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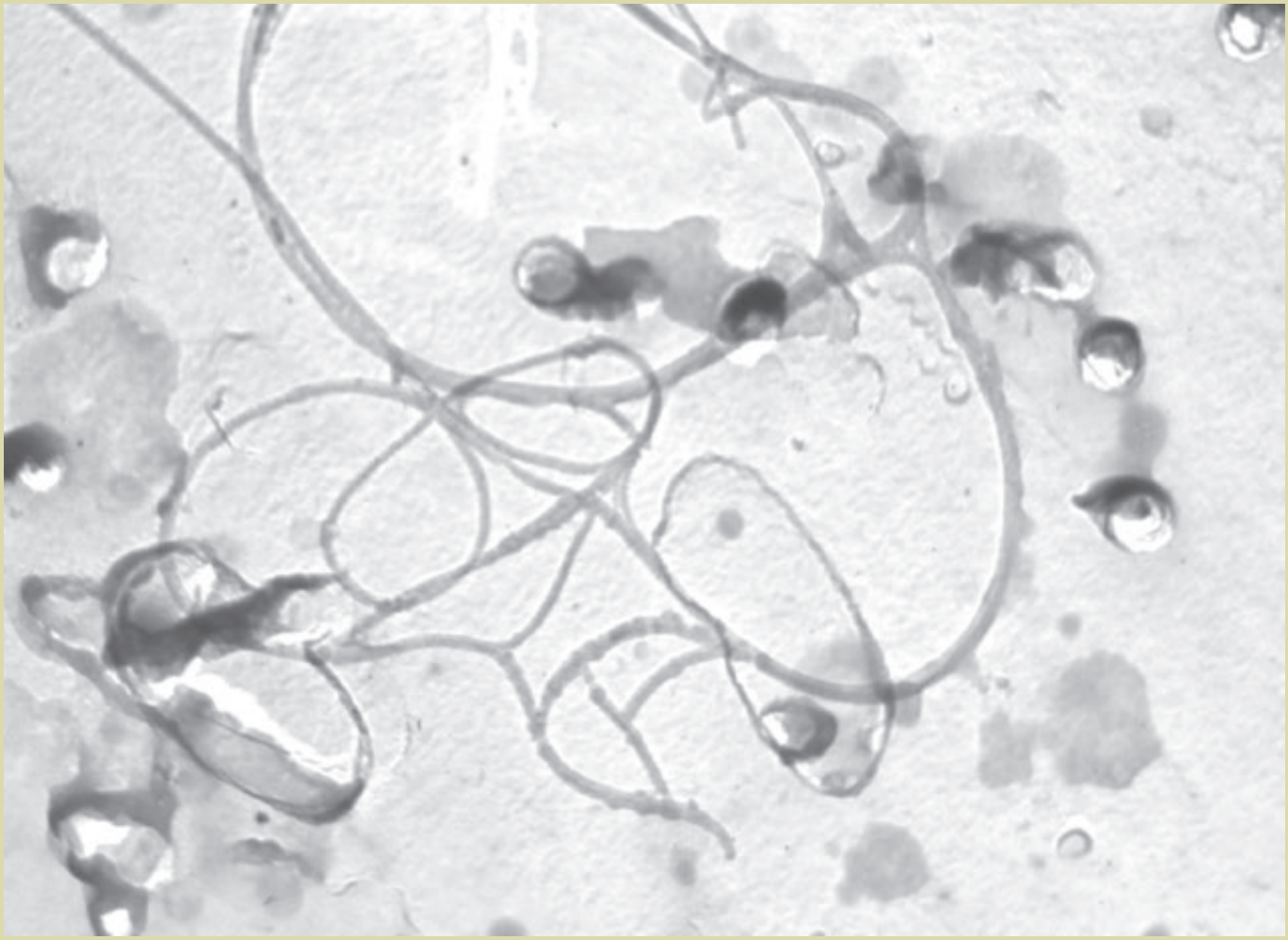
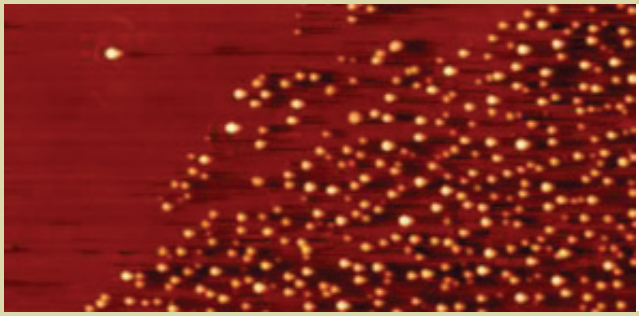
Characterising the Potential Risks posed by Engineered Nanoparticles

A Second UK Government Research Report





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Main cover image: Airborne carbon nonotube fibres collected by drawing a known volume of air through a polycarbonate filter using a sampling pump.

Bottom image: Atomic Force Microscope image of diamond nanoparticles.
Image courtesy of the National Physical Laboratory.

Foreword image: Atomic Force Microscope image of a bundle of carbon nanotubes.
Image courtesy of the National Physical Laboratory.

This report is published by the Department for Environment, Food and Rural Affairs on behalf of the Department for Business, Enterprise and Regulatory Reform, the Department for Innovation, Universities and Skills, the Department for Work and Pensions and the Department of Health.

Further copies of this publication are available from:
Defra Publications
Admail 6000
London
SW1A 2XX
Tel: 08459 556000

This document is also available on the Defra website.

Published by the Department for Environment, Food and Rural Affairs. Printed in the UK, December 2007, on material containing 80% post-consumer waste and 20% Elemental Chlorine-Free pulp.

Product code PB12901

Foreword

Nanotechnology undoubtedly presents a major opportunity for the economic and sustainable development of many countries; current predictions estimate the value of the global nanotechnology industry at $1 trillion by 2015. It also presents many challenges. If the UK is to take full advantage of the opportunities, we must identify and manage potential risks before harm is done to human health or the environment.

That is why the UK research programme is so vital and timely. The programme is truly a cross-government effort. It is being steered by the Nanotechnology Research Coordination Group (NRCG) and draws upon expertise from Government Departments and Agencies, the Research Councils, academia and industry to characterise the potential risks posed by engineered nanoparticles and to consider the social, economic and ethical dimensions.

We are pleased to present this second Government research report which was promised as part of the review process for the research programme. It reviews the status of research pertaining to the environmental, health and safety issues relating to engineered nanoparticles. The report places the UK research programme in an international context and we are collaborating with international partners, particularly through the Organisation for Economic Co-operation and Development (OECD) and the International Standards Organisation (ISO), to share data and experiences. In this way we will be able to maximise the effectiveness and speed with which potential risks may be identified and managed. The report also responds to the recommendations made by the Council for Science and Technology (CST) review (March 2007) on the UK research programme and the activities of the NRCG.

The report clearly shows that the UK is actively pursuing relevant research. Government Departments and Agencies will have funded around £10 million of Environment, Health and Safety related research between 2005 and 2008 with a number of projects having been completed or well under way. This funding sits alongside major funding for research into the fundamental science behind the nanotechnologies through the UK Research Councils, which provide the bedrock on which nanotechnology research is growing in the UK, and the research delivered through the EU Framework Programmes.

There is still a way to go but we can be encouraged that we have got the programme off to a good start. Advances in hazard and risk identification have been made but we still require knowledge and understanding of the underpinning science necessary for the characterisation of nanomaterials and work on human health impacts remains a priority. Both of these aspects continue to present major challenges and will remain a focus for future activities.

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Executive Summary

In October 2005 the Government published 'Characterising the potential risks posed by engineered nanoparticles: A first Government research report'[1], in which a set of 19 Environmental, Health and Safety research objectives were described together with ongoing research in this area and proposed research activities to be taken forward by the Nanotechnology Research Co-ordination Group (NRCG). Funding opportunities were also summarized. This was followed in October 2006 by the publication of a report[2] setting out progress made to meet these 19 objectives.

This report builds on the 2006 publication, providing an update on the NRCG's objectives and associated programme of work. It sets out an updated approach for funding additional research and places UK activities in an international context. It also responds to the recommendations made by the Council for Science and Technology (CST) review[3] published in March 2007 of the UK research programme which was instigated following publication of the Royal Society and Royal Academy of Engineering Report 'Nanoscience and Nanotechnologies: opportunities and uncertainties'[4].

The five Task Forces, set up to take forward the work of the NRCG, have benefited from a broader range of membership, and they now include representatives from industry and additional members from the academic community. This report covers the activities of the five Task Forces and progress on their action plans set out in the 2006 report to meet the 19 objectives.

Task Force 1 (Metrology, Characterisation, Standardisation and Reference Materials): A key output has been a report related to the metrology and characterisation aspects which deals with defining a set of reference nanomaterials and related issues as a means to focus the way forward to establish a bank of reference materials for toxicology studies and other purposes. In addition, standardisation work, particularly at the international level is proceeding very strongly with the UK taking a lead role.

Task Force 2 (Exposures: Sources, Pathways and Technologies): A concerted body of work has begun or is proposed. However, the difficulties in distinguishing between engineered and naturally occurring nanoparticles complicates the assessment of exposure to humans and the environment. Nevertheless, the range of projects and proposals in this area, particularly in the occupational setting, will provide a sound starting point to address many of the uncertainties in our understanding of such exposure to engineered nanoparticles. Exposure in the workplace is an area of work where there has been considerable progress made at an international level.

Task Force 3 (Human Health Hazard and Risk Assessment): The world literature on human toxicology on nanomaterials has been growing, building on work undertaken on combustion derived particles in the atmosphere. The toxicological properties of nanomaterials, like those of other toxicologically active substances, seem to be controlled by dose although the most appropriate metric for dose may be, for example, surface area rather than the mass which is the usual measure of dose. Within the UK, two calls for research proposals have been made and work has now started. Reviews of issues surrounding *in vivo* and *in vitro* toxicology studies on nanomaterials have been undertaken and a proposal to establish a national nanotechnology inhalation research centre has been accepted for funding. The issues surrounding the characterisation of nanoparticles will have a significant impact on the ability to perform human toxicity studies.

Task Force 4 (Environmental Hazard and Risk Assessment): The range of work undertaken and in progress in the UK on environmental hazard and risk assessment supports a number of research priorities on the evaluation of ecohazard and fate and behaviour in the environment. This has seen the successful launch of the Environmental Nanoscience Initiative (ENI), designed for capacity building, pump priming and knowledge transfer activity to drive forward research programmes in this area. An assessment of the fitness for purpose of current ecotoxicological methods for hazard assessment of nanomaterials has been undertaken.

Task Force 5 (Social and Economic Dimensions of Nanotechnologies): The UK has been active in engaging with the public in nanoscience. Few such initiatives have taken place elsewhere. Currently the results of the Demos' People's Inquiry are being considered, both in terms of their implications for Government policy and for the future of public engagement activities. High quality studies by the Economic and Social Research Council (ESRC) and the United Nations Educational Scientific and Cultural Organization (UNESCO) on the social and economic aspects of nanotechnologies have highlighted a number of further concerns and priorities for research. Key priorities for this Task Force will be the economic clustering of the UK innovation community and the consumer and regulatory implications of further nanotechnology development.

Government Departments funded around £10 million of Environment, Health and Safety related research between 2005 and 2008. The Research Councils have also funded significant nanotechnologies research under their responsive mode programmes. These cover a wide range of activities, not only those focused on by the NRCG, and we recognise that more needs to be done to improve understanding, particularly on characterisation of nanoparticles and human health impacts. Progress has been made in joint and collaborative working, upon which we will build, to increase research opportunities and capacity. This will include both directed and responsive mode funding in the UK and via the EU Framework Programme. Discussions are underway to explore more collaborative ways of working between Government Departments, their Agencies, the Research Councils and industry. Opportunities are being explored to support projects through the cross-Government LINK programmes where it is intended to use these platforms as a baseline for any ensuing joint research proposals.

This report places the UK research programme in an international context. Other countries, particularly the US, Japan and Germany, also have strong research programmes on nanotechnologies and it is essential that we work together to pool resources and share results. The UK has been active in the Working Party on Manufactured Nanomaterials (WPMN) set up under the auspices of the Organisation for Economic Co-operation and Development (OECD) to consider the human health and environmental safety issues associated with manufactured nanomaterials. Members of the NRCG have joined the steering groups set up to take projects forward under the WPMN. This offers a unique chance to combine international resources for research and to ensure no unnecessary duplication of effort. The NRCG has also been active in encouraging the UK research community to engage with the EU 7th Framework Programme which has a significant theme on nanomaterials, including EHS aspects with associated funding. The responses to the first call for proposals are currently under evaluation.

The Council for Science and Technology's March 2007 review[3] of the Government's progress on nanotechnologies contained some specific recommendations for the NRCG and UK research programme. This report takes the opportunity to respond directly to those recommendations setting out what changes have already been made or will be considered in the future.

This second research report provides an update on the activities carried out so far and highlights key priorities to be taken forward in the future. Significant progress has already been made, both within the UK and internationally, but research programmes are generally still in their infancy and it will be a while before concrete data is available upon which to base an appropriate appraisal of the potential risks posed by manufactured nanoparticles. With a raft of international research underway, there is a need to undertake a comprehensive review of completed research in the field to guide us on future activities. This will be taken forward over the coming year. Results from the individual projects reported in this document will be made publicly available and references for further information are included throughout.

