

REPORT OF FSA REGULATORY REVIEW

A review of potential implications of nanotechnologies for regulations and risk assessment in relation to food.

Food Standards Agency

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Summary

1. This report presents the findings of a review by the Food Standards Agency to identify potential gaps in regulation or risk assessment relating to the use of nanotechnologies and the potential deliberate or adventitious presence of manufactured nanomaterials in food.
2. This review is part of the Agency's contribution to the UK government strategy on nanotechnologies, as set out in the government response to the Royal Society and the Royal Academy of Engineering's 2004 report on nanotechnologies.
3. The conclusions of this review will inform the Agency's ongoing work in relation to nanotechnologies, and will also feed into an overall, cross-Government review of regulatory gaps co-ordinated by the Nanotechnology Issues Dialogue Group.
4. On the basis of current information, most potential uses of nanotechnologies that could affect the food area would come under some form of approval process before being permitted for use.
5. This review has not identified any major gaps in regulations but there is uncertainty in some areas whether applications of nanotechnologies would be picked up consistently. In these cases there are relatively straightforward options to address this uncertainty. As food regulations are harmonised at EU level, the Agency will seek to address them at EU level through the European Commission and other Member States. The Commission's Nanotechnology Action Plan commits it to co-ordinating an approach to such issues.
6. The view of the independent advisory Committees on Toxicity, on Carcinogenicity and on Mutagenicity of Chemicals in Food, Consumer Products and the Environment, is that the existing model for risk assessment is applicable to nanomaterials although there are major gaps in information for hazard identification. Risk assessment relies on provision of sufficient reliable information to inform an assessment in each case. Risk assessment procedures will need to include procedures for provision of information to inform risk assessments, for example in relation to an application for approval for a new product or process. The Agency will support the development of risk assessment in this area in close partnership with other Departments and the independent advisory bodies in the UK and the EU.

Introduction

7. In June 2003, Lord Sainsbury, the UK Minister for Science and Innovation, asked the Royal Society and the Royal Academy of Engineering (RS/RAEng) to consider the potential opportunities and uncertainties associated with nanoscience and nanotechnologies.
8. The resulting RS/RAEng report '*Nanoscience and Nanotechnologies: opportunities and uncertainties*'¹, made a number of recommendations aimed at ensuring the responsible development and management of nanotechnologies. Many of these centred on the need for a programme of research and public engagement to better understand the potential risks posed by nanotechnologies. Particular emphasis was given to the risks posed by free engineered nanoparticles to human health and the environment, a view recently supported by the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR).²
9. The Government published its response to the RS/RAEng report in February 2005³. This included a commitment to a number of actions including a review of existing regulations to identify any gaps to ensure that human health and the environment are adequately protected from any potential risks from nanotechnologies. UK government activities to fulfil these commitments are co-ordinated by the Nanotechnology Issues Dialogue Group (NIDG) and its sub-group the Nanotechnology Research Co-ordination Group (NRCG). The Food Standards Agency is a member of the NIDG and NRCG.
10. As part of its contribution to the UK government strategy on nanotechnologies, the Agency has carried out a review to identify potential gaps in regulation or risk assessment relating to the use of nanotechnologies and the potential deliberate or adventitious presence of manufactured nanomaterials in food. The conclusions of this review will inform the Agency's ongoing work in relation to nanotechnologies and will feed into the cross-Government review of regulatory gaps co-ordinated by the NIDG.

¹ The Royal Society and Royal Academy of Engineering (2004) *Nanoscience and Nanotechnologies: opportunities and uncertainties*. London: The Royal Society. See: <http://www.nanotec.org.uk/finalReport.htm>

² SCENIHR (2005) *Opinion on the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies*. Brussels: European Commission. See: http://europa.eu.int/comm/health/ph_risk/committees/04_scenihhr/docs/scenihhr_o_003.pdf

³ HM Government (2004) *Response to the Royal Society and Royal Academy of Engineering Report: 'Nanoscience and nanotechnologies: opportunities and uncertainties'*. London: DTI. See: <http://www.ost.gov.uk/policy/issues/index.htm>

Aims and scope

11. The Food Standards Agency is responsible for food safety, nutrition (jointly with the UK health departments) and protecting the interests of consumers in relation to food. As part of this work the Agency advises the Government and the public on risks from food and takes a lead in the UK for regulations relating to food safety, consumer protection in relation to food, and animal feed.⁴
12. The Agency review covered all areas within its responsibility. The Agency decided to review risk assessment as well as regulation, since regulation in the food area is closely linked to risk assessment. As far as possible the review considered potential uses or releases even if such uses are not known to exist or to be planned at present. Uses could involve materials that are nano-scale in one dimension (films, coatings) two dimensions (nanofibres/tubes) or three dimensions (nanoparticles).
13. The aims of the Agency's review were to
 - assess whether current procedures in the areas for which the Agency is responsible would be able to identify, assess and control any potential risks and other issues arising from the use of nanotechnologies or the presence of manufactured nanomaterials in food;
 - identify any gaps in regulation or risk assessment;
 - set out the actions currently in train or planned to address these gaps and any other issues both in the UK and internationally.
14. The review considered areas where regulations require some form of formalised 'prior approval' or 'positive list' of permitted products or processes as well as those relying on case-by-case assessment, including deliberate use or adventitious/accidental presence of nanomaterials, for example through planned or unplanned release into the environment.
15. The review also considered wider issues of openness and transparency of regulation and risk assessment in an area where high technical innovation may give rise to competing demands for commercial confidentiality for new nano-materials or nanotechnology.
16. Regulation in the food area is largely decided at European Union level, and UK food law generally implements in the UK the measures that have been agreed at European level. Risk assessment is also co-ordinated at European level in many areas. The Agency works closely with its partners in other European Member States, the European Commission and the European Food Safety Authority, EFSA. Any regulatory gaps in the food area in relation to nanotechnologies would need a response at

⁴ A detailed guide to food law is available on the Agency's website at: <http://www.food.gov.uk/multimedia/pdfs/foodlaw.pdf>

the EU level. The review also took account of current and planned activities at the EU level.

