

**State of the art on the initiatives and activities
relevant to risk assessment and risk management of
nanotechnologies
in the food and agriculture sectors**

Draft Version for Public Review

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Food and Agriculture
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1. Background

2 An international expert meeting on the potential food safety implications of the application of
3 nanotechnologies in the food and agriculture sectors was convened by the Food and Agriculture
4 Organization of the United Nations (FAO) and the World Health Organization (WHO) in June 2009.
5 The key findings, conclusions and recommendations of the meeting were published in 2010
6 (FAO/WHO, 2010) and are briefly summarized in section 1b below.

7 a. Methodology

8 This report was commissioned by FAO and WHO with the objective of summarizing and analysing
9 the information that has become available since the 2009 expert meeting and determining possible
10 courses of action to be followed by FAO and WHO in this matter.

11 Following up on one of the recommendations of the 2009 FAO/WHO expert meeting, the present
12 report reviews national and international activities on the risk analysis of nanomaterials in the food
13 and agriculture sectors that have been carried out since the meeting. It presents national and
14 international risk assessment and risk management approaches that identify and implement strategies
15 to address potential hazards associated with the use of nanotechnology-related products or techniques.

16 Information on relevant regulations and risk assessment activities was gathered from the web sites of
17 national and international institutions, organizations and governments. Specific reference to these web
18 sites is given in the respective sections of this report. It should be noted that terms used in this report
19 reflect the definitions applied within the various sources of information; no attempt was made to align
20 the terminology with definitions agreed to by the 2009 expert meeting or other definitions applied
21 internationally—for example, by the Codex Alimentarius Commission.

22 Information on actual and planned uses of nanomaterials resulting in human exposure through food or
23 food packaging/contact materials since 2009 was collected from a variety of sources, including the
24 scientific literature, web sites, patent databases, market analysis reports and material presented at
25 conferences, workshops and symposia.

26 b. Summary of the FAO/WHO expert meeting in 2009

27 *Use of nanotechnology*

28 The expert meeting agreed that nanotechnology offers considerable opportunities for the development
29 of innovative products and applications for agriculture, water treatment and food production,
30 processing, preservation and packaging, and its use may benefit farmers, the food industry and
31 consumers alike. It was noted that nanotechnology-derived food products will be increasingly
32 available to consumers worldwide.

33 It was recognized that there was a need for clear and internationally recognized definitions and that
34 gaps in definitions in the food area could be addressed by the Codex Alimentarius Commission.

35 *Assessment of human health risks*

36 Materials that are produced intentionally with structural features at a nanoscale range (between 1 and
37 100 nm) may have properties that are different from those of their conventional counterparts. Such
38 differences may have an impact on human health following consumer exposure to nanomaterials.

39 Current risk assessment approaches used by FAO, WHO and the Codex Alimentarius Commission
40 were considered to be suitable for engineered nanomaterials used in food and agriculture. Additional
41 safety concerns may arise owing to the characteristic properties of nanomaterials that make them
42 different from their microscale/macroscale counterparts. For example, the very high surface area of
43 engineered nanomaterials has consequences that need to be considered in their risk assessment.
44 Nanoparticles may interact with other substances present in the food matrix, and such effects and
45 interactions of engineered nanomaterials need to be characterized. Understanding their fate in the
46 environment is also important, as it may result in indirect human exposure.

47 The experts agreed that risk assessment strategies might benefit from the use of a tiered approach for
48 prioritization of the types or classes of material for which additional data are likely to be necessary to
49 reduce uncertainties in the risk assessment. Further research could lead to novel risk assessment
50 strategies; the development of validated testing methods and guidance would help to address specific
51 data gaps.

52 *Stakeholder confidence and dialogue*

53 Engagement of stakeholders was acknowledged as imperative for any emerging or controversial issue
54 in the area of food safety. Critical to the success of a research strategy for nanomaterials would be
55 addressing the key interests, priorities and concerns of stakeholders and ensuring that all potential
56 pathways and risks are addressed.

57 Consumer attitudes towards the application of nanotechnology in food and agriculture were seen as
58 complex; consumer understanding of the potential risks and clear, tangible benefits of nanotechnology
59 was key. It was noted that advocacy groups had expressed the desire for industry and governments to
60 implement measures to protect consumers from the consequences of the unregulated release of
61 commercial nanoproducts.

62 Greater access of scientists to the public debate was needed. A forum for continued international
63 dialogue to develop strategies to address stakeholder issues was proposed, and it was noted that the
64 public should be engaged at the national level. Also, the existing FAO/WHO food safety risk analysis
65 framework might be reviewed in particular with regard to engaging stakeholders. Mechanisms should
66 be identified to support the need for transparency and traceability of nano-enabled products or
67 engineered nanomaterials in food and agriculture and their associated risks.

68 **2. Application of nanomaterials in food: current status**

69 Food can be cultivated, produced, processed or packaged with nanotechnology, or engineered
70 nanomaterials can be added to food. The list of current and projected nanotechnology applications in
71 the food and agriculture sectors in Appendix 4 of the report from the FAO/WHO expert meeting
72 (FAO/WHO, 2010) was found to be accurate and up to date.

73 Within the period 2009–2011, 183 patents were published that contain the keywords “nano* AND
74 food*” in the patent title (<http://wokinfor.com/>, accessed 2 January 2012). Among these patents, 47
75 related to packaging or coating applications. Furthermore, 19 patents concerned nano-additives, and
76 10 patents covered nanotechnology applications for the detection of compounds in food.

77 Examples of nanomaterials in food and beverages, for food storage and for food preparation on the
78 United States market can be found on the web site of the Project on Emerging Nanotechnologies of
79 the Woodrow Wilson International Center for Scholars (<http://www.nanotechproject.org/>). A report
80 from the European Consumer Voice in Standardisation and the European Consumers’ Organisation
81 contains several lists of consumer products, among them food supplements, that claim to contain
82 nanomaterials (ANEC/BEUC, 2009).

83 In general, more research on the application of nanomaterials in food is expected. In particular,
84 research on nanoemulsion will increase because of the transfer from parallel efforts in the drug
85 delivery sector (ObservatoryNANO, 2010). However, there are some barriers to commercialization
86 for nanoemulsions. First, suitable food-grade ingredients must be identified for formulating food
87 nanoemulsions. Second, many of the approaches that have been developed within research
88 laboratories may not be suitable for scale-up to industrial production; suitable processing operations
89 must be identified for economic production of food-grade nanoemulsions on an industrial scale. Third,
90 as nanodroplets may have an enhanced bioavailability, in vivo evaluation of nanoemulsion droplets is
91 required; however, such studies are limited (McClements & Jiajia, 2011).

92 With respect to the use of nanotechnology, it is important to consider all areas potentially associated
93 with food safety; such areas may to a certain extent go beyond the borders of traditional activities.

94 One specific area of interest is the use of nanomaterials in wastewater treatment to improve the
95 quality and safety of water used for agriculture, aquaculture and human consumption. It might be
96 possible to develop, for example, low-cost nanofilter/nanomembrane materials that could be of
97 interest to developing countries. However, such new materials and uses may pose safety issues not
98 related to food safety, such as their disposal at the end of their life cycle (FAO/WHO, 2012).

99 For animal health, the development of so-called “nanovaccines” with improved delivery routes to
100 target animals of small size in aquaculture (e.g. fish larvae, shrimp) could be of benefit from a cost
101 and animal welfare point of view. However, research seems to be in an early conceptual stage; no
102 information is available on already ongoing technical projects (FAO/WHO, 2012). Testing kits to
103 identify animal or zoonotic pathogens and nanoscale drug delivery routes have been identified as
104 application areas of potential benefit for animal husbandry in developing countries (FAO/WHO,
105 2012).

106 Technological solutions using nanotechnology in packaging to reduce food losses or facilitate
107 traceability could be of interest (FAO/WHO, 2012).

108 The future use of nanomaterials, especially for industrial purposes, has recently raised specific
109 concerns regarding their disposal at the end of their life cycle. Such materials may not be degradable
110 and may persist in the environment. This is already causing concern in developing countries to which
111 such waste may be exported (FAO/WHO, 2012).