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Introduction

1.1 Background

1. In November 2005, the Government, through the Nanotechnology Research Coordination Group (NRCG), published its first research report[1] which identified 19 objectives to address research requirements to understand the potential risks to human health and the environment from manufactured free nanomaterials. The driver for the research report was the 2004 Royal Society and Royal Academy of Engineering (RS/RAEng) report[4] on Nanotechnology which highlighted the need to match the development and commercialisation of the new technology with an understanding of potential risks to human health and the environment. The Government responded by setting up the Nanotechnology Issues Dialogue Group (NIDG) and the NRCG to coordinate policy and research respectively across Government Departments, their agencies and the Research Councils. To avoid duplication of research effort and ensure common, appropriate standards are developed for nanotechnologies, the UK has also engaged in dialogue in international fora, particularly with the Organisation for Economic Co-operation and Development (OECD) and the International Standards Organisation (ISO). This second research report follows the publication of an interim progress report[2] in 2006 and takes stock of progress on objectives and presents an updated look at the UK research programme and its place in the international arena.

2. Development of materials and products based on the nanoscale has become a major investment area on a global scale and there are many products already on the market which use materials in this size range. The ability to manipulate chemicals into nanostructures has many applications and a number of reviews have been written on the topic[5,6,7]. Applications in medicine, cosmetics and personal care products, materials science, energy production and storage and electronics are just a few examples where benefits to society, human health and the environment are predicted. However, what is also needed is assurance that the many current and foreseen applications are safe to use. Nanotechnology presents a major opportunity for the economic and sustainable development of many countries (estimates have predicted the value of the global nanotechnology industry at $1 trillion by 2015[8]) and there could be very significant implications for business and the wider community if potential risks are not identified and managed before any harm to the environment or human health may be done.

3. In March 2007, the Council for Science and Technology (CST) reviewed the progress of UK commitments to nanotechnology[3] as outlined in the Governments response to the RS/RAEng report. This document considers the recommendations made by the CST for the research programme, the NRCG and associated activities.

4. This report follows a similar structure to the 2006 progress report where an overall introductory consideration of the research strategy, including funding issues, is followed by contributions from the individual Task Forces on their research priorities and position in meeting objectives. This has inevitably led to some differences in style and format within the document but attention has been paid to the accuracy of information provided. Details of specific research programmes, results, reports and publications are provided in Annexes at the end of the report.

1.2 UK Strategy and Approach to Research

5. Evidence is required to support decisions on appropriate controls that might be necessary for the nanotechnology industries and their products and the NRCG has been, over the past two years, formulating and taking forward an approach to the challenges presented. The priority is to increase our understanding of the hazards and risks of manufactured nanomaterials and

to have investigated the options for appropriate regulation where it may be necessary to prevent harm to human health and/or the environment. This is in the interests of producers, consumers and the general public ensuring the benefits of this new technology are gained without detriment to society. All stakeholders should have the opportunity to be party to the oversight of the process. The Government, in acknowledging the extent of the field that nanotechnologies embrace, has encouraged and participated in international co-operation and collaboration on research requirements especially through the EU Nanoscience and Nanotechnologies Action Plan 2005-2009 and the OECD, which has set up a Working Party on Manufactured Nanomaterials (WPMN).

6. In the longer term, there is a need to build research capacity to be able to understand the more fundamental aspects of the properties, toxicokinetics, and fate and behaviour of nanomaterials in the environment, to be able to develop models for the prediction of impacts and to design new materials that are inherently safe to human health and the environment. A detailed consideration of the safe handling of nanomaterials over different time frames has been recently published[9] which encapsulates the research needs in this area over the next 10-15 years. There have been various other reports on the needs and strategies for addressing the risks from nanotechnologies[10,11,12] which present broadly similar objectives and priorities for the required research.

7. The NRCG set up five Task Forces early in 2006 to take forward the 19 objectives outlined in its first research report. The membership of the Task Forces is listed in Annex K. Each Task Force has members from academic institutions, industry, Government Departments, their Agencies and the Research Councils to get the widest possible input and buy in to their work programmes. The five Task Forces and their research areas are:

   Task Force 1: Metrology, Characterisation, Standardisation and Reference Materials

   Task Force 2: Exposures – Sources, Pathways and Technologies

   Task Force 3: Human Health Hazard and Risk Assessment

   Task Force 4: Environmental Hazard and Risk Assessment

   Task Force 5: Social and Economic Dimensions of Nanotechnologies.

   The research areas breakdown into the 19 objectives which are listed by Task Forces at Annex J.

8. The Task Forces have developed action plans, which were set out in the Government's 2006 progress report and which identified priority areas for research. It became clear to all the Task Forces that there are seven overarching requirements common to them all if we are to understand Environment, Health and Safety (EHS) issues:

   - A fundamental requirement to be able to measure and characterise nanomaterials in a range of media (air, soil, water and in testing nanoparticles for toxicity). This includes having appropriate methods and instrumentation, the ability to differentiate manufactured materials from naturally occurring nanoparticles in the environment and the ability to measure nanomaterials in biological systems.
   - A critical need to understand which physico/chemical properties of nanomaterials are important for toxicity/ecotoxicity such as particle size and size distribution, surface area, surface properties, aspect ratio, surface charge etc.

- A means of prioritising nanomaterials for EHS studies and identifying a set of 'reference' or representative materials for testing. This requires separate consideration for occupational exposure and exposure from consumer products and via the environment.
- A need to know whether methods used in hazard assessment of chemicals, specifically OECD test guidelines (or their equivalents), are fit for purpose for use with nanomaterials.
- A testing plan for 'reference' or representative materials to establish potential hazards to human health and the environment for a range of nanoparticles through an agreed set of toxicity methods.
- The requirement for a review of current risk assessment approaches and associated methodologies for chemicals with regard to their potential suitability for dealing with nanomaterials.
- To understand the economic, social and ethical implications of nanotechnologies through a programme of public dialogue, social and economic research.

9. The Task Forces noted an overarching imperative for standards for nanotechnology nomenclature, characterisation and measurement methods and for codes of practice for safe handling and development of new materials. Progress on the development of standards is considered under the section for Task Force 1.

10. Many of the above seven actions need to be undertaken in parallel to arrive at a position where evaluation of hazard, exposure and risks can be based on evidence from widely agreed and accepted characterisation procedures and testing protocols. In the generation of hazard data there is also an important need to look at the role that in *vitro* methods can play to reduce the reliance on animal testing.

11. In considering these research requirements, the Task Forces took account of the need for the UK to play its part in the wider international research effort. They were also mindful of the potential problem of capacity and capability of the UK research community to undertake the work required and of the competing demands on the various forms of funding available to meet the priorities set for nanotechnology EHS research.

1.3 Funding the research

12. There are a number of funding opportunities available to support research work in the UK and these are not specific to nanotechnology. What is unusual in the present situation is the identification of and need for a very significant programme of work in a rapidly developing area of technology and concerns about the limited capacity of the research community to respond quickly enough to the many questions that arise. Industry, Government Departments and their Agencies, the Research Councils and EU funding Framework programmes all have a role to play and it is clear that the best way ahead is to work collaboratively making best use of the various resources available in a shared responsibility for capacity building and to fund the necessary research work.

13. The responsibility for funding research into EHS implications of nanotechnologies will remain with the appropriate department, agency or Research Council and not through a single department, body or agency with power to allocate funds and instigate action as recommended by the CST. This makes it all the more important to collaborate and share the funding of projects in the UK. This approach also holds true at the international level where collaboration will lead to a more efficient use of funds and will avoid unnecessary duplication of effort, particularly where the use of animals for hazard identification and characterisation cannot be avoided.

14. In the UK, therefore, the NRCG will strive to strengthen joint working on Environmental, Health and Safety Research to draw further together those responsible for the various funding streams. Examples to build on include the 'directed call' approach adopted by the Natural Environment Research Council (NERC) in conjunction with the Environment Agency (EA) and Defra for the Environmental Nanoscience Initiative to focus proposals in a particular area of research; the MRC (Medical Research Council) Highlight Notice framed around the relevant NRCG objectives and the industry/Government collaborative research programmes run by the Technology Strategy Board and Research Councils and Defra's LINK programmes with industry. The intention with these programmes will be to ensure that the balance of the research towards safe and responsible development is appropriate as recommended in the CST review.

Government and Agency funding

15. Government Departments and Agencies fund research to answer specific policy questions. Defra, the Health and Safety Executive and the Environment Agency have all committed funds for nanotechnology research over the past few years and this has been reported on in the previous two Government reports. The National Measurement System (NMS) in the Department for Innovation University and Skills (DIUS) funds nanometrology activities in a number of programmes: Innovation R&D, Chemical & Biological Metrology, Engineering & Flow Metrology, Materials & Thermal Metrology, Physical Metrology, Quantum Metrology and Measurements for Innovation.

16. Total funding from Government Departments and Agencies on EHS work between 2005 and 2008:

Defra	Approximately £1.5m from 2005/2006 to 2008
DH	£250k for 2007/2008.
DIUS	Approximately £6.2m spend on nanometrology activities from 2005/2006 to 2008 (includes £2.6m prediction for 2007/2008).
MoD	Approximately £50k.
EA	£100k total between 2005 and 2006.
FSA	£106k total for 2007/2008.
HPA	Approximately £300k allocated.
HSE	Approximately £1.63m between 2006 and 2008.
Total	**£10.136m**

17. Although nanotoxicology lies outside the Department of Health's (DH) usual sphere of funding, DH recognises that without cross-Government support in this area it will be difficult to move the subject forward. DH has therefore recently committed to providing £1.25m over 5 years to support the health-related research needs identified by the NRCG. Future funding beyond this commitment would expect to be targeted on areas that are regarded within DH's usual remit.

18. The Ministry of Defence (MoD), Biotechnology and Biological Sciences Research Council (BBSRC), Engineering and Physical Sciences Research Council (EPSRC) and Medical Research Council (MRC) contribute funds totalling £19.4m (3.4m, 3.0m, 10.0m and 3.0m, respectively) towards running the Interdisciplinary Research Centres (IRCs) in nanotechnology at Oxford and Cambridge Universities. However, only a small proportion of these costs are devoted to EHS research.

19. Similarly, the Technology Strategy Board is funding three UK based Micro and Nano Technology open access facilities on Micro and Nano Technology. SAFENANO is an information centre (http://www.safenano.org/) with a focus on capturing emerging scientific evidence and translating it in a way that enables industry to develop nanoscale technology safely and responsibly. SAFENANO exists as a free information service through its website. The project cost over its three year life is £318k which is 100% funded by the Technology Strategy Board.

20. The Technology Strategy Board is also funding two centres offering services on Micro and Nano scale materials characterisation. The two centres – CEMMNT (http://www.lboro.ac.uk/research/cemmnt/) and Begbroke Nano (http://www.begbroke.ox.ac.uk//), based at Loughborough and Oxford Universities respectively - have total project costs of £12m over their project lives of five years, with £6m grant support from the Technology Strategy Board. CEMMNT attributes approximately 2% of its enquiries to Health and Safety issues. Begbroke Nano attributes approximately 5%.

21. The CST review supported the RS/RAEng recommendation in 2004 that Government should spend a minimum of £5m/year over the next ten years to achieve the research aims. The amounts to be spent in the future will depend on an analysis of available resources following the announcement of the 2007 Spending Review. In analysis preceding the Review, Her Majesty's Treasury (HMT) had regard to eight science and technology clusters identified by the Government Office for Science. These clusters, which include nanotechnologies, are areas where developments affecting wealth creation, changing society or transforming public services are to be expected in the next decade.

Research Council funding

22. The Research Councils provide funding for high quality research. Their coordinating body, Research Councils UK (RCUK), has established a Nanotechnology Group in order to facilitate cross Council working in the area. The Group meets regularly to exchange information and to consider the possibility of cross Council initiatives in the area. The Environmental Nanoscience Initiative and the Interdisciplinary Research Centres in nanotechnology are examples of existing cross Council initiatives. Progress with cross Council initiatives will be considered following the announcement of the Comprehensive Spending Review 2007. Councils will be contributing to the cross-Council priorities, one of which is 'nanoscience through engineering to application', and Councils will be agreeing individual contributions which will be outlined in the updated RCUK Delivery Plan which will be submitted to DIUS in the near future.

23. Typically, the Research Council funded projects' usefulness in providing the high quality research base on which others (e.g. Defra, Technology Strategy Board) can build is very high, although the projects might not address NRCG Research Objectives explicitly. Both the Research Councils and the Technology Strategy Board support a number of nano characterisation facilities that are available to a wide range of researchers, including those in the EHS domain. It is not possible to quantify the extent of future usage of such facilities by EHS researchers. However, this substantial investment of public funds provides a valuable underpinning resource for EHS researchers.

24. The Engineering and Physical Sciences Research Council (EPSRC) has established a strategy for nanotechnology; this is described in detail at: http://www.epsrc.ac.uk/ResearchFunding/Programmes/Materials/ReviewsAndConsultations/Nanotechnology/NanotechnologyStrategy.htm

25. EPSRC has already started to implement this strategy through the appointment of a Senior Strategy Adviser, the creation of a Strategic Advisory Team, and the launch of calls for equipment sharing and the first Grand Challenge in the area of large-scale, integrated projects exploiting nanotechnology to enable cheap, efficient and scalable ways to harvest solar energy. EPSRC will also start to consult on the scope of the second Grand Challenge, which will be in the area of healthcare. In addition to working with funders, users and researchers, the EPSRC will also seek to secure an input from the public on the choice of areas. This will build upon completed work on public engagement through, amongst other things, the Nanotechnology Engagement Group.

26. Further details of nanotechnology EHS and economic and social research supported by the BBSRC, EPSRC, ESRC, MRC and NERC are contained in the relevant Task Force sections of the report and a summary of research relevant to NRCG objectives funded since 2004 can be seen in Annex H.