17. The European Commission published a Nanosciences and Nanotechnologies Action Plan in June 2005, in support of its Nanotechnology Strategy for Europe.⁵ Among other things the Action Plan recognises the Commission will have a role in co-ordinating activities in many regulatory areas. The Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) has issued for consultation an opinion on the appropriateness of existing methodologies to assess the potential risks associated with engineered and adventitious products of nanotechnologies.

18. A public consultation exercise on this nanotechnologies regulatory review report was conducted by the Agency in 2006 which has been finished and updated in July 2008.

REGULATION

Novel foods and processes

19. The Novel Foods Regulation (EC) 258/97 applies to foods or ingredients (other than food additives) not consumed within the EU before 15th May 1997. It establishes a mandatory pre-market approval system for all novel foods and processes that applies and is legally binding to all EU Member States.

20. The Agency is the UK competent authority for this regulation. It is advised in this role by the independent Advisory Committee on Novel Foods and Processes (ACNFP), which carries out a thorough safety evaluation based on rigorous scrutiny of scientific data (eg toxicological, allergenicity and nutritional information). As well as the scientific safety assessment, the committee also takes into account issues of consumer concern and ethical issues. Decisions regarding approval are made by Member States using a qualified majority vote at the EC Standing Committee on the Food Chain and Animal Health.

21. There are no specific criteria to consider particle size under this legislation. However, the assessment of the food or food ingredient includes details of the composition, nutritional value, metabolism, intended use and the level of microbiological and chemical contaminants. Where appropriate, this might also include studies on the toxicology and allergenicity of the novel food. In addition, details of the manufacturing process used to process the food or food ingredient are also considered and novel food production processes can render a food novel if it alters the final composition of the food.

⁵ 'Nanosciences and nanotechnologies: An action plan for Europe 2005-2009' (COM(2005) 243). Available at:

http://europa.eu.int/comm/research/industrial_technologies/lists/list_108_en.html

Gaps in regulation

22. On the whole this process is considered adequate to identify any potential risk associated with the presence of newly designed nanomaterials that might be used as food ingredients. It is less certain that this regulatory framework would apply to ingredients that have a history of use and which might in future be marketed in smaller particle sizes of 100nm or below. Nevertheless, in such cases, the general safety articles of the EU Food Law Regulation (178/2002) would apply, which require that food placed on the market is not unsafe. Other applications of nanotechnology in food processing would require evaluation under the novel foods regime only if they significantly affect the properties of the final product.
23. The novel foods Regulation is currently being reviewed. A proposal to replace this Regulation was published in January 2008 and this clarifies that nanoparticles are to be included within its remit.

Food additives

24. The use of food additives in the EU is controlled by European Parliament and Council legislation, which sets out lists of permitted additives, the foods in which they can be used, and maximum levels of use. All permitted additives have been assessed for safety by the independent Scientific Committees that advise the European Commission. Assessments are now carried out by EFSA. In addition, each additive must comply with specific purity criteria laid down in corresponding European Commission Directives. The criteria dictate the chemical structure and purity of each additive. However, minimum particle size is only specified in the case of microcrystalline cellulose (E460 (i)), while the specification for carrageenan (E407) limits the molecular weight distribution (which may indirectly limit particle size).
25. Food Additives are controlled in the UK by the Sweeteners in Food Regulations 1995 (as amended), the Colours in Food Regulations 1995 (as amended), and the Miscellaneous Food Additives Regulations 1995 (as amended), with smoke flavourings being specifically controlled by the Smoke Flavourings (England) Regulations 2005. A recently proposed amendment to EU food additives legislation states that when a food additive is already included in a Community list and there is a significant change in the production methods or the starting materials, or a change in particle size, for example through nanotechnology, the food additive prepared by those new methods or materials shall be considered as a different additive, and a new entry in the Community lists or change in the specifications shall be required before it can be placed on the market.
26. Positive lists control miscellaneous additives, colours, sweeteners and smoke flavourings. Any new nanomaterials would need to undergo safety assessments by EFSA before they were included on the relevant

positive list and so be permitted in foods. For the majority of additives, specifications have also been elaborated for the material as used.

27. The only examples in the food additives area that specifically limits the presence of small particles is the specification for microcrystalline cellulose, where the presence of particles <5 microns (5000 nm) is limited because of uncertainties over their safety. There is a limit on the molecular weight distribution of carrageenan (which could be regarded as a size limitation) based on concerns over potential toxicity in the gut associated with the smaller “degraded” components.

Gaps in regulation

28. As none of the other permitted additives include limitation on the size of particles, it could be argued that in principle there are gaps in the legislation. The proposed amendment mentioned in paragraph 23, which would require an existing food additive produced through nanotechnology to be assessed by EFSA as a new additive, is intended to clarify the legislative situation. Individual specifications, which are set out in Commission Directives, may be amended at Standing Committee and this is a straightforward process. Therefore, action could be taken fairly quickly if EFSA recommended that amendments were required to address the issue of particle size, whether as a result of its own assessment or on the basis of information or a request from a Member States.
29. In order to inform the assessment of any issues associated with this new technology, the Agency has issued a call for research proposals to: "Assess potential applications of nanotechnology for food additives and other (novel) food ingredients, considering the consumer safety and regulatory implications of their possible use." This research will help us to identify how near to the market any developments are, and any gaps in procedures and is due to be published summer/autumn 2008.

Food contact materials

30. Current controls stem mainly from Regulation (EC) 1935/2004. This covers materials and articles that are intended to be, already are, or can reasonably be expected to be brought into contact with food and those that might reasonably be expected to transfer their constituents to food.
31. This Regulation is drawn widely enough to deal with the migration of ‘nanocomponents’ into food from food contact materials and articles. This is because the legislation deals with the material or the article and its components in general rather than any component or type of component in particular. It requires that these materials and articles may not transfer their constituents to foods under normal and foreseeable conditions of use in quantities that could endanger human health, or bring about an unacceptable change in the composition of the food or deterioration in the organoleptic properties of the food.