112 3. Relevant activities at the national/regional level since 2009

113 This section briefly summarizes national and regional initiatives and activities related to the risk
114 assessment and risk management of nanomaterials, such as research projects, development of
115 guidance documents and drafting of regulations, that have been carried out since the FAO/WHO
116 expert meeting in 2009. Emphasis is placed on issues that contribute to the definition of the term
117 “nanomaterials” (to be subjected to specific risk assessments) and case-studies where a risk
118 assessment has been undertaken for a defined material.

119 One needs to keep in mind that these national and regional initiatives were not undertaken in a
120 regulatory or scientific vacuum. The countries concerned usually have regulatory frameworks in place
121 that deal with food safety and consumer protection, such as risk assessments for food chemicals,
122 product labelling and market access authorization. The absence of legislation dealing specifically with
123 nanomaterials used in foods does not mean that such products fall into a regulatory gap. Modern food
124 legislation regulates many issues related to, for example, consumer health, consumers’ right to
125 information, fair trade practices and the environment, many of which may be applied to
126 nanotechnology and nanomaterials used in foods.

127 a. Australia/New Zealand

128 *Risk management*

129 All food supplied in Australia and New Zealand must comply with the Australia New Zealand Food
130 Standards Code and be safe for human consumption. Any new food substances manufactured using
131 nanotechnologies that may present safety concerns will have to undergo a comprehensive scientific
132 safety assessment under the appropriate standard before they can be legally supplied in Australia and
133 New Zealand (FSANZ, 2011).

134 Food Standards Australia New Zealand (FSANZ) recently published an article describing its
135 regulatory approach to nanoscale materials in the *International Food Risk Analysis Journal* (Fletcher
136 & Bartholomaeus, 2011). The primary focus is not on the size of the material per se, but on materials
137 likely to exhibit physicochemical and/or biological novelty. FSANZ differentiates between nanoscale
138 materials that undergo dissolution in water or oil in the final food or in the gastrointestinal tract and
139 nanoscale or microscale materials that are insoluble in water and oil and non-biodegradable,
140 particularly those that may not be readily excreted. The latter type of material may require additional
141 regulatory examination due to its particulate nature.

142 *Risk assessment*

143 FSANZ has not yet received any applications to approve any novel type of engineered nanoscale
144 particles for food use. Therefore, no risk assessments have been undertaken.

145 b. Brazil

146 On 9 August 2011, experts from the Brazilian Competitiveness Forum on Nanotechnology met in São
147 Paulo to address the issue of regulating nanotechnology for the industrial sector (NIA, 2011). The
148 meeting was attended by representatives of the working groups of the forum, who discussed a study

149 funded by the Brazilian Agency for Industrial Development on the development of possible standards,
150 laws and guidelines for nanotechnology regulation in Brazil (ABDI, 2010).

151 **c. Canada**

152 *Risk management*

153 Regulations in Canada make no explicit reference to nanomaterial at this time. Health Canada helps
154 protect and promote health by using existing legislative and regulatory frameworks to mitigate the
155 potential health risks of nanomaterials and to help realize their health benefits.

156 Health Canada considers any manufactured substance or product and any component material,
157 ingredient, device or structure to be a nanomaterial if it is at or within the nanoscale in at least one
158 external dimension or has internal or surface structure at the nanoscale; or it is smaller or larger than
159 the nanoscale in all dimensions and exhibits one or more nanoscale properties/phenomena (Health
160 Canada, 2011).

161 Health Canada encourages stakeholders to communicate with the responsible regulatory authority
162 early in the development process, especially for combination products that are, contain or make use of
163 nanomaterials. In order to identify and assess potential risks and benefits of nanotechnology-based
164 health and food products, Health Canada encourages manufacturers to request a pre-submission
165 meeting with the responsible regulatory authority to discuss the type of information that may be
166 required for their product's safety assessment.

167 **d. China**

168 *Risk management*

169 In China, a general Food Safety Law came into effect on 1 June 2009 (Food Safety Law of China,
170 2009). According to this law, risk assessment has to be conducted by the Ministry of Agriculture and
171 the Ministry of Health (Articles 4–17) (Poto, 2011). The law will enhance monitoring and supervision
172 and strengthen safety standards (Qian et al., 2011). The law does not contain any legislation relating
173 to nanomaterials (Food Safety Law of China, 2009). Until now, applications for using nanominerals
174 or food ingredients have been rejected by regulatory authorities, but the safety evaluation of
175 nanotechnology in foods continues to be discussed.

176 **e. European Union**

177 *Risk management*

178 Regarding the definition of nanomaterials, the Scientific Committee on Emerging and Newly
179 Identified Health Risks published the opinion “Scientific basis for the definition of the term
180 nanomaterial” in 2010 (SCENIHR, 2010). Based on this, the European Commission adopted the
181 following recommendation on the definition of nanomaterial in 2011 (EC, 2011):

182 “Nanomaterial” means a natural, incidental or manufactured material containing particles, in an
183 unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in
184 the number size distribution, one or more external dimensions is in the size range 1 nm–100 nm.

185 The European Commission recommends that this definition, which is complemented by further
186 definitions for terms used, such as aggregate, be used as a reference to determine whether a material is
187 considered as a nanomaterial for legislative and policy purposes in the European Union.

188 The European Union action plan on nanotechnologies for the next few years is currently under
189 preparation. Results from the public consultation launched to support the preparation of the new
190 action plan are available in a summary paper (EC, 2010). Responses were received from the general
191 public, individual researchers, research organizations, industry, public authorities and
192 nongovernmental organizations.

193 Very recently adopted new legislation that regulates food information also addresses the presence of
194 engineered nanomaterials in foods (EU, 2011). Article 18 of Regulation (EU) No. 1169/2011 states
195 that “All ingredients present in the form of engineered nanomaterials shall be clearly indicated in the
196 list of ingredients. The names of such ingredients shall be followed by the word ‘nano’ in brackets”
197 (EU, 2011). This regulation is going to apply from 13 December 2014. It also provides, for food, a
198 legal definition of an “engineered nanomaterial”, which

199 means any intentionally produced material that has one or more dimensions of the order of 100 nm or
200 less or that is composed of discrete functional parts, either internally or at the surface, many of which
201 have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or
202 aggregates, which may have a size above the order of 100 nm but retain properties that are
203 characteristic of the nanoscale.

204 Properties that are characteristic of the nanoscale include (1) those related to the large specific surface
205 area of the materials considered and/or (2) specific physicochemical properties that are different from
206 those of the non-nanoform of the same material.

207 An up-to-date overview of European policies for nanomaterials in food and feed with a focus on
208 comparing lessons learnt from the regulatory approach to genetically modified organisms was
209 completed recently by Bucatariu (2011). The author argues that a coherent approach to ensuring the
210 safety and security of food and consumers in the European Union should also support active and
211 responsible involvement in the global perspective (e.g. trade, innovation, sustainability) along with
212 European Union research and development funding and partnerships.

213 *Risk assessment*

214 In 2011, the European Food Safety Authority (EFSA) published a scientific opinion with the title
215 “Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food
216 and feed chain” (EFSA Scientific Committee, 2011). The guidance is a practical approach to
217 assessing potential risks when nanomaterials are applied in the food and feed chain. It builds upon the
218 scientific opinion from 2009 (EFSA, 2009).

219 EFSA concluded in both reports that “the risk assessment paradigm (hazard identification and hazard
220 characterisation followed by exposure assessment and risk characterisation) is appropriate for these
221 applications” of nanoscience and nanotechnologies in the food and feed chain.

222 Therefore, the risk of an engineered nanomaterial will be determined by its chemical composition,
223 physicochemical properties, interactions with tissues and potential exposure levels. EFSA states that
224 there are currently uncertainties related to the identification, characterization and detection of
225 engineered nanomaterial because of the lack of suitable and validated test methods. For these reasons,

226 EFSA recommends that additional research is needed to address the many current uncertainties and
227 limitations. In general, EFSA supports the use of conventional risk assessment while acknowledging
228 the limited knowledge on exposure to nanofood applications.