EU Framework Research Programme

27. Members of the NRCG have been strongly supportive of the submission by UK institutions of proposals under the New Materials and Nanotechnologies theme of the EU 7th Framework Research Programme (FP7) which has €3.5bn available for research in this field. Responses to the first call for proposals will be finally evaluated by November 2007 and a second call for proposals will go out in December. It is expected that a number of projects to support EHS objectives will be funded and the NRCG will be keeping a close watch on these and how they will fit into its own and the broader research agenda. A number of collaborative projects have been funded under the EU FP6 programme including Impart, Nanotox, Nanosafe 2, NANOSH and these are considered within the appropriate Task Force sections.

OECD Working Party on Manufactured Nanomaterials (WPMN)

28. The very large potential number and variety of new nanomaterials poses a real issue of capacity and capability for any one country to carry out the work necessary to understand the EHS aspects of nanomaterials. It is for this reason that the international community has come together under the Organisation for Economic Co-operation and Development (OECD) to formulate programmes of work to address the knowledge gaps. The OECD Working Party on Manufactured Nanomaterials (WPMN) was set up at a meeting in London in October 2006.

29. The WPMN, through its 6 projects each overseen by a Steering Group (SG), has drawn up operational plans which are being actively worked on. The six Steering Group topics are as follows:

    SG1 Database on Environment Health & Safety (EHS) Research

    SG2 EHS Research strategies on manufactured nanomaterials

    SG3 Safety testing of a representative set of manufactured nanomaterials.

    SG4 Manufactured nanomaterials and test guidelines.

    SG5 Co-operation on voluntary schemes and regulatory programmes. A drafting group on co-operation on exposure measurement and exposure mitigation will have inputs from SG5.

    SG6 Co-operation on risk assessment.

30. The operational plans from the Steering Groups are in the main part in line with similar approaches and strategies from the UK NRCG and other bodies such as the US Environmental Protection Agency[12], the German Government[13] and the US National Science and Technology Council[14] which have produced their own research reports.

31. The UK is well represented on the OECD WPMN having members on the managing bureau and each of the 6 Steering Groups with the lead on one of them. This will enable the UK to contribute to and learn from this internationally shared responsibility for understanding hazard, exposure and risk assessment of manufactured nanomaterials. The Steering Groups have frequent teleconferences and occasional meetings to take the operational plans forward and ensure no overlap of responsibilities. The WPMN meets twice a year to review progress and the third meeting was held in November 2007.

1.4 International Research

32. An attempt has been made to identify ongoing research and proposals for new projects outside the UK. The intention was to broadly identify some of the more important activities and not to catalogue an exhaustive list of research work of other countries – indeed this is an exercise which the OECD will be attempting as part of its operational plans. The table at Annex F lists projects which are funded by other international Governments, research institutes or consortia of industry, public bodies or Government and work being carried out within academic institutions. It is not clear just how much research is going on within industry as this information is not always publicly available. Internationally it is recognised that there are three main priorities for research:

- There is a widespread lack of evidence of research on human health aspects of nanomaterials and the sharing of research results in this field. A recently published report[15] of a study carried out on behalf of the Swiss Federal Offices for the Environment (FOEN) and of Public Health (SFOPH) confirmed the limited data available on the toxicology, release, environmental behaviour and safety of nanoparticles. Furthermore, it questioned the meaningfulness of the results of the few studies carried out, particularly those using high concentrations of particles, and with samples or materials that had not been adequately characterised.

- Given the fast pace of developments in nanotechnology applications and an ever increasing market for nanotechnology products, there is an urgent need for more international collaboration to accelerate the process of risk assessment. With the majority of current research proposals projected to run over a span of a few to several years, the urgency to generate key EHS data can not be overemphasized. One of the recommendations flowing from the paper "EPA and Nanotechnology: Oversight for the 21st Century"[16] is for the U.S. Environmental Protection Agency (EPA) working with State Departments and other agencies to fully support the OECD's developing mechanisms for exchange of nano research results.

- It is widely accepted by the international community that the development of appropriate reference materials and characterisation methodology, is lagging behind, and remains a significant factor hindering the design and execution of experiments and interpretation of research results.

33. Within Europe, the UK and German Governments have been actively involved in driving research over a number of years, the latter having brokered a partnership approach with industry, examples of which include the recently initiated projects Nanocare, Tracer and Inos, which draw upon the research expertise from industry, research institutes and universities.

A paper (Annex G) released in July 2007 by DECHEMA (Society for Chemical Engineering and Biotechnology) and VCI (German Chemical Industry Association) outlines the "Roadmap of the Dechema-VCI Working Group on safety research on nanomaterials" detailing industry involvement in national as well as EU 7th Framework Programmes to assess the potential risks posed by nanomaterials.

34. Elsewhere in Europe, where Government interest has been identified, it has not translated into significant action yet, and for most of these nations, the process of formulating action plans is just beginning. Nevertheless, projects in research institutes and universities can be identified. These are in the main funded through the EU FP6 programmes and include: NANOSAFE 2 (France, Belgium, Germany, Slovenia, Switzerland, Finland, UK); NanoInteract "Development of a platform and toolkit for understanding interactions between nanoparticles and the living world" (Ireland); DIPNA "Development of an Integrated Platform for Nanoparticle Analysis (Italy); NANOSH (Finland, Germany, Netherlands, Poland, UK). More details about other existing EU programmes can be found at: (http://cordis.europa.eu/nanotechnology/src/safety.htm).

35. The European Commission has also committed to boost support for collaborative risk related research on nanotechnology through the FP7 programme for which first calls for proposals were published in December 2006, details of which can be found at: (http://cordis.europa.eu/fp7/cooperation/nanotechnology_en.html). In addition, DG Research of the European Commission recently circulated, for comments, a report on the research efforts at EU level.

36. The Nanotechnology and Molecular Imaging Unit is one of five Scientific Units of the Institute for Health and Consumer Protection of the European Commission's Joint Research Centre (JRC). The unit provides scientific support in key technologies for JRC priority areas related to Environment and Health, alternative methods, exposure monitoring and security. In the area of nanobiotechnology, based on extensive experience in surface engineering and biophotonics, new bio-interfaces, biosensors and diagnostic systems are developed and tailored to specific applications in toxicology (high throughput screening), exposure assessment and monitoring, toxicity of nanoparticles, and health.

37. The Swiss Government is one of the latest entrants in developing a plan of action for research priorities. This progresses the Swiss "Risk Assessment and Risk Management for Synthetic Nanomaterials 2006 – 2009" plan and will be informed by the findings of the study[15] mentioned above. The Research Council in Norway has adopted a national strategy which is awaiting consideration by Government, whereas in the Netherlands, an inter-departmental working group on possible risks is due to produce an action plan for the Government.

38. The Swedish Government has commissioned a review of available knowledge and identification of gaps with a view to formulating proposals for filling gaps, whereas in Italy, a Commission has been set up to cover the range of risk issues.

39. In France, the National Institute for Industrial Environment and Risks (INERIS) and other French partners to the EU funded NANOSAFE 2 programme, as well as national agencies such as the National Research and Safety Institute (INRS, http://en.inrs.fr/) are working separately or together to identify and develop the metrology needed to characterise human exposure and enhance knowledge of the toxicity of nanoparticles and nanotubes. Some research on exposures and human health issues is already underway in conjunction with NANOSAFE 2 which is coordinated by the Commissariat à l'Energie Atomique (CEA, Atomic Energy Commission) in France. In Spain, a number of initiatives with a focus on networking/information sharing are in

place, and it is anticipated that increased funding will be made available for EHS through the renewal of the strategic action on Nanoscience and Nanotechnology (2004 -2007).

40. In Denmark, the National Research Centre for the Working Environment's (NFA) programme of work (http://www.arbejdsmiljoforskning.dk/?lang=en) focuses on integrating research on nanoparticles, aerosol science and molecular biology. The Technical University of Denmark is leading on some research covering metrology, exposure and human health.

41. In Finland the nanotechnology programme (FinNano) was started in 2005 and consists of research and technology development. It is carried out in close co-operation with the Academy of Finland's Nanoscience Research Programme (http://akseli.tekes.fi/opencms/opencms/OhjelmaPortaali/ohjelmat/NANO/en/etusivu.html) which combines nanoscale research in chemistry, physics and biosciences and supports the overall development of the field in Finland. Details of the FinNano projects can be found at: http://www.aka.fi/en-gb/Science-in-society/Research-programmes/Ongoing/FinNano/

42. In the US, the Woodrow Wilson International Center for Scholars through its Project on Emerging Nanotechnologies has been pivotal in not only informing and driving forward the direction of research in the USA, but also in providing a platform for information sharing for the international community.

43. Within the US, there is a level of collaboration between industry and the Government, with a fairly active programme in place, particularly in occupational exposure and human toxicology issues. A number of existing projects have been extended, as new projects start to come on line. Records held on the Woodrow Wilson Inventory of Nanotechnology Environment, Health and Safety research[17] indicate approximately 17% (environmental hazard), 10% (metrology and characterisation) and 3% (social and economic related issues) percent respectively of the total number of projects.

44. A range of US Government agencies, namely, the Environmental Protection Agency (EPA), the National Institute of Occupational Health and Safety (NIOSH), the National Institute of Health (NIH), the National Science, Engineering and Technology Committee (NSET), the Food and Drug Administration (FDA), the Occupational Health and Safety Administration (OHSA), etc., are involved in funding or administering research. A Government call (http://www.nano.gov/html/society/ehs_priorities/) for comments on the prioritisation of the Environmental Health and Safety research needs was issued in August 2007 to inform the focus of continued research.

45. In Canada, the National Sciences and Engineering Research Council (NSERC) is funding a number of research projects in metrology and characterisation as well as a few related to human and environmental health hazard issues.

46. Within the Asia Pacific Region, 13 economies (Australia, China, Hong Kong, India, Indonesia, Korea, Japan, Malaysia, New Zealand, Singapore, Taiwan, Thailand and Vietnam) have come together to form the Asia Nano Forum (ANF), a network organisation now established as a Non-Government Organisation in Thailand, to foster collaboration and act as a focus for regional and global nanotechnology issues for its members. The 3rd International Symposium on Nanotechnology and Occupational and Environmental Health held in the region between 29 August and 1 September 2007, was organised by the Taiwan National Nanoscience and Nanotechnology programme and the National Chaio Tung University. Details of the symposium can be found at: http://nano-taiwan.sinica.edu.tw/2007_EHS2007/index.htm. The findings of a number of projects being pursued by NRCG Task Force 2 to progress Research Objectives 6 and 7 were presented at the Symposium.

47. In general, demonstrable activity amongst ANF members appears to be focused on occupational and human health aspects: a response to the paper "Options for a National Nanotechnology Strategy" being prepared by the Australian Government; the Laboratory for Bio-Environmental Health Sciences of Nanoscale Materials in China offers a facility for scientists to conduct multidisciplinary studies on the biological effects of nanomaterials with regard to human toxicology; a 5 year project encompassing research on metrology, exposure and human health aspects launched by the Japanese Government; a project on human health and environmental safety set up within the framework of the previous Eco-technopia21 in Korea; Coordination of research effort in studying EHS issues from different agencies overseen by the National Nanotechnology Program (http://nano-taiwan.sinica.edu.tw/) in Taiwan; focus on nanosafety issues in the 3rd phase of the Thailand Government's strategic plan (NANOTEC, 2004 – 2013).

1.5 Council for Science and Technology (CST) Review of March 2007 – issues for research and the NRCG

48. The CST review of March 2007[3] covered the whole range of Government's policy commitments on nanotechnology but it is intended here to address only the comments and recommendations made on issues relating to the research programme and the NRCG. An initial response to the overall recommendations from the CST review was given by the then Science Minister, Malcolm Wicks, in May 2007.

49. The CST was generally supportive of the approach the Government had adopted so far but was critical in particular of funding for research and the co-ordination of activities across different departments and agencies. In addition there were particular recommendations for the NRCG.

The CST recommended that:

> *The Government must cease to rely primarily on responsive mode funding to fill the knowledge gaps.*
>
> *The Government must embark upon an immediate programme of strategic research spending in order to achieve the NRCG objectives.*
>
> *Government programmes that support the nanotechnology industry should consider ring-fencing a proportion of the budget – which could still be channelled through industry-to research toxicology and health and environmental impacts of nanomaterials.*
>
> *Government must continue to engage proactively with the European 7th Framework Programme to ensure that sufficient funding is allocated to the responsible development of nanotechnologies.*

50. The earlier section under Funding the Research (see section 1.3) addressed the above recommendations. It gives notice of the Government's intention for a more joined up approach to optimise the use of available funding for more directed programmes of work, the intention to engage more closely with industry on EHS issues through joint funding mechanisms and the broad encouragement via the NRCG for maximum interaction with the EU Framework programme.

For the NRCG the CST made the following recommendations:

> *The Government should explore the possibility of making the NRCG more directly involved in awarding research funding, in order that its valuable work in identifying research priorities will have an immediate impact.*

The NRCG should adopt a higher profile within the research community in order to increase awareness of its work.

The NRCG is encouraged to continue its recent efforts to include more social and independent scientists on its Task Forces.

51. As explained above, the Government considers that responsibility for funding research into the health, safety and environmental implications of nanotechnologies should remain with the appropriate department, agency or Research Council and not be administered by a single body such as the NRCG.

