6-2 Choose the number of the applicable item from below concerning the payrolls (including researchers, employee researchers, and research assistants, as of the end of September 2009) directly engaged in R&D in your company. (Please encircle only one number that applies.)

	Single choice (N = 204)	Number of responses	Ratio
1)	None	50	24.5%
2)	Not more than 50	118	57.8%
3)	51–100	19	9.3%
4)	101–300	12	5.9%
5)	301–1000	2	1.0%
6)	1001–3000	2	1.0%
7)	3001–5000	0	0.0%
8)	Not less than 5001	1	0.5%

6.3 Companies paying attention to the use of nanotechnology

Q6-3 In the food sector, which companies are making advanced efforts toward the use of nanotechnology? (Please enumerate a couple of companies that you know including foreign ones.)[3]

Name of company	Total number	Name of company	Total number
Fujifilm	8	Buhler (Switzerland), Nisshin SeifunGroup Inc., Masuko Sangyo Co., Ltd., Shiseido Co., Ltd., Yamamoto Kogaku Co., Ltd., San-Ei Gen F.F.I.,Inc., Nakata MFG. Co., Ltd., Takenaka Seisakusho Co., Ltd., Yakult Honsha Co. Ltd., Pokka Corp., Nipponluna. Inc., Nisshoku Co., Ltd., Natures Inc., Jet Mill Manufacturing CompanyC-Tech Corp., Suntory, NOF Corp., KAGOME Co., Ltd., Asahi Breweries, Ltd., Aishin Corp., Mars/Weigley, Tsuji Oil Mill co., Ltd., Nikkiso Co., Ltd.	1
Ajinomoto Co.Inc.	5		
Kirin Beverage Nestle Group Hosokawa Micron Corp.	4		
Taiyo	3		
DHC J-Oil Mills Inc. Toray Industries Inc.	2		

* Others: Emulsifying agent maker, grinder mill maker and flavor maker were found in the expressions of the respondents.

6.4 Effectiveness expected of nano-substances (nanotechnology using companies only)

Q6-4 What effects do you expect of the nano-substances your company is using? (Please encircle <u>every</u> item applicable.)[4]

	Multiple choice (N = 48)	Number of responses	Ratio
1)	Absorption efficiency enhancement	21	45%
2)	Flavor enhancement	14	30%
3)	Reactivity enhancement	6	13%

[3] These company names were enumerated in the questionnaire responses, and we didn't confirm whether they are actually using nanotechnology individually.

[4] Though the Survey Slips originally asked for "making only one choice," considering the possibility of multiple choices, we again asked the responding companies to submit their multiple choices and collected the responses.

	Multiple choice (N = 48)	Number of responses	Ratio
4)	Solubility enhancement	17	36%
5)	Transparency enhancement	10	21%
6)	Stability enhancement	19	40%
7)	Detection by food containers	1	2%
8)	Sterilization, antibacterial, freshness preservation by container/packaging materials	4	9%
9)	Others	6	13%

* Others: Separation/generation of trace constituents, food products with oxidizing/reducing properties, creation of appropriate reaction systems and functionality, classification per preservability, sterilization/antimicrobial activity (These properties/effects are enhanced by using some surfactants.), enhancement of functionality/safety more than the existent general technologies (nano-bubble washing etc.), no new effects to expect in particular, immunity activity, etc.

6.5 Indication of nanotechnology use (nanotechnology using companies only)

Q6-5 Does your company indicate the use of nano-substances on your final (commercial) products using nano-substances? (Please encircle only one number that applies.)

	Single choice (N = 46)	Number of responses	Ratio
1)	Without fail	5	11%
2)	Some with indication and others without it	2	4%
3)	No indication	38	83%
4)	No idea (not manufacturing the final products)	1	2%

6.6 Considerations at the site of nanotechnology use (nanotechnology using companies only)

Q6-6 In using or conducting the research/manufacturing of nano-substances, does your company have any special considerations (e.g., countermeasures against exposure to nanoparticles) for workers (researchers) in their workplaces (laboratories)? (Please encircle only one number that applies.)

	Single choice (N = 47)	Number of responses	Ratio
1)	Yes	9	19%
2)	Nothing in particular	38	81%

Q6-6a What are the considerations, and what are the reasons? (Please write freely.)

1) Companies that chose “Yes”

- We are giving adequate considerations taking into account the safety.
- We have separated the manufacturing plants so that no cross-contaminations with other products will take place. We disclose MSDS and provide supporting information for the safety treatment in other manufacturing plants.
- We encourage the workers to use glasses and gloves.
- We obtain MSDS, ensure product safety, and take measures against exposure during working hours. (masks, glasses, long-sleeved fatigues, cotton work gloves, etc.)
- We use dust-protective masks.
- We address the issues according to the notification by the Ministry of Health, Labour and Welfare, "Notification on present preventive measures for the prevention of exposure at workplaces manufacturing and handling nanomaterials."
- We use masks and ventilation for preventing inhalation of substances.
- We use the related materials in agglomerated forms by kneading them into resins, etc. so as not to let them fly in all directions.

2) Companies that chose "Nothing in particular"

- We have no concerns over the exposure since they are treated in water.
- We have not started any specific steps.
- The nano-substances we are using are the means to control the substances that originally have solubility, and these entail no safety problems.
- We do not deal with any harmful constituents at present.
- In our products, they are treated as general powders with average particle diameter of not less than 3 μm.
- We have not initiated any protective measures as the materials are still at a research stage.

6.7 Safety ensuring activities concerning nano-substances (nanotechnology using companies only)

Q6-7 Does your company conduct any activity to secure safety with relation to the nano-substances used?
(Please encircle only one number that applies.)

6-7a What are the reasons for making your choices in 6-7? (Please write freely.)

	Single choice (N = 46)	Number of responses	Ratio
1)	Not conducting at present	20	44%
	Main reasons: • We have not initiated any activity in a specific way. • We see no danger. • Because of the size of fat emulsions, they are not likely to exert any influence on the human body. And they won't have influence because the parts concerned are derived from foods. • Because we have a long experience of eating the substances. • We have seen no problems for 100 years of manufacturing/marketing, and we believe we will see none in future either.		
2)	Conducting toxicity tests	8	17%

	Single choice (N = 46)	Number of responses	Ratio
	Main reasons: • We have confirmed the safety of 9 items and 90 days of successive oral administration/intraperitoneal administration, and we are conducting safety as food products. We have no concerns over our nano-products. • Because we believe it our obligation to ensure safety as a manufacturer of food raw materials. • We examine acute toxicity in combination with the confirmation of absorbability of active constituents. This is because side effects could be found if the activity should be too strong.		
3)	Purchasing products whose safety is warranted	10	22%
	Main reasons: • In order to secure the safety of products. • We believe retailers should make purchases as surrogate purchasers for consumers. Safety and a sense of security are prerequisites for purchases; so we confirm the safety of new technologies that have no past records by asking the manufacturers for the information. • Because we just deal with ordinary edible oils and fats. • Product safety certificates.		
4)	Collecting safety information	7	15
	Main reasons: • Because we do not deal with food itself. • Because it is still at a research stage.		
5)	Others (used in agglomerated form)	1	2%
	• Unlikely to be scattered and easy to handle		

III. Reference materials

Survey Slip (The final page of the Survey Slip is omitted because it has no questions.)

Reference materials (Further notes on food nanotechnology)

Please send back these Survey Slips by November 25 (Wed.)
in the envelope enclosed herewith.
(Please contact the person in charge
if you need an electronic file version of the Survey Slips.)

A Comprehensive Study for Ensuring Food Safety
The Cabinet Office Food Safety Commission (FY 2009)
A Basic Survey Report on Safety Assessment Information on the Use of Nanotechnology in the Food Sector

Survey Slips

Name of your company	
Location of the headquarters	
Unit of the respondent	

These Survey Slips are composed of Part 1 (Fundamental items) and Part 2 (Specific items).

Part 1 … We sincerely wish to ask you kindly to cooperate with us in our efforts to collect general information on the current status of the use of "nanotechnology" in the food sector. You might just choose to fill in only Part 1.

Part 2 … These are the question items for which the Food Safety Commission wishes to have your cooperation to the extent possible. You might choose only those parts that you can answer. We would highly appreciate your kind understanding and cooperation on this survey.

[Notes for filling in the form]

1. We would like to ask the representative officers or those who understand the company's overall manufacturing processes and R&D activities, and are in a position to review the future directions of the efforts to fill in this form.
2. All the information you give us will be processed as statistical figures and we will never publish any information from which specific businesses can be identified. Besides, the information will never be diverted to any other uses than the purposes of this fundamental survey.
3. As for the method of answering, please encircle the number of the choices or make specific mention according to the explanation of each of the questions.

[Sample (encircle the number of the choice)] 1) Yes 2) No

[Sample (Please be specific)] ABC Company, etc.

[Sample (Please supplement it in the parentheses of "Others (_____)")]

4) Others (We would hope for △△△ as a manufacturer of ○○)

4. Please fill in the answers directly in these Survey Slips. And when you fill in, please use writing instruments with indelible ink such as ball-point pens. (Please contact the person in charge shown on the final page of these Survey Slips if you need an electronic file version.)
5. Please fill in your answers to the applicable questions without skipping.
6. If you cannot possibly answer some of the questions, then you may give comments like "No idea" in the blank spaces.
7. If you have any questions, then please inquire the person in charge shown on the final page of these Survey Slips or on the letter of request enclosed.

I. Questions on your company

1-1 Choose the number of the item included in your company's business mix from the food industry activities shown below. (Please encircle every item applicable.)

1) Manufacturing/processing and packaging of prepared food that consumers directly purchase
2) Manufacturing/processing of prepared food (raw) materials that are supplied to companies in 1)
3) Manufacturing of functional food materials that are supplied to companies in 1) or 2)
4) Manufacturing of food container/packaging (materials)
5) Manufacturing of food processing machinery
6) Others (_____)

1-2 Choose the number of the item applicable on the payrolls of your company (as of the end of September 2009, excluding part-timers). (Please encircle only one number that applies.)

1) Not more than 50 2) 51–100 3) 101–300
4) 301-1000 5) 1001–3000 6) 3001–5000
7) Not less than 5001

II. We would like to ask for the opinion of the respondent who answered the questions of this questionnaire survey.

Please refer to the reference material documents for the supplemental descriptions on food nanotechnology.

2-1 Do you think the use of nanotechnology will increase (not only in your company but also in your industry) in future? (Please encircle only one number that applies.)

1) Definitely 2) Yes 3) Yes and no
4) No 5) Not at all

2-2 Do you see some noteworthy nanotechnology use related to food products? (Please encircle every item applicable.)

1) Food raw materials (structure, emulsion, etc.)
2) Food manufacturing/processing (micromachining and tiny bubbles, etc.)
3) Food function (nano-order capsule, etc.)
4) Container/packaging materials
5) Measurement (nano-sensor, etc.)
6) Others (_____)
7) Nothing in particular

2-3 How do you think the substances (including food raw materials and additives etc.) in nano-order size of which respondents have a long eating experience (e.g., dextrin and homogenized milk) should be treated? (Please encircle either necessary or unnecessary in each of the choices.)

2-3a "Substances in nano-order size for which respondents have a long eating experience as such"

1) Some regulation is (necessary/unnecessary)
2) Some indication obligation is (necessary/unnecessary)
3) Scientific safety assessment before launching into market is (necessary/unnecessary)

2-3b "Substances for which respondents have a long eating experience, processed in nano-order size anew"

1) Some regulation is (necessary/unnecessary)
2) Some indication obligation is (necessary/unnecessary)
3) Scientific safety assessment before launching into market is (necessary/unnecessary)

2-4 Do you have any opinion about the use or regulation of nanotechnology in the food sector?
(Please write freely.)

III. We would like to ask about the status of nanotechnology use in your company.

Please refer to the reference material documents for the supplemental descriptions on food nanotechnology.

3-1 Does your company use nanotechnology or nanomaterials (1 nm to several μm) in the manufacturing or research and development of food products? (Please encircle only one number that applies.)

1) Using
2) Not using (with development plan)
3) Not using (without development plan)

3-1a For respondents who chose "Using," what is the objective of the use? (Please encircle every item applicable.)

1) Food raw materials (structure, emulsion, etc.)
2) Food manufacturing/processing (micromachining and tiny bubbles, etc.)
3) Food function (nano-order capsule, etc.)
4) Container/packaging materials
5) Measurement (nano-sensor, etc.)
6) Others (_____)

If you chose "Using," then please go on to the questions on the following pages.

■ **If you chose "Not using," then please go on to page 6 (Questionnaire Part 2).**

→ **If you do not respond to the Questionnaire Part 2, then please go on to page 8 (the final page: the back side of this booklet).**

IV. We would like to ask about the nano-substances of which your company is manufacturing/using or is engaged in the research & development.

Please refer to the reference material documents for the supplemental descriptions on food nanotechnology.