229 Opinions on four nanomaterials from two EFSA panels have been published so far (L. Djien, EFSA,
230 personal communication, 2011). For silicon dioxide coating (maximum thickness 100 nm) on the
231 inner surface of polyethylene terephthalate articles, the Panel determined that the tested substance was
232 not genotoxic (AFC, 2007). Regarding nanoparticles of titanium nitride used in polyethylene
233 terephthalate bottles at concentrations up to 20 mg/kg, the Panel considered that the intended use of
234 this substance would not give rise to exposure via food and hence was not of toxicological concern
235 (CEF, 2008). For the nanoparticle silver hydrosol, the Panel concluded that due to the lack of an
236 appropriate dossier supporting its use, its safety and the bioavailability of silver from silver hydrosol
237 could not be assessed (ANS, 2008). For calcium carbonate, the Panel noted that the presence of
238 unintentional nanoscale particles at trace levels in food additive grade calcium carbonate could not be
239 excluded. While the data were inadequate to reach definitive conclusions on calcium carbonate
240 predominantly in the nanoscale, the Panel concluded that the available data were sufficient to
241 conclude that the current levels of adventitious nanoscale material within microscale calcium
242 carbonate would not be of additional toxicological concern (ANS, 2011).

243 Although not food related, it is of interest to note that risk assessments are ongoing on three specific
244 manufactured nanomaterials (ultraviolet filters) for authorization of their use in cosmetics. These are
245 the first nanomaterial products to be assessed in the European Union. In October 2011, the European
246 Commission's Scientific Committee on Consumer Safety was requested to develop guidance on
247 manufactured nanomaterial for the safety assessment of nanomaterials in cosmetic products (SCCS,
248 2011). In this document, the Scientific Committee on Consumer Safety is going to provide guidance
249 on the development of criteria and conditions that would allow the risk assessment of nanomaterials
250 using a category-based approach rather than on a case-by-case basis.

251 *Research on nanomaterials*

252 The FAO/WHO expert meeting in 2009 called for innovative and interdisciplinary research that may
253 lead to novel risk assessment strategies for the application of nanotechnologies in food and feed.
254 Several corresponding research projects on nanomaterials were funded by the European Union's
255 framework programmes for research and technological development. Ongoing and finished projects
256 related to nanotechnology are provided on the European Commission's web site on nanotechnology
257 (<http://cordis.europa.eu/nanotechnology/home.html>).

258 One of these projects, called NanoLyse, focuses on nanoparticles in food and is dedicated to the
259 development of analytical methods for the detection and characterization of engineered nanoparticles
260 in food. The NanoLyse consortium comprises 10 universities and research centres from Europe and
261 Canada. The project started in January 2010 and will last for three years (NanoLyse, 2011).
262 According to NanoLyse, very limited knowledge is available on the potential impact of engineered
263 nanoparticles on consumers' health. The NanoLyse project will develop a toolbox of methods to
264 detect and characterize different types of engineered nanoparticles in food. Recent project outcomes
265 have been presented in several scientific publications (Allmaier et al., 2011; Dudkiewicz et al., 2011;
266 Linsinger et al., 2011; Peters et al., 2011; Von der Kammer et al., 2011).

267 Another project funded by the European Union’s framework programme is ObservatoryNANO. The
268 project is led by the United Kingdom’s Institute of Nanotechnology; it has as a final goal the
269 establishment of a permanent European Observatory on Nanotechnologies. ObservatoryNANO
270 publishes factsheets that provide information on nanotechnology developments in different sectors,
271 including the agrifood sector (ObservatoryNANO, 2010, 2011).

272 The Joint Research Centre of the European Commission maintains a repository of nanomaterials
273 (Gilliland, 2012). These reference nanomaterials enable the accurate comparison of data obtained in
274 different test laboratories worldwide. The 25 types of material include silver nanoparticles, silicon
275 dioxide and titanium dioxide (JRC, 2011).

276 **f. Indonesia**

277 No safety assessments or regulations specific to nanomaterials in the food and agriculture sectors
278 were found on the Indonesian government’s web site (<http://www.indonesia.go.id/en.html>) or on a
279 cooperative web site between the private sector and the research community (<http://www.nano.or.id/>).

280 **g. Japan**

281 *Risk management*

282 Nanotechnology was specified as one of the priority research targets in the third *Science and*
283 *Technology Basic Plan* for 2006–2010 by the Japanese government (Government of Japan Council for
284 Science and Technology Policy, 2006). In response to this plan, the Japanese Ministry of Agriculture,
285 Forestry and Fisheries (2007) funded the research project “Food nanotechnology project” in 2007.
286 Scientific papers published under this project evaluate and analyse nanoscale food products.

287 The Japanese Ministry of Health, Labour, and Welfare launched a six-year programme (2009–2014)
288 called the “Research project on the potential hazards, etc. of nanomaterials”, which focuses on the
289 carcinogenicity of nanomaterials. The Japanese Ministry of Economy, Trade and Industry published
290 the results of voluntary information gathering on industry activities on its web site in March 2010
291 (only in Japanese) (OECD, 2010a).

292 The fourth *Science and Technology Basic Policy Report*, published in October 2010, stated that the
293 government will promote research and development into nanotechnology (Government of Japan
294 Council for Science and Technology Policy, 2010). In December 2010, the Japanese Center for
295 Research and Development Strategy published a nanotechnology report (Japan Science and
296 Technology Agency, 2010). According to this report, the annual investment in nanotechnology in the
297 United States, China and the Republic of Korea has exceeded that of Japan (Japan Science and
298 Technology Agency, 2010).

299 *Risk assessment*

300 The Food Safety Commission, the Japanese organization that undertakes risk assessment, published a
301 survey report on the use of nanotechnology in the food sector in March 2010 (FSC, 2010). From the
302 replies to the questionnaire by the domestic industry on the use of engineered nanomaterial, it was
303 concluded that there was no need for specific nanomaterial regulation at present. However, the report
304 also concluded that there were questions on the classification of nanotechnology-using food products

305 as well as significant data gaps, which precluded the drawing of firm conclusions. If any regulation
306 needed to be introduced, safety assessment methods would need to be established first (FSC, 2010).

307 **h. Malaysia**

308 No safety assessments or regulations specific to nanomaterials in the food and agriculture sectors
309 were found on Malaysian government web sites for the Ministry of Science, Technology and
310 Innovation (<http://www.mosti.gov.my/mosti/index.php>) or the Ministry of Health
311 (<http://www.moh.gov.my/>).

312 **i. Mexico**

313 No safety assessments or regulations specific to nanomaterials in the food and agriculture sectors
314 were found on government web sites relating to food and agriculture: the Mexican Ministry of
315 Agriculture, Livestock, Rural Development, Fisheries and Food (<http://www.sagarpa.gob.mx/>) and the
316 Mexican National Institute of Public Health (<http://www.insp.mx/>).

317 **j. Republic of Korea**

318 No regulations relating to nanomaterials were found on government web sites: the official web site of
319 the Republic of Korea (<http://www.korea.net/index.html>), the Korean Ministry for Food, Agriculture,
320 Forestry and Fisheries (<http://english.mest.go.kr/web/40724/en/board/enlist.do?bbsId=276>) and the
321 Korean Ministry of Education, Science and Technology (<http://english.mest.go.kr/enMain.do>).

322 The 3rd International Nanomaterials Ethics Workshop, a gathering of international experts in
323 nanotechnology and science ethics, was held on 14 January 2011 in the Republic of Korea. Topics
324 included changes in safety regulation regarding nanomaterials in European countries. Companies'
325 responses and strategies with respect to the launch and export of nanotechnology products were
326 discussed at the workshop (Korean Ministry of Education, Science and Technology, 2011).

327 The Korean Ministry of the Environment developed a document on the *Guideline for the life cycle*
328 *assessment (LCA) of nanomaterials*, as reported in OECD (2011b).

329 **k. South Africa**

330 No safety assessments or regulations specific to nanomaterials in the food and agriculture sectors
331 were found on the Government of the Republic of South Africa's web site
332 (<http://www.info.gov.za/view/DynamicAction?pageid=528>). The *Foodstuffs, Cosmetics and*
333 *Disinfectants Amendment Act, 2007* contains no regulations on nanomaterials (Government of the
334 Republic of South Africa, 2008).