32. In addition, where the 'nanocomponent' might be intended to migrate into the food as part of an 'active' packaging system, it must only do so to improve the shelf life or to maintain or improve the condition of the food. However, any change to the food must comply with EC provisions applicable to food. Where that 'nanocomponent' is part of an 'intelligent' packaging system the material or article may only monitor the condition of the food in the packaging or the environment around the food. Furthermore it may not give information to the consumer that could mislead about the condition of the food. Both types of material or article must be labelled to say that they are 'active' or 'intelligent'.
33. Provision exists for the European Commission, acting at its own behest or in response to a request from a Member State, to ask the European Food Safety Authority to conduct an independent, expert human health risk assessment of any substance or compound used in the manufacture of a food contact material or article. This risk assessment is published and provided to the Commission so that, in co-operation with the Member States, suitable measures may be put in place across the EU to deal with any public health or food issues arising from that risk assessment. There is also provision for the UK and any other EU Member State to act on its own behalf in relation to any perceived health risk pending assessment of that risk at the European level. Any unilateral UK action would only be taken after taking into account data on the migration of the substance or nanomaterial into food, or if necessary an established simulant for the food, expert analysis of the scientific data on the health effects and assessment of the public's exposure to the risk. The wider ramifications of courses of action on other aspects of food safety and public health would also be considered where they apply. For instance it would be necessary to ensure that any action taken against, say a particular nanomaterial in a food contact material, did not lead to the food safety related function of that material being unwittingly compromised.
34. Some materials and articles are subject to specific measures. Different requirements may apply to 'nanocomponents' incorporated into these materials or articles, as set out below.
- i. Plastic materials and articles.* These are subject to the rules contained in Commission Directive 2002/72/EC, these rules are implemented in Great Britain by The Plastic Materials and Articles in Contact with Food Regulations 1998, as amended. The provisions in the legislation for these materials and articles do not yet differentiate between nanoscale components and others. It is possible within the legislation as framed for a nanosubstance to be treated separately from the normal scale substance from which it is derived. In this case it would have to be approved for use in food contact plastics separately. Otherwise, monomers or starting substances have to be included in a positive list and if they are not on that list they cannot be used. Additives to the polymer in order to achieve a technical effect are currently subject to an open list system. This will change in the future but the Commission has not set a date for this. In the case of substances not included in

the lists in the legislation, i.e. those that directly influence the formation of the polymer and colorants and solvents, they are subject to the requirements of the general Regulation (EC) 1935/2004 described above.

ii. Ceramic materials and articles. These are covered by their own specific legislation that controls the migration of lead and cadmium into foodstuffs from the ceramic ware. Other issues affecting the safety, quality and nature of food with which these materials come into contact are covered by the provisions of the European Regulation No. (EC) 1935/2004. The Department of Trade and Industry have led historically on food contact ceramics, and recently revoked the original Regulations that applied across the United Kingdom, the Ceramic Ware (Safety) Regulations 1988 that were made under the Consumer Protection Act 1987, and, in co-operation with the Agency, made new regulations under the Food Safety Act 1990. This will ensure that the regulations on these materials and articles is grounded in the same enforcement, offence and penalty regime as applies to other food contact materials and articles. In future the food safety aspects of rules on food contact ceramics will be the responsibility of the Food Standards Agency. Substances in food contact ceramics are not subject to positive listing, as is the case for other food contact materials.

iii. Regenerated cellulose film materials and articles. These and any cellulose coating are subject to manufacture only from substances on a positive list. Exceptions are colorants and adhesives, but these must be non-detectable in the food using a validated method. Any plastic coating of regenerated cellulose film on the food contact side may only be manufactured using substances listed in Directive 2002/72/EC on food contact plastics (see (i) above).

Gaps in regulation.

35. The legislation as it stands does not differentiate between chemicals produced routinely by current methods and those that may be developed by nanotechnology. There is currently no specific scope in the European legal framework for food contact materials and articles to develop specific measures to deal with 'nanocomponents' on their own, however the possibility to develop rules on the use of them should not be ruled out. Until such a development, the products of nanotechnology would have to be dealt with by the specific controls on particular materials and articles. The negotiation and adoption of all the specific measures on all the materials and articles for which harmonised EU legislation is envisaged could take many years.

Actions

36. We will work with the European Commission and other Member States to develop necessary harmonised EU controls on food contact materials for the protection of public health. A harmonised approach will help ensure

consistent and enforceable controls. The European Commission has informally declared its intention to develop controls for the application of nanotechnology in the manufacture of food contact materials and articles, although unless a real problem arises from the use of this technology, specific rules are likely to take some time to put in place.

37. A potential solution would be to amend the European Regulation (EC) 1935/2004 to require that all nanocomponents are subject to their own risk assessment. This would bring all nanocomponents within scope of the requirement regardless of the material they are incorporated into. This would also apply to those materials and articles not already covered by the specific measures currently in place. However, this would require a Commission proposal that would be subject to the co-decision procedure between the Council and the Parliament and could also take considerable time to put in place.
38. Engineering at the nanoscale creates new opportunities for the packaging industries, and various potential food contact applications have been suggested. These include: improved barrier properties; better temperature performance; thinner films for flexible packaging; and nanoscale pigments for inks. However, little is known about the impact on chemical migration into food from such applications. In order to inform the assessment of any migration issues associated with this new technology, the Agency has funded a research project entitled: "Assessment of Current and Projected Applications of Nanotechnology for Food Contact Materials in Relation to Consumer Safety and Regulatory Implications." This work has been undertaken by a Panel of Experts from SnIRC (Safety of nanomaterials Interdisciplinary Research Centre) that was led for this project by Central Science Laboratory, York. The study involved collation of information on the current and projected processes, products, and applications of nanotechnologies for FCMs through extensive searches of published literature, industry information, and key market reports. Information on the potential migration of nanoparticles from food contact materials was also obtained as part of this study through experimental testing of nanomaterial migration in two typical nanotechnology-derived food contact materials. The findings of the study were disseminated and discussed at a workshop, attended by representatives from academia, consumer forums, industry, regulatory agencies, and R&D stakeholders. Some of the information gathered has been published as a review article in a peer-reviewed journal (Chaudhry, Q; Scotter, M; Blackburn, J; Ross, B; Boxall, A; Castle, L; Watkins, R; Aitken, R (2008) Applications and implications of nanotechnologies for the food sector. *Food Additives and Contaminants* 25(3): 241-258). The final report on this project will be published by the Agency in summer 2008.
39. We will consider any further actions in light of the results of this work and the other relevant work carried out under the co-ordination of the NRCG.