52. The Government will raise the profile of its work on nanotechnologies through establishing a Ministerial Group from the Department of Health, Defra, the Department for Work and Pensions, the Department for Innovation, Universities and Skills and the Department for Business, Enterprise and Regulatory Reform to bring together the Ministers responsible for the research base, innovation, health, safety and the environment. The NRCG will report to the Ministerial Group. In addition, the NRCG will continue to provide regular updates of activities and progress to the Nanotechnology Stakeholder Forum. Further organisations are being invited to join the Forum to include a broader range of members with interests in the topic including the Royal Society of Chemistry and the Institute of Physics.

53. The NRCG will continue to engage as widely as possible with the academic and industrial communities to synergise outputs in research both in quantity and in quality. The NRCG has welcomed further members from the academic community and from industry on to its Task Forces to enable a wider input into their action plans and to contribute ideas for research priorities and funding mechanisms. The NRCG, in commissioning research work, aims to give the outputs maximum exposure and review through the convening of open workshops and seminars. Where appropriate Government Scientific Advisory Bodies, such as the Advisory Committee on Hazardous Substances (ACHS), are asked to review research project specifications and reports and their views are taken on board.

On research priorities the CST recommended that Government must ensure that the following research priorities are achieved:

An urgent priority is formulating short-term toxicity protocols, focussing on the types of nanomaterials – including metals, metal oxides and carbon nanotubes – currently on the market and being used by industry.

A longer term need for substantive research into the toxicology, health and environmental impacts and environmental fate of nanomaterials.

Development of methodologies for life cycle assessments involving nanomaterials and the carrying out of life cycle assessments would also be valuable, though is of lower priority than the above.

Although much work remains to be done in the field of nanometrology, discussions with HSE and with industry indicate that the substantive investment up to this point has succeeded in developing the field to the extent that responsive mode and demand from industry should be sufficient to develop the capabilities to the required standard, with only minimal further directed programmes from Government.

Introduction

54. The Government has just completed a study[18], funded by Defra, to look at those nanomaterials that are presently being used commercially and are likely to be in the future and combined this with an estimation of likely environmental exposure through production and use (see Task Force 2 section for details). This will enable the focus of attention for further study to be placed on the materials with greatest potential for environmental exposure. Defra has also commissioned research to look into the fitness for purpose of currently used ecotoxicity testing methods in order to assist with the development of protocols suitable for use with nanomaterials and this is reported under Task Force 4. There has also been an overview by the European Commission's Scientific Committee on Newly Identified and Emerging Health Risks (SCENIHR)[18] of the Technical Guidance Documents used in chemical hazard and risk assessment for their appropriateness for dealing with nanomaterials.

    The report has been the subject of a public consultation and the final document published in June 2007 will be used to further guide the development and use of existing methods of human health and environmental hazard assessment.

55. Longer term research into EHS issues will be achieved as a result of capacity building and responsive mode funding, some directed, through the UK Research Councils, FP7 and other international research programmes as discussed elsewhere in this report. A large amount of research will be needed into the toxicology and ecotoxicology of nanoscale materials, but the community of toxicologists in the UK is small. To encourage the development of this community, the MRC issued a Highlight Notice in March 2007 encouraging the submission of research proposals aligned with the NRCG research objectives.

56. In contrast to the CST view, the Government believes that there is still much to be done on nanometrology and related issues of characterisation and preparation of materials for testing. There has been significant progress in this area but there needs to be a comprehensive review of what measurements are needed in the various environmental and testing matrices and what instruments are available to make those measurements. Task Force 1 considers this item and highlights the gaps in our capability. It incorporates views from Task Forces 2, 3 and 4 about what needs to be measured in toxicology studies and what methods are available.

57. The Task Forces have identified life cycle assessments (LCA) as research priorities and will seek to address this aspect through collaborative programmes with industry. An important part of LCA is in understanding the potential for exposure and impact from nano products throughout their life cycle from production, use and disposal/recycling.

58. Since its establishment in 2005, the NRCG has reviewed the research needs on EHS for nanomaterials and developed plans for taking this forward; this 2nd Government Report flags up progress made by each of the Task Force areas and records results achieved so far.

Task Force 1: Metrology, Characterisation and Standardisation, Reference materials

2.1 Research priorities and proposals

59. Task Force 1, and indeed the other 4 Task Forces, have repeatedly identified metrology issues as being fundamental to make progress across the whole set of NRCG Research objectives. They are also unanimous in recognising that there are critical gaps in the metrology tools for these measurements – for example quantification of dose by surface area, and quantification of engineered nanoparticles amid a background of particles of similar size that are products of incomplete combustion from road transport and elsewhere.

60. Task Force 1 emphasises the need for the development of measurement methods, particularly in

- The **quantification of dose in toxicology studies.**
- The **quantification and characterisation of engineered nanoparticles against a larger background of particles of similar size but less aggressive chemistry** (typically products of incomplete combustion).
- The characterisation of **Surface Area** and **Surface Chemistry.**
- **Compact, rapid and inexpensive measurement methods** that can form the basis for future workplace risk assessments.
- **Documentary standards** describing the above methods, and appropriate **reference materials to validate them.**

2.2 Background and brief summary of current status of research including issues arising in progressing the programme of UK research activities

61. The remit of Task Force 1 is Metrology, Characterisation, Standardisation and Reference Materials. Progress in issues of metrology and characterisation continues steadily, while developments in standardisation and reference materials have accelerated over the period since the last NRCG research report.

2.2.1 Reference Materials

62. The REFNANO[20] project that took place in the first half of 2007 has been a major step forward in the prioritisation of needs for reference materials and measurement methods in support of nanoparticle toxicology and risk assessment. Since it has direct impact on three of the Task Force's Research Objectives, REFNANO is discussed in depth in sections 2.3.1 and 2.3.2 below.

2.2.2 UK and International Standardisation Activities

63. The UK has the highest international profile in nanotechnology standards activities. Progress has been rapid in this area, with most initiatives being proposed by the UK, and in around half of cases the UK making the predominant contribution to the development of the relevant standards.

64. Developments have been particularly rapid since the establishment of the ISO (International Standards Organisation) committee TC229 on Nanotechnologies in June 2005 following the UK's proposal. The UK holds both the chair and the secretariat. The UK hosted the first meeting of the new committee in London in November 2005, submitted the first new work item proposal on terminology and definitions for nanoparticles, and has provided leadership roles in task groups for roadmapping and for identifying the work programme for one of its working groups.

UK experts are participating in the majority of the 12 work items so far approved for development, and will participate in all relevant future work items, provided resources are available. The volume of work in this and other standards bodies is now extensive, and reported in further detail under item 2.8.

2.3 Summary of current position by research objective (RO, UK projects)

2.3.1 RO2: To identify the most suitable metrics and associated methods for the measurement and characterisation of nanoparticles

65. The REFNANO research project that took place in the first half of 2007 has been a major step forward in the prioritisation of needs for reference materials and measurement methods, including in support of nanoparticle toxicology and risk assessment. An important output has been the prioritisation of metrics and associated measurement methods[21]. The priority list includes;

- a minimum set of six characteristics to be determined for the reference/test materials:
  - Aerodynamic equivalent diameter
  - Absolute length
  - Specific surface area
  - Number of particles per unit mass
  - Concentration of bulk and/or surface contaminants
  - Polymorphic composition
- a further ten lower priority parameters for characterisation;
- the appropriateness and availability of characterisation methods.

2.3.2 RO3: To develop standardised, well-characterised reference nanoparticles

66. The REFNANO project was based on an informed discussion and opinion-gathering activity with representatives from the toxicology, metrology and nanomaterials producer/user communities. A critical aspect was that these communities understand the needs and capabilities of each other. This was achieved through representation of the communities on the Project Management Group, the preparation of five topic briefing papers designed to inform discussion at two workshops attended by key opinion-leaders in the field, and consultation with other internationally-recognised reference material initiatives.

67. As part of the REFNANO review of toxicology needs, a questionnaire survey of 22 opinion leaders in particle toxicology, who are currently working on nanoparticles was carried out. There was unanimous agreement that a reference bank of nanoparticle materials was needed. There was also strong agreement that the bank should contain particles selected around 3 main criteria:

1. **Industrial Nanomaterials:** to select reference nanomaterials on the basis of scale of production and likelihood of exposure;
2. **Hypothesis Driven:** to select reference nanomaterials on the basis of how their physicochemical properties are expected to interact with the living system, and that will be useful in answering particular toxicology (and eco-toxicology) questions, e.g. length distribution and its effect on carbon nanotube toxicity;

3. **Distributed Analysis:** to select reference nanomaterials in the context of standardised comparative studies. The bank should contain benchmark control particles such as polystyrene latex, or reporter nanoparticles such as quantum dots.

68. Based on the discussions and recommendations arising from the two workshops, the REFNANO project developed a series of outputs including:

- a rationale and set of criteria for selection of priority reference/test materials associated with high production volume (HPV) industrial nanomaterials, hypothesis-testing, and distributed analysis.
- a list of seven high priority reference/test materials to meet the needs of toxicology and metrology:
  - carbon black
  - TiO_2
  - ZnO
  - Single-walled and multi-walled carbon nanotubes
  - Polystyrene
  - Metal & metal oxide
  - Combustion-derived nanoparticles
- a further eight lower priority materials to meet the needs of toxicology and metrology;
- information relating to the quantities of materials needed and the matrix in which they are present;
- a proposed development schedule for nanoparticle reference materials.

2.3.3 RO4: Understand the properties of nanoparticles in the context of their ignition and explosion potential, and assess/develop methods for evaluating this

69. The Health and Safety Laboratory (HSL) published an extensive review[22] of the issues associated with the explosive potential of nanoparticles in 2004. HSL announced in 2007 the launch of the Centre for Interdisciplinary Nano-Research (CINR) which includes expertise and work on explosion risk assessment[23].

70. HSL have designed an explosion test vessel specifically for nanopowders under a project started in December 2006, which will run for 2 years and cost £305k. The test chamber has an internal volume of 2 litres and incorporates an external dust injection system that will enable nanopowders to be safely handled within a glove box and safely introduced into the test chamber within a sealed system. The rate of pressure rise and maximum explosion pressure are the parameters measured. The minimum ignition energy test apparatus is being modified to enable nanopowders to be similarly handled within a glove box and introduced into the apparatus in a sealed system.

2.3.4 RO9: Optimisation, development and application of technologies that enable the measurement of exposure to nanoparticles in soil and water

71. These are particularly challenging measurement problems. In many cases instruments are commercially available but require the development of validated measurement and extraction protocols.

72. Work in progress includes the development of Quartz Crystal Microbalance (QCM) methods at the University of Birmingham, as part of work on understanding the environmental behaviour and biological impacts of manufactured nanoparticles in natural aquatic systems (NERC funded, 2006-2009).

73. A meeting on Environmental Effects of Nanoparticles and Nanomaterials organised jointly by the Environment Agency and The University of Plymouth in Sept. 2006 discussed a number of measurement techniques, particularly field-flow fractionation.

2.4 Research Council and other funding

74. The larger part of the Research Councils' grant funds are spent on responsive mode research i.e. research proposals submitted at any time. In the area covered by this Task Force, the primary Research Council is the Engineering and Physical Sciences Research Council (EPSRC). Initiatives of, or in collaboration with, other Research Councils have less of a metrology focus, and are described in the following Task Force sections.

75. The EPSRC research is generally of a more fundamental, innovative nature. A typical EPSRC-funded project on nanometrology, the DyMARS project at Newcastle University, is a good example of an EPSRC supported project. This aims to develop new measurement capability for the dynamic measurement of stress in micro-and nanodevices (typically fabricated from silicon, using integrated circuit-type techniques) by time-resolved analysis of Raman spectra. This is a truly challenging project, with many potential applications in the development of new silicon biosensors. It is also a good example of a collaborative research project, having as it does, Qinetiq and the National Physical Laboratory as project partners. Although this project does not directly address the NRCG research objectives, it will develop useful measurement techniques.

76. A table of EPSRC Nanotechnology related awards directly related to NRCG objectives can be seen in Annex H.

2.5. Summary of other programmes of work internationally

2.5.1 EU 7th Framework Programme

77. UK partners are involved in a number of proposals related to Task Force 1 research objectives. The NANOBADGE project aims to develop small, portable nanoparticle measurement equipment, and has been successful in proceeding to the next stage of examination. The NANODEVICE project proposal has a main goal of developing new and innovative concepts and methods to measure exposure to and characterise airborne engineered nanoparticles (ENP) with novel, portable and easy-to-use devices at workplaces.

2.5.2 Organisation for Economic Co-operation and Development (OECD)

78. Of particular interest to Task Force 1 is Project 3 of the OECD's Working Party on Manufactured Nanomaterials (WPMN). This is entitled "*Safety testing of a representative set of reference materials*". The expected outputs of the OECD project are:

- A working definition of "manufactured nanomaterials" (MN) for use by the working party;
- Description of the information on intrinsic properties that are relevant for exposure and effects assessment of different groups of nanomaterials (foundation data set) and the corresponding methods of measurement;

- Identification of a representative set of manufactured nanomaterials;
- Testing of a number of representative nanomaterials using the foundation data set;
- Identification of the combination of physical- chemical properties having a major impact on adsorption, distribution, metabolism and elimination (ADME) of manufactured nanomaterials.

79. OECD is aware of the REFNANO project and the project is specifically identified in their plans as feeding into a process for the identification of an agreed representative set of nanomaterials.

2.6 Conclusion

80. Standardisation is proceeding very strongly, with the UK in a leading position. Substantial progress has been made in 2007 on issues of the provision of reference materials, largely through the Defra-funded REFNANO project.