335 South Africa's national nanotechnology strategy runs until 2014. The main objective of this strategy is
336 to support long-term nanoscience research (Department of Science and Technology of the Republic of
337 South Africa, 2011).

338 **I. Switzerland**

339 *Risk management*

340 There is no Swiss legislation that incorporates specific safety provisions for nanomaterials; however,
341 the Federal Office of Public Health and the Federal Office for the Environment in Switzerland
342 published a precautionary matrix to assist authorities, industry, trade, commerce and research
343 laboratories in the preliminary clarification of any need for action. The questionnaire is based on a
344 limited number of evaluation parameters, including size of the particles, the number of particles, their
345 reactivity and their release potential. The Federal Office of Public Health and the Federal Office for
346 the Environment recommend that the precautionary matrix is to be used for all synthetic
347 nanomaterials smaller than 500 nm (Höck et al., 2011). Retailers in Switzerland use the precautionary
348 matrix for nanomaterials for their suppliers, and Swiss retailers have developed codes of conduct for
349 nanomaterial applications in food (IG DHS, 2011).

350 **m. United States of America**

351 *Risk management*

352 In addressing issues raised by nanomaterials, United States agencies adhere to the principles for
353 regulation and oversight of emerging technologies, as summarized by Holdren, Sunstein & Siddiqui
354 (2011).

355 The United States government founded the National Nanotechnology Initiative 10 years ago to
356 leverage the research programmes on nanotechnology (Tinkle & Carim, 2011). In October 2011, the
357 National Nanotechnology Initiative released a national strategy for ensuring the responsible
358 development of nanotechnology and to support regulatory decision-making (NSET/NEHI, 2011). The
359 2011 strategy, which revises and replaces the 2008 strategy, concerns environmental, health and
360 safety issues. The report identified that more research is required to develop tools for the
361 determination of the physicochemical properties of engineered nanomaterials and for the detection
362 and monitoring of engineered nanomaterials in realistic exposure media. In terms of human exposure
363 assessment, the report recognized that more research is needed to understand the processes and factors
364 that determine exposures to nanomaterials. In relation to human health, the most important research
365 need is to identify or develop appropriate, reliable and reproducible in vitro and in vivo assays and
366 models to predict in vivo human responses to engineered nanomaterials. Relating to risk assessment
367 and risk management methods, more safety evaluation of nanomaterials is needed, with incorporated
368 hazard identification, exposure science and risk modelling (NSET/NEHI, 2011).

369 *Risk management: FDA*

370 In June 2011, the United States Food and Drug Administration (FDA) issued for public comment a
371 draft guidance document on considering whether an FDA-regulated product contains nanomaterials or
372 otherwise involves the use of nanotechnology. According to the FDA, the guidance document does
373 not establish any regulatory definitions. Rather, it is intended to help industry and others identify
374 when they should consider potential implications for regulatory status, safety, effectiveness or public
375 health impact that may arise with the application of nanotechnology in FDA-regulated products. The
376 draft guidance document is intended to be broadly applicable to all FDA-regulated products, including
377 food substances. According to this draft guidance document (FDA, 2011a):

378 ...when considering whether an FDA-regulated product contains nanomaterials or otherwise involves
379 the application of nanotechnology, FDA will ask:

- 380 1. Whether an engineered material or end product has at least one dimension in the nanoscale
381 range (approximately 1 nm to 100 nm); or
- 382 2. Whether an engineered material or end product exhibits properties or phenomena, including
383 physical or chemical properties or biological effects, that are attributable to its dimension(s),
384 even if these dimensions fall outside the nanoscale range, up to one micrometer.

385 The FDA's consumer update from June 2011 stated that the agency plans to develop additional
386 guidance for specific products, as needed, in the future. The FDA is working with the White House,
387 the National Nanotechnology Initiative, other United States government agencies and international
388 regulators to focus on generating data and coordinating policy approaches to ensure the safety and
389 effectiveness of products using nanomaterials (FDA, 2011b).

390 The draft guidance on substances to be used in dietary supplements, published in July 2011, proposes
391 to include issues related to nanotechnology, if such use of nanotechnology results in new or altered
392 properties of the ingredient (FDA, 2011c).

393 The FDA is in the process of preparing another guidance document that addresses the impact that
394 manufacturing changes, including a change in particle size, would have on the regulatory status of
395 authorized materials, which will address nanomaterials (A. McCarthy, FDA, personal communication,
396 2011).

397 *Risk assessment: FDA*

398 The FDA does not maintain a list of nanomaterials that it has assessed (A. McCarthy, FDA, personal
399 communication, 2011).

400 *Risk management and assessment: EPA*

401 The nanomaterial research strategy from 2009 defines the United States Environmental Protection
402 Agency's (EPA) nanotechnology research programme to conduct focused research on nanomaterial
403 safety (EPA, 2009). The EPA has identified five nanomaterial types for investigation that are widely
404 used in products or have been recognized for their potential uses (EPA, 2011c). The materials being
405 studied are:

- 406 1. *Carbon tubes and fullerenes*: Carbon materials have a wide range of uses, ranging from
407 composites for use in vehicles and sports equipment to integrated circuits for electronic
408 components.
- 409 2. *Cerium oxide*: Nano cerium is being investigated for uses ranging from drug delivery to
410 automobile catalytic converters. One use currently on the market in some countries is as a
411 diesel fuel additive to reduce exhaust particulates and increase fuel mileage.
- 412 3. *Titanium dioxide*: Nano titanium dioxide is currently used in many products. Depending on
413 the type of particle, it may be found in sunscreens, cosmetics, and paints and coatings. It is
414 also being investigated for use in removing contaminants from drinking-water.
- 415 4. *Silver*: Silver has long been known for its antimicrobial properties. Nanosilver is being
416 incorporated into textiles and other materials to eliminate bacteria and odour from clothing,
417 food packaging and other items where antimicrobial properties are desirable. The EPA has

418 approved the use of a nanosilver-based antimicrobial product that is incorporated into textile
419 as long as the company performs some required studies during the period of conditional
420 registration (EPA, 2011a). Before this assessment, the EPA registered all silver particles using
421 ionic risk assessment, without consideration of the particle size (Costanza, 2012).

422 5. *Iron*: While nanoscale iron is being investigated for many uses, including “smart fluids” for
423 uses such as optics polishing and as better-absorbed iron nutrient supplements, one of its more
424 prominent current uses is to remove contamination from groundwater. This use, supported by
425 EPA research, is being piloted at a number of sites across the country.

426 EPA research will determine whether these materials present a potential environmental hazard or
427 exposure over their life cycles and how these materials, when used in products, may be modified or
428 managed to avoid or mitigate potential human health or ecological impacts.

429 Researchers in the EPA’s Nanotechnology Research Program are studying nanomaterials to
430 understand the potential unintended consequences from accidental or intentional exposure of humans.
431 The research programme has the following approach for assessing the potential toxicity of
432 nanomaterials:

- 433 • Identify and characterize the physical and chemical properties of manufactured nanomaterials.
- 434 • Identify alternative testing methods and approaches to predict toxicity in humans, which
435 includes identification of biomarkers of nanomaterial exposure and/or toxicity.
- 436 • Assess the toxicity of nanomaterials in animals. These studies will include research to identify
437 host susceptibility and sensitivity factors that may influence toxicity.

438 For a comprehensive environmental assessment, the EPA conducted two case-studies on titanium
439 dioxide. One examined nano titanium dioxide use for water treatment, and the other looked at its use
440 as an ingredient in sunscreens (EPA, 2010). The case-studies incorporated a comprehensive
441 environmental assessment framework, which combines a product life cycle perspective with the risk
442 assessment paradigm. This document will be used as part of a process to identify and prioritize
443 research needs in developing data to inform nanomaterial risk assessment (OECD, 2011b).

444 In the *Federal Register* on 17 June 2011, the EPA’s Office of Pesticide Programs proposed several
445 approaches to obtain information on what nanoscale materials are present in pesticide products and
446 requested comments from stakeholders (EPA, 2011b).