Other areas

Animal feed

40. EU legislation on animal feed covers the additives (vitamins, colourants, flavourings, binders, and so on) authorised for use in animal feed; the maximum levels of various contaminants (e.g. arsenic, lead, dioxins); ingredients that may not be used in feed; nutritional claims that can be made for certain feeds; the names and descriptions which must be applied to various feed materials; and the information to be provided on feed labels.
41. The European Commission White Paper on Food Safety (January 2000) contains a number of proposals to strengthen feedingstuffs legislation. These are now in force, and/or are being implemented in national legislation. The chief measures are:
- EC Regulation 178/2002 laying down the general principles of food and feed law, which includes provisions on feed for food-producing animals. This prohibits the marketing of unsafe feed and requires feed businesses to have traceability procedures in place.
 - EC Regulation 882/2004 on official food and feed controls, which consolidates existing enforcement and inspection measures, lays down the principles and powers for carrying out these controls, and specifies the action to be taken both to check businesses' compliance with the rules and when breaches are found.
 - EC Regulation 183/2005 on feed hygiene, which requires all feed businesses, including farms involved in making or marketing feeds, to be registered. Feed businesses will have to comply with standards in respect of facilities, storage, personnel and record-keeping. This Regulation applies throughout the feed chain, including to food manufacturers selling material into the feed chain and all livestock and some arable farmers.
42. We are not aware of any specific applications in the pipeline with respect to the use of nanotechnology directly in animal feed. However, current procedures would allow a proper risk assessment to be performed on such products if and when they appear.
43. Since 2004, candidate feed additives have been assessed for safety to the consumer, to target species and to the environment by the European Food Safety Authority (EFSA), prior to possible authorisation. Dossiers for new feed bioproteins ('certain products') are assessed jointly by EFSA and the Member States. While the manufacture of additives and bioproteins via the use of nanotechnology might pose new risks to consumers, workers, animal health and to the environment, the risk assessment system is sufficiently flexible to be able to encompass these – EFSA can co-opt appropriate scientists and technologists if expertise for assessment needs to be augmented. The fact that changes to the assessment procedure can be made where new potential risks are identified has been demonstrated by the way that feed products consisting of, or derived from *Bacillus* species are now assessed for their

potential to contain or produce toxins. The changes to the assessment procedure were started in 2000, following heightened concerns in Member States. The manufacture of currently authorised additives and bioproteins by new methods would require reassessment.

Pesticides, veterinary medicines and biocides

44. If manufactured nanomaterials were used as pesticides, veterinary medicines or biocides then the current authorisation processes would apply, and any product would be assessed before approval for use by the relevant independent advisory committees: the Advisory Committee on Pesticides, the Veterinary Product Committee and the Biocides Consultative Committee. The Department for Environment, Food and Rural Affairs, with the Pesticides Safety Directorate and Veterinary Medicines Directorate, lead on these regulations. The Agency works with Defra and the advisory and regulatory bodies in these areas to ensure that food safety is given top priority during the authorisation and monitoring of pesticides, veterinary medicines and biocides.

Food hygiene

45. New EU legislation on food hygiene comes into force on 1st January 2006. This consists of Regulation 852/2004 (which covers the general food hygiene rules for all foodstuffs), Regulation 853/2004 (which covers additional specific rules for products of animal origin) and Regulation 854/2004 (which sets out the official controls for products of animal origin).

46. Although none of these Regulations has provisions specifically relating to nanotechnologies, nor any prior approval requirements for the use of such processes, each of them gives powers to the Commission to amend the Regulations to take account of scientific or technological progress. There is therefore the potential for the EU to legislate quickly in this area, either to regulate the food business operator's use of nanotechnologies or to impose additional official control procedures in relation to them. Furthermore, Regulation 852/2004 obliges food business operators not to accept raw material or ingredients if they are known to be, or might reasonably be expected to be, contaminated with toxic or other foreign substances to such an extent that the final products would be unfit for human consumption.

47. However, in practice the marketing of products of animal origin produced using nanotechnologies should be covered by the prior approval requirements of other legislation such as the EU Novel Foods Regulation (see above). Uses of nanotechnologies in the production of products of animal origin would be covered by the prior approval/positive list requirements in that regulation or in legislation such as that on veterinary medicines and animal feedingstuffs (see above). Similarly, potential food safety risks associated with veterinary medicines employing nanotechnology should be addressed in the approval process, and any residues could be monitored via the Veterinary Medicines Directorate's

national surveillance scheme (provided of course appropriate methods were available for detection).

Labelling

48. Under the food labelling legislation (Directive 2000/13/EC - implemented in the UK by the Food Labelling Regulations 1996, all ingredients in packaged food need to be declared, including nanomaterials. However, the labelling need not include details of the particle size of the ingredients. Any proposal to introduce mandatory labelling requirements would need to be implemented separately, as with GM ingredients. General labelling provisions exist which require the true nature of food to be declared which includes any processing or treatment. However, this would not necessarily be required for constituent ingredients in a food product (Article 5 (1a) of 2000/13/EC). Regulation 178/2002 on general food law also requires that consumers are not misled. Existing legislation should account for traceability of materials added to food (Regulation 178/2002 would be applicable for nano food ingredients or nano food additives).
49. The European Commission has recently completed a review of existing food labelling legislation, and on 30 January 2008, it published a proposal for a regulation on the Provision of Food Information to Consumers. Nanotechnology is not mentioned in the proposal as it deals with horizontal labelling considerations rather than specific issues. Should consumers start to demand to know whether or not a food or food ingredient has been produced through nanotechnology, then the Commission might be able to bring in specific rules to enable this to happen.

Exposure through potential release into the environment

50. Many existing environmental contaminants are present in food in very small quantities, at molecular or fine particle level. These may be regarded as nanomaterials in the wider sense but are not deliberately manufactured nanomaterials. If they are constructed of a material that is considered sufficiently undesirable then they will be subject to regulation as contaminants under the current framework for contaminants.
51. The existing framework for regulation of food contaminants could be applied to any emerging risks from manufactured nanomaterials present in food as a result of deliberate or unplanned releases into the environment.
52. Emergency powers also exist to address any potential immediate risks to consumer in the event of a significant release of nanomaterials into the environment. The Food and Environment Protection Act 1985 empowers Ministers to make emergency orders where they consider that circumstances exist, or may exist, which are likely to create a hazard to human health through the consumption of contaminated food. Such orders prohibit the distribution of affected produce from an area where foodstuffs have, or may have, been contaminated. In practice these

powers are used only where there are no other statutory means of dealing with contaminated food (e.g. sector-specific legislation under the Food Safety Act 1990). Part I of the Food and Environment Protection Act was amended by Section 51 of the Food Safety Act 1990. The Act also applies in Scotland and Northern Ireland.