81. The REFNANO project provided a priority list of candidates for inclusion in a set of reference materials to support measurement, toxicology and risk assessment of engineered nanoparticles in the UK. Consensus has been reached between the toxicology and metrology communities on the rationale for reference materials, a list of priority candidates, their selection criteria and the suitability of existing instrumental techniques for characterisation. The prioritised candidates are toxicologically and industrially relevant at the nano-scale and focus on materials produced and used in the UK.

2.7 Analysis and recommendations

82. The REFNANO project has identified a series of requirements for the further development and promulgation of reference materials for nanoparticles. These requirements have been grouped according to the following themes:

- Existing reference & test materials;
- New reference & test materials;
- Measurement techniques;
- Guidance;
- Strategic developments.

2.8 UK National and International Standardisation Impact

2.8.1 BSI British Standards NTI/1

83. The UK committee for standardization for nanotechnologies, NTI/1, was established by the British Standards Institute (BSI) in June 2004 and has the following Terms of Reference:

- To mirror the work of the CEN, ISO and IEC Technical Committees for Nanotechnologies – CEN/TC 352, ISO/TC 229 and IEC/TC 113.
- To formulate a UK strategy for standardization in nanotechnologies through a broad consultation with relevant stakeholders.
- To ensure the UK view is given due consideration within the European Union, CEN, ISO and IEC.
- To develop and support formal standards and other standardization documents in the area of nanotechnologies and to promote their use by industry and other potential users.

- To ensure due consideration of the need for standards and standardization is given by UK nanotechnology networks and organisations, and to coordinate activities and actions in this area.

84. The membership of NTI/1 currently comprises representation from a wide range of nanotechnology stakeholders, including Universities, Defra, the Environment Agency, Institute of Nanotechnology, Nanotechnology Industries Association, NPL, and HSE.

85. Besides monitoring the work of the European and International Standardization committees, NTI/1 is also responsible for developing UK standards documents. Thus far the committee has delivered one Publicly Available Specification (PAS) – Vocabulary for Nanoparticles, published by BSI as PAS 71 in 2005 – see www.bsi-global.com/nanotechnologies – and is currently developing another 9 documents, listed below, all of which are scheduled to be published before the end of 2007. Like PAS 71, all will be made freely available on the internet. These are:

- Sector specific terminologies for
  - Medical, health and personal care applications of nanotechnologies;
  - The bio-nano interface;
  - Carbon nanostructures;
  - Nanofabrication;
  - Nanomaterials;
  - Common nanoscale measurement terms, including Instrumentation.

These terminology documents will be published as PAS and used as the first drafts for New Work Item Proposals for ISO standards.

- Guides for
  - Labelling of manufactured nanoparticles and products containing manufactured nanoparticles (to be published as a PAS);
  - Safe handling and disposal of manufactured nanoparticles (to be published as a PD – Published Document);
  - Specifying manufactured nanomaterials (to be published as a PD).
- Plans are in preparation for the development of further UK National standards, including detection of manufactured nanoparticles in environmental media (in so far as methods exist at present), dose metrics for nanomaterials ecohazard studies, a guide to human and eco-toxicology testing, risk management for nanotechnologies, certification of consumer products, nanomaterials specifications, product assessment, nanometrology, and societal engagement, which will be published over the next two to three years.

2.8.2 ISO/TC 229 – Nanotechnologies

86. NTI/1 was instrumental in the establishment of this committee in June 2005 and the UK holds both the chair and the secretariat as indicated in Section 2.2.2. The current work programme and new work items awaiting approval, indicated by *, are given in Table 1 below.

Table 1: Standardization projects being developed by ISO/TC 229 Nanotechnologies

- Terminology and definitions for nanoparticles
- Current Practices in Occupational Settings Relative to Nanotechnologies
- Nanotechnologies -- Endotoxin test on nanomaterial samples for in vitro test systems
- Use of Transmission Electron Microscopy (TEM) in the Characterization of Single Walled Carbon Nanotubes (SWCNTs)
- Use of Scanning Electron Microscopy (SEM) and Energy Dispersive X-ray Analysis (EDXA) in the Characterization of Single Walled Carbon Nanotubes (SWCNTs)
- Use of UV-Vis-NIR absorption spectroscopy in the Characterization of Single-Walled Carbon Nanotubes (SWCNTs)
- Photoluminescence (NIR-PL) Spectroscopy in the Characterization of Single-Walled Carbon Nanotubes (SWCNTs)
- Measurement Methods for the Characterization of Multi-Walled Carbon Nanotubes (MWCNTs)
- Nanotechnologies – Generation of silver nanoparticles for inhalation toxicity testing
- Nanotechnologies – Monitoring silver nanoparticles in inhalation exposure chambers for inhalation toxicity testing
- Terminology and nomenclature for nanotechnologies – Framework and core terms
- Use of Thermo Gravimetric Analysis (TGA) in the purity evaluation of Single Walled Carbon Nanotubes*
- Use of Evolved Gas Analysis-Gas Chromatograph Mass Spectrometry (EGA-GCMS) in the Characterization of Single-Walled Carbon Nanotubes*
- Use of Raman Spectroscopy in the Characterization of Single Walled Carbon Nanotubes (SWCNTs)*
- Terminology and definitions for carbon nanomaterials*
- Outline of Nanomaterials classification ("Nano tree")*
- Guidance on physico-chemical characterization of engineered nanoscale materials for toxicological assessment.

2.8.3 IEC/TC 113 – Nanotechnology standardization for electrical and electronic products and systems

87. NTI/1 provides the UK input to this committee, which was established in 2006 with a US chair and German secretariat. The committee held its first meeting in March 2007, at which time it approved the establishment of two joint working groups (JWG) with ISO/TC 229 – JWG1 terminology and nomenclature, and JWG2 – measurement and characterization, together with a third working group, WG3, on product performance. A meeting of WG3 was held in July 2007, at which the scope and modified title were developed. A New Work Item Proposal – *Guide for Carbon Nanotube Specification for Electrotechnical Applications* is expected to be submitted by Germany shortly.

2.8.4 CEN/TC 352 – Nanotechnologies

88. As with ISO/TC 229, NTI/1 was instrumental in the establishment of this committee and as with the ISO committee, the UK holds both the chair and secretariat. The proposal for this committee was made following the delivery of a European strategy for nanotechnologies standardization, developed by CEN Technical Board Working Group (BTWG) 166, which was led by the UK between 2004 and 2005. The committee was established by unanimous approval of the 28 members of CEN on the understanding that work items of mutual interest to CEN and ISO will be developed under the "Vienna Agreement" (an agreement on joint working between the two committees) with an ISO lead. This will limit the work of the committee but will ensure that topics of international, as opposed to regional, significance will be given international recognition through ISO, whilst topics of specific interest to Europe will be developed by CEN. So far CEN/TC 352 has adopted all of the ISO approved work items for development under the Vienna Agreement, and has also approved three work items of its own:

- Format for reporting the engineered nanomaterials content of products
- Guide to nanoparticle measurement methods
- Guide to methods for nano-tribology measurements

UK experts will participate in all of these work items, with the latter two being led by the UK.

3.1 Research priorities and proposals

89. Task Force 2 is focused on the sources, pathways and technologies associated with human and environmental exposure to engineered nanoscale materials. The current key priorities for the Task Force are:

- **Discrimination between** ambient nanoparticles and those engineered.
- **Which exposure metric to use?**
- **Addressing potential exposure** through developing the techniques for a life-cycle approach.
- **Modelling and generation of real exposure data** including environmental emissions data.
- **Efficiency of control measures.**

3.2 Background and brief summary of current status of research including issues arising in progressing the programme of UK research activities

90. Full details of current research projects and proposals can be found in Annex A. In summary, the Task Force considers that the current projects and proposals represent a sound body of work which starts to address many of the uncertainties in our understanding of the exposure of people and the environment to manufactured nanomaterials. As results become available from ongoing research work, as developments occur on the international stage (particularly through the OECD, International Standards Organisation (ISO) and EU research initiatives) and as funding opportunities arise the Task Force will review current work from around the globe and develop further priority proposals.

3.3 Summary of current position by research objective (RO, UK Projects)

91. Greater detail of the status and findings of the full Task Force 2 portfolio of research projects can be found in the table in Annex A. The following are brief highlights.

3.3.1 RO5: Further identification of sources of nanoparticles

NanoAlert (Helpdesk)

92. The aim of this work supported by the HSE is to provide an information bulletin service reviewing studies on exposure and potential health effects of nanomaterials relevant to the occupational setting. The first two bulletins have been issued and can be found at: http://www.hse.gov.uk/horizons/nanotech.htm. A mailing list is being created to inform customers when a new bulletin is available. Funding for a second year has been agreed. The NanoAlert project also forms part of an EU FP 7 funding bid as part of a larger communications project.

An analysis of potential exposures throughout the lifecycle of engineered nanoscale materials. (Part of NANOSAFE 2)

93. A Review by University College London of existing Life Cycle Analysis programmes (i.e. encompassing manufacture, through use, to waste removal or recycling, and which highlights links between air, land and water and between measurement and exposure) has been carried out and found to be in need of modification. Work has started on modification of these programmes with the intention of using the incorporation of carbon nanotubes into tyres as a practical case study.

94. This project represents a first step in the identification of a suitable approach for Life Cycle Analysis of nanoparticles. As the CST review notes, it is important to coordinate UK efforts in this area with those from international colleagues. The OECD Working Party on Manufactured Nanomaterials provides one forum where the UK and many others could achieve this.

3.3.2 RO6: Optimisation and development of technologies that enable the measurement of occupational and environmental exposure to nanoparticles via air, and RO7: Understanding of fate and behaviour of nanoparticles in air

NOSH (Nanoparticle Occupational Safety & Health) Consortium

95. This multi group "club" project consists of a consortium of companies (largely US), Government (including HSE), academia, and public interest groups, led by DuPont. The project is ongoing at DuPont's Experimental Station Laboratories in the US. With respect to research objectives 6&7 the project has developed methods for the reproducible generation of a number of nanoparticles, which are useful as reference methods for particle generation. The aerosols generated have been used to characterise performance of a range of instruments and also used to investigate the fate of nanoparticle aerosols i.e. rate of transport, and loss mechanisms. The project has recently been extended to the end of 2007 as new partners have joined.

NANOSH: Inflammatory and genotoxic effects of engineered nanomaterials. (includes work on workplace exposure assessment and associated control)

96. NANOSH is a 7-partner project funded under the EU 6th Framework Programme. The outline sampling strategy for work place exposure monitoring including contextual information (sampling instruments, where to sample and for how long, etc) has been agreed using experience gained in NANOSAFE 2 and other Health and Safety Laboratory (HSL) work. All partners have concluded pilot studies. HSL carried out a monitoring programme in the nanotechnology laboratories of a university in February 2007. Initial results show rush hour peaks in traffic in the detection of nanoparticles but no increase over background due to work activities. The difficulties of determining exposure to *engineered* nanoparticles are very clear. The initial results from the second monitoring campaign carried out in a different university using improved methodology included observations in one clean room where no particles were detected and in another where carbon nanotube agglomerate aerosols were detected.

HSL Monitoring Equipment

HSL Investment Research Programme – Nanochallenge.

97. This series of projects whose 3 main areas are Exposure Assessment and Control, Fire and Explosion and *in vitro* Toxicology Assays, falls under The Centre for Interdisciplinary NanoResearch at HSL (CiNR http://www.hsl.gov.uk/nanotech/index.htm). This was established in Spring 2007 to bring together expertise across the whole laboratory and is uniquely placed to address the potential health and safety risks from nanoparticles.

98. For the improved collection/characterisation of nanoparticles element of the programme, a start has been made on assessing collection methods (electrostatic and thermal precipitators made or refurbished for use in collecting nanoparticles in the NANOSH exposure study). The project will also trial methodologies developed in NOSH (with their permission).

Assessment of the potential use of nanomaterials as food additives or food ingredients in relation to consumer safety and implications for regulatory control.

99. This project has been completed and the final report is due out soon.

Assessment of current and projected applications of nanotechnology for food contact materials in relation to consumer safety and regulatory implications.

100. This project is due to be completed in Spring 2008.

3.3.3 RO8: Development of exposure control devices

NOSH Consortium

101. Work on respiratory protective equipment (RPE) proceeds with results showing an unusual pattern of efficiency with an increase in exposure when the unit is used after a break in use. The hypothesis is that it might be the loss of static charge that reduces filter efficiency.

NANOSH

102. A programme to assess the performance of respiratory protective equipment (RPE) and protective clothing in real conditions has been discussed for implementation in the second year of the project.

NANOSAFE 2

103. The project has included work on efficiency of RPE and personal protective equipment (PPE) systems. Improved designs for total containment of processes have been explored by industrial partners producing nanoparticles.

Effectiveness of current control measures: a review of control measures currently used for the production, handling and end use of nanoparticles.

104. This project is only a proposal, and was always envisaged to follow on from the exposure assessment work conducted as part of NANOSH. However, in preparation, the range of control measures used in UK university research laboratories are being collated by HSL.

3.3.4 RO10: Research to understand the environmental fate, behaviour and interactions of nanoparticles in soils and water

The Environmental Nanoscience Initiative: mechanism to address basic research into fate and behaviour of nanomaterials in the environment.

105. The Environmental Nanoscience Initiative has been set up by NERC, Defra and the Environment Agency. Ten grants have been awarded following the first call. A second call for proposals has just been completed and a further 8 grants awarded. The focus of the second call was on impacts and interactions of nanoparticles with microbial communities in soils and water. More details can be found in Task Force 4's section.

Current and Predicted Environmental Exposure to Engineered Nanomaterials

106. This Defra funded project[18] has used simple models based on levels of pharmaceuticals in water bodies along with water concentration data and usage scenarios of current products to make predictions of worst case concentrations of nanoparticles in the environment.

3.4 Research Council and other funding – projects summary

107. Summary details of projects are noted above, with fuller details and funding sources in Annex H.

3.5 Summary of other programmes of work internationally

3.5.1 Organisation for Economic Co-operation and Development (OECD)

108. *Of particular interest to Task force 2 are the outputs from projects under the OECD Working Party on Manufactured Nanomaterials, especially:*

   i) Steering Group 1 who are developing a database on EHS research (which links to the NanoAlert project and its FP7 project bid).

   ii) Steering Group 2 who are developing EHS Research Strategies on Manufactured Nanoparticles. At present details are being collected of ongoing work. A discussion for exchanging and identify principles for setting priorities amongst the different themes and research projects will follow. This will include discussion on urgent short term research priorities.

   iii) Steering Group 5 who have a drafting group on Co-operation on Exposure has prepared a first draft on *Co-operation on Exposure Measurements and Exposure Mitigation* which will be published in 2008.

3.5.2 EU 7th Framework Programme

109. The European Commission has adopted the "Nanosciences and nanotechnologies: An action plan for Europe"[24]. This Action Plan defines a series of interconnected actions for the immediate implementation of a safe, integrated and responsible strategy for nanosciences and nanotechnologies, based on the priority areas identified in the Communication "Towards a European Strategy for Nanotechnology"[25]. Two of the projects detailed above and in Annex 1 (NANOSH, NANOSAFE2) are co-funded by the EU and form part of their research plan.

3.5.3 National Institute for Occupational Safety and Health (NIOSH) http://www.cdc.gov/niosh/topics/nanotech/)

110. NIOSH is the leading US agency conducting research and providing guidance on the occupational safety and health implications and applications of nanotechnology. The NIOSH Nanotechnology and Health & Safety Research Program is a five-year multidisciplinary study into the toxicity and health risks associated with occupational nanoparticle exposure. Research will include aerosol generation and characterisation plus studies in the laboratory and in the field. In addition, NIOSH have produced handling and use documentation that is under consultation at the moment and will be available on their website soon.

3.5.4 US Environmental Protection Agency

111. The US EPA has a number of research projects within the environmental field including projects on Life Cycle Analysis. Details can be found at: http://es.epa.gov/ncer/nano/research/index.html

3.5.5 Standards Organisations

112. Task Force 2 has good links with representatives on the International Standards Organisation's nanotechnology technical committee (TC 229). The work here links with the UK's own nanotechnology standards group NTI/1 (http://www.bsi-global.com/en/Standards-and-Publications/Industry-Sectors/Nanotechnologies/BSI-Committee-for-Nanotechnologies/). Active work is progressing in many areas, but of particular note for Task Force 2's remit is the draft ISO Technical Report "Current Practices in Occupational Settings Relative to Nanotechnologies" and the BS NTI/1 project to draft guidance for handling and disposal of nanoparticles. It is hoped that these documents will be complementary and will refer to the detailed documentation from both OECD and NIOSH and produce a practical guide for industry and researchers. Further details on activities on standards can be seen under Task Force 1.

3.6 Analysis and Conclusion

113. Overall, the Task Force considers that a concerted and reasoned body of work is being proposed and conducted addressing a number of the major uncertainties in the field. Ongoing projects are starting to provide interesting and valuable results and in many cases provide examples of the value of multi-partner projects with a variety of funding sources. The Task Force has links to much international work not least the OECD and Standards initiatives.

114. However, there are some issues that presently limit the ability of the available techniques to assess exposure to manufactured nanoparticles. The most immediate ones are the inability to distinguish readily between natural and man made nanoparticles and the uncertainty over which metric is the most appropriate to measure exposure. Efforts to address these are currently being undertaken by Task Force 1 and wider international groups.

115. There is an increasing body of information and advice on ways to handle and use nanoparticles. The ISO Technical Report will be the main source of practical guidance but the British Standards Institute guidance project in particular offers the promise of a user's guide which will advise those using nanoparticles on risk reduction options and disposal issues.

116. The Task Force will continue to meet and review both UK research and that of other international groups and develop proposals for further research to fill gaps in our understanding.

4.1 Research priorities and proposals

117. Task Force 3 is focused on the potential human health hazard of nanoparticles and in particular research objectives 11 to 16. This second report focuses on a limited number of issues that we think need urgent consideration. It is worth noting that achieving definitive outcomes on any of these will take some years of research due to the difficulties in defining the characteristics of nanomaterials.

- **Determining the characteristics of nanomaterials that confer toxicity.** This will not be possible until a set of nanomaterials with properly defined physico–chemical properties are available for use in toxicology studies: *in vitro and in vivo*. The characteristics or features that need to be defined for each type of nanomaterial include: composition, solubility, morphology (size and size distribution and shape), surface area per unit mass, surface layer composition (especially important if this differs from general composition) and surface charge. We think that until such a set of characterised nanomaterials are available it will be difficult or impossible to develop any general understanding of nanoparticle toxicology. We note that the history or provenance of samples needs to be carefully defined. Variations in key characterisations from batch to batch and with time since production are seen as real problems. The work of the Defra funded REFNANO[20] project, led by the Institute of Occupational Medicine in Edinburgh is taking this area forward.

- **Inhalation studies using nanomaterials are a priority.** Special attention is needed regarding toxicokinetics ("partico-kinetics") and the distribution of inhaled particles in the body. Transfer across biological barriers (e.g. to the brain or foetus) should be studied. Studies of bio-persistence are urgently needed.

- **Studies of the transfer of nanoparticles across skin are also needed.** Such work could involve animal or *in vitro* studies. Labelled particles are needed for these studies. *In vitro* models have been developed for healthy skin but it has been claimed that mechanical aspects such as skin-flexing are important for nanomaterial behaviour on skin and that the current *in vitro* models for skin absorption are inappropriate. Research is urgently needed to ascertain if this is indeed the case since an *in vitro* model is a high priority.

4.2 Summary of current status of research including issues arising in progressing the programme of UK research activities

118. A detailed report on in vitro methods for assessing the toxicology of nano-particles was provided in the NRCG Progress Report (2006)[2]. A short paper (Annex B) on the key aspects of *in vitro* studies has been prepared. We have reviewed our thinking on *in vitro* testing of nanoparticles. It is felt that in vitro studies have the potential for use as a screening tool to provide information on the relative toxicity of manufactured nanomaterials (MN) compared to the corresponding bulk material. Some *in vivo* data would, however, be needed before definite conclusions could be drawn for hazard assessment.

119. Investigations relating to cells/tissues of initial contact (respiratory tract, gastro-intestinal tract, skin) together with cells/tissue from potential target organs, would be appropriate; ideally the latter would be based on information available from studies on the distribution of absorbed MN.

120. A short paper (Annex C) on key factors likely to be important in the *in vivo* testing of nanoparticles has also been prepared. A number of recent reports have concluded that current methods used to assess the health effects of chemicals, based largely on experimental studies in animals, are generally appropriate for manufactured nanomaterials. However special attention needs to be given to metrology and dosimetry aspects. Also to certain types of toxic effects that may arise from nanomaterials that would be poorly detected in conventional toxicology studies.

121. It is recognised that there is a need for more targeted work on human toxicology; however, this has proven more problematic in moving forward due to the issues of characterisation, compounded by profound difficulties in accessing relevant funding for these longer term projects. Some projects on a smaller scale are in the pipeline.

4.2.1 Current developments and thinking

122. The world literature on nanotoxicology is expanding rapidly and includes a number of detailed reviews published by experts in the field[26,27,28].

123. Nanotoxicology is being funded on a large scale in the United States.
Most areas covered by the UK programme of work are being considered by US workers. A summary of areas being studied and a list of at least some of the key workers are provided in the monograph "Particle Toxicology"[29]. Another recently published monograph "Nanotoxicology"[30] also provides a state of the art description of the field and sets out the gaps that need to be filled.

124. It is recognised by most toxicologists that nanoparticles represent a subgroup of particles likely to have, or known to have, biological effects. Focusing on advances in the nanotoxicology area alone is likely to be unwise as developments in "ordinary" particle toxicology may well impact on thinking in the nanotoxicology area. Current thinking is tending towards a unifying approach to particle toxicology: fitting nanoparticle effects into this broad approach is difficult but very important[29,31].

125. The idea that nanoparticles have unique properties that set them apart from all other particles in terms of the nature and extent of their toxicity, now seems increasingly unlikely to be true: this represents a change in thinking over the past ten or so years. Work using surface area as the dose metric, for example, has allowed nanosized titanium dioxide particles to be placed on the same dose-response curve as regards pulmonary inflammation as larger titanium dioxide particles[27,32,33].

126. The small radii of curvature of nanoparticles have been thought by some to affect the activity or reactivity of the surface molecules[34]. It was thought that even generally inert materials such as titanium dioxide might be reactive if their molecules were exposed to the forces necessary to produce small radii of curvature. This idea seems less popular now than it was a few years ago. It seems to be thought, now, that the reactivity of the particle surface, expressed in units of reactivity per unit surface area, is unchanged by reducing particle size to nano-dimensions. Whether all nanoparticles express surface reactivity in the same way, for example, by participating in or catalysing free radical generation is unknown but it seems likely that some materials act in this way[35].

127. It is accepted that nanoparticles can:

- gain access to cellular and tissue locations that are inaccessible to larger particles. Nanoparticles, for example, have been found in mitochondria and in the Central Nervous System (CNS)[36,37]. The CNS is defended by the blood brain barrier, albeit that this is deficient in some circum-ventricular areas, but nanoparticles may enter via the olfactory and trigeminal nerve endings found in the nose and naso-pharynx.
- enter the interstitium of the lung to a greater extent than can larger particles: One of the early findings in the field was that nanoparticles could set up an interstitial inflammatory response in the lung[38].
- enter the blood stream, either directly via the lung and gut or perhaps via the lymphatic system. The fate of nanoparticles in the blood is imperfectly known; uptake by the reticulo-endothelial system of the spleen, bone marrow and liver sinusoids has been demonstrated but excretion via the kidney requires further study. Whether nanoparticles can enter the bile is unknown as is, therefore, the likelihood of an entero-hepatic circulation. Translocation across the placenta to the foetus has been suggested but more work is needed on this[39].

128. Because nanoparticles will differ with respect to their pharmacokinetic properties, predicting from data for one nanoparticle to another is likely to be difficult.

129. Nanotubes/fibres and rods have been produced from a range of substances and combinations of substances. Some authors have asked whether "form" is likely to be a controlling factor in nanoparticle toxicity and have asked whether a parallel should be drawn with asbestos fibres where form is certainly a key factor.

130. Nanofibres and tubes have large length to diameter ratios. In the case of asbestos fibres a length of greater than 5μ is needed before the ratio becomes toxicologically important. It is thus important to consider fibre or tube length as well as the length to diameter ratio. This may be important as long as the fibres maintain durability in the intra/extra cellular environment. A project (see below, under Section 4, Current Research in the UK) to undertake a scoping study on whether any parallels can be drawn with asbestos, has recently begun. The importance of wall configuration (single or multiple) needs further study with regard to nanotubes.

131. The toxicological properties of nanomaterials seem to be controlled by:

i. Dose: as with other toxicologically active materials, though the most applicable metric for dose may be surface area rather than mass.

ii. Composition: controlling surface reactivity expressed in units of reactivity per unit surface area.

iii. Kinetics and distribution in the body.

iv. Shape and form.

132. None of these are in fact novel but neither has any been sufficiently studied to allow accurate prediction of the toxicological properties of a new nanomaterial.

4.3 Current Research in the UK

133. Research on nanotoxicology is developing in the UK and the picture is significantly better than it was a year ago as reflected in our first report. Key developments have been;

134. Defra has let the following projects:

(a) An outline scoping study to determine whether high aspect ratio nanoparticles (HARN) should raise the same concerns as do asbestos fibres

There is concern over the potential adverse effects of human exposure to nanoparticles but special concern has been expressed regarding nanoparticles with a high aspect-ratio (high aspect ratio nanoparticles; HARN) i.e. nanoparticles that are fibrous in shape. This concern is based on the potential for such fibre-shaped nanoparticles to behave like asbestos fibres. Exposure to airborne asbestos fibres is associated with a number of lung diseases including fibrosis (asbestosis), lung cancer and mesothelioma.

The Objective is to undertake a scoping study that reviews the existing literature and sets out a research strategy towards determining whether such concerns about HARN are well–founded.

(b) A study to identify physicochemical factors controlling the capacity of nanoparticles to penetrate cells of the respiratory epithelium, especially those of first contact on inhalation of the particles

One of the major concerns regarding the possible toxic effects of nanoparticles is the capacity of these materials to translocate into cells. This may be a necessary step in the movement of particles deposited in the lung into the blood stream and thence to other tissues. Research on the mechanisms involved in translocation across the respiratory epithelium is needed.

This study will scope the feasibility of achieving the following end-points:

- Identify which features of nano-particles/tubes/fibres (NP) are important in particle-cell interactions. NP chemistry, structure, mass, numbers, shape, surface area, surface charge and surface functionalisation may all be important.
- Suggest how NPs may be modified to enhance or reduce their capacity to enter cells.
- Suggest how interactions between NPs and cultured human cells might be studied.

135. A proposal to establish a National Nano-toxicology Inhalation Research Centre (N-NIRC) is being funded by HPA. N-NIRC will be sited at HPA Chilton and funding (circa 300k) has been allocated to the project. This facility will allow UK research workers to collaborate with the HPA research group in studies that would otherwise be very difficult or impossible in the UK today. Studies of the deposition of nanoparticles in the airways and of their kinetics following inhalation exposure will be undertaken in animal models and results linked with those from studies in volunteers. Five leading UK academic research groups have agreed, in principle, to collaborate with N-NIRC. Funding for collaborative research programmes will be sought from UK Research Councils, from the EC and from industry.

136. The Ministry of Defence has made around £50k available to the Defence Science and Technology Laboratory (DSTL) to study the behaviour of NP in biological systems in order to inform later risk assessments of products containing nanomaterials. The work will involve studies of NP kinetics in lung tissue to further elucidate the extent of penetration of particles into the cells.

137. UK research workers have made bids for EC Framework 7 Programme funding: several proposals have passed the first hurdles.

138. Funding by charitable foundations has also been made available: The Colt Foundation is funding work at the University of Edinburgh on the mechanisms of lung injury produced by nanotubes and nanoparticles.

139. Research Council Funded Projects
The Physiological Systems and Clinical Sciences Board of the MRC issued a policy highlight notice (http://www.mrc.ac.uk/ApplyingforaGrant/HighlightNotices/Nanotoxicology/MRC003580#P17_1483) in partnership with the Department of Health to encourage innovative, high quality research proposals in nanotoxicology in March 2007. The highlight notice has already stimulated a substantial increase in the number applications addressing the health risk of nanotechnologies and several proposals are currently under consideration by the Board.

A number of nanotoxicology proposals were funded through the NERC led Environment and Human Health Programme to which the MRC contributes. Details of these are outlined at Annex H.

4.4 International activities

140. Task Force 3 is involved with Steering Group 4 of the OECD's Working Party on Manufactured Nanomaterials. This Steering Group is taking work forward by four subgroups namely physiochemical properties; effects of biotic systems; degradation and accumulation; and health effect. Initially work will concentrate on test guidelines relevant to characterisation (i.e. the existing guidelines on physiochemical properties of substances that need expansion/modification or new guidelines that may be needed). The aim is to produce a draft document for consideration at the OECD WPMN meeting in November 2007. Dosimetry and sample preparation will also be priority areas with interim reports due in 2008.

4.5 Problems and recommendations

141. Work funded through the NRCG work programme is in very early stages. Two calls for proposals have been published and work has now started. However, there remains a need for a significant expansion of central funding in this area. Although research in the nanotoxicology area is developing in the UK, there is a need for better coordination of resources which can be facilitated by the NRCG to ensure that there is no unnecessary overlap between projects. It is important that UK researchers be in close contact with work done abroad for example in the US and funding for an exchange scheme would be useful.

142. The need for a major stock-take of results obtained around the world is now pressing. The monographs mentioned above go some way to meeting this need but a systematic appraisal looking for overlap, answered questions and gaps has yet to be undertaken.

143. In coordinating work in this area the need to share results as early as possible is paramount. This is difficult to achieve pre-publication, because of the competitive nature of research publication. The feasibility of establishing a secure network for the exchange of pre-publication findings should be explored.

144. It is important that *in vivo* work should be funded to follow up in vitro work already underway.

145. Epidemiological studies are needed to help to generate hypotheses that can be tested in the laboratory. Only a very limited amount of epidemiological work on the effects of nanoparticles (manufactured or environmental) on health is underway in the UK or, indeed, abroad.

Task Force 4: Environmental hazard and risk assessment

5.1 Research priorities and proposals

146. Task force 4 is focussed on environmental hazards and risk assessment. Key priorities of this group are:

- **Phase 2 of the Environmental Nanoscience Initiative.**
- **Development of infrastructural support** for nanomaterials characterisation and analysis for the environmental sciences, notably for dosimetry (supporting Task Force 1).
- **Guidance on nanomaterials preparation and dose metrics** for ecohazard studies and on associated abiotic and biotic parameters to be measured.
- **Standard Reference Materials for benchmarking ecotoxicological studies** (Task Force 1 is taking this forward).
- **Case studies of ecohazard and risk assessment** using nanomaterials in current production.
- **Further studies to evaluate the fitness for purpose** of current methods for environmental hazard assessment of nanomaterials.

5.2 Background and brief summary of current status of research including issues arising in progressing the programme of UK research activities

147. Task Force 4 is charged with defining priority strategic research needs within the areas of environmental risk assessment of nanotechnologies across Government. It is also accountable for ensuring timely delivery of research to meet the priorities. The objective of the Task Force is to support the development of appropriate environmental controls for nanotechnologies as needed through provision of robust, high quality evidence.

148. Membership includes Government Department and Agency scientists, representatives of the Research Councils, academics working in this area and industry specialists. In 2007 the membership was increased in response to recommendations from the CST.

149. Both the 2004 RS/ RAEng[4] and 2005 NRCG[1] Research reports (amongst others) recognised the almost complete absence of scientific data on environmental exposure, hazard and risks of free manufactured nanomaterials. A *first key objective* identified within the first NRCG report was therefore the need to develop fundamental understanding on the environmental fate, behaviour and ecotoxicology of manufactured nanomaterials (NRCG Objective 18). A *second key* NRCG objective was to focus on one important subset of this, namely impacts on microbial communities, flora and fauna in soils and groundwaters, reflecting the use of nanoparticles in remediation, where deliberate introduction into the environment can occur as well as other potential sources, (for example through the spreading of sewage sludge that might be contaminated with nanoparticles). (NRCG Objective 17).

150. Developing a fundamental understanding of environmental fate, behaviour and ecotoxicology of manufactured nanomaterials is dependent on there being an active, interdisciplinary community of scientists working in this area in the UK. It also requires the monitoring, collation and synthesis of evidence developed by international environmental scientists. While there is a community of UK scientists working on measurement, fate, behaviour and impact of naturally occurring and incidentally produced nanoparticles (e.g. 'ultrafines' in atmospheric pollution and aquatic colloids), at the time of writing the 2005 NRCG report few UK scientists were undertaking studies with manufactured nanoparticles.

151. It was therefore recognised that developing capacity in the UK research base was an immediate priority if the Task Force was to meet the two key objectives above. Encouraging knowledge transfer and interdisciplinary working were acknowledged as important components of this, reflecting the fact that nanotechnologies environmental risk research sits at the interface of several disciplines, from materials science through ecotoxicology to hazard and risk assessment. We proposed and established a collaborative UK Environmental Nanoscience Initiative to meet these needs, co-funded by NERC, Defra and the Environment Agency and in partnership with EPSRC. The outputs from this directed programme are described in more detail below.

152. In addition to developing a UK based programme of environmental nanosciences work, the Task Force is monitoring scientific work funded by industry and others in the UK and work being undertaken internationally. This is again described below. One important aspect of this has been the establishment of the International Conference series on Environmental Effects of Nanoparticles and Nanomaterials, co-sponsored by the Society of Environmental Toxicology and Chemistry (SETAC), the Society of Experimental Biology, the Environment Agency and others. The first conference was held in London in September 2006, and its success has led to continuation of the series, with a second conference being held at the Natural History Museum in London in September 2007.

153. The *third key* NRCG objective being implemented by the Task Force is an evaluation of how fit for purpose current ecotoxicological methods are for assessing the hazards of nanomaterials (NRCG Objective 19). This supports any requirement for hazard assessment (for example under regulatory regimes such as REACH, under review at an EU Commission level). It also supports the development of guidance for those industries wishing to proactively undertake an ecohazard assessment. Work commissioned by the Task Force and funded by Defra to address this objective is again discussed in more detail below.

5.3 Progress to date and Forward Look

154. The Environmental Nanoscience Initiative launched its first call in September 2006. The focus of this first call was on small, exploratory research proposals that address generic aspects of environmental risk of nanoparticles and nanotubes, specifically addressing NRCG Objective 18. This was designed to be a capacity building, pump priming activity to enable researchers to generate initial datasets that could support high quality submissions through responsive mode routes to the Research Councils and others.

155. The first call was very successful, with 37 submissions. Ten grants were made in April 2007, in a number of disciplines and to a number of UK academic institutions. Details of these are given in the table at Annex H. A second call was announced in June 2007, specifically addressing impacts of nanoparticles on environmental microbial communities, addressing NRCG Research Objective 17. This was again extremely well subscribed, with 23 expressions of interest received and a further 8 grants awarded.

156. In addition to the ENI, grants have also been awarded to 4 academic institutions under the NERC collaborative Environment and Human Health Programme. These will investigate environmental behaviour and impacts of manufactured nanoparticles and toxicology of nanoparticles in general. These are listed in Annex H.

157. This portfolio of environmental nanoscience research has been supplemented by 4 grants made by NERC through responsive mode since publication of the first NRCG report. RCUK have also recently awarded funds for a full time Research Fellow at the University of Plymouth for 5 years in nano ecotoxicology, leading to a permanent position in this area.

158. Academic Institutions have also gained grants from other sources of funding, including industry and from Europe. Details of these are again given below.

159. The number of proposals submitted to the directed and responsive mode programmes above and to other sources of funding in the UK and internationally (e.g. to the EU Framework Programme) is strongly welcomed. The UK environmental research community has actively engaged with this issue over the last 12 months, submitting a large number of high quality proposals. Given this, the Task Force recommends that the Government, through mechanisms such as the Environmental Research Funders Forum should further encourage and develop this community, reflecting that this is an area where the UK can take a strong lead globally. This should use the directed programme and knowledge transfer funding mechanisms described above, in keeping with the recommendations of the Royal Society / Royal Academy of Engineering and the Council of Science and Technology.

160. In addition to the fundamental science programmes described above work appraising the fitness for purpose of current ecotoxicological methods for hazard assessment of nanomaterials has been taken forward by Defra, who funded a study to undertake this evaluation and a report[40] has been published.

161. The work areas outlined above have independently converged on a number of key enabling research priorities. These are needed to both support the research community as it is further developed through programmes such as the Environmental Nanoscience Initiative and to support the undertaking and evaluation of ecohazard test methods. There is a critical need *to develop nanomaterials characterisation and analysis infrastructural support*. This includes both the necessary instrumentation and associated expertise for analysis of nanomaterials in biological media and in environmental matrices, including soils, sediments, water and air. This should be matched to the nanomaterials in production now and in the near future and to those most likely to give rise to environmental exposure. This is a fundamental requirement for the provision of high quality, robust environmental fate, behaviour and ecotoxicological studies, notably to support dosimetry, an essential component of ecohazard assessment.

162. In addition to infrastructural support, there is an associated need for development of expertise and knowledge transfer across disciplines in the *area of abiotic and biotic controls of nanomaterial behaviour*, notably discipline hopping between environmental nanochemistry and ecotoxicology. A number of important abiotic and biotic factors can influence nanomaterial behaviour (e.g. pH, ionic strength and ligand interactions that may be important determinands of agglomeration behaviour in aquatic systems). Understanding these factors and measuring them accordingly in hazard studies is an important need. The development of guidance on this issue is a recommendation.

163. Thirdly there is a need for *guidance on an agreed suite of dose metrics* for reporting in ecohazard studies. A number of metrics have been suggested (e.g. surface area, particle number, mass concentration, surface reactivity) and early consensus and guidance is needed. *Guidance is also needed on preparation of nanomaterials for ecotoxicological studies*, in the context of the form in which they occur in the environment. The need for development of standard reference materials for benchmarking ecotoxicological studies has been acknowledged as an ongoing priority by the Task Force and is covered elsewhere in this report under Task Force 1.

164. Finally, the Task Force strongly recommends the undertaking of *several case studies of environmental hazard and risk assessment* to empirically test the appropriateness of underlying methodologies. This may be best undertaken in collaboration with industry, and would complement work being undertaken at OECD under the Working Party on Manufactured Nanomaterials (Steering Group 3).

165. Many of these recommendations are concerned with the enabling science, guidance and infrastructural needs that support environmental hazard and risk assessment.

5.4 Summary of current position by objective (UK projects)

166. The status of Government funded projects addressing NRCG objectives that fall within the remit of the Task Force are summarised in Annex D.

5.5 Research Council and other Government funding – projects summary

Environmental Nanoscience Initiative

167. Tabulated at Annex H

Environment and Human Health Programme

168. Tabulated at Annex H

NERC Responsive Mode Funding and Knowledge Transfer

169. Tabulated at Annex H

5.6 Other UK projects meeting NRCG research objectives 17 – 19

University of Exeter

170. BBSRC / DTA Case studentship, How do nanoparticles disrupt key functions within microbial communities and affect virulence genes?

Napier University

PhD Ecotoxicology of Nanoparticles (funded by Central Science Laboratory) – 2005/2008

171. Project focus on fluorescent nanoparticles, titanium dioxide and carbon black.
Test organism is *Daphnia magna*.
Studies on uptake, lethal and sublethal endpoints, including biochemical biomarkers.

PhD Ecotoxicology of Nanoparticles (funded by RAE) – 2006/2009

172. Project focus on titanium dioxide and carbon black.
Test organism is the freshwater snail *Lymnaea stagnalis*.
Studies on uptake, lethal and sublethal endpoints, including biomarkers.

Postdoctoral project Ecotoxicology of Nanoparticles (funded by the Danish Government Research Fund) – 2006/2008

173. Project focus on titanium dioxide and carbon black.
Test organism is the marine macroalgae *Fucus serratus*
Studies focus on uptake, reproduction and development

PhD Ecotoxicology of Nanoparticles (funded by Unilever) – 2007/2010

174. Project focus on a range of nanoparticles (still to be confirmed).
Range of test organisms including *Daphnia Magna*.
Studies on uptake, lethal and sublethal endpoints, including biochemical biomarkers.

University of York / Central Science Laboratory

PhD – Fate and bioavailability of nanomaterials in the environment (funded by Unilever) – 2005/2008)

175. Project focuses on a range of commercially available nanoparticles.
Aim to identify suitable quantitative and qualitative analytical methods for NPs in the environment, to understand the environmental fate and impact of NPs.

University of Birmingham

176. NERC Quota/algorithm PhD studentship – Behaviour of nanoparticles in the natural aquatic environment (start date October 2007).

CEFAS

177. Project focuses on obtaining information on the effect of manufactured Nanoparticles (NPs) (cadmium sulphide and silver) on biological systems in the aquatic environment in a structured reproducible manner appropriate for developing risk management.

- Provide comparative data on the acute toxicity of well-characterised manufactured metal-containing NPs on cultured cells, a crustacean species, algae, and fish.
- Develop cell systems for toxicity and genotoxicity testing of NP's and the potential for these to replace or supplement whole animal testing.
- Provide comparative data on the chronic toxicity of NPs on a commonly-tested crustacean species.
- Evaluate biomarkers and histopathology as monitoring tools for exposure to NMs in the environment. A tissue bank of biological material exposed to metallic NPs will be preserved and archived for comparison with field-collected samples.

5.7 Analysis and recommendations

178. The Task force has commissioned a number of key initiatives in the period since the publication of the November 2005 NRCG research strategy report[1]. It is now critical to build on this platform through a) comprehensive funding of the Environmental Nanoscience Initiative b) provision of support for characterisation and metrology and development of good practice guidance on ecotoxicological methodological approaches and reporting and c) interfacing work undertaken on the appropriateness of ecotoxicological methods with important international initiatives in this area within OECD.

Task Force 5: Social and Economic Dimensions of Nanotechnologies

6.1 Research priorities and proposals

179. The remit of Task Force 5 is the social and economic dimensions of nanotechnologies. There have been a number of public engagement activities underway over the last few years and the group is reflecting on how best to take these forward. In the meantime the group has identified two broad themes for priority research in this area:

- **Commercialisation and development of nanotechnologies in the UK:** This would include an examination of the UK's nanoscience research and innovation base with a view to predicting social and economic impacts;
- **Consumer & Regulatory effects:** This would include: an examination of the role of the media, NGOs and other external influences on the public acceptability of risk and scientific uncertainty in innovation; consider what lessons from past experience (e.g. asbestos) are transferable to nanoscience and nanotechnologies; life cycle analyses to ensure that savings in resource consumption during use of nanoproducts are not offset by increased consumption during manufacture and disposal; and how to engage most effectively further public engagement.

6.2 Background and brief summary of current status of research including issues arising in progressing the programme of UK research activities

180. The first research report of the NRCG[1] emphasised the Government's commitment to "understand the social and ethical implications of nanotechnologies, through a programme of public dialogue and social research." Following the report's publication, Task Force 5 on Social and Economic Dimensions of Nanotechnologies was convened to consider the implications of work in this wide-ranging area for Government policy and to take forward appropriate research.

181. Whilst a great deal of work has been done on public engagement in this area, little progress has been made beyond understanding the 'upstream' concerns over the socially responsible and ethically minded development of nanoparticle applications.

182. The Government has already made a considerable commitment to a programme of public dialogue on nanotechnologies as set out in the first Government research report'[1]. This has been designed to inform both the policies for addressing the implications of nanotechnologies and the development and use of nanotechnologies themselves. The Government is committed to enabling public and corporate R&D organisations to access information about societal aspirations and concerns, and hence take account of these in their policy and decision-making early in the nanotechnologies development process. We are of a view that we need to learn from the activities taking place under this programme, as well as those funded by other organisations, to maximise the benefits of any new public dialogue initiatives.

183. Two key activities have recently been reported:

- Nanodialogues: Experiments in public engagement with science', published by Demos (http://www.demos.co.uk/files/Nanodialogues%20-%20%20web.pdf).
- Democratic technologies? The final report of the Nanotechnology Engagement Group', published by Involve (http://83.223.102.125/involvenew/mt/archives/blog_37/Democratic%20Technologies.pdf).

184. Both reports were launched at an event hosted by Demos and Involve at the Institute of Physics on 26 June 2007. The following overall messages arise from the 2 reports[41,42].

- People's attitudes to nanotechnology are not significantly different from their attitudes to any new technology, and are generally positive.
- There are concerns about the lack of knowledge about the human health and environmental risks arising from nanotechnologies.
- There is strong support for fundamental science to arrive at answers to these questions.

185. Task force 5 is in the process of reflecting on the outputs of Demos' People's Inquiry on Nanoremediation, both in terms of what it means for Government policy on nanotechnologies and the future of public engagement activities more generally. This process of reflection is being informed by our knowledge and experience of previous public engagement activities, including the outcomes of the UK NanoJury and a citizen's jury that Defra has recently funded on air quality issues. We will also draw on the discussions and publications of the Nanotechnology Engagement Group, which was a multistakeholder group, charged with supporting *"public bodies in developing a coherent programme of social and ethical research and public dialogue around nanotechnology; and transferring this learning to wider science and technology arenas."*

186. Although upstream engagement provides useful perspectives, these can be difficult to connect to policy. Public engagement outputs have greater value and policy relevance when dealing with processes and applications which are 'out there' and known to the audience. There is a tendency to reduce the social issues associated with innovation to ethics, as the focus is on risk and safety, rather than broader social questions.

6.3 Summary of current position by research objective (RO, UK Projects)

6.3.1 RO1: Nanotechnologies and public engagement

187. A summary of the activities undertaken is provided at Annex E. In their 2004 report[4], 'Nanoscience and Nanotechnologies: Opportunities and Uncertainties', the Royal Society (RS) and the Royal Academy of Engineering (RAEng) examined the implications of nanotechnology and its potential uses. Among its 21 recommendations, the report recommended that Government initiate adequately funded public dialogue around the development of nanotechnologies. In responding, the Government committed to facilitate dialogue to enable both the science community and the public to explore together the aspirations and concerns around the development of nanotechnologies.

188. Since 2004 Government has funded a number of public dialogue initiatives including:

- **Nanodialogues** (as part of the Sciencewise programme), supported by a £120k grant from the DTI with matched funding from other sources, to look at a variety of applications of nanotechnology;
- **Small Talk,** a £50k project involving discussing nanotechnologies with the public and scientists;
- **Sciencehorizons,** a £330k programme which forms the public engagement section of the Wider Impacts of Science and Technology (WIST) programme that considers nanotechnologies as one of eight key emerging science and technology clusters;

- **The Nanotechnology Engagement Group** (NEG), funded with a grant of approximately £90k is made up of people with expertise in this area and is charged with mapping out and analysing current practices of public engagement on nanotechnologies. It has published a number of reports considering various methods of public engagement on nanotechnologies and held a workshop with interested parties;
- **Nanojury UK,** although not Government funded, brought together fifteen randomly selected people to discuss issues related to nanotechnologies.

Council for Science and Technology review

189. Although complimentary about the above activities, the Council for Science and Technology's (CST) recent review of Government's progress on its nanotechnology commitments expressed concern that, in many cases, public engagement has not had a major impact on policy. The CST were also concerned that a number of public engagement initiatives are drawing to an end and that it is not yet clear what will replace them. With regard to public engagement, the CST specifically recommended:

- *Maintaining an ongoing programme of public engagement;*
- *Carefully formulating future public engagement initiatives so that they are useful to policy makers;*
- *Conducting deeper and more in depth deliberative dialogue processes to deliver results of greater value to policy makers*
- *Considering how best to involve industry and NGOs in engagement processes.*

190. The CST will be keeping an eye on the Government's further progress on its Nanotechnology commitments, particularly assessing the impact of the recently established Ministerial group.

6.4 Research Council and other funding – projects summary

191. The ESRC, with its sister Research Councils plan a series of at least three 'Grand Challenges' of large multidisciplinary investments in specific areas of nanotechnology, beginning with energy. The social sciences will contribute fully and effectively to each of these 'Grand Challenges' to both research and development for capacity for interdisciplinary work. The ESRC will build on its existing achievements by ensuring each 'Grand Challenge' addresses research questions including:

- what are the key drivers of public and scientists' perceptions of risks and opportunities of nanotechnologies in this application?
- what is the likely impact on industry and economies, including from the convergence of nano with other technologies?
- how will the global development of science and innovation -and their multi level regulation-affect these technologies?
- how, when and why will public engagement and social influences affect development of these technologies?

192. In addition, the ESRC will take forward an international partnership of social science funders interested in these important questions.

193. The ESRC Centre for Business Relationships, Accountability, Sustainability and Society is currently undertaking work that builds on regulatory studies carried out on behalf of the DTI[43].

194. The ESRC has also carried out the world's most authoritative review of the social, ethical and economic aspects of development of nanosciences and nanotechnologies. The reports, published in 2003[44] and a follow-up in 2007[45], explain what nanotechnology is as well as its existing and potential consequences, and identify important issues for research and society.

195. The ESRC is currently funding a Science in Society Initiative in the area of 'Converging Technologies (CT)' – the convergence of nanotechnology, genomics, cognitive systems, neuroscience and information technology. All the uncertainties surrounding nanotechnology apply even more strongly to CT. The project aims to build scenarios to identify the scientific and economic activities that are likely to be relevant for social sciences research and, if so, how social sciences research topics relating to CT differ to those concerning nanotechnologies and other previous 'novel' technologies. This work is being taken forward by the James Martin Institute for Science and Civilisation, Oxford, and will report in late 2007[46].

196. The ESRC is also exploring opportunities to work with the International Risk Governance Council on 'Appropriate risk governance strategies for nanotechnology applications in food and cosmetics'.

197. Past research supported by ESRC has included shaping public attitudes and awareness; learning the real life lessons from the Genetically Modified Organisms debate, and a study of scientists', journalists' and editors' views on nanotechnology and news production.

6.5 Summary of other programmes of work internationally

198. The UK is ahead of other countries in engaging with the public on nanoscience. Few such initiatives have taken place elsewhere. The US has not yet carried out any public engagement activities. Preliminary studies at Universities in the US and beyond are reviewed within the NEG Report. Nanologue is a Europe-wide public engagement project, and the Rathenau Institute in the Netherlands is undertaking public consultation on the social issues surrounding nanotechnology.

199. UNESCO (2006) recently published 'The Ethics and Politics of Nanotechnology'[47], which indexed international work in this area.

200. Desk-based literature reviews are also available from the European Commission, Enterprise and Industry Directorate-General; Unit Chemicals – Environmental & Economic Issues Team; Brussels.

201. The Canadian Government[48] has also examined the social and ethical research questions posed by nanotechnologies. However, this and other international efforts have been assessed within what remains the most comprehensive study to date; the ESRC's (2007) work in this area led by Profs. Wood and Jones at Sheffield with Alison Geldart.

202. The nanoscience research agenda is wide reaching and is more than any single country can pursue. The UK is recognised as having taken a lead on international engagement and, through the OECD's Working Party on Manufactured Nanomaterials, has driven forward the shared international research effort.

6.6 Conclusion

203. Whilst the various lessons of public engagement on nanotechnology are absorbed by Government and the research community, high quality studies by the ESRC and UNESCO on the social and economic aspects of nanotechnologies have highlighted a number of further concerns and priorities for research. In support of the Government's commitments, both nationally and internationally we have concluded that there are two broad themes for priority research in this area; the economic clustering of the UK innovation community and the consumer and regulatory effects of further nanotechnology development.

6.7 Analysis and recommendations

204. In considering the two broad themes above, both of the thematic assemblages could be divided into smaller projects, though the linkages between each theme are apparent and we would prefer to see an holistic approach taken. Such an approach would capture the relationships between international regulatory demands (such as reference materials) with the ethics of intellectual property protection and the (in) equity of global technology markets and applications.

7. Next Steps

205. Since the publication of the Government's 1st Research report[1], the UK and the international community have identified the key priorities for EHS research in nanotechnology and the current report illustrates the extent of agreement achieved. It is clear that the next steps are to put in place the work required to fill the knowledge gaps and to address the seven overarching requirements outlined in the introduction. The top priority will be to put resources into the issues in metrology and characterisation that are needed to underpin the other research strands.

206. Joint working and collaborative funding will be the main avenue for taking the programme forward in the UK and there are a number of initiatives in place to achieve this. Government Departments, their Agencies, the Research Councils and Industry are focussing on the NRCG objectives and seeking flexible approaches to funding them.

207. We will actively continue participation in international collaboration in this area, mainly through the OECD Working Party on Manufactured Nanomaterials and its Steering Groups, and play our role in influencing the programme and in taking on a share of the workload as part of the ongoing UK effort. We will also seek to encourage the broadest possible sharing of data generated whether it is through public or private funding. UK and international voluntary reporting programmes or schemes for industry will be looked to as important sources of information in this regard.

208. We intend to review more fully, over the next twelve months, research work that has been completed and in progress in the UK and internationally. We will take stock of action towards meeting the NRCG and broader objectives with a view to considering what evidence of hazard, exposure or risk may be available that might indicate the need for controls on manufactured nanomaterials. This will be in the form of a report to Government Ministers.

209. We have already taken a new look at the remit, membership and objectives of the NRCG but we will continue to look for more efficient ways of working and to greater involvement of all stakeholders in decision making in research and for opportunities to raise the profile of the Group.

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Summary Status: Progress update and review (Task Force 2)		
Objective: RO5 Further identification of sources of nanoparticles.		
Project Description	**Active/Proposed/Completed (with costs in £s committed, proposed or spent)**	**Progress/Outcome/Next Steps**
1) NanoAlert – information bulletin service on exposure and human health	Active – HSE 52,000 year 1 Second year funding agreed	First two bulletins available on HSE Nanotechnology web site