447 In the *Federal Register* on 26 October 2011, the EPA requested information on the discharge of
448 nanosilver (an from industrial manufacturing) (EPA, 2011d). The EPA is interested in collecting as
449 much information as possible on the fate, transport and effects of nanosilver on the aquatic
450 environment and human health.

451 The National Research Council performed an independent study for the EPA to develop a research
452 strategy to address the environmental, health and safety aspects of engineered nanomaterials. The
453 comprehensive report summarized the current state of the science and identified research that needs to
454 be undertaken and the resources needed (NRC, 2012). Relating to food, the report concluded that little
455 is known about ingestion exposures and the transport and distribution of engineered nanomaterials in
456 the human body. It was identified that research is needed to understand the biomolecular
457 modifications of engineered nanomaterials in the human body.

458 **4. Relevant activities by international governmental and**
459 **nongovernmental organizations since 2009**

460 **a. Institute of Food Technologists**

461 In the last few years, the Institute of Food Technologists (IFT) has supported research and published
462 several articles on nanotechnology relating to an ongoing project on safety assessment:

- 463 • “Proposed minimum characterization parameters for studies on food and food-related
464 nanomaterials” (Card & Magnuson, 2009);
465 • “A method to assess the quality of studies that examine the toxicity of engineered
466 nanomaterials” (Card & Magnuson, 2010);
467 • “An appraisal of the published literature on the safety and toxicity of food-related
468 nanomaterials” (Card et al., 2011);
469 • “A brief review of the occurrence, use and safety of food-related nanomaterials” (Magnuson,
470 Jonaitis & Card, 2011).

471 IFT offers an on-demand online course entitled “Introduction to Nanoscience” that provides an
472 introduction to the subject and addresses fabricating and characterizing nanomaterials and
473 nanoscience application challenges ([http://www2.ift.org/PersonifyEbusiness/OnlineLearning/
474 LearnOnline/FoodScienceCourses/Description/tabid/364/Default.aspx?ProductId=1198](http://www2.ift.org/PersonifyEbusiness/OnlineLearning/LearnOnline/FoodScienceCourses/Description/tabid/364/Default.aspx?ProductId=1198)). An on-
475 demand webcast entitled “Nanoscience as an Emerging Food Industry Driver” addresses defining and
476 describing nanoscale science and technology, applications and challenges facing the food industry
477 ([http://www2.ift.org/PersonifyEbusiness/OnlineLearning/LearnOnline/OnDemandWebcasts/Descripti
478 on/tabid/377/Default.aspx?ProductId=862](http://www2.ift.org/PersonifyEbusiness/OnlineLearning/LearnOnline/OnDemandWebcasts/Description/tabid/377/Default.aspx?ProductId=862)).

479 Furthermore, IFT has held meetings and conferences that highlighted recent advances in safety and
480 toxicological assessment of nanomaterials relevant to food application. Since 2006, IFT has organized
481 an International Food Nanoscience Conference in conjunction with the IFT Annual Meeting & Food
482 Expo. The fifth IFT International Food Nanoscience Conference was held in Chicago, Illinois, in July
483 2010. It focused on advances in safety and toxicological assessment of nanomaterials for food and
484 food-related applications, the current regulatory guidelines in the United States and Europe and their
485 legal implications for industry and other stakeholders, and investments in nanotechnology research
486 and development initiatives worldwide (Bugusu, 2010). IFT is in the process of initiating planning for
487 the next International Food Nanoscience Conference, which will be convened in the fall of 2012 in
488 Washington, DC (R. Newsome, IFT, personal communication, 2011).

489 At the IFT Annual Meeting & Food Expo that took place in June 2011, several scientific sessions
490 were held, and the following nanotechnology-related presentations were given:

- 491 • “Development of nanoengineered surfaces and evaluation of the effect of nanoscale
492 topography on the attachment of pathogenic and biofilm-forming bacteria” (Moraru, 2011);
493 • “Carbohydrate nanoparticle-mediated colloidal assemblies to deliver antimicrobial peptide”
494 (Yao, 2011);
495 • “Development and application of food-grade antimicrobial nanoparticles” (McClements,
496 2011);
497 • “Self-sanitizing food processing surfaces” (Goddard, 2011);

- 498 • “Overview of the science and technology in food and food products at the nanoscale level”
499 (Yada, 2011);
- 500 • “Issues and challenges for food product applications of nanomaterials” (Magnuson, 2011);
- 501 • “Novel nanoscale structures inspired by biological systems” (Batt, 2011);
- 502 • “Diverse applications of DNA-based nanobiomaterials” (Luo, 2011);
- 503 • “Processing and characterization of nanostructured food materials” (Padua, 2011).

504 In addition to the above-mentioned scientific literature and conferences, IFT is supporting the
505 development of a framework for implementing standard characterization of and reporting for
506 nanomaterials. Referred to as the NanoCharacter project, this activity, which is in an initial stage, is
507 being led by the International Life Sciences Institute (ILSI) Research Foundation (R. Newsome, IFT,
508 personal communication, 2011; see also next section).

509 **b. International Life Sciences Institute**

510 The NanoRelease project from the ILSI Research Foundation’s Center for Risk Science Innovation
511 and Application aims to promote the safe development of nanomaterials by supporting the
512 development of methods to understand the release of nanomaterials used in products. As part of the
513 NanoRelease project, data, methods, guidance, standards and links are collected. The NanoRelease
514 Steering Committee is composed of risk management experts from government, industry,
515 nongovernmental organizations and international organizations (ILSI, 2011).

516 In a white paper providing background on the state of the science for nanomaterial release
517 measurement, published on the ILSI web site, it is stated that “At the time of writing, there were over
518 3,500 studies that investigated nanoparticle release. However, nearly all of these research efforts
519 focused on release in a targeted drug therapy context and less than 20 focused on release from
520 consumer products” (Froggett, 2011).

521 The NanoRelease project is currently evaluating multiwalled carbon nanotube release from consumer
522 products. The project is planning to undertake similar evaluation of engineered nanomaterial release
523 from food matrices in the gastrointestinal tract (R. Canady, ILSI, personal communication, 2011). In
524 the NanoCharacter project, the Center for Risk Science Innovation and Application has collected
525 leading experts in nanotechnology environmental, health and safety research to develop a framework
526 and road map for the staged implementation of consistent nanomaterial characterization and reporting
527 practices. Over the course of the coming years, the road map will lay out the steps that need to be
528 taken for funding, standardization, instrumentation, regulatory specifications and journal review so
529 that studies use consistent methods for measuring physical properties to facilitate inter-study
530 comparisons. More recently, a NanoRelease Food Additive project was launched that is evaluating
531 and developing methods to characterize nanomaterials released from food in the gut (R. Canady, ILSI,
532 personal communication, 2011).

533 NanoCharacter is another project aimed at developing a framework and road map for implementing
534 widespread adoption of principles of reporting characteristics of nanomaterials in studies of
535 commercial nanoproducts. The project builds on Organisation for Economic Co-operation and
536 Development (OECD), International Organization for Standardization (ISO), Minimum Information
537 on Nanoparticle Characterization (MINChar) and other efforts to establish “the list” of what to
538 measure and will lay out how to get from concept to reality of consistent reporting. The project was
539 initiated in response to a study of nanoparticle research in foods and will target food additives as one

540 of the areas where consistent reporting is needed. A workshop is planned for August 2012 to draft a
541 first framework document (R. Canady, ILSI, personal communication, 2011).

542 ILSI Europe initiated the Novel Foods and Nanotechnology Task Force (ILSI Europe, 2011), which
543 started its work focusing on new technologies for the safety/nutritional assessment of novel foods and
544 food ingredients. The aim of the activity will be to:

- 545 • review the applicability of new technologies for generating data and for integrating new types
546 of data for safety (risk-based) and nutritional assessment;
- 547 • understand the role that other new and emerging technologies (e.g. tissue engineering, micro-
548 ribonucleic acid, stem cells) may play in assessments in the future.