53. Corresponding powers also exist to impose emergency measures at EU level.
54. Any recommendation from the Agency to use emergency powers would be based on an assessment of the potential risks from any contamination. Risk assessment is discussed in the next section.

RISK ASSESSMENT

55. The previous section reviewed regulations and other controls on food in relation to potential risks from uses of nanotechnologies in food or food production and the presence of nanomaterials in food or feed. Clearly, the application of these regulations and controls, as well as the provision of advice to government and to the public, depends on the assessment of potential risks. In several cases – for example novel foods – regulations explicitly require a risk assessment of products or processes before their use is permitted.
56. As well as considering any gaps in the regulations, it is necessary to consider any gaps in the supporting risk assessment.
57. The independent advisory Committees on Toxicity, on Carcinogenicity and on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COT, COC and COM), have jointly considered generic issues around nanomaterials. The COT identified risk assessment of nanomaterials as an area of interest during horizon scanning discussions in February 2004, prior to the publication of the RS/RAEng review of nanotechnology.
58. The European Food Safety Authority's (EFSA) scientific committee is preparing an opinion on the risks arising from nanoscience and nanotechnologies on food and feed safety and the environment. A draft is due to be put for public consultation in October 2008 and EFSA intends to finalise the opinion before the end of 2008.
59. The terms of reference of the COT, COC and COM includes "to assess and advise on the toxic/carcinogenic/mutagenic risk to man of substances" that could be present in food. The use of the term "substances" encompasses nanomaterials and it was not considered necessary or appropriate to modify this broad remit.
60. The Committees have produced a joint COT/COM/COC statement, which was published early in January 2006, with a supplementary statement issued in March 2007. The Committees noted that particle

size, surface area and surface chemistry are important in determining nanomaterial toxicity and suggested that toxicological studies with nanomaterials should be carried out using a systematic tiered approach. A copy of this report and supplementary statement can be found in Annex I.

61. An important conclusion is that current approaches to risk assessment would be appropriate for nanomaterials, but there are limited toxicological data on nanomaterials available at present. COT members have proposed a systematic approach to toxicological testing of nanomaterials, to support risk assessment however, the highest concern is over non-biodegradable nanoparticles rather than those that are biodegradable.
62. Current procedures would allow the COT to evaluate available information in order to assess any potential risks. Information on nanomaterial usage would need to be provided by the relevant policy division within the Agency, as occurs with other chemicals in food. Information for risk assessment would be considered in light of current knowledge including any relevant published data on other materials. However it is likely that there will be considerable gaps in the database, and hence uncertainty in the risk assessment.
63. The risk assessment will identify key gaps in the information. There are likely to be particular problems with identifying what people are actually exposed to in different matrices, especially environmental samples, and how that compares with the materials that have been tested (where testing has actually been conducted). Much of the published work has focussed on risks due to inhalation of nanomaterials, and there is also interest in medicines and cosmetics. There is a need for more information on possible effects following ingestion (i.e. dietary exposure). The Committees have agreed that they wish to keep the subject of nanomaterial toxicology under regular review.
64. If there are major gaps in the information required for risk assessment, then it should be for the manufacturers to provide the data. Experience in other areas suggests that responsible manufacturers are often willing to commission the work requested, even when there is no statutory obligation. However, there have been some exceptions to this. The Agency will need to consider if additional regulatory measures are required. This will be done through the NIDG in the UK and the European Commission at EU level to ensure a consistent approach across all areas.

OTHER ISSUES

65. The review has also identified some other issues that should be taken into account in pursuing the actions identified above.

66. Commentators on nanotechnologies have highlighted the importance of definitions for nanoparticle and nanotechnology for the purposes of regulation. The Royal Society defined nanomaterials as having one dimension less than 100 nanometres, however, it was agreed by the COT, COC, COM that this definition should not be regarded as rigid and that a case-by-case approach would be more appropriate.
67. Some commentators have suggested that a separate regulatory framework needs to be in place which would cover risk assessment and labelling of nanomaterials used in food production and that a moratorium be in place on the use of nanotechnology applications and the release of nanomaterials into the environment until such regulations exist.
68. As noted above, food regulations are harmonised at the EU level. In seeking to ensure an appropriate and consistent approach to regulation and risk assessment in the EU, we will need to consider how these procedures would deal with foods imported from outside the EU. Other countries may be developing applications that are different from or emerging earlier than in the EU. We need to be able to monitor developments elsewhere and ensure that means are in place to pick these up.

Summary of conclusions

69. On the basis of current information, most potential uses of nanotechnologies that could affect the food area would come under some form of approval process before being permitted for use.
70. This review has not identified any major gaps in regulations in principle, but there is uncertainty in some areas whether applications of nanotechnologies would be picked up consistently. In these cases relatively straightforward options are available to address this uncertainty.
71. As food regulations are harmonised at EU level, these would need to be addressed through the European Commission. The Commission's Nanotechnology Action Plan commits it to co-ordinating an approach to such issues.
72. The view of the independent advisory committees the COT, COC and COM on risk assessment is that the existing paradigm for risk assessment is applicable to nanomaterials although there are major gaps in information for hazard identification.
73. Risk assessment relies on provision of sufficient reliable information to inform an assessment in each case. Development of risk assessment procedures will need to include procedures for provision of information to inform risk assessments, for example in relation to an application for approval for a new product or process.

74. The onus should be on the manufacturers of new products or processes to supply the information needed for risk assessment. A model balancing openness in the interests of consumers and the public and commercial confidentiality exists under the current regulations on novel foods.