This questionnaire form has 2 spaces to fill in the nano-substances (Please fill in the second material on page 5.). If applicable substances are more than one, please fill in the representative 2 substances.

<Nano-substance: first substance>

	No.	Questions	Spaces to fill in your answers (Please describe or encircle the number)
Nano-Substance: first substance	4-1	What is the nano-substance in the area of nanotechnology for which your company is engaged in the manufacture or research/development? (Sample answers) Calcium, platinum colloid, ○○ extract, △△ emulsion, ×× capsule, □□ sheet, etc.	Please fill in reference to the sample answer.
	4-2	What is the approximate average size of the nano-substance (primary particle)? (Please encircle only one number that applies.) If only the average size of agglomerates is known, or if it is unclear whether the obtained data is on primary particles or agglomerates, then please check either of the following and choose the size. □ agglomerate □ unknown	1) Not more than 10 nm 2) 10–100 nm 3) 100–500 nm 4) 500–900 nm 5) around 1000 nm (1 μm) 6) around several μm
	4-3	What is the purpose of the use of the nano-substance/nanotechnology using products? (Please encircle every item applicable.)	1) Health food 2) Food products other than health food 3) Food container/packages 4) Apparatuses other than food container/packages 5) Nanoparticle formation 6) Others ( )

If your company's products have already been launched in the market, then please answer the following questions too.

Nano-Substance: first substance	4-4	How do you obtain the nano-substances you use? (Please encircle only one number that applies.)	1) Manufacturing in-house 2) Both manufacturing in-house and purchasing 3) Purchasing without manufacturing in-house
	4-5	What is the annual production of the nanotechnology using food products? (If you ship nano-substances as food raw materials, then please fill in the production amount.)	Please choose either of the following: [as food/as nano-substance food raw material] Unit: _____ tons, kg, liters, etc.

■ **If your company uses only one nano-substance, then please go on to page 6 (Questionnaire Part 2).**

If your company uses more than one nano-substance, then please answer the questions on the next page too.

<Nano-substance: second substance>

	No.	Questions	Spaces to fill in your answers (Please describe or encircle the number)
Nano-Substance: second substance	5-1	What is the nano-substance in the area of nanotechnology for which your company is engaged in the manufacture or research/development? (Sample answers) Calcium, platinum colloid, ○○ extract, △△ emulsion, ×× capsule, □□ sheet, etc.	Please fill in reference to the sample answer.
	5-2	What is the approximate average size of the nano-substance (primary particle)? (Please encircle only one number that applies.) If only the average size of agglomerates is known, or if it is unclear whether the obtained data is on primary particles or agglomerates, then please check either of the following and choose the size. □ agglomerate □ unknown	1) Not more than 10 nm 2) 10–100 nm 3) 100–500 nm 4) 500–900 nm 5) around 1000 nm (1 μm) 6) around several μm
	5-3	What is the purpose of the use of the nano-substance/nanotechnology using products? (Please encircle every item applicable.)	1) Health food 2) Food products other than health food 3) Food container/packages 4) Apparatuses other than food container/packages 5) Nanoparticle formation 6) Others ( )

If your company's products have already been launched in the market, then please answer the following questions too.

Nano-Substance: second substance	5-4	How do you obtain the nano-substances you use? (Please encircle only one number that applies.)	1) Manufacturing in-house 2) Both manufacturing in-house and purchasing 3) Purchasing without manufacturing in-house
	5-5	What is the annual production of the nanotechnology using food products? (If you ship nano-substances as food raw materials, then please fill in the production amount.)	Please choose either of the following: [as food/as nano-substance food raw material] Unit: _____ tons, kg, liters, etc.

5-6 Does your company use more than two nano-substances? (Please encircle either one.)

1) Yes 2) No

Thank you for your cooperation. This is the end of the Survey Slip 1.

We hope to have your answers on the following questions to the extent possible.

■ **If you do not answer these, then please go on to page 8 (the final page: the back side of this booklet).**

The following part is the Survey Slip Part 2.
We hope to have your answers on the following questions to the extent possible.

6-1 Considering some review processes on the safety of nanotechnology are to be initiated in Europe and the United States, how do you collect food safety-related information (including nanotechnology) from abroad? (Please encircle every item applicable.)

1) Subscription of specialized journals (mail magazines, magazines, newspapers) and news coverage
2) Procurement of information released by foreign organizations concerned on a regular basis
3) Information exchange among industry groups, etc.
4) Database searches on a regular basis
5) Not collecting

6-2 Choose the number of the applicable item from below concerning the payrolls (including researchers, employee researchers and research assistants, as of the end of September 2009) directly engaged in R&D in your company. (Please encircle only one number that applies.)

1)	None	2)	Not more than 50	3)	51–100
4)	101–300	5)	301–1000	6)	1001–3000
7)	3001–5000	8)	Not less than 5001		

6-3 In the food sector, which companies are making advanced efforts toward the use of nanotechnology? (Please enumerate a couple of companies that you know, including foreign ones.)

In question 3-1(page 3),

- **If you answered your company is using nanotechnology or nanomaterials, then**
  → **please go on to the questions on the following pages.**
- **If you answered your company is not using nanotechnology or nanomaterials, then**
  → **please go on to page 8 (the final page: the back side of this booklet).**

Please refer to the reference material documents for the supplemental descriptions on food nanotechnology.

6-4 What effects do you expect from the nano-substances your company is using? (Please encircle only one number that applies.)

1)	Absorption efficiency enhancement	2)	Flavor enhancement	3)	Reactivity enhancement
4)	Solubility enhancement	5)	Transparency enhancement	6)	Stability enhancement
7)	Detection by food containers	8)	Sterilization, antibacterial, freshness preservation by container/packaging materials		
9)	Others ( )				

6-5 Does your company indicate the use of nano-substances on your final (commercial) products using nano-substances? (Please encircle only one number that applies.)

1)	Without fail	2)	Some with indication and others without it
3)	No indication	4)	No idea (not manufacturing the final products)

6-6 In using or conducting the research/manufacturing of nano-substances, does your company have any special considerations (e.g., countermeasures against exposure to nanoparticles) for workers (researchers) in their workplaces (laboratories)? (Please encircle only one number that applies.)

1) Yes 2) Nothing in particular

6-6a What are the considerations, and what are the reasons? (Please write freely.)

6-7 Does your company conduct any activity to secure safety with relation to the nano-substances used?
(Please encircle only one number that applies.)

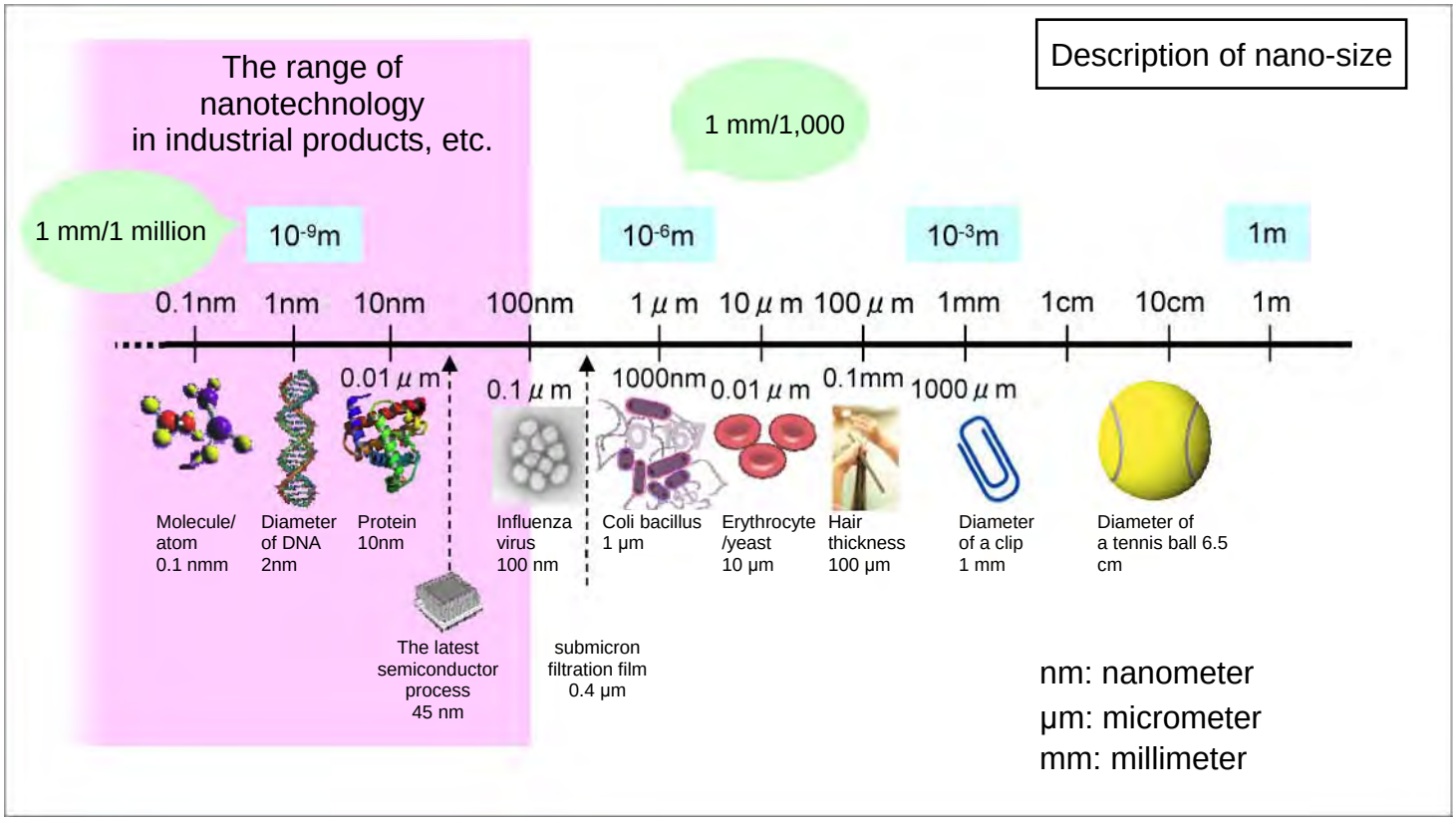
1)	Not conducting at present	2)	Conducting toxicity tests
3)	Purchasing products whose safety is warranted	4)	Collecting safety information
5)	Others ( )		

6-7a What are the reasons for making your choices in 6-7? (Please write freely.)

Supplemental description of food nanotechnology

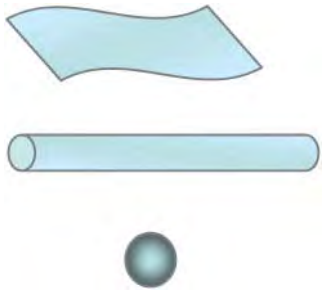
1. Nanotechnology

Nanotechnology is a technology for controlling substances freely in the range of one nanometer (nm, 1 nm = 10^{-9}m).



Industrial products and raw materials using nanotechnology generally refer to the substances that have a characteristic size below 100 nm and those materials containing these substances.

Types of nanotechnology using products in terms of the forms.



Nano membrane・・・Membrane with thickness less than 100 nm

Nano textile・・・Bar or ribbon form with diameter less than 100 nm

Nanoparticle・・・Particle with diameter less than 100 nm

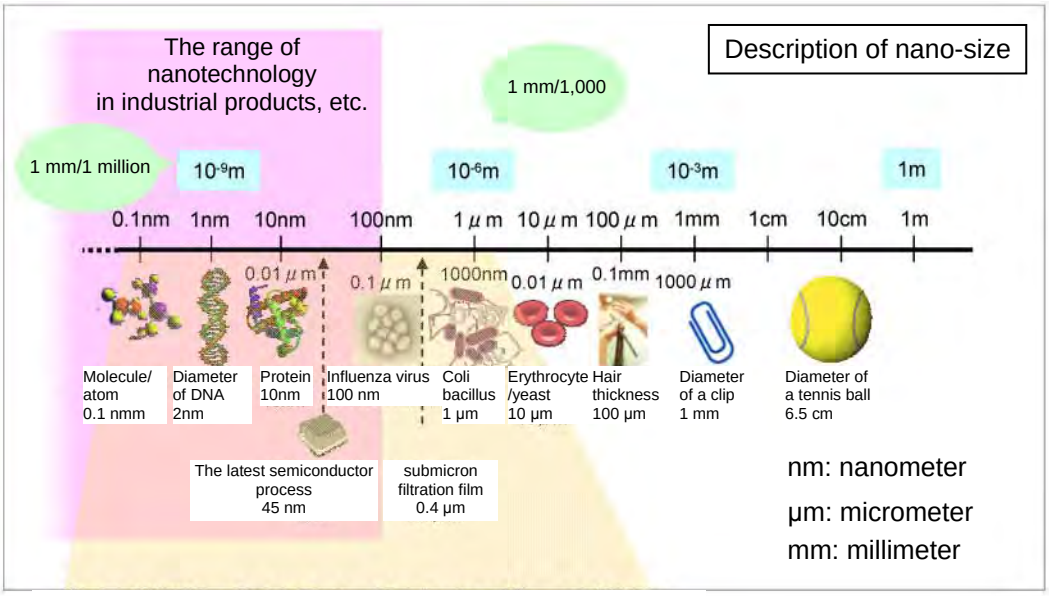
The image of a new type of influenza virus (A/H1N1swl) was provided by National Institute of Infectious Diseases.