549 The brief on this activity is currently under development (A. Chiodini, ILSI, personal communication,
550 2011). This expert group previously discussed guidance for the safety assessment of engineered
551 nanomaterials in food and developed a manuscript that was reviewed at a workshop that took place on
552 13–15 April 2011 in Cascais, Portugal, by participants from academia and industry, national
553 authorities and representatives from the European Commission and EFSA. The expert group
554 considered the outcome of the workshop discussions for the finalization of the article, which was on
555 “Approaches to the safety assessment of engineered nanomaterials (ENM) in food” (Cockburn et al.,
556 2012).

557 The task force’s proposal for the safety assessment of engineered nanomaterials involves five steps. In
558 step 1, all available and relevant data for the material are collected. In step 2, the physical and
559 chemical characterization of the nanomaterial is conducted. In step 3, with the help of a decision-tree,
560 this available information on physicochemical properties (especially solubility in water), data on
561 bioavailability and comparison with existing “non-nano” versions of the material in question are used
562 to decide what safety assessment approach is adequate. From this decision-tree, three scenarios
563 follow: (i) if the nanomaterial’s dissolution (rate, location) is comparable with that of the conventional
564 material, it should be covered by the previous risk assessment for that material; (ii) if the
565 nanomaterial’s dissolution (rate, location) differs from the behaviour of the conventional material, a
566 re-evaluation of the existing risk assessment with particular emphasis on absorption is advisable; and
567 (iii) if the engineered nanomaterial is insoluble or partly insoluble, a tiered assessment addressing
568 potential specific hazards is foreseen. In step 4, for materials for which at step 3 the existing risk
569 assessment has been found not to cover the novel nanomaterial, a two-tiered testing scheme is used.
570 At tier 1, the potential hazards are investigated in in vitro and short-term (<28 days) in vivo studies.
571 At tier 2, if needed, the engineered nanomaterial is evaluated in more detail involving, as a minimum,
572 a 90-day study in rodents and other focused and mechanistic studies. In the final step 5, an overall
573 safety assessment of the engineered nanomaterial as consumed in food is described that takes into
574 account the interaction with the food matrix (all components), the impact on solubility/bioavailability
575 at local and systemic levels and the exposure to the engineered nanomaterial from food (A. Chiodini,
576 ILSI, personal communication, 2011; FAO/WHO, 2012).

577 **c. Organisation for Economic Co-operation and Development**

578 OECD activities do not address food directly. OECD has two relevant working parties: (1) the
579 Working Party on Nanotechnology and (2) the Working Party on Manufactured Nanomaterials. Both
580 working parties do not have food as a main subject; nevertheless, OECD’s work on the testing and

581 assessment of nanomaterials can be used for food-related nanomaterial applications (M. Gonzalez,
582 OECD, personal communication, 2011).

583 The Working Party on Nanotechnology has, since 2007, advised on emerging policy issues of science,
584 technology and innovation related to the responsible development of nanotechnology (OECD, 2011c).
585 It provides to members socioeconomic analysis of nanotechnology and the facilitation of international
586 collaboration in research and development and science and technology policies. The project from the
587 Working Party on Nanotechnology on “Regulatory Tools for Nanotechnology in Food and Medical
588 Products” aims at creating and maintaining inventories that will include information regarding:

- 589 • current regulatory frameworks in place for regulating the use of nanotechnology in food and
590 in medical products;
- 591 • current legislative regimes relevant to regulatory frameworks in place for regulating the use of
592 nanotechnology in food and in medical products;
- 593 • government-supported research institutions related to nanotechnology in food and in medical
594 products, including current and future research strategies, programmes and activities.

595 The inventories will assist the Working Party on Nanotechnology in identifying areas of shared
596 interest and highlight opportunities for enhancing communication related to regulation and
597 applications of nanotechnology in food and medical products. The report analysing the survey’s
598 results is currently in development (M. Gonzalez, OECD, personal communication, 2011).

599 OECD’s Working Party on Manufactured Nanomaterials, established in 2006, concentrates on the
600 human health and environmental safety implications of manufactured nanomaterials, mainly with
601 regard to the chemicals sector. The Working Party on Manufactured Nanomaterials aims to ensure
602 that the approach to hazard, exposure and risk assessment is of a high, science-based and
603 internationally harmonized standard. Its programme seeks to promote international cooperation on the
604 human health and environmental safety of manufactured nanomaterials and involves the safety testing
605 and risk assessment of manufactured nanomaterials. It is a subsidiary group of, and receives its
606 mandate from, the Chemicals Committee (OECD, 2011c).

607 The Working Party on Manufactured Nanomaterials is active in a number of different areas. The
608 following summaries are a selection of topics that are related to food. A more comprehensive
609 description of all activities can be found at <http://www.oecd.org/env/nanosafety>.

610 *OECD database on research into the safety of manufactured nanomaterials*

611 The objective of this project is to develop a global resource for research projects that address
612 environmental, human health and safety issues of manufactured nanomaterials. This database helps to
613 collect research information, search details by categories (e.g. nanomaterials, test methods, themes),
614 identify gaps and assist in future collaborative efforts. Besides experimental studies, the database
615 includes projects relevant to comprehensive risk assessments of specific substances, risk mitigation
616 measures, regulatory aspects, international standard setting and reports on public dialogues. The
617 database was publicly launched in April 2009 and now includes data on more than 700 research
618 projects (OECD, 2009).

619 *Safety testing of a representative set of manufactured nanomaterials*

620 The “Sponsorship Programme for the Testing of Manufactured Nanomaterials” involves OECD
621 member countries, as well as some non-member economies and other stakeholders, with the goal to
622 pool expertise and fund the safety testing of specific manufactured nanomaterials. In initiating this
623 programme, the Working Party on Manufactured Nanomaterials agreed on a priority list of 13
624 manufactured nanomaterials for testing, based on materials that are in or close to the market, such as
625 fullerenes, single-walled carbon nanotubes, silver nanoparticles, titanium dioxide, silicon dioxide and
626 nanoclays (OECD, 2010c). In addition, a number of end-points were selected for their relevance in
627 providing crucial information related to environmental and human health safety. Therefore, each
628 selected manufactured nanomaterial will be tested for its physicochemical properties, environmental
629 degradation and accumulation, environmental toxicology and mammalian toxicology. As part of the
630 programme, a *Guidance manual for the testing of manufactured nanomaterials* has been developed
631 (OECD, 2010b). The programme is in its first phase, and dossiers for each sponsored nanomaterial are
632 under preparation (M. Gonzalez, OECD, personal communication, 2011).

633 *The role of alternative test methods in nanotoxicology*

634 This project addresses the use of alternative methods and integrated testing strategies for
635 manufactured nanomaterials. It is focused on in vitro or other alternative methods for the reduction,
636 refinement or replacement of animals in test approaches that could be further explored with respect to
637 manufactured nanomaterials. An outcome of this project will be guidance on integrated testing
638 strategies, which will focus on those manufactured nanomaterials currently sponsored through the
639 Sponsorship Programme (M. Gonzalez, OECD, personal communication, 2011).

640 *Manufactured nanomaterials and test guidelines*

641 Through this project, OECD is carefully evaluating any concrete proposals for the development or
642 revision of test guidelines and/or guidance documents, which need to take into account existing
643 information and results coming from the scientific community. A preliminary review of 115 OECD
644 test guidelines has shown that most of them are suitable, but that, in some cases, modification will be
645 needed for their applicability to manufactured nanomaterials. Because the information concerning the
646 properties of nanomaterials and their effects is still being developed, for example, through the
647 Sponsorship Programme described above, the process to move ahead is flexible and able to adapt new
648 information. Therefore, some of the outcomes being made available are expected to be revised as new
649 information becomes available. For example, the document *Preliminary guidance notes on sample
650 preparation and dosimetry for the safety testing of manufactured nanomaterials* has been published;
651 as new information becomes available, it will be incorporated into a revised version (OECD, 2010d).