Proposed actions

75. The Agency will undertake the following :

- Approach the Commission (SANCO) at the earliest opportunity to clarify and contribute to plans for regulation to address any gaps – backed up with a copy of our review;
- Support the development of risk assessment approaches in this area in close partnership with other Departments and the independent advisory bodies in the UK and the EU (EFSA, SCENIHR);
- Continue to co-ordinate approach through NIDG and NRCG but we would probably want to be pro-active and take a lead in food issues rather than waiting for UK wide response where we can (though there are advantages to having a consistent approach with non-food uses as far as possible).

76. The Agency has commissioned research on new and potential uses of nanotechnology in relation to food contact materials and food additives/novel ingredients. This research considered the consumer safety and regulatory implications of potential uses. We will consider any further actions in light of this research and other relevant work carried out under the co-ordination of the NRCG.

**Food Standards Agency
August 2008**

Glossary

A **nanometre** (nm) is one thousand millionth of a metre. For comparison, a single human hair is about 80,000 nm wide, a red blood cell is approximately 7,000 nm wide and a water molecule is almost 0.3nm across.

Nanoscale may be defined as from 100 nm down to the size of atoms (approximately 0.2nm). At this scale the properties of materials can be very different from those at a larger scale.

Nanoscience is the study of phenomena and manipulation of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale.

Nanotechnologies are the design, characterisation, production and application of structures, devices and systems by controlling shape and size at the nanometre scale.

Nanomaterials have been defined by the Royal Society as having one dimension less than 100nm, but this is not a rigid definition and may change as the science evolves. Nanomaterials may be produced either by reducing the size of larger particles, or by combining individual molecules.

Materials can be produced that are nanoscale in one dimension (for example, very thin surface coatings), in two dimensions (for example, nanowires and nanotubes) or in all three dimensions (for example, nanoparticles).



Annex I

COMMITTEES ON TOXICITY, MUTAGENICITY AND CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT, COM, COC)

JOINT STATEMENT ON NANOMATERIAL TOXICOLOGY

Background

1. In June 2003 the UK Government commissioned the Royal Society, the UK national academy of science, and the Royal Academy of Engineering, the UK national academy of engineering, to carry out an independent study of likely developments in nanotechnology and of whether nanotechnology raises or is likely to raise new ethical, health and safety or social issues which are not covered by current regulation.¹ Their report "Nanoscience and nanotechnologies: opportunities and uncertainties" - was published on 29 July 2004.² The UK Government's response to the joint Royal Society and Royal Academy of Engineering report was published on 25 February 2005.³ The Committees on the Toxicity, Carcinogenicity and Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COT, COC and COM) were identified in an annex to the Government report along with six other independent expert scientific committees as relevant scientific committees to provide advice on the development of nanotechnology. The Government stated in its reply to the Royal Society that it would ask for advice from COT/COC/COM on issues as they arise and seek to ensure that nanotechnologies will be explicitly mentioned in their terms of reference.

2. The COT, COC and COM carry out regular horizon scanning exercises as part of their annual remit (see appended internet links at the end of this statement). The COT identified nanomaterials as an emerging issue at its February 2004 meeting. Following the Royal Society's review of nanotechnology in 2004 (which was discussed at the COT's September 2004 meeting), all three committees identified the risk assessment of nanomaterials as an area of interest and asked for appropriate information to be provided for consideration.

Introduction to current review.

3. Overview papers on the available toxicological data were prepared for the committees to assist in preparing an initial joint statement.⁴⁻⁶ The information presented to the committees was based on a hazard assessment document published by the Health and Safety Executive (HSE)⁷, a literature review prepared by the secretariat which identified a number of additional

published scientific papers (which are cited in the overview papers) and information published in abstracts from the US Society of Toxicology (SOT) meeting held March 6–10, 2005, in New Orleans, Louisiana, USA.⁸ The HSE captured published information up to July 2004 and the additional review prepared for the committees captured information up to March 2005.

4. The Royal Society defined nanomaterials as having one dimension less than 100 nanometres (nm) or 0.1 micrometre (µm).² However, the Committees (COT, COC, COM) agreed that this should not be viewed as a rigid definition and that a pragmatic case-by-case approach should be adopted with regard to nanomaterials. There are two basic approaches to generating novel nanomaterials. ‘Top down’ technologies use machining and etching methods to create particulates which are usually found in micrometre sizes, but can also be produced in nanometre dimensions. Examples include engineered surfaces and surface coatings (e.g fuel cells and catalysts) and microcrystalline materials (potential uses are in textiles, cosmetics, and paints). ‘Bottom-up’ nanotechnologies involve the production of nanomaterials from individual molecules. The nanomaterials thus generated are novel, e.g. carbon nanotubes and nanofoam, nanodots and fullerenes. Some examples of ‘bottom up’ nanomaterials are shown below. The committees noted that nanoparticles were also produced during combustion, food cooking and from vehicle exhausts.

	Carbon nanotubes	Fullerenes	Nanodots	Carbon nanofoam
Structure	Rolled up sheets of graphite, with one end capped	Molecules of carbon formed into hollow cage like structures	Crystalline structures of compounds eg cadmium, selenium, tellurium, sulphur	Clusters of carbon atoms in a web like structure
<u>Properties</u>	Extreme strength and electrical conductivity. Insoluble in water. Biologically non-degradable			Lightweight, spongy solid, can act as semiconductor. Magnetic property

5. Nanomaterials have a high surface to volume ratio. This means that a high proportion of the atoms will be at the particle surface, and consequently surface reactivity will be high. These particles may adopt structures that are different to the bulk form, with different physical and chemical properties. The kinetic behaviour of nanoparticles follows basic laws of gaseous diffusion, with extensive interactions between particles. It is likely these collisions lead to agglomeration, and reactions between nanoparticles and other airborne molecules (water or pollutants).⁷

COT/COC/COM Review of toxicological information on nanomaterials

Proposed approach to initial toxicological studies with nanomaterials

6. The Committees agreed that the objective of the review was to provide a baseline statement on the available information on nanomaterials toxicology. At the present time, there are considerable limitations in the number of materials tested, and in the toxicology data available. However, it is expected there will be considerable growth in the number of nanomaterials produced industrially and their potential commercial applications. There is also virtually no information on potential human exposure resulting from environmental exposure. To some extent this reflects the limited commercial applications to date (excluding medicinal/cosmetic uses which are considered under regulatory assessment schemes). In addition the review provided to COT/COC/COM did not cover the exposure to nanoparticulate material present in air pollution (e.g. resulting from industrial processes, diesel emissions etc). The Committees noted the importance of particle size, surface area and surface chemistry as determinants of nanomaterial toxicity. The main methods of hazard identification used included comparison of hazard data for micrometre sized and nanometre sized equivalent materials.