2. Use of nanotechnology in food products

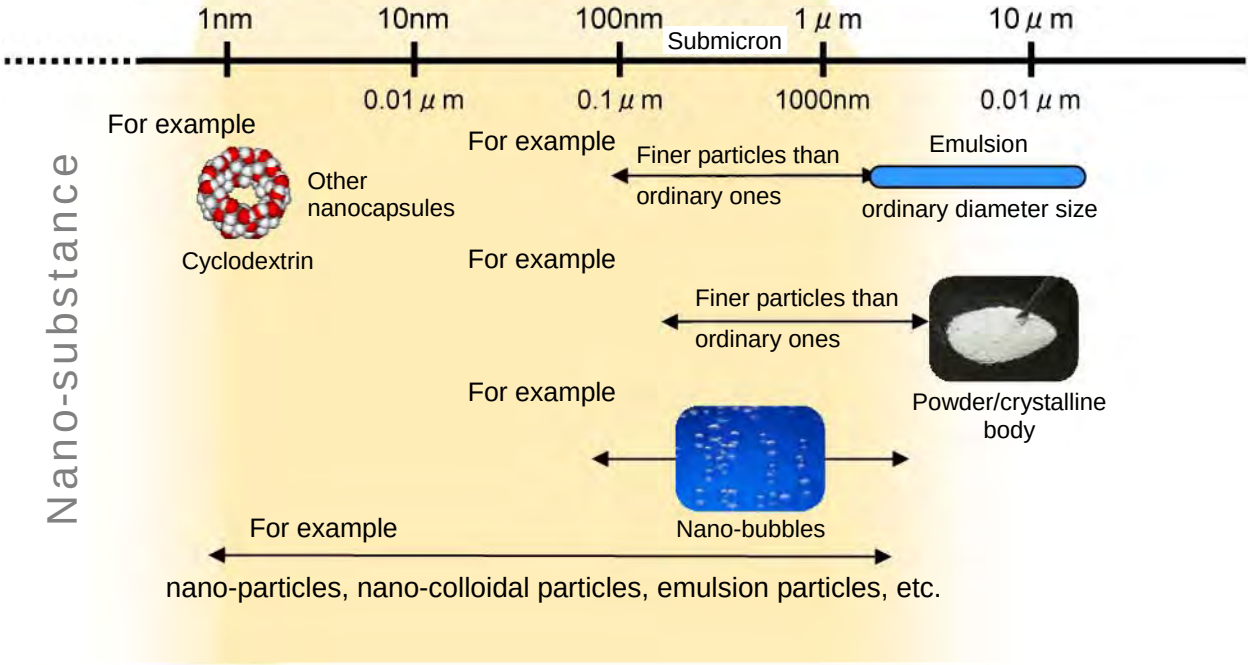
Use of nanotechnology in the food sector has just begun, and therefore the clear definition of nanotechnology has not been established yet.

However, unlike industrial materials, even if the size is not reduced to as small as less than 100 nm, just by reducing it to smaller-than-ordinary size is sometimes enough for food materials to provide new functions different from the conventional ones.

In light of this fact, we decided to conduct a questionnaire survey defining the use of nanotechnology in food products as “using particles with the diameter ranging from nm order to not more than several μm.”



The range of nanotechnology in the food sector



Drink or eat nano-substances in food products, use them for food containers/packages or the researches on them

Food products

Health foods

Food containers/packages

Appendix II　A List of the Reports Produced by International Organizations, etc.

No.	Nation	Name of international organization	Abbreviation	Document	Publication year
1	International organization	FAO/WHO Expert Meeting on the Application of Nanotechnologies in the Food and Agriculture Sectors	FAO/ WHO	FAO/WHO Expert Meeting on the Application of Nanotechnologies in the Food and Agriculture Sectors: Potential Food Safety Implications	2009
2	International organization	International Risk Governance Council	IRGC	Risk Governance of Nanotechnology Applications in Food and Cosmetics	2008
3	EU	Nanoforum/European Nanotechnology Gateway		Nanotechnology in Agriculture and Food	2006
4	EU	European Food Safety Authority	EFSA	The Potential Risks Arising from Nanoscience and Nanotechnologies on Food and Feed Safety	2009
5	EU	Scientific Panel on food additives, flavorings, processing aids and materials in contact with food	EFSA	Inability to assess the safety of a silver hydrosol added for nutritional purposes as a source of silver in food supplements and the bioavailability of silver from this source based on the supporting dossier	2008
6	EU	Observatory NANO		Nanotechnology in Agrifood.	2009
7	EU	European Commission		Novel foods, MEPs set new rules	2009
8	United Kingdom	British Food Standards Agency	FSA	A review of potential implications of nanotechnologies for regulations and risk assessment in relation to food. (August 2008)	2008
9	United Kingdom	British Food Standards Agency	FSA	Nanotechnology	2009
10	United Kingdom	ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES		NANOPARTICLES IN FOODS	2005
11	United Kingdom	HOUSE OF LORDS Science and Technology Committee		Nanotechnologies and Food	2010.1
12	United Kingdom	Department for Environment, Food and Rural Affairs	DEFRA	Environmentally beneficial nanotechnologies: barriers and opportunities	2007
13	United Kingdom	Department for Environment, Food and Rural Affairs	DEFRA	EMERGNANO A review of completed and near completed environment, health and safety research on nanomaterials and nanotechnology	2009

No.	Nation	Name of international organization	Abbreviation	Document	Publication year
14	United Kingdom	Royal Society for Chemistry	RSC	RSC Nanoscience & Nanotechnology Nanotechnologies in Food (Summary only)	2010.5(Scheduled for publication)
15	Germany	Federal Institute for Risk Assessment	BfR	The data to evaluate the application of nanotechnology in food and food commodities is still insufficient	2008
16	France	Food Safety Agency of France	AFSSA	Nanotechnologies et nanoparticules dans l'alimentation humaine et animale	2009
17	Ireland	Food Safety Authority of Ireland	FSAI	The Relevance for Food Safety of Application of Nanotechnology in the Food and Feed Industries	2009
18	The Netherlands	Institute of Food Safety Wageningen University and Research Centre (RIKILT)/RIVM (National Institute for Public Health and the Environment)	RILILT/ RIVM	Health impact of nanotechnologies in food production (September 2007)	2007
19	Switzerland	Center for Technology Assessment	TA-SWISS	Dinner is served! Nanotechnology in the kitchen and in the shopping basket, Abridged version of the TA-SWISS study "Nanotechnology in the food sector "	2009
20	The United States	Woodrow Wilson International Center for Scholars (WWICS)/Project on Emerging Nanotechnologies (PEN)	WWICS /PEN	A Hard Pill to Swallow: Barriers to Effective FDA Regulation of Nanotechnology-Based Dietary Supplements	2009
21	The United States	Woodrow Wilson International Center for Scholars (WWICS)/Project on Emerging Nanotechnologies (PEN)	WWICS /PEN	Assuring the safety of nanomaterials in food packaging: The regulatory process and key issues	2008
22	The United States	Woodrow Wilson International Center for Scholars (WWICS)/Project on Emerging Nanotechnologies (PEN)	WWICS /PEN	nanotechnology in agriculture and food production	2006

No.	Nation	Name of international organization	Abbreviation	Document	Publication year
23	The United States	National Academies/National Academy of Science/Institute of Medicine	IOM	Nanotechnology in Food Products	2009
24	The United States	Food and Drug Administration	FDA	Nanotechnology: A report of the U. S. FDA Nanotechnology Task Force	2007
25	The United States	Food and Drug Administration	FDA	FDA Nanotechnology public meeting (Briefing paper at the meeting (multiple documents))	2008
26	Australia New Zealand	Food Standards Australia New Zealand	FSANZ	Small Particles, Nanotechnology and Food (HP information)	2008
27	Others	Friends of the Earth	FoE	OUT OF THE LABORATORY AND ON TO OUR PLATES Nanotechnology in Food & Agriculture	2008
28	Others	ETC Group	ETC	DOWN ON THE FARM The Impact of Nano-Scale Technologies on Food and Agriculture	2004
29	The United States	U.S. Environmental Protection Agency	EPA	U.S. Environmental Protection Agency Nanotechnology White Paper	2007
30	The Netherlands	National Institute for Public Health and the Environment	RIVM	Nanotechnology in perspective. Risks to man and the environment	2009

Appendix III A List of Literature on Safety

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
1	Alexander T. Florence	Nanoparticle uptake by the oral route: Fulfilling its potential?	Drug Discovery Today: Technologies, Volume 2, Issue 1, Spring 2005, Pages 75-81	2005	Nanoparticle/solid lipid nanoparticle/nanocrystal/ nano-suspension (liquid)/microemulsion/ carbon nanotube/polymer micelle
2	Angeles-Agdeppa I, Capanzana MV, Barba CV, Florentino RF, Takanashi K.	Efficacy of iron-fortified rice in reducing anemia among schoolchildren in the Philippines.	Int J Vitam Nutr Res. Mar;78(2):74-86.2008	2008	Ferric pyrophosphate
3	Ankola D D; Viswanad B; Bhardwaj V; Ramarao P; Kumar M N V Ravi	Development of potent oral nanoparticulate formulation of coenzyme Q10 for treatment of hypertension: can the simple nutritional supplements be used as first line therapeutic agents for prophylaxis/therapy?.	Eur J Pharm Biopharm. 2007 Sep;67(2):361-9.	2007	CoQ10
4	Aprahamian, M., Michel, C., Humbert,W., Devissaguet, J.P., Damge, C.	Transmucosal passage of polyalkylcyanoacrylate nanocapsules as a new drug carrier in the small intestine.	Biology of the Cell 61, 69-76	1987	Iodized lipid (lipidol), poly (alkylcyanoacrylate)
5	Araujo, L., Lobenberg, R. and Kreuter, J.	Influence of the surfactant concentration on the body distribution of nanoparticles.	J Drug Target 6(5):373-385.	1999	Polymethyl methacrylate (coated with non-ionic surfactant)
6	Araujo, L., Sheppard, M., Lobenberg, R. and Kreuter, J.	Uptake of PMMA nanoparticles from the gastrointestinal tract after oral administration to rats: modification of the body distribution after suspension in surfactant solutions and in oil vehicles.	International Journal of Pharmaceutics 176 (2): 209-224.	1999	Polymethyl methacrylate
7	Ashwood, P., Thompson, R.P. and Powell, J.J.	Fine particles that adsorb lipopolysaccharide via bridging calcium cations may mimic bacterial pathogenicity towards cells.	Exp Biol Med (Maywood.) 232(1): 107-1 17.	2007	Titanium oxide
8	Avella, M., De Vlieger, J., Errico, M., Fischer, S., Vacca, P. and Volpe, M.	Biodegradable starch/clay nanocomposite films for food packaging applications.	Food Chemistry 93 (3): 467-474.	2005	Clay

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
9	BACK Evelyn I., NOHR Donatus, BIESALSKI Hans K. (Univ. Hohenheim, Stuttgart, DEU), FRINDT Claudia, STERN Martin (Univ. Children's Hospital Tuebingen, Tuebingen, DEU), OCENASKOVA Erika (Fac. Hospital, Hradec Kralove, CZE)	Can changes in hydrophobicity increase the bioavailability of α–tocopherol?	European Journal of Nutrition, Volume 45, Number 1, p.1-6	2005	Vitamin E
10	Ballou B, et al.	Noninvasive imaging of quantum dots in mice	Bioconjugate Chem. 15(1): 79-86 (2004).	2004	Quantum dot
11	Balogh, L., Nigavekar, S. S., Nair, B. M., Lesniak, W., Zhang, C., Sung, L. Y., Kariapper, M. S., Elawahri, A., Llanes, M., Bolton, B., Mamou, F., Tan, W., Hutson, A., Minc, L. and Khan, M. K.	Significant effect of size on the in vivo biodistribution of gold composite nanodevices in ouse tumor models.	Nanomedicine 3 (4): 281-96.	2007	Metal dendrimer
12	Baun, A., Sorensen, S.N., Rasmussen, R.F., Hartmann, N.B. and Koch, C.B.	Toxicity and bioaccumulation of xenobiotic organic compounds in the presence of aqueous suspensions of aggregates of nano-C(60).	Aquat. Toxicol. 86(3):379-387.	2008	Fullerene
13	Behsens, I., Pena, A.I., Alonso, M.J. and Kissel, T.	Comparative uptake studies of bioadhesive and non-bioadhesive nanoparticles in human intestinal cell lines and rats: the effect of mucus on particle adsorption and transport.	Pharm. Res 19(8): 1 185-1 193.	2002	Three substances: Polystyrene, chitosan and PLA-PEG
14	Bockmann, J., Lahl, H., Eckert,T., Unterhalt. B.	Blood titanium levels before and after oral administration titanium dioxide.	Pharmazie 55(2), 140-3	2000	Titanium oxide
15	Bouwmeester Hans; Dekkers Susan; Noordam Maryvon Y; Hagens Werner I; Bulder Astrid S; de Heer Cees; ten Voorde Sandra E C G; Wijnhoven Susan W P; Marvin Hans J P; Sips Adrienne J A M	Review of health safety aspects of nanotechnologies in food production.	Regulatory toxicology and pharmacology : RTP, (2009 Feb) Vol. 53, No.1, pp. 52-62.	2009	

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
16	Boyd, B.J., Kaminskas, L.M., Karellas, P., Krippner, G., Lessene, R. and Porter, C.J.	Cationic poly-L-lysine dendrimers: pharmacokinetics, biodistribution, and evidence for metabolism and bioresorption after intravenous administration to rats.	MOLECULAR PHARMACEUTICS VOL. 3, NO. 5, 614-627	2006	Poly (L-lysine) dendrimer
17	Bravo-Osuna I; Vauthier C; Chacun H; Ponchel G	Specific permeability modulation of intestinal paracellular pathway by chitosan-poly(isobutylcyanoacrylate) core-shell nanoparticles.	European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, (2008 Jun) Vol. 69, No. 2, pp. 436-44.	2008	
18	BUGUSU Betty (Inst. Food Technol., Washington, DC)	Improving Food Through NANOSCIENCE	Food Technology, 34-39, 09.08	2008	
19	BUGUSU Betty, MEJIA Carla (Inst. Food Technol., Washington, D.C.), MAGNUSON Bernadene, TAFAZOLI Shahrzad (Cantox Health Sci. International, ON, CAN)	GLOBAL REGULATORY POLICIES ON FOOD NANOTECHNOLOGY	Food Technology, 24-28, 05.09	2009	
20	Carr KE, Hazzard RA, Reid S, Hodges GM	The effect of size on uptake of orally administered latex microparticles in the small intestine and transport to mesenteric lymph nodes.	Pharmaceutical Research 13, 1205-1209.	1996	
21	Carrero-Sanchez, J., Elias, A., Mancilla, R., Arrellin, G., Terrones, H., Laclette, J. and Terrones, M.	Biocompatibility and toxicological studies of carbon nanotubes doped with nitrogen.	Nano letters 6 (8): 1609-1616.	2006	Carbon nanotube
22	Cedervall T, Lynch I, Lindman S, Berggård T, Thulin E, Nilsson H, Dawson K, Linse S.	Understanding the nanoparticle-protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles.	Proceedings of the National Academy of Sciences 104(7):2050-2055.	2007	N-Isopropylacrylamide/ N-t-butyl-acrylamid copolymer

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
23	Cedervall, T., Lynch, I., Foy, M., Berggard, T., Donnelly, S. C., Cagney, G., Linse, S. and Dawson, K. A.	Detailed identification of plasma proteins adsorbed on copolymer nanoparticles.	Angew chem Int Ed Engl 46 (30): 5754-6.	2007	N-Isopropylacrylamide/ N-t-butyl-acrylamid copolymer
24	Chalasani Kishore B; Russell-Jones Gregory J; Jain Akhlesh K; Diwan Prakash V; Jain Sanjay K	Effective oral delivery of insulin in animal models using vitamin B12-coated dextran nanoparticles.	Journal of controlled release : official journal of the Controlled Release Society, (2007 Sep 26) Vol. 122, No. 2, pp. 141-50.	2007	Vitamin B_{12}
25	Chau, Chi-Fai; Wu, Shiuan-Huei; Yen, Gow-Chin	The development of regulations for food nanotechnology	Trends in Food Science & Technology, (2007) Vol. 18, No. 5, pp. 269-280.	2007	
26	CHAUDHRY Qasim, SCOTTER Michael, BLACKBURN James, CASTLE Laurence, WATKINS Richard (Defra Central Sci. Lab., York UK), ROSS Bryony, AITKEN Robert (Inst. of Occupational Medicine, Edinburgh, GBR), BOXALL Alistair (Univ. York, York, GBR)	Applications and implications of nanotechnologies for the food sector	Food Addit Contam Pt A Chemistry Analysis Control Expo Risk Assess, 25, 3, 241-258, 2008.03	2008	
27	Chen, H.,Weiss, J., Shahidi, F.	Nanotechnology in nutraceuticals and functional foods	Food Technology, 3, 30-36	2006	
28	Chen, Z., Meng, H., Xing, G., Chen, C., Zhao, Y., Jia, G., Wang, T., Yuan, H., Ye, C., Zhao, F., Chai, Z., Zhu, C., Fang, X., Ma, B. and Wan, L.	Acute toxicological effects of copper nanoparticles in vivo.	Toxicol Lett 163 (2): 109-20.	2006	Copper
29	Chen, Z., Meng, H.,Yuan, H., Xing, G., Chen, C., Zhao, F.,Wang,Y., Zhang, C., Zhao,Y.	Identification of target organs of copper nanoparticles with ICP-MS technique	J. Radioanalytical Nuclear Chem., 272, 599-603	2007	Copper

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
30	Chia-Ding Liao, Wei-Lun Hung, Wen-Chien Lu, Kuo-Ching Jan, Daniel Yang-Chih Shih, An-I Yeh, Chi-Tang Ho and Lucy Sun Hwang	Differential Tissue Distribution of Sesaminol Triglucoside and Its Metabolites in Rats Fed with Lignan Glycosides from Sesame Meal with or without Nano/Submicrosizing	J. Agric. Food Chem., 2010, 58 (1), pp 563–569	2009	Lignan glycoside (sesame extract)
31	Chithrani, B.D. and Chan, W.C.	Elucidating the mechanism of cellular uptake and removal of protein-coated gold nanoparticles of different sizes and shapes.	Nano. Lett 7(6): 1542-1550.	2007	Gold (coated with transferrin)
32	Cho, W.S., Cho, M., Jeong, J., Choi, M., Cho, H.Y., Han, B.S., Kim, S.H., Kim, H.O., Lim, Y.T., Chung, B.H. and Jeong, J.	Acute toxicity and pharmacokinetics of 13 nm-sized PEG-coated gold nanoparticles.	Toxicol Appl Pharrnacol.	2009	Gold
33	CHOI Soo-Jin, OH Jae-Min, CHOY Jin-Ho (Ewha Womans Univ., Seoul, KOR), CHOI Soo-Jin (Seoul Women's Univ., Seoul, KOR)	Human-related application and nanotoxicology of inorganic particles: complementary aspects	J Mater Chem, 18, 6, 615-620	2008	Layered double hydroxide (LDH)
34	Christine Hotz, Maribel Porcayo, Germán Onofre, Armando García-Guerra, Terry Elliott, Shirley Jankowski, and Ted Greiner	Efficacy of iron-fortified Ultra Rice in improving the iron status of women in Mexico	Food and Nutrition Bulletin, vol. 29, no. 2, p140-148, 2008	2008	Ferric pyrophosphate
35	Colas Jean-Christophe; Shi Wanlong; Rao V S N Malleswara; Omri Abdelwahab;Mozafari M Reza; Singh Harjinder	Microscopical investigations of nisin-loaded nanoliposomes prepared by Mozafari method and their bacterial targeting.	Micron (Oxford, England : 1993), (2007) Vol. 38, No. 8, pp. 841-7.	2007	
36	Costantino Luca; Gandolfi Francesca; Bossy-Nobs Leila; Tosi Giovanni; Gurny Robert; Rivasi Francesco; Vandelli Maria Angela; Forni Flavio	Nanoparticulate drug carriers based on hybrid poly(D,L-lactide-co-glycolide)-dendron structures.	Biomaterials, (2006 Sep) Vol. 27, No. 26, pp. 4635-45.	2006	
37	Damge, C., Aprahamian, M., Humbert, W. and Pinget, M.	Ileal uptake of polyalkylcyanoacrylate nanocapsules in the rat.	J Pharm. Pharmacol. 52(9): 1049-1 056.	2000	Poly (alkylcyanoacrylate)
38	Das, M., Saxena, N. and Dwivedi, PD.	Emerging trends of nanoparticles application in food technology: Safety paradigms.	Nanotoxicology 3(1):10-18. Infoma Healthcare	2009	

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
39	De Jong WH, Hagens WI, Krystek P, Burger MC, Sips AJ, Geertsma RE	Particle size-dependent organ distribution of gold nanoparticles after intravenous administration.	Biomaterials 29, 1912-1919.	2008	Gold
40	Demoy, M., AndreuxJ,. P., Weingarten, C., Gouritin, B., Guilloux, V. and Couvreur, P.	Spleen capture of nanoparticles: influence of animal species and surface characteristics.	Pham. Res 1 6(1):37-4 1.	1999	Polystyrene (coated with surfactant)
41	des Rieux, A., Fievez, V., Garinot, M., Schneider, Y.J. and Preat, V	Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach.	J Control Release 1 16(1): 1-27.	2006	
42	Desai, M. P., Labhasetwar, V., Amidon, G. L. and Levy, R. J.	Gastrointestinal uptake of biodegradable microparticles: effect of particle size.	Pharm Res 13 (12): 1838-45.	1996	Poly-lactic acid, glycolic acid
43	Desai, M.P., Labhasetwar, V., Walter, E., Levy, R.J. and Amidon, G.L.	The mechanism of uptake of biodegradable microparticles in Caco-2 cells is size dependent.	Pharm.Res 14(11):1568-1573.	1997	PLGA (Poly-lactic acid-polyglycolic acid copolymer)
44	Dingman Jim	Nanotechnology: its impact on food safety.	Journal of environmental health, (2008 Jan-Feb) Vol. 70, No. 6, pp. 47-50.	2008	
45	Dobrovolskaia, M.A. and McNeil, S.E.	Immunological properties of engineered nanomaterials.	Nat. Nanotechnol. 2(8):469-478.	2007	
46	Doyle-McCullough, M., Smyth, S.H., Moyes, S.M. and Carr, K.E.	Factors influencing intestinal microparticle uptake in vivo.	Int J Pharm. 33 5(1-2): 79-89.	2007	Latex
47	DUTTA P.k., TRIPATHI Shipra, MEHROTRA G.k. (Dep. of Chemistry, Motilal Nehru National Inst. of Technol., Allahabad 211004, IND), DUTTA Joydeep (Regenerative Medicine, Reliance Life Sciences Pvt. Ltd., R-282, TTC Area of MIDC, Thane Belapur Road, Rabale, Navi ...)	Perspectives for chitosan based antimicrobial films in food applications	Food Chemistry 114 (2009) 1173–1182	2009	Chitosan

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
48	Dutta, T., Garg, M., Dubey, V., Mishra, D., Singh, K., Pandita, D., Singh, AK., Ravi, AK., Velpandian, T. and Jain, NK.	Toxicological investigation of surface engineered fifth generation poly (propyleneimine) dendrimers in vivo.	Nanotoxicology 2(2):62-70.	2008	Poly (propyleneimine) Dendrimer
49	Fabian, E., Landsiedel, R., Ma-Hock, L., Wiench, K., Wohlleben, W. and van Ravenzwaay, B.	Tissue distribution and toxicity of intravenously administered titanium dioxide nanoparticles in rats.	Arch Toxicol 82 (3): 151-7.	2008	Titanium oxide
50	FLANAGAN John, SINGH Harjinder (Massey Univ., Palmerston North, NZL)	Microemulsions: A Potential Delivery System for Bioactives in Food	Critical Reviews in Food Science and Nutrition, 46:221-237 (2006)	2006	
51	Florence, A.T. and Hussain, N.	Transcytosis of nanoparticle and dendrimer delivery systems: evolving vistas.	Adv Drug Deliv. Rev 50(2001) :S69-S89.	2001	
52	FSA (United Kingdom)	Assessment of the potential use of nanomaterials as food additives or food ingredients in relation to consumer safety and implications for regulatory control.	OECD Budget Database on Nano Risk Research (project)	2006- 2007	
53	FSA (United Kingdom)	Assessment of current and projected applications of nanotechnology for food contact materials in relation to consumer safety and regulatory implications	EmergeNano (2009)(project)	2006- 2008	
54	Furumoto, K., Ogawara, K., Nagayama, S., Takakura, Y., Hashida, M,, Higaki, K. and Kimura, T.	Important role of serum proteins associated on the surface of particles in their hepatic disposition.	J Control Release 83(1):89-96.	2002	Polystyrene (coated with cystine)
55	Furumoto, K., Ogawara, K., Yoshida, M., Takakura, Y., Hashida, M., Higaki, K. and Kimura, T.	Biliary excretion of polystyrene microspheres depends on the type of receptor-mediated uptake in rat liver.	Biochim.Biophys. Acta 1526(2):221-226.	2001	Polystyrene
56	Garcia-Garcia, E., Andrieux, K., Gil, S., Kim, H.R., Le, D.T., Desmaele, D., dlAngelo, J., Taran, F., Georgin, D. and Couvreur, P.	A methodology to study intracellular distribution of nanoparticles in brain endothelial cells.	Int J Pharm. 298(2):3 10-3 14.	2005	Poly (hexadecyl cyanoacrylate) (coated with PEG)

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
57	Gatti Antonietta M; Tossini Daniela; Gambarelli Andrea; Montanari Stefano; Capitani Federico	Investigation of the presence of inorganic micro- and nanosized contaminants in bread and biscuits by environmental scanning electron microscopy.	Critical reviews in food science and nutrition, (2009 Mar) Vol. 49, No. 3, pp. 275-82	2009	
58	Gatti,A.M.	Biocompatibility of micro- and nano-particles in the colon. Part II	Biomaterials, 25, 385-392	2004	Silicon, aluminum, zirconium
59	Geiser, M., Rothen-Rutishauser, B., Kapp, N., Schurch, S., Kreyling, W., Schulz, H., Semmler, M., Im, H., V, Heyder, J. and Gehr, P.	Ultrafine particles cross cellular membranes by nonphagocytic mechanisms in lungs and in cultured cells.	Environ Health l Perspect. 113(11):1555-1560.	2005	Titanium oxide
60	GROVES Kathy (Leatherhead Food International)	Potential benefits of micro and nanotechnology for the food industry: does size matter?	New Food, 11, 4, 49-52, 2008.11	2008	
61	H.S. Chen, J.H. Chang, and J.S.B. Wu	Calcium Bioavailability of Nanonized Pearl Powder for Adults	Journal of Food Science, Volume 73 Issue 9, Pages H246 - H251	2008	Pearl
62	Heinlaan, M., Ivask, A., Blinova, I., Dubourguier, H. C. and Kahru, A.	Toxicity of nanosized and bulk ZnO, CuO and TiO2 to bacteria Vibrio fischeri and crustaceans Daphnia magna and Thamnocephalus platyurus.	Chemosphere 71 (7): 1308-16.	2008	Zinc oxide/titanium oxide/copper oxide
63	Hillery,A.M., Jani, P.U., Florence,A.T.	Comparative, quantitative study of lymphoid and non-lymphoid uptake of 60nm polystyrene particles.	J Drug Target, 2,151-156	1994	Polystyrene
64	Hillyer, J. F. and Albrecht, R. M.	Gastrointestinal persorption and tissue distribution of differently sized colloidal gold nanoparticles.	Journal of Pharmaceutical sciences, vol. 90, No.12, December 2001	2001	Gold
65	Hoet, P. H., Bruske-Hohlfeld, I. and Salata, O. V.	Nanoparticles - known and unknown health risks.	J Nanobiotechnology 2 (1): 12.	2004	

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
66	Hussain, N. and Florence, A.T.	Utilizing bacterial mechanisms of epithelia1 cell entry: invasin-induced oral uptake of latex nanoparticles.	Pharm. Res 15(1):153-156.	1998	Latex
67	Hussain, N., Jani, P.U. and Florence, A.T.	Enhanced oral uptake of tomato lectinconjugated nanoparticles in the rat.	Pharm. Res 14(5):613-618.	1997	Polystyrene (tomato-lectin bond)
68	Hussain, S.M., Hess, K.L., Gearhart, J.M., Geiss, K.T., Schlager, J.J.	In vitro toxicity of nanoparticles in BRL3A rat liver cells.	Toxicology in vitro 19, 975-983	2005	Silver, Molybdenum oxide, aluminum, Ferric oxide, Titanium oxide
69	Jain K K	Stability and delivery of RNA via the gastrointestinal tract.	Current drug delivery, (2008 Jan) Vol. 5, No. 1, pp. 27-31	2008	
70	Jani, P., Halbert, G.W., Langridge, J. and Florence, A.T.	Nanoparticle uptake by the rat gastrointestinal mucosa: quantitation and particle size dependency.	J Pharm. Pharmacol. 42(12):821-826.	1990	Polystyrene
71	Jani, P. U., McCarthy, D.E., Florence,A.T.	Titanium dioxide (rutile) particle Uptake from the rat GI tract and translocation to systemic organs after oral administration.	International Journal of Pharmaceutics 105, 157-168	1994	Titanium oxide
72	Jani, P., Halbert, G.W., Langridge, J., Florence,A.T.	The uptake and translocation of latex nanospheres and microspheres after oral administration to rats.	J. Pharm. Pharmacol., 41, 809-812	1989	Polystyrene
73	Jia, X., Li, N., Chen, J.	A subchronic toxicity study of elemental Nano-Se in Sprague- Dawley rats.	Life Sci. 76(17),1989-2003	2005	Selenium
74	Kaminskas, L.M., Wu, Z., Barlow, N., Krippner, G.Y., Boyd, B.J. and Porter, C.J.	Partly-PEGylated Poly-L-lysine dendrimers have reduced plasma stability and circulation times compared with fully PEGylated dendrimers.	J Pharm. Sci. Volume 98 Issue 10, Pages 3871 - 3875	2009	Poly (propyleneimine) Dendrimer
75	KAMPERS Frans (Wageningen Univ., Wageningen, NLD)	Micro- and nanotechnologies for food and nutrition in preventative healthcar	Food Sci Technol, 21, 1, 20-23, 2007.03	2007	

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
76	Kim, Dong-Heui; Song, Soon-Bong; Qi, Xu-Feng; Kang, Wie-Soo; Jeong, Yeon-Ho; Teng, Yung-Chien; Lee, Seon-Goo; Kim, Soo-Ki; Lee, Kyu-Jae	The Food Safety of Superfine Saengshik Processed by Top-down Technique in Mice	Molecular & Cellular Toxicology, (MAR 31 2009) Vol. 5, No. 1, pp. 75-82	2009	Saengshik (functional food manufactured by powderizing dried grain, beans, vegetable, fungus, etc.)
77	Kim, Y. S., Kim, J. S., Cho, H. S., Rha, D. S., Kim, J. M., Park, J. D., Choi, B. S., Lim, R., Chang, H. K., Chung, Y. H., Kwon, I. H., Jeong, J., Han, B. S. and Yu, I. J.	Twenty-eight-day oral toxicity, genotoxicity, and gender-related tissue distribution of silver nanoparticles in Sprague-Dawley rats.	Inhal Toxicol 20 (6): 575-83.	2008	Silver
78	Kotyla,T., Kuo, F., Moolchandani,V.,Wilson, T., Nicolosi, R.	Increased bioavailability of a transdermal application of a nano-sized emulsion preparation.	International Journal of Pharmaceutics, 347, 144-148	2008	Vitamin E
79	Kreyling,W. G., Semmler, M., Erbe, F., Mayer, P.,Takenaka, S., Schulz, H., Oberdorster, G. and A. Ziesenis,A.	Translocation of ultrafine insoluble iridium particles from lung epithelium to extrapulmonary organs is size dependent but very low.	J.Toxicol. Environ. Health.A 65(20),1513-30	2002	Iridium
80	Kuzma Jennifer; Romanchek James; Kokotovich Adam, Upstream oversight assessment for agrifood nanotechnology: a case studies approach., Risk analysis : an official publication of the Society for Risk Analysis,	Upstream oversight assessment for agrifood nanotechnology: a case studies approach.	Risk analysis : an official publication of the Society for Risk Analysis, (2008 Aug) Vol. 28, No. 4, pp. 1081-98.	2008	DNA-containing nanoparticle for monitoring agroecosystem, agrochemical nanocapsule, food additive nanocapsule, medical cellulose nano-crystalline composite, nanoparticles for eliminating O175:H7 coli bacillus from livestock, nanoparticles for food packaging film coating
81	LaCoste,A., Schaich, K., Zumbrunnen, D., Yam, K.	Advancing controlled release packaging through smart blending.	Packaging Technology Sci 18, 77-87	2005	Nano-scaled material (without clear notification)

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82	Lagaron J M; Cabedo L; Cava D; Feijoo J L; Gavara R; Gimenez E	Improving packaged food quality and safety. Part 2: nanocomposites.	Food additives and contaminants, (2005 Oct) Vol. 22, No. 10, pp. 994-8	2005	Nanocomposite (ethylene vinyl alcohol copolymer and amorphous poly-lactic acid incorporated with clay)
83	Lai, S.K., O'Hanlon, D.E., Harrold, S., Man, S.T., Wang, Y .Y ., Cone, R. and Hanes, J.	Rapid transport of large polymeric nanoparticles in fresh undiluted huinan mucus.	Proc.Natl.Acad.Sci US A 104(5): 1482-1487.	2007	Polystyrene (coated with PEG)
84	Layre A-M; Couvreur P; Richard J; Requier D; Eddine Ghermani N; Gref R	Freeze-drying of composite core-shell nanoparticles.	Drug development and industrial pharmacy, (2006 Aug) Vol. 32, No. 7, pp. 839-46.	2006	
85	Lei Ronghui; Wu Chunqi; Yang Baohua; Ma Huazhai; Shi Chang; Wang Quanjun; Wang Qingxiu; Yuan Ye; Liao Mingyang	Integrated metabolomic analysis of the nano-sized copper particle-induced hepatotoxicity and nephrotoxicity in rats: a rapid in vivo screening method for nanotoxicity.	Toxicology and applied pharmacology, (2008 Oct 15) Vol. 232, No. 2, pp.292-301.	2008	Copper
86	Limbach L, Li Y, Grass R, Brunner T, Hintermann M, Muller M, Gunther D, Stark W.	Oxide Nanoparticle Uptake in Human Lung Fibroblasts: Effects of Particle Size, Agglomeration, and Diffusion at Low Concentrations	Environ Sci Technol 39(23): 9370-9376.	2006	Cerium oxide
87	Lin,W., Huang,Y-W., Zhou, X-D, Ma,Y.	In vitro toxicity of silica nanoparticles in human lung cancer cells.	Toxicology and Applied Pharmacology 217, 252-259	2006	Silica
88	Linse, S., Cabaleiro-Lago, C., Xue, W. F., Lynch, I., Lindman, S., Thulin, E., Radford, S. E. and Dawson, K. A.	Nucleation of protein fibrillation by nanoparticles.	Proc Natl Acad Sci U S A 104 (21): 8691-6.	2007	Cerium oxide, carbon nanotube

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89	Lippacher A; Muller R H; Mader K	Semisolid SLN dispersions for topical application: influence of formulation and production parameters on viscoelastic properties.	European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, (2002 Mar) Vol. 53, No. 2, pp. 155-60	2002	
90	Liu Huiting; Ma Linglan; Zhao Jinfang; Liu Jie; Yan Jingying; Ruan Jie;Hong Fashui	Biochemical toxicity of nano-anatase TiO2 particles in mice.	Biological trace element research, (2009 Summer) Vol. 129, No. 1-3, pp.170-80.	2009	Titanium oxide
91	Lockman PR, et al.	Nanoparticle surface charges alter blood-brain barrier integrity and permeability	J. Drug Target. 12(9-10): 635-641 (2004).	2004	Emulsified wax
92	LOMER M C E, THOMPSON R P H (St. Thomas' Hospital, London, GBR), POWELL J J (King's Coll. London, London, GBR),	Fine and ultrafine particles of the diet: Influence on the mucosal immune response and association with Crohn's disease.	Proc Nutr Soc, 61, 1, 123-130, 2002.02	2002	
93	Long, T.C., Saleh, N., Tilton, R.D., Lowry, G.V. and Veronesi, B.	Titanium dioxide (P25) produces reactive oxygen species in immortalized brain microglia (BV2): implications for nanoparticle neurotoxicity.	Environ Sci Techno l40 (14):4346-4352.	2006	Titanium oxide
94	Loretz, B. and Bemkop-Schniirch, A.	In vitro cytotoxicity testing of non-thiolated and thiolated chitosan nanoparticles for oral gene delivery.	Nanotoxicology, June 2007; 1(2): 139 148	2007	Chitosan, DNA
95	Lu Wei; Tan Yu-zhen; Jiang Xin-guo	Establishment of coculture model of blood-brain barrier in vitro for nanoparticle's transcytosis and toxicity evaluation.	Yao xue xue bao Acta pharmaceutica Sinica, (2006 Apr) Vol. 41, No. 4, pp. 296-304.	2006	Coumarin

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
96	Luykx Dion M A M; Peters Ruud J B; van Ruth Saskia M; Bouwmeester Hans,	A review of analytical methods for the identification and characterization of nano delivery systems in food.	Journal of agricultural and food chemistry, (2008 Sep 24) Vol. 56, No. 18, pp. 8231-47.	2008	
97	Lynch, I. and Dawson, K. A.	Protein-nanoparticle interactions.	Nano Today 3 (1-2): 40-47.	2008	
98	Lynch, I., Cedervall,T., Lundqvist, M., Cabaleiro-Lago, C., Linse, S., Dawson, K.A.	The nanoparticle-protein complex as a biological entity; a complex fluids and surface science challenge for the 21st Century.	J. Colloid Interface Sci. 134-135, 167-174	2007	
99	Lynch, I., Dawson, K. A. and Linse, S.	Detecting cryptic epitopes created by nanoparticles.	Sci STKE 2006 (327): pe14.	2006	
100	Mark A. Roe, Rachel Collings, Jurian Hoogewerff and Susan J. Fairweather-Tait	Relative bioavailability of micronized, dispersible ferric pyrophosphate added to an apple juice drink	European Journal of Nutrition, Vol.48, p115-119, 2009	2009	Ferric pyrophosphate
101	Matschulat, D., Prestel, H., Haider, F., Niessner, R. and Knopp, D.	Immunization with soot from a non-combustion process provokes formation of antibodies against polycyclic aromatic hydrocarbons.	J Immunol Methods 310 (1-2): 159-70.	2006	Soot
102	Maynard,A.D.,Aitken, R.J., Butz,T., Colvin, V., Donaldson, K., Oberdorster, G., Philbert, M.A., Ryan, J., Seaton,A., Stone, V.,Tinkle, S.S.,Tran, L.,Walker, N.J., Warheit, D.B.	Safe handling of nanotechnology.	Nature, 144, 267-269	2006	
103	Meng, H., Chen, Z., Xing, G.,Yuan, H., Chen, C., Zhao, F., Zhang, C., Zhao,Y.	Ultrahigh reactivity provokes nanotoxicity: Explanation of oral toxicity of nano-copper particles	Toxicology Letters, 175, 102-110	2007	Copper
104	Meredith C. Fidler, Thomas Walczyk, Lena Davidsson, Christophe Zeder, Noboru Sakaguchi, Lekh R. Juneja and Richard F. Hurrell	A micronised, dispersible ferric pyrophosphate with high relative bioavailability in man	British Journal of Nutrition, Volume 91, Issue 01, January 2004, pp 107-112	2004	Ferric pyrophosphate

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105	Michaelis, K., Hoffinann, M.M., Dreis, S., Herbert, E., Alyautdin, R.N., Michaelis, M., Kreuter, J. and Langer, K.	Covalent linkage of apolipoprotein e to albumin nanoparticles strongly enhances drug transport into the brain.	J Pharmacol. Exp Ther. 3 17(3):1246-1253.	2006	Apolipoprotein, E-human serum albumin
106	MORRIS Vic (Inst. Food Res., Norwich, GBR)	Nanotechnology and its future in New Product Development	Food Sci Technol, 20, 3, 15-17, 2006.09	2006	
107	MORRIS Victor J (Inst. Food Res.)	Nanotechnology in the food industry	New Food, 11, 4, 53-55, 2008.11	2008	
108	Moyes, S.M., Smyth, S.H., Shipman, A., Long, S., Morris, J.F. and Carr, K.E.	Parameters influencing intestinal epithelial permeability and microparticle uptake in vitro.	Int JPharm. 337(1-2):133-141.	2007	Latex
109	Mozafari M, Flanagan J, Matia-Merino L, Awati A, Omri A, Suntres Z, Singh H.	Recent trends in the lipid-based nanoencapsulation of antioxidants and their role in foods	J Sci Food Ag 86:2038-2045.	2006	
110	Mozafari, M.R., Johnson, C., Hatziantoniou, S. and Demetzos, C.	Nanoliposomes and their applications in food nanotechnology	J. Liposome Res. 1 8(4):3 09-327.	2008	
111	Nefzger, M., Kreuter, J., Voges, R., Liehl, E. and Czok, R.	Distribution and elimination of polymethyl methacrylate nanoparticles after peroral administration to rats.	J Pharm Sci 73 (9): 1309- 11.	1984	Polymethyl methacrylate
112	Nel, A., Xia, T., Madler, L. and Li, N.	Toxic potential of materials at the nanolevel.	Science 311 (5761): 622-7.	2006	
113	Niidome, T., Yamagata, M., Okamoto, Y., Akiyama, Y., Takahashi, H., Kawano, T., Katayama, Y. and Niidome, Y.	PEG-modified gold nanorods with a stealth character for in vivo applications.	J Control Release 114 (3): 343-7.	2006	Gold

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114	NISHIMURA Asako, YANAGAWA Haruna, FUJIKAWA Naoko, SHIBATA Nobuhito (Dep. of Biopharmaceutics, Fac. of Pharmaceutical Sciences, Doshisha Women's Coll. of Liberal Arts), KIRIYAMA Akiko (Dep. of Pharmacokinetics, Fac. of Pharmaceutical Sciences, Doshisha Women's Coll. of Liberal Arts)	Pharmacokinetic Profiles of Coenzyme Q10: Absorption of Three Different Oral Formulations in Rat	J Health Sci , Vol.55, No.4, Page540-548	2009	CoQ10
115	NUKUI Kazuki, MATSUOKA Yuki, YAMAGISHI Toshihiko, SATO Kiyoshi (Nisshin Pharma Inc., Tokyo, JPN), MIYAWAKI Hiromi (Miyawaki Orthopedic Clinic, Hokkaido, JPN	Safety Assessment of PureSorb-Q`TM´40 in Healthy Subjects and Serum Coenzyme Q10 Level in Excessive Dosing	J Nutr Sci Vitaminol Vol.53, No.3, Page198-206	2007	(Literature on excess symptom)
116	Oberdörster G, Stone V, Donaldson K.	Toxicology of nanoparticles: An historical perspective.	Nanotoxicology 1(1):2-25.	2007	
117	Oberdorster, G., Maynard, A., Donaldson, K., Castranova, V., Fitzpatrick, J., Ausman, K., Carter, J., Karn, B., Kreyling, W., Lai, D., Olin, S., Monteiro-Riviere, N., Warheit, D. and Yang, H.	Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy.	Part Fibre Toxicol 2: 8.	2005	
118	Oberdorster, G., Oberdorster, E. and Oberdorster, J.	Nanotoxicology: An emerging discipline evolving from studies of ultrafine particles.	Environmental Health Perspectives 113 (7): 823-839.	2005	
119	Oberdorster, G., Sharp, Z., Atudorei, V., Elder, A., Gelein, R., Lunts, A., Kreyling, W. and Cox, C.	Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation exposure of rats.	J Toxicol Environ Health A 65 (20): 1531-43.	2002	^{13}C (Carbon)
120	Ogawara, K., Yoshida, M,, Higaki, K., Kimura, T., Shiraishi, K., Nishikawa, M,, Takakura, Y. and Hashida, M.	Hepatic uptake of polystyrene microspheres in rats: effect of particle size on intrahepatic distribution.	J Control Release 59(1): 15-22.	1999	Polystyrene

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121	Ogawara, K., Yoshida, M., Furumoto, K., Takakura, Y., Hashida, M., Higaki, K. and Kimura, T.	Uptake by hepatocytes and biliary excretion of intravenously administered polystyrene microspheres in rats.	J Drug Target 7(3):2 13-22 1.	1999	Polystyrene
122	Pante, N. and Kann, M.	Nuclear pore complex is able to transport macromolecules with diameters of about 39 nm.	Mol Biol Cell 13 (2): 425-34.	2002	Gold (coated with nucleoplasmin or BSA)
123	Papageorgiou, I., Brown, C., Schins, R., Singh, S., Newson, R., Davis, S., Fisher, J., Ingham, E. and Case, C. P.	The effect of nano- and micron-sized particles of cobalt-chromium alloy on human fibroblasts in vitro.	Biomaterials 28 (19): 2946-58.	2007	Cobalt-chromium
124	PEHANICH Mike	Small gains in processing, packaging	Food Process 67(11): 46-48	2006	
125	Poland, C., Duffin, R., Kinloch, I., Maynard, A., Wallace, W., Seaton, A., Stone, V., Brown, S., MacNee, W. and Donaldson, K.	Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study.	Nature Nanotechnology: 1-6.	2008	Carbon nanotube
126	Qingrong Huang, Hailong Yu , and Qiaomei Ru	Bioavailability and Delivery of Nutraceuticals Using Nanotechnology	Journal of Food Science, Volume 75 Issue 1, Pages R50 - R57	2009	
127	Rohner F, Ernst FO, Arnold M, Hilbe M, Biebinger R, Ehrensperger F, Pratsinis SE, Langhans W, Hurrell RF, Zimmermann MB.	Synthesis, Characterization, and Bioavailability in Rats of Ferric Phosphate Nanoparticles	J Nutr. 2007 Mar;137(3):614-9.	2006	Ferric pyrophosphate $FePO_4$
128	Russell-Jones, G. J., Arthur, L. and Walker, H.	Vitamin B 12-mediated transport of nanoparticles across Caco-2 cells.	Int J Pharm. 179(2):247-255.	1999	Surface modified with vitamin B_{12}
129	Russell-Jones, G.J., Veitch, H. and Arthur, L.	Lectin-mediated transport of nanoparticles across Caco-2 and OK cells.	lnt J Pharm. 190(2): 165-174.	1999	Surface coated with lectin
130	Sadauskas, E., Wallin, H., Stoltenberg, M,, Vogel, U., Doering, P., Larsen, A. and Danscher, G.	Kupffer cells are central in the removal of nanoparticles from the organism.	Part Fibre. Toxicol 4: 10.	2007	Gold

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131	Sato, Y., Yoltoyarna, A., Shibata, K., Akimoto, Y., Ogino, S., Nodasaka, Y., Kohgo, T., Tamura, K., Akasaka, T., Uo, M., Motomiya, K., Jeyadevan, B., Ishiguro, M., Hatakeyama, R., Watari, F. and Tohji, K.	Influence of length on cytotoxicity of multi-walled carbon nanotubes against human acute monocytic leukemia cell line THP-1 in vitro and subcutaneoustissue of rats in vivo.	Mol Biosyst. l(2): 176-182.	2005	Carbon nanotube
132	SCHULZ Christiane, BERNHARDT Juergen (BioTeSys GmbH, Esslingen, DEU), OBERMUELLER-JEVIC Ute C., HASSELWANDER Oliver (BASF Aktiengesellschaft, Limburgerhof, DEU), BIESALSKI Hans K. (Univ. Hohenheim, Stuttgart, DEU)	Comparison of the relative bioavailability of different coenzyme Q10 formulations with a novel solubilizate (Solu™ Q10)	Int J Food Sci Nutr. 2006 Nov-Dec;57(7-8):546-55.	2006	CoQ10
133	Semmler-Behnke, M., Kreyling, W.G., Lipka, J., Fertsch, S., Wenk, A., Takenaka, S., Schmid, G. and Brandau, W.	Biodistribution of 1.4- and 18-nm gold particles in rats.	Small 4(12):2108-2111.	2008	Gold
134	Semmler-Behnke, M., Takenaka, S., Fertsch, S., Wenk, A., Seitz, J., Mayer, P., Oberdorster, G. and Kreyling, W. G.	Efficient elimination of inhaled nanoparticles from the alveolar region: evidence for interstitial uptake and subsequent reentrainment onto airways epithelium.	Environ Health Perspect 115 (5): 728-33.	2007	Iridium
135	Shi, Y. H. [Reprint Author]; Xu, Z. R.; Feng, J. L.; Wang, C. Z.	Efficacy of modified montmorillonite nanocomposite to reduce the toxicity of aflatoxin in broiler chicks	Animal Feed Science and Technology, (AUG 4 2006) Vol. 129, No. 1-2, pp.138-148.	2006	Montmorillonite
136	Shipley, H.J., Yean, S., Kan, A.T. and Tomson, M.B.	Adsorption of arsenic to magnetite nanoparticles: effect of particle concentration, pH, ionic strength, and temperature.	Envivon. Toxicol. Chem. 28(3):509-515.	2009	Magnetite

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137	Shvedova,A.A., Kisin, E.R., Mercer, R., Murray,A.R., Johnson,V.J., Potapovich,A.I., Tyurina,Y.Y., Gorelik,O.,Arepalli, S., Schwegler-Berry, D., Hubbs,A.F.,Antonini, J., Evans, D.E., Ku, B.-K., Ramsey, D., Maynard,A., Kagan,V.E., Castranova,V., Baron, P.	Unusual inflammatory and fibrogenic pulmonary responses to singlewalled carbon nanotubes in mice.	American Journal of Physiology: Lung Cellular and Molecular Physiology 289, 698-708	2005	Carbon nanotube
138	Simon, P. and Joner, E	Conceivable interactions of biopersistent nanoparticles with food matrix and living systems following from their physicochemical properties.	Journal of Food and Nutrition Research 47 (2): 51-59.	2008	
139	Simon, P., Chaudhry, Q. and Bakos, D.	Migration of engineered nanoparticles from polymer packaging to food - a physicochemical view.	Journal of Food and Nutrition Research 47 (3): 105- 113.	2008	
140	Singh, R., Pantarotto, D., Lacerda, L., Pastorin, G., Klumpp, C., Prato, M., Bianco, A. and Kostarelos, K.	Tissue biodistribution and blood clearance rates of intravenously administered carbon nanotube radiotracers.	Proc. Natl. Acad.Sci U. S A 103(9):3357-3362.	2006	Carbon nanotube
141	Smyth, S.H., Doyle-McCullough, M., Cox, O.T. and Carr, K.E.	Effect of reproductive status on uptake of latex microparticles in rat small intestine.	Life Sci 77(26):3287-3305.	2005	
142	Smyth, S.H., Feldhaus, S., Schumacher, U. and Carr, K.E.	Uptake of inert microparticles in normal and immune deficient mice.	Int J Pharm. 346(1-2): 109- 1 1 8.	2008	Latex
143	Sugibayashi Kenji; Todo Hiroaki; Kimura Eriko	Safety evaluation of titanium dioxide nanoparticles by their absorption and elimination profiles.	The Journal of toxicological sciences, (2008 Aug) Vol. 33, No. 3, pp. 293-8	2008	Titanium oxide
144	Szentkuti, L.	Light microscopical observations on luminally administered dyes, dextrans, nanospheres and microspheres in the pre-epithelial mucus gel layer of the rat distal colon.	J Control Release 46(3):233-242.	1997	Latex

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145	Takagi, A., Hirose, A., Nishimura, T., Fukumori, N., Ogata, A., Ohashi, N., Kitajima, S. and Kanno, J.	Induction of mesothelioma in p53+/mouse by intraperitoneal application of multi-wall carbon nanotube.	J Toxicol Sci 33 (1): 105-16.	2008	Carbon nanotube
146	TAKAHASHI Makoto (Kagoshima Univ.)	Characterization and Bioavailability of Liposomes Containing a Ukon Extract	Bioscience, Biotechnology, and Biochemistry 72(5) pp.1199-1205 2008	2009	Curcumin
147	Taylor,T.M., Davidson, P.M., Bruce, B.D., and Weiss, J.	Liposomal Nanocapsules in Food Science and Agriculture	Crit. Rev. Food Sci. Nutr. 45, 1-19	2005	
148	The Danish Strategic Research Council (Denmark)	Biopolymer Nanocomposite Films for use in Food Packaging Applications	OECD Budget Database on Nano Risk Research, EmergeNano(2009) (project)	2007-2010	
149	Tiede Karen; Boxall Alistair B A; Tear Steven P; Lewis John; David Helen; Hassellov Martin	Detection and characterization of engineered nanoparticles in food and the environment	Food additives & contaminants. Part A, Chemistry, analysis, control, exposure & risk assessment, (2008 Jul) Vol. 25, No. 7, pp. 795-821. Ref:213	2008	
150	TIWARI Rashmi (Rutgers Univ., NJ)	The Hurdles of Using Nanodelivery Vehicles for Nutraceuticals	Cereal Foods World, 53, 3, 152-154, 2008.05	2008	
151	Tsuchiya, T., Oguri, I., Yamakoshi, Y .N. and Miyata, N.	Novel harmful effects of [60]fullerene on mouse embryos in vitro and in vivo.	FEBS Lett 393 (1): 139-145.	1996	Fullerene
152	Uchida T; Serizawa T; Ise H; Akaike T; Akashi M	Graft copolymer having hydrophobic backbone and hydrophilic branches. 33. Interaction of hepatocytes and polystyrene nanospheres having lactose-immobilized hydrophilic polymers on their surfaces.	Biomacromolecules, (2001 Winter) Vol. 2, No. 4, pp. 1343-6.	2001	
153	USDA (U.S.)	Application Of Nanotechnology, Antimicrobial, And Polymer Films In Food Safety And Quality	OECD Budget Database on Nano Risk Research (project)	2003-2008	

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154	USEPA/USDA	Increasing Scientific Data on the Fate, Transport and Behavior of Engineered Nanomaterials in Selected Environmental and Biological Matrices	USEPA/USDA (project)	2009-	
155	Valdes, Mayra Granda; Valdes Gonzalez, Aristides Camilo; Garcia Calzon, Josefa Angela; Diaz-Garcia, Marta Elena	Analytical nanotechnology for food analysis	Microchimica Acta, (2009) Vol. 166, No. 1-2, pp. 1-19	2009	
156	van Hasselt, P.M., Jailssens, G.E., Slot, T.K., van der Ham, M., Minderhoud, T.C., Talelli, M., Akkermans, L.M., Rijcken, C. J. and van Nostrum, C.F.	The influence of bile acids on the oral bioavailability of vitamin K encapsulated in polymeric micelles.	J. Control Release 133(2):161-168.	2009	Vitamin K
157	Vernikov V M; Arianova E A; Gmoshinskii I V; Khotimchenko S A; Tutel'ian V A	Nanotechnology in food production: advances and problems.	Voprosy pitaniia, (2009) Vol. 78, No. 2, pp. 4-17.	2009	
158	Volkheimer, G.	Hematogenous dissemination of ingested polyvinyl chloride particles.	Ann N YAcad.Sci 246: 164-1 71.	1975	Polyvinyl chloride, Irish potato starch
159	Wajda, R., Zirkel, J. and Schaffer, T.	Increase of bioavailability of coenzyme Q(10) and vitamin E	J. Med. Food 10(4):73 1-734.	2007	CoQ10, Vitamin E
160	Wang Yanbo	Differential effects of sodium selenite and nano-Se on growth performance, tissue se distribution, and glutathione peroxidase activity of avian broiler.	Biological trace element research, (2009 May) Vol.128, No. 2, pp. 184-90.	2009	Selenium
161	Wang, B., Feng, W. Y., Wang, M., Wang, T. C., Gu, Y. Q., Zhu, M. T., Ouyang, H., Shi, J. W., Zhang, F., Zhao, Y. L., Chai, Z. F., Wang, H. F. and Wang, J.	Acute toxicological impact of nano- and submicro-scaled zinc oxide powder on healthy adult mice.	Journal Of Nanoparticle Research 10 (2): 263-276.	2008	Zinc oxide
162	Wang, B., Feng, W. Y., Wang, T. C., Jia, G., Wang, M., Shi, J. W., Zhang, F., Zhao, Y. L. and Chai, Z. F.	Acute toxicity of nano- and micro-scale zinc powder in healthy adult mice.	Toxicol Lett 161 (2): 115-23.	2006	Zinc

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
163	Wang, B., Zhang, L., Bae, S.C. and Granick, S.	Nanoparticle-induced surface reconstruction of phospholipid membranes.	Proc. NatL Acad. Sci. U. S. A 105(47): 18171-18175.	2008	
164	Wang, J., Zhou, G., Chen, C., Yu, H., Wang, T., Ma, Y., Jia, G., Gao, Y., Li, B., Sun, J., Li, Y., Jiao, F., Zhao, Y. and Chai, Z.	Acute toxicity and biodistribution of different sized titanium dioxide particles in mice after oral administration.	Toxicol Lett 168 (2): 176-85.	2007	Titanium oxide
165	Wegmüller R, Zimmermann MB, Moretti D, Arnold M, Langhans W, Hurrell RF.	Particle Size Reduction and Encapsulation Affect the Bioavailability of Ferric Pyrophosphate in Rats	J Nutr. 2004 Dec; 134(12):3301-4.	2004	Ferric pyrophosphate
166	Weiss, J.,Takhistov, P., McClements. J.	Functional materials in food nanotechnology.	J Food Sci 71(9), R107-R116	2006	
167	Werner I. Hagensa, Agnes G. Oomena, Wim H. de Jongb, Flemming R. Casseec and Adriënne J.A.M. Sipsa	What do we (need to) know about the kinetic properties of nanoparticles in the body?	Regulatory Toxicology and Pharmacology, Volume 49, Issue 3, December 2007, Pages 217-229	2007	
168	Xia, T., Kovochich, M., Brant, J., Hotze, M., Sempf, J., Oberley, T., Sioutas, C., Yeh, J. I., Wiesner, M. R. and Nel, A. E.	Comparison of the abilities of ambient and manufactured nanoparticles to induce cellular toxicity according to an oxidative stress paradigm.	Nano Lett 6 (8): 1794-807.	2006	Titanium oxide, carbon black, fullerene, polystyrene
169	Xia, T., Kovochich, M., Liong, M., Zink, J.I. and Nel, A.E.	Cationic polystyrene nanosphere toxicity depends on cell-specific endocytic and mitochondrial injury pathways.	ACS Nano. 2(1): 85-96.	2008	Polystyrene
170	Yamago, S.,Tokuyama, H., Nakamura, E., Kikuchi, K., Kananishi, S., Sueki, K., Nakahara, H., Enomoto, S.,Ambe, F.	In vivo biological behavior of a water-miscible fullerene: 14C labeling, absorption, distribution, excretion and acute toxicity.	Chem Biol. 2(6), 385-9	1995	Fullerene
171	Yoksan, R. and Chirachanchai, S.	Amphiphilic chitosan nanosphere: studies on formation, toxicity, and guest molecule incorporation.	Bioorg Med Chem 16 (5): 2687-96.	2008	Chitosan

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
172	Yu Chiun-Chieh; Wang Jyh-Jye; Lee Chun-Lin; Lee Shu-Hui; Pan Tzu-Ming	Safety and mutagenicity evaluation of nanoparticulate red mold rice	Journal of agricultural and food chemistry, (2008 Nov 26) Vol. 56, No. 22, pp. 11038-48.	2008	Red yeast rice
173	Zhang, G., Yang, Z., Lu, W., Zhang, R., Huang, Q., Tian, M., Li, L., Liang, D. and Li, C.	Influence of anchoring ligands and particle size on the colloidal stability and in vivo biodistribution of polyethylene glycol-coated gold nanoparticles in tumor-xenografted mice.	Biomaterials 30(10): 1928- 1936.	2009	Gold (coated with PEG)
174	Zhang, J., Wang, H., Yan, X. and Zhang, L.	Comparison of short-term toxicity between Nano-Se and selenite in mice.	Life Sci 76 (10): 1099-109.	2005	Selenium
175	Zhang, K., Fang, H., Chen, Z., Taylor, J.S. and Wooley, K.L.	Shape Effects of Nanoparticles Conjugated with Cell-Penetrating Peptides (HIV Tat PTD) on CHO Cell Uptake	Bioconjug. Chem 19(9): 1 880- 1887.	2008	
176	Zolnik Banu S; Sadrieh Nakissa	Regulatory perspective on the importance of ADME assessment of nanoscale material containing drugs	Advanced drug delivery reviews, (2009 Jun 21) Vol. 61, No. 6, pp. 422-7.	2009	
177	Shigeru Ishida, Yuichi Tsuda, Kazuhisa Hatayama, Yuko Yamaguchi, Minenobu Okayama, , Masami Hattori (Bozo Research Center Inc., Apt Corp.)	Toxicity test of Apt 231 – Repeated oral toxicity test over 13 weeks using rats	Pharmacogenetics and medical treatment (Jpn Pharmacol Ther), vol.35 no.12, 1227-1240 (2007)	2007	Platinum nanocolloid

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
178	Yasuhiro Abe 1,Tomoaki Yoshikawa 1,2, Hiromi Nabeshi 1,2, Keigo Matsuyama 1,2, Sayuri Kondo 1,2, Kazuya Nagano 1, Yasuo Yoshioka 1,3, Takayoshi Imazawa 1, Shin-ichi Tsunoda 1,3, Yasuo Tsutsumi 1,2,3 (1 National Institute of Biomedical Innovation, 2 Graduate School of Pharmaceutical Sciences, Osaka University, 3 MEI Center, Osaka University)	Toward ensuring safety of nanomaterials - 3 Intracellular dynamic state of nanomaterials and genotoxicity	List of academic lectures, Japanese Society for Food Hygiene and Safety Vol.98th, Page 93	2009	Silica
179	Masaaki Oka*1,2, Isao Makino*1,3, Tadao Baba*1,4, Yasuyuki Arakawa *1,5, Hiroshi Atomi*1,6, Teruaki Matsui*1,5, Tetsuya Suga*1,7, Saburo Nakazawa*1,8 (*1 “The Food and Medicine Study Group on Gastroenterology”, Study Group under The Japanese Society of Geneatric Gastroenterogy,*2 Dept. Digestive Surgery and Surgical Oncology, Yamaguchi University Graduate School of Medicine,*3 Hokushinkai Megumino Hospital, *4 Shiga University of Medical Science, *5 Nihon University Itabashi Hospital, *6 Kyorin University Hospital, *7 Pharmaceutical Business Division, Ajinomoto Co., Inc., *8 Yamashita Hospital)	Studies on Safety and Benefits of Particulated Lentinan (β-1,3-glucan)-Containing Food Products for Patients with Cancer – Coordinated National Multicenter Protocol Study -	BIOTHERAPY, 20(6): 590-606, 2006.	2006	β-glucan

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
180	Shin-ichi Tsunoda 1,2,3, Tomoaki Yoshikawa 1,2, Hiromi Nabeshi 1,2, Takanori Akase 1,2, Kazuya Nagano 1, Yasuhiro Abe 1, Yasuo Yoshioka 1,3, Takayoshi Imazawa 1, Yohei Mukai 1,2, Naoki Okada 2, Shinsaku Nakagawa 2,3, Yasuo Tsutsumi 1,2,3 (1 National Institute of Biomedical Innovation, 2 Graduate School of Pharmaceutical Sciences, Osaka University, 3 MEI Center, Osaka University)	Toward ensuring safety of nanomaterials -1 Percutaneous absorbability/disposition and acute toxicity/liver toxicity of nanomaterials	List of academic lectures, Japanese Society for Food Hygiene and Safety Vol.98th, Page 91	2009	Silica
181	Masayoshi Kajita, Mio Kato (Kajita Eye Clinic), Hiroki Tsukahara (Fuji Chemical Industry Co., Ltd.), Tanihiro Yoshimoto (Department of Molecular Pharmacology, Graduate School of Medical Science, Kanazawa University)	Safety of the excessive ingestion of astaxanthin	Journal of Clinical Therapeutics and Medicine Vol.25, No.8, Page 691-698	2009	(Literature on excess symptom)
182	Yasuo Yoshioka 1,2,3, Tomohiro Morishige 2, Hiroshi Inekura 2, Tokuyuki Yoshida 2,3, Maho Fujimura 2,3, Hiromi Nabeshi 2,3, Yasuhiro Abe 3,Kazuya Nagano 3, Tomoaki Yoshikawa 2,3, Takayoshi Imazawa 3, Shin-ichi Tsunoda 1,3, Yohei Mukai 2,Naoki Okada 2,Yasuo Tsutsumi 1,2,3, Shinsaku Nakagawa 1,2 (1 MEI Center, Osaka University, 2 Graduate School of Pharmaceutical Sciences, Osaka University, 3 National Institute of Biomedical Innovation)	Toward ensuring safety of nanomaterials - 4 Dynamical feature and immunotoxicity of nanomaterials	List of academic lectures, Japanese Society for Food Hygiene and Safety Vol.98th, Page 94	2009	Silica

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
183	Tomoaki Yoshikawa 1,2, Hiromi Nabeshi 1,2, Toshiro Hirai 1,2, Kazuya Nagano 2, Yasuhiro Abe 2, Yasuo Yoshioka 2,3, Shin-ichi Tsunoda 2,3, Masao Kondo 1, Kiyohito Yagi 1, Yasuo Tsutsumi 1,2,3 (1 Graduate School of Pharmaceutical Sciences, Osaka University, 2 National Institute of Biomedical Innovation, 3 MEI Center, Osaka University)	Toward ensuring safety of nanomaterials - 2 Interaction analysis and study on acute toxicity/liver toxicity formation mechanism of nanomaterials	List of academic lectures, Japanese Society for Food Hygiene and Safety Vol.98th, Page 92	2009	Silica
184	Tadakazu Tamai, Itsuki Murota, Takashi Baba, Yoshikazu Sato (Central Research Institute ,Maruha Nichiro Holdings, Inc.), Tatsuya Tsuzuku (Fuji Biomedix Co., Ltd.), Yoshio Ohashi (Kohokai Tokyo Ekimae-building Clinic), Hitomi Nagaoka (Fuji Clinical Support Co., Ltd.)	Effects of Fish Hamburger Enriched with Docosahexaenoic Acid and Eicosapentaenoic Acid on Serum Lipids in Clinical Trials of Intake for Three Months, and Safety Evaluation of Excessive Intake	Japanese Pharmacology and Therapeutics Vol.36, No.4, Page 333-345	2008	(Literature on excess symptom)
185	Tadakazu Tamai , Itsuki Murota , Takashi Baba, Nozomi Hiura, Yoshikazu Sato (Central Research Institute, Maruha Nichiro Holdings, Inc.), Ken-ichi Shionoya (Seikokai Clinic), Hironari Sano (Maruha Otemachi Clinic), Hideyuki Ikematsu (Clinical Study Division, Haradoi Hospital), Hideki Nozaki (Nozaki Clinic)	Effect of Fish Sausage Enriched with DHA (docosahexaenoic acid) on Serum Lipids (I) : Determination of Effective dose of Docosahexaenoic Acid, and Safety Evaluation of Excessive Intake	Journal of Japanese Society of Clinical Nutrition Vol.25, No.4, Page 293-302	2004	(Literature on excess symptom)
186	Naoki Takaishi, Katsuyuki Mukai (Yunitika), Makoto Shimizu (the University of Tokyo)	Mechanisms for the Intestinal Absorption of Emulsified β-cryptoxanthin	Food Style 21 Vol.11, No.11, Page 35-39	2007	β-cryptoxanthin
187	Keiji Terao (CycloChem)	Safety Assessment of Cyclodextrin and Functionality Being Clarified (Part One)	Food and Development, Vol.38, No.9, p70-73	2003	Cyclodextrin

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188	Masaki Akino, Koji Ebitani, Takuma Imamura (Fisheries Experiment Station of Abashiri, Hokkaido), Tomoyuki Uchiyama, Keiichiro Matsusima (Industrial Experiment Station of Hokkaido), Hiroshi Hara (Hokkaido University Graduate School of Agriculture)	Effects of Salmon Bone Processing Methods on Intestinal Calcium Absorption in Rats	Journal of the Japanese Society for Food Science and Technology, 56, 3, 155-162, 2009.03.15	2009	Middle bone of salmon
189	Manabu Ogawa, Masao Sato, Keiichi Suzuki (Life Science Systems, Fujifilm Corp.)	Development of Astaxanthin Nano Emulsion with Improved Shelf Life and Enhanced Absorbability	FUJIFILM RESEARCH & DEVELOPMENT, No.52: 26-29	2007	Astaxanthin
190	Yasuteru Odagiri*1, Orie Yokoi*1, Hajime Sui*2, Koji Yamakage*2, Tetsuya Suga*3, Tsuyoshi Masuyama*1 (*1 Pharmaceutical Research Laboratories, Ajinomoto Co., Inc., *2 Hatano Research Institute, Food and Drug Safety Center, *3 Pharmaceutical Business Division, Ajinomoto Co., Inc.)	Genotoxicity Test- Reverse Mutation Test, Chromosomal Aberration Test and Micronucleus Test Using Particulated Lentinan (β-1,3-glucan)-Containing Food Products	BIOTHERAPY, 20(6) : 557-567, 2006.	2006	β-glucan
191	Yasuteru Odagiri*1, Tsuyoshi Masuyama*1, Kazuo Oishi*2, Tetsuya Suga*3, Kuninobu Yasuda*4 (*1 Pharmaceutical Research Laboratories, Ajinomoto Co., Inc., *2 Clinical Development Division, Ajinomoto Co., Inc., *3 Pharmaceutical Business Division, Ajinomoto Co., Inc., *4 Kannnonndai Clinic, Medical Corporation of Yakugawakai)	Safety Assessment of Particulated Lentinan (β-1,3-glucan)-Containing Food Products Repeated Dose Test on Healthy Adults	BIOTHERAPY, 20(6) : 578-589, 2006	2006	β-glucan

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
192	Yasuteru Odagiri *1, Nobuaki Watari *2, Tetsuya Suga *3, Tsuyoshi Masuyama *1 (*1 Pharmaceutical Research Laboratories, Ajinomoto Co., Inc., *2 Biosafety Research Center Foods, Drugs and Pesticides, *3 Pharmaceutical Business Division, Ajinomoto Co., Inc.)	Repeated Dose Test of Particulated Lentinan (β-1,3-glucan)-Containing Food Products in Drinking Water over 4 Weeks Using Rats	BIOTHERAPY, 20(6) : 568-577, 2006	2006	β-glucan
193	Ogami Kazuhiro, Kenji Shiratori, Takuya Nitta, Yasuhiro Shinmei, Chin-Hui Chen, Kazuhiko Yoshida, Shigeaki Ohno (Department of Ophthalmology, Graduate School of Medicine, Hokkaido University), Hiroki Tsukahara (Fuji Chemical Industry Co., Ltd.)	Study on the Safety of High Dose Administration of Astaxanthin	Journal of Clinical Therapeutics and Medicine Vol.21, No.6, Page 651-659	2005	(Literature on excess symptom)
194	Kazuya Nagano 1, Yasuo Yoshioka 1,3, Kohei Yamashita 1,2, Kazuma Higashisaka 1,2, Yuki Morishita 1,2, Hiromi Nabeshi 1,2, Yasuhiro Abe 1, Tomoaki Yoshikawa 1,2, Shin-ichi Tsunoda 1,2,3, Shigeru Saito 5, Yuichi Kawai 4, Tadanori Mayumi 4, Yasuo Tsutsumi 1,2,3 (1 National Institute of Biomedical Innovation, 2 Graduate School of Pharmaceutical Sciences, Osaka University, 3 MEI Center, Osaka University, 4 Graduate School of Pharmaceutical Sciences, Kobe Gakuin University, 5 Graduate School of Medical Pharmaceutics, Toyama University)	Toward ensuring safety of nanomaterials - 5 Dynamical feature and reproductive development toxicity of nanomaterials	List of academic lectures, Japanese Society for Food Hygiene and Safety Vol.98th, Page 95	2009	Silica

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
195	Hiromi Nabeshi, Tomoaki Yoshikawa, Yasutaro Nakazato, Keigo Matsuyama, Norio Ito, Yasuo Tsutsumi (Graduate School of Pharmaceutical Sciences, Osaka University), Yasuhiro Abe, Shin-ichi Tsunoda (National Institute of Biomedical Innovation), Tadanori Mayumi (Graduate School of Pharmaceutical Sciences, Kobe Gakuin University), Yasuo Yoshioka (MEI Center, Osaka University)	Association analysis of solid-state properties and bioinfluence of nano-silica as a food additive	List of academic lectures, Japanese Society for Food Hygiene and Safety, 97th, , 40, 2009.04.20	2009	Silica
196	Hiromi Nabeshi 1,2, Tomoaki Yoshikawa 1,2, Yasutaro Nakazato 1,2, Saeko Tochigi 1,2, Kazuya Nagano 1, Yasuhiro Abe 1, Yasuo Yoshioka 1,3, Takayoshi Imazawa 1,2, Shin-ichi Tsunoda 1,3, Yasuo Tsutsumi 1,2,3 (1 National Institute of Biomedical Innovation, 2 Graduate School of Pharmaceutical Sciences, Osaka University, 3 MEI Center, Osaka University)	Toward ensuring safety of nanomaterials - 6 Safety assessment of surface-modified nano-silica and development assistance for safe nanomaterials	List of academic lectures, Japanese Society for Food Hygiene and Safety Vol.98th, Page 162	2009	Silica
197	Hironobu Nanbu (Taiyo Kagaku Co., Ltd.)	“Health Depends on Medicine and Diet”—The current status and future of functional food — absorbability and bioavailability of particulated disperse ferric pyrophosphate	Journal of Chemical Engineering of Japan, vol 68, 9th issue, 481-483. 2004	2004	Ferric pyrophosphate
198	Hironobu Nanbu (Taiyo Kagaku Co., Ltd.)	Development of Water-Dispersible/Absorbable Iron Supplement Materials	Science & Industry, 77, 5, 240-246, 2003.05.20	2003	Ferric pyrophosphate

No.	Author	Title	Bibliographic information	Publication year	Nano-substance to be assessed
199	Mikihiko Hattori (Shinagawa Seaside Central Clinic), Minenobu Okayama, Masami Hattori (Apt Corp.), Arimasa Miyamoto (Graduate School of Frontier Sciences, the University of Tokyo)	Studies on Safety and Influence of Repeated Dose of Platinum Nano-Colloids (CPt) for 2 Weeks	Excerpts of the Program, General Meeting of Japanese Society of Anti-Aging Medicine, Vol.8th, p.202 (2008)	2008	Platinum nanocolloid
200	Yoshinobu Kiso (Institute for Health Care Science, Suntory Ltd.)	Essentiality and excess symptoms of n-6 fatty acid – essentility of arachidonic acid in particular–	Lipid Nutrition Vol.16, No.2, Page145	2007	(Literature on excess symptom)

This report summarizes the results of “A Basic Survey Report on Safety Assessment Information on the Use of Nanotechnology in the Food Sector” conducted by Toray Research Center as “A Comprehensive Study for Ensuring Food Safety under the Cabinet Office Food Safety Commission (FY 2009).” Therefore, reproduction, reprinting, quotation, etc. of this report needs approval from the secretariat of the Cabinet Office Food Safety Commission.