652 *Voluntary schemes and regulatory programmes*

653 This project has examined various national voluntary reporting schemes and regulatory programmes
654 to assess the safety of manufactured nanomaterials. To date, the main outputs of this project have
655 been (1) the analysis of information-gathering initiatives on manufactured nanomaterials, which
656 includes a table of comparison of information-gathering schemes; and (2) the report of the
657 questionnaire on regulatory regimes for manufactured nanomaterials, including legislative features
658 identified in legislation on regulatory oversight of nanomaterials/nanoproducts. Two documents were

659 published in December 2011: *Regulated nanomaterials: 2006–2009* (OECD, 2011d) and *Information*
660 *gathering schemes on nanomaterials: lessons learned and reported information* (OECD, 2011a).

661 *Risk assessment*

662 The overall objectives of this project are to evaluate risk assessment approaches for manufactured
663 nanomaterials through information exchange and to identify opportunities to strengthen and enhance
664 risk assessment capacity. Through this project, it is expected that the outcomes of the work of the
665 other Working Party of Manufactured Nanomaterials projects will be integrated into an overall
666 framework within which risks of manufactured nanomaterials are assessed, ensuring good practice
667 across OECD countries and other interested parties.

668 The document *Important issues on risk assessment of manufactured nanomaterials* has been
669 developed (OECD, 2012). This document aims to introduce the current practices and challenges with
670 respect to the risk assessment of manufactured nanomaterials as well as strategies for assessing risk in
671 circumstances where data are limited. Furthermore, this document makes clear the necessity of direct
672 research on specific risk assessment issues in concert with current efforts to develop basic data sets.

673 *Environmentally sustainable use of nanotechnology*

674 The aim of this project is to investigate the potential benefits of applications based on the use of
675 manufactured nanomaterials. The expected outcome is the development of tools and frameworks
676 based on life cycle considerations for different nano-enabled applications that either directly address
677 an environmental problem or indirectly contribute to environmental objectives. As such, the project
678 will address environmental benefits, sustainability and life cycle-related issues. Through this project,
679 the Working Party on Manufactured Nanomaterials seeks to complement current working party work
680 regarding the potential positive and negative impacts on the environment and health of certain nano-
681 enabled applications at their different stages of development.

682 As part of this project, the document *National activities on life cycle assessment of nanomaterials* was
683 compiled from delegations and was published in December 2011 (OECD, 2011b).

684 **5. Scientific reviews addressing risk assessment of** 685 **nanotechnologies in the food and agriculture sectors**

686 Recent scientific reviews on risk assessment of nanotechnologies in the food and agriculture sectors
687 confirm that information on this topic is limited (Tran & Chaudhry, 2010; Card et al., 2011; Horie &
688 Fujita, 2011; Magnuson, Jonaitis & Card, 2011; Morris, 2011; Rico et al., 2011; Krug & Wick, 2011).

689 A review on the interaction of nanoparticles with edible plants found that understanding of plant
690 toxicity is at the early stages. Few studies have been performed on the accumulation of engineered
691 nanomaterials in crop plants such as rape, radish, lettuce, corn and cucumber (Rico et al., 2011). Rico
692 et al. (2011) noted that among the studied nanomaterials, the carbon-based nanomaterials fullerenes
693 C₇₀ and fullerols C₆₀(OH)₂₀ and most of the metal-based nanomaterials (titanium dioxide, cerium
694 oxide, magnetite, zinc oxide, gold, silver, copper and iron) accumulated in the plants. These
695 compounds stored in the plants can be transferred to consumers. Depending on the studied

696 nanomaterial and plant, negative effects of the nanoparticles on the food crops were observed, such as
697 reduced germination, reduced root growth and delayed flowering.

698 Card et al. (2011) evaluated published literature on the safety of oral exposure to food-related
699 nanomaterials and found that there are currently insufficient reliable data to allow a clear safety
700 assessment. Card et al. (2011) also considered that non-food-related engineered nanomaterials require
701 evaluation of oral toxicity in light of possible contamination of the food supply. Morris (2011)
702 concluded that the lack of information on the possible toxicity of nanomaterials makes it difficult to
703 assess the safe or acceptable daily intake.

704 According to Magnuson, Jonaitis & Card (2011), the literature on the safety of oral exposure to
705 nanomaterials inadequately characterizes nanomaterials with insufficient physicochemical parameters,
706 concluding that “Unless nanomaterials are adequately characterized, the results of the toxicology
707 studies cannot be utilized to predict toxicity of other nanomaterials as changes in any of the
708 characteristics may result in changes in biological activity”.

709 Horie & Fujita (2011) reasoned that in vitro and in vivo tests with no characterization of the
710 nanomaterial are meaningless; for example, metal oxide nanoparticles with the same chemical
711 composition are likely to have different effects depending on the manufacturer. Therefore, at the
712 present time, risk evaluation requires characterization of each substance and each product (Horie &
713 Fujita, 2011).

714 There has been more interest in occupational health, such as nanoparticle toxicology in the lung, and
715 less research has been published on nanomaterial toxicity in the gut.¹ According to the review by
716 Morris (2011), there is at present little information on the effect of antimicrobial nanomaterials such
717 as nanosilver on normal microbial populations in the mouth and gut. Few studies have attempted to
718 find a relationship between the presence of nano-sized particulate materials in food and the initiation
719 and/or worsening of certain gut diseases, such as Crohn disease and irritable bowel syndrome. Studies
720 have produced contradicting results; therefore, there is a requirement for considerable further research
721 (Tran & Chaudhry, 2010).

722 The safety assessment of nanomaterials will depend on their adequately characterized chemical
723 properties; critical parameters include biopersistence and digestibility. Based on the development of
724 nano forms of trace minerals, the group led by D. Pereira at MRC Human Nutrition Research
725 identified three different scenarios. Digestible, non-biopersistent nanomaterials such as nano forms of
726 a salt will be digested (dissolve) prior to any cellular exposure; for cells and tissues, there will be no
727 difference if compared with conventional forms. A second type of digestible, non-biopersistent
728 nanomaterial, such as micellar nano formulations or ferritin, will only partially degrade in the gut;
729 they may therefore be absorbed as nano structures but will be rapidly broken down in cells. A third
730 type, non-digestible, biopersistent nanomaterials, may remain intact and will raise different issues, an
731 important one being their adsorbed surface materials, which may be removed in the stomach and
732 replaced in the gut by luminal molecules before cellular uptake (FAO/WHO, 2012).

733 The above-described scenarios would be part of the first principle identified by Krug & Wick (2011),
734 the transport principle. The authors identified three principles that in their view describe specific

¹ Search for literature with [Topic=(toxicology) AND Title=(nano*, lung)] or [Topic=(toxicology) AND Title=(nano* intestin* or gut)] within the years 2009 and 2011 (<http://wokinfo.com/>, accessed 6 February 2011).

735 aspects of the separate discipline of “nanotoxicology”. The principle of transport requires an
736 understanding of whether and in what form nanomaterials will enter into cells where they may elicit a
737 toxic response. The second principle of the surface reflects the fact that for smaller particles with
738 active molecules on their surface, the proportion of atoms or molecules that are exposed and may
739 therefore react with biological structures increases exponentially with decreased diameter if the same
740 amount is administered. The third principle of material states that changes in dimensions (i.e. going
741 towards nano) will not have the same effects but will depend on the properties of the material and its
742 composition, including impurities.

743 **6. Conclusions and recommendations**

744 The review of national and international scientific (i.e. risk assessment related) and regulatory (i.e.
745 risk management) activities on applications of nanotechnology in food and agriculture that have been
746 undertaken since 2009 demonstrates that progress has been made in all three major areas addressed by
747 the joint FAO/WHO expert meeting in 2009.

748 **a. Use of nanotechnology**

749 The concepts of potential use of nanomaterials in food and the implied benefits for stakeholders
750 including consumers have not changed significantly. The main areas, as summarized in Appendix 4 of
751 the FAO/WHO (2010) report, remain valid. New products are being developed and probably enter the
752 market, but the available data from published sources do not allow an assessment of whether product
753 ideas are just concepts or are already resulting in exposure of consumers to food being produced with
754 nanotechnology/nanomaterials at any significant rate.

755 Whether a product would be considered to be a nanomaterial or representing an application of
756 nanotechnology also depends on available definitions applied by regulators. Several regulatory bodies
757 have meanwhile introduced or proposed definitions of nanomaterials for regulatory purposes that
758 reflect one of the two main issues of the discussion: whether the dimension of materials of nanometer
759 scale or the change of the properties of materials due to smaller particle size is more relevant. One
760 definition extends the possible range of materials of concern to dimensions that are 10 times higher
761 than the nanoscale range of 1–100 nm that was defined by the 2009 expert meeting. There is a trend to
762 apply in the definitions two criteria, an altered or new dimension at nanoscale and a concurrent
763 change of properties due to the change of dimension. A true nanomaterial that requires the attention of
764 regulators and a specific risk assessment would need to meet both criteria. This was not fully clarified
765 by the definitions as discussed and proposed by the 2009 expert meeting, but the discussion did
766 address this issue, which was reflected in the proposal of a tiered approach for classifying
767 nanomaterials for risk analysis purposes. Such a tiered approach would apply several criteria, of
768 which dimension and change of properties expected to result in a modified hazard identification and
769 characterization would be two important ones.

770 **b. Assessment of human health risks**

771 The statement by the 2009 joint FAO/WHO expert meeting (FAO/WHO, 2010) that current risk
772 assessment approaches were suitable to assess nanomaterials and nanotechnologies used in food is
773 supported by those agencies/institutions that have investigated this issue in more detail. National and

774 regional food safety agencies increased their focus during the past few years on investigating the
775 implications of nanomaterials added to or used with food. Policies and guidance documents have been
776 published that allow a better understanding of how risk assessment of nanomaterials will be
777 performed in the future.

778 Significant progress was made by OECD, which provides the globally accepted testing guidelines for
779 hazard identification and characterization of food chemicals, such as additives, pesticides and
780 veterinary drugs, and other substances resulting in human exposure, such as cosmetic ingredients.
781 OECD reviewed these guidelines and found them to be generally applicable for the testing of
782 nanomaterials. Other research-oriented projects initiated by OECD will provide valuable insights into
783 aspects of risk assessment specific to engineered nanomaterials.

784 The approach to be published by ILSI for nanomaterials to be used in food is interesting, as it tries to
785 systematically review the information already available for conventional material and discusses what
786 properties would allow extrapolation from conventional to novel nanomaterials. Further development
787 and implementation of this concept may lead to reduced animal testing.

788 Whether the paradigm of testing materials in animals at a toxic dose, determining a no-effect level and
789 applying an uncertainty factor to establish a safe intake for humans is applicable to all nanomaterials
790 continues to be challenged. The tiered approaches that are discussed may allow in vivo testing for
791 specific groups such as nano-salts of micronutrients to be waived.

792 The number of published risk assessments of products that are nanomaterials or contain particles that
793 fall within applicable definitions is growing slowly. As agencies apply different strategies with
794 respect to communication, it is difficult to develop a clear picture of the true number of substances
795 assessed and the issues discussed that are specific for nanomaterials. Particle risk assessment is a new
796 field; risk assessment has always been done with defined chemicals, with no attention paid to particle
797 size. There is not enough known about nanomaterial toxicity to be able to group the particles into low-
798 toxicity or high-toxicity groups. Therefore, nanomaterial risk assessment currently needs to be done
799 on a case-by-case basis, as size, shape, chemical composition, surface area and surface charge
800 influence the toxicity of nanomaterials (Park et al., 2010). With respect to the three different exposure
801 routes, more risk assessment has been done for inhalation and dermal exposure and less for ingestion
802 exposure, because there are more nanomaterial products on the market in textiles, cosmetics and
803 sprays than in food and food contact materials.

804 The main areas of chemical risk assessment at the international level address food additives, pesticide
805 residues, veterinary drug residues, some processing aids, such as enzymes, and occasionally micro-
806 nutrients. Nanomaterials would be within the scope of such activities; for example, a nanoscale food
807 additive could be addressed by the Joint FAO/WHO Expert Committee on Food Additives, and
808 residues from a nanoscale pesticide could be addressed by the Joint FAO/WHO Meeting on Pesticide
809 Residues. There are, however, some areas of food chemicals, such as materials in contact with foods
810 (e.g. food packaging), that occasionally are addressed by FAO/WHO expert bodies, but for which no
811 comprehensive and systematic programme is in place; for a “nano-plastic material” to be used in food
812 packaging, there is no risk analysis framework at the international level currently in place.

813 c. Stakeholder confidence and dialogue

814 A key finding of the 2009 FAO/WHO expert meeting was that public confidence in engineered
815 nanomaterials can be supported through institutional efforts to provide an overview of applications of
816 nanotechnology in food and packaging that are transparent and allow public involvement
817 (FAO/WHO, 2010). However, for this report, it was difficult to assess the extent to which engineered
818 nanomaterials are already being used in the food and agriculture sectors. Inventories that register
819 nanotechnology in consumer products are scarce; only one database is publicly available.

820 Besides inventories, mandatory labelling would lead to greater transparency for the consumer and
821 enable consumer freedom of choice. However, mandatory labelling could also lead to the avoidance
822 of the use of nanotechnologies in consumer products, including those that are beneficial (Gruère,
823 2011). So far, apart from the European Union, no country has set a regulatory framework for the
824 mandatory labelling of nanomaterials in food (EU, 2011).

825 The mandatory labelling of materials that meet a definition that reflects only dimension (i.e. is not risk
826 based) provides a new element in the discussion that might be of interest to the Codex Alimentarius
827 Commission, as it could result in technical barriers to trade of foods to which nanomaterials have been
828 added.

829 In a report on the European Commission's public online consultation among key stakeholders about
830 nanomaterials, the majority of the 716 respondents regarded applications in agriculture and food with
831 more scepticism than applications in other areas (EC, 2010). The major concern was the possible
832 toxicity of poorly understood nanomaterials.

833 In accordance with the recommendations of the Science and Technology Committee of the United
834 Kingdom Parliament, it may be valuable to develop a database of information on nanomaterials in
835 development, in collaboration with the food industry, to anticipate future safety assessment needs and
836 to aid in the prioritization of research (United Kingdom Parliament, 2010).

837

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1125 Upcoming conferences relating to nanotechnology: <http://www.nanotech-now.com/events-2012.htm>

1126 Nanotech Regulatory Document Archive: <http://nanotech.law.asu.edu>. This database is a collaboration of the
1127 Center for the Study of Law Science & Technology at Arizona State University, USA, the Centre of Regulatory
1128 Studies in the Monash University Law School, Australia, and the Institute of Environmental and Energy Law at
1129 K.U. Leuven, Belgium.

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| ABDI | Brazilian Agency for Industrial Development |
| AFC | (former) Panel on food additives, flavourings, processing aids and materials in contact with food, EFSA (replaced by two separate Panels, ANS and CEF, in 2008) |
| ANS | Panel on food additives and nutrient sources added to food, EFSA |
| CEF | Panel on food contact materials, enzymes, flavourings and processing aids, EFSA |
| EC | European Commission |
| EFSA | European Food Safety Authority |
| EPA | United States Environmental Protection Agency |
| EU | European Union |
| FAO | Food and Agriculture Organization of the United Nations |
| FDA | United States Food and Drug Administration |
| FSANZ | Food Standards Australia New Zealand |
| FSC | Food Safety Commission, Japan |
| IFT | Institute of Food Technologists |
| IG DHS | Interessengemeinschaft Detailhandel Schweiz |
| ILSI | International Life Sciences Institute |
| ISO | International Organization for Standardization |
| JRC | Joint Research Centre, European Commission |
| MINChar | Minimum Information on Nanoparticle Characterization |
| NEHI | Nanotechnology Environmental and Health Implications (working group of the NSET Subcommittee) |
| NIA | Nanotechnology Industries Association |
| NRC | National Research Council, USA |
| NSET | Nanoscale Science, Engineering, and Technology |
| OECD | Organisation for Economic Co-operation and Development |
| SCCS | Scientific Committee on Consumer Safety, European Commission |
| SCENIHR | Scientific Committee on Emerging and Newly Identified Health Risks, European Commission |
| WHO | World Health Organization |