7. Possible biological effects were discussed, including a contribution of nanoparticles in the genesis of oxidative stress processes. It was suggested that the mechanisms leading to these processes probably depend on particle size and chemical composition. Some of the SOT abstracts reported studies suggesting that surface area might not be the most appropriate metric for describing the dose of nanoparticles, which contrasted with the information available in the HSE review document.^{7,8} The Committees noted the “Seaton” hypothesis regarding potential cardiovascular effects of inhaled particles.⁹ The Committee considered that there was scope for further research into the potential systemic effects associated with inhalation of nanomaterials. This would include information on uptake and systemic distribution and potential for systemic effects (such as procoagulation).

8. The Committees suggested a systematic tiered approach to initial toxicological studies with nanomaterials. Given the paucity of toxicological data indicating which are the vulnerable cell types, and the likelihood that this will be variable depending on nanoparticle surface properties, *in-vitro* assessment should initially be directed towards those cell types shown to receive the highest nanoparticle dose in biodistribution studies (where this information is available). Because of the likely routes of exposure, such an approach would normally involve epithelial cells (e.g. respiratory and gastrointestinal tract) and macrophages (i.e. professional phagocytic cells) for assessment of cytotoxicity, adsorption/uptake, changes in oxidative status, release of mediators. Such studies would provide basic data that could be used for comparison between nanomaterials. This would be followed by a second tier of *in-vivo* studies using appropriate routes of exposure. It was noted that evidence of oral uptake of one type of single-walled carbon nanotube (SWCNT) had been identified.¹⁰ The Committees recognised the need for identifying ranges of standardised nanomaterials for these initial investigations to produce baseline information on structural influences on

toxicological responses (e.g. the impact of surface chemistry). It was acknowledged that the range of nanomaterials and uses would be very diverse. This approach can be summarised in the following figure.

Proposed approach to initial toxicological studies with nanomaterials

9. The Committees confirmed that there was no need to develop a new approach to risk assessment of nanomaterials but there was a clear need to provide hazard identification data on the widest possible range of nanomaterials. It was noted that in the absence of such data it was not possible to derive conclusions about the spectrum of toxicological effects which might be associated with nanomaterials. Thus it was noted that nanoparticles resistant to degradation could accumulate in secondary lysosomes, which in cells with a long survival such as neurones or hepatocytes might lead to chronic toxicity.

Additional comments from COM on mutagenicity evaluation.

10. The COM reviewed a number of publications where mutagenic effects *in vitro* had been specifically attributed to nanoparticulate titanium dioxide¹¹ and zinc oxide¹². However the COM noted inconsistency in the available mutagenicity data and in the information on the specification of the test materials used. It was therefore not able to conclude that any specific mutagenic activity had been documented which would not also be reported for studies using micrometre sized equivalents.

11. The COM considered that specific information on particle size was required to assess mutagenicity studies undertaken with nanomaterials. Thus, there was insufficient information on titanium dioxide to allow an assessment of the agglomeration/disagglomeration of particles in the vehicles used and it was not possible to conclude which particles had been tested. The COM agreed that it might be appropriate to support *in-vitro* mutagenicity tests with imaging data on particle sizes.

12. The Committees agreed that particle size was a generic factor which should be considered with all *in-vitro* testing of nanomaterials.

Additional comment from COC on carcinogenicity evaluation.

13. The Committees discussed whether SWCNTs and other carbon nanotubes might have carcinogenic potential analogous to fibres such as asbestos. Some recent information from the SOT abstracts using gold labelled SWCNT had demonstrated that some of these fibres may evade macrophage engulfment, although granuloma formation was still reported. It was considered they would not reach the mesothelium. The COC considered that more information (including detailed structural data, and absorption and cellular response in macrophages) was required on a range of single- and double-walled carbon nanotubes before any definite conclusions could be reached.

Epidemiological aspects of exposure to nanomaterials.

14. The Committees noted that there were no published epidemiological studies of nanomaterials available. They also noted that the Royal Society report had highlighted problems in the detection of nanoparticles. It was agreed that estimating human exposure to nanoparticles would be exceptionally difficult particularly where there was exposure to a range of both nanometre-sized and micrometre-sized particles. Similarly, assessment of the toxicity would need to distinguish effects arising from the nanoparticle form and those due to chemical composition. HSE have confirmed that the Health and Safety Laboratory (HSL) in Buxton is working with the US National Institute for Occupational Safety and Health (NIOSH) to develop techniques to carry out such monitoring in the future.

Concluding remarks

15. The Committees noted that the current review did not include information on mixtures of nanoparticles such as in environmental air pollution. Members considered that information from environmental epidemiology and volunteer studies of nanomaterials, predominantly from the field of air pollution research, might be informative in identifying end points for initial screening and possible hazards. It was suggested that liaison with other relevant expert groups such as the Committee on the Medical Effects of Air Pollutants (COMEAP) would be valuable. In addition information on medical applications of nanoparticles might be important to the COT discussions. Such information might be potentially relevant with regard to information on structure activity. The secretariat was asked to liaise with the Medicines and Healthcare products Regulatory Agency (MHRA).

16. The Committees reached the following overall conclusions:

i) We note that there is the potential for a wide range of nanomaterials to be produced by many different methods and that there is also the potential that they may be used for many different purposes. Two safety concerns arise: firstly, the intrinsic toxicity of the nanomaterial itself and secondly, the fact that products with potential for widespread human exposure (e.g. paints) may be delivered in future using nanotechnology.

ii) We have proposed a systematic tiered approach for initial toxicological studies on novel nanomaterials based on *in-vitro* screening of selected materials supported by biodistribution studies to aid in the identification of cell types for study, followed by appropriate *in-vivo* testing.

iii) We believe from the available toxicological data that current approaches to risk assessment should be appropriate for nanomaterials. However there are limited toxicological data on nanomaterials at present and we consider it is necessary to keep a watching brief of the developing area of nanomaterial toxicology.

iv) We note the difficulties in determining exposures to nanomaterials but consider this to be a high priority for further research so that appropriate risk assessments can be undertaken.

v) We suggest close collaboration and exchange of information between COT/COC/COM and COMEAP and the MHRA so that information on environmental air pollution and human medicines can be included in further reviews of nanomaterials. Such information may help to identify potential areas of hazard and risk assessment for nanomaterials used in manufactured products.

vi) We consider this subject should be subject to regular reviews by COT/COC/COM.

December 2005

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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

COT ADDENDUM TO JOINT STATEMENT OF THE COMMITTEES ON TOXICITY, MUTAGENICITY AND CARCINOGENICITY ON NANOMATERIAL TOXICOLOGY

Background

1. In December 2005 the Committees on the Toxicity, Carcinogenicity and Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COT, COC and COM) published a joint statement on nanomaterial toxicology <http://www.food.gov.uk/multimedia/pdfs/cotstatements2005nanomats.pdf>.
2. The objective was to provide a baseline statement on the available information on nanomaterials toxicology. The Committees suggested a systematic tiered approach to initial toxicological studies with nanomaterials. The Committees stated that there was no need to develop a new approach to risk assessment of nanomaterials but there was a clear need to provide hazard identification data on the widest possible range of nanomaterials. It was noted that in the absence of such data it was not possible to derive conclusions about the spectrum of toxicological effects which might be associated with nanomaterials. Thus it was noted that nanoparticles resistant to degradation could accumulate in secondary lysosomes, which in cells with a long survival such as neurones or hepatocytes might lead to chronic toxicity.
3. In the concluding remarks the COT indicated additional information on medical applications of nanoparticles might be important to their discussions and might be potentially relevant with regard to information on structure activity.

MHRA review.

4. Following discussions between the secretariat and Medicines and Healthcare products Regulatory Agency (MHRA), the MHRA produced a review of information on the toxicology of nanoparticles used in healthcare. This MHRA review aimed to identify whether healthcare nanoparticles introduced any new toxic hazards and was based on published literature from the last five years supplemented by additional

specific product information. The review excluded healthcare products where the administered product is a single large molecule or entity that just happens to fall in the nanoparticulate scale such as pro-drugs, biological macromolecules and viral transfection agents. Many publications involved *in vitro* proof of principle with incidental cytotoxicity information. The review can be found at <http://www.food.gov.uk/multimedia/pdfs/TOX-2006-28.pdf>.

COT discussion.

5. Based on this comprehensive review, the toxicological database to date was considered to be still inadequate to indicate whether nanoparticles have a specific form of toxicity. The apparent emphasis on an initial wide ranging *in vitro* investigation in nanotoxicology testing strategies might represent a misunderstanding of the role of *in vitro* data since animal studies remained the key hazard identification studies. The role of *in vitro* testing is as part of a tiered approach to decision making and not a means of detecting toxicity endpoints other than genotoxicity hazards.
6. Having considered the new data on healthcare nanoparticles, there were limited data on extrapolation from animals to humans and therefore the implications of such extrapolation and use of standard uncertainty factors would need further consideration as data emerged. Bioavailability and biodistribution studies have a critical role in evaluation of nanoparticles and such information is not obtained from *in vitro* studies. Common mechanisms of toxicity, for example, oxidative stress might also provide a method for prioritisation of those nanoparticles that need further testing.
7. The approach to biodegradable and non-biodegradable nanoparticles might need to be different. There is no evidence that biodegradable nanoparticles have toxicity intrinsic to their nanoparticulate state. In contrast, the evidence indicates that non-biodegradable nanoparticles can cause cell death due to their physical nature by accumulating and overloading lysosomes. Although there was an extremely limited database some studies on nanoparticles had shown evidence of potential shape-specific biological properties.
8. The information reviewed indicated there was a need to consider formulation effects which can affect surface charge and particle size and influence the resulting toxicity. Product specific assessments would be needed as well as clarity on the formulations tested. The COT was informed that this could raise difficulties for evaluating nanoparticles in cosmetics since current EU legislation does not allow *in vivo* testing on cosmetic formulations.
9. The mechanisms of toxicity seen with healthcare nanoparticles were not unique. There is a need for sufficiently sensitive endpoints to identify

effects which had predictive validity for potential adverse effects in humans.

10. Conventional toxicological assessment should be sufficient to identify toxic hazards from biodegradable healthcare nanoparticles. However, it was important to ensure study designs were appropriate to the nanoparticle under investigation. Whilst the standard toxicological test batteries would detect possible effects from healthcare nanoparticles, there was as yet, insufficient information to exclude the possibility of effects not detectable by these methods. The COT was not currently aware of such effects being reported.
11. For pharmaceuticals it has been shown that incorporation into nanoparticle formulations can greatly influence the biodistribution (and hence toxicity) of included chemicals. Indeed the intention behind many such formulations is to facilitate drug delivery across tissue barriers. There is little evidence that the biodistribution of other chemicals not physically included in the original formulations, but accidentally present in the body at the same time as the nanoparticles, can be so influenced. However there is at least a theoretical possibility that freshly generated nanoparticles with reactive surfaces could significantly bind and alter the biodistribution of other xenobiotics. Such effects would not represent nanoparticle toxicity per se, but would represent a consequence of co-exposure.
12. The COT reached the following conclusions in addition to those in paragraph 12 of the joint statement on nanomaterial toxicology <http://www.food.gov.uk/multimedia/pdfs/cotstatements2005nanomats.pdf>
 - I. We wish to emphasise that the role of *in vitro* testing is part of a tiered approach to decision making and not a means of detecting toxicity endpoints other than genotoxicity.
 - II. We concluded that the approach to the risk assessment of biodegradable and non-biodegradable nanoparticles should be different, since the available evidence indicates that non-biodegradable nanoparticles can cause cell death due to their physical interaction with cells. In contrast, biodegradable nanoparticles are less likely to have toxicity intrinsic to their nanoparticulate state.
 - III. There is some limited evidence available to indicate that formulation, i.e. the matrix in which the nanomaterial is present, can affect surface charge and particle size and influence the resulting toxicity. Therefore we conclude that available evidence on formulation effects on toxicity of nanoparticles should be monitored.

COT Statement 2007/01
March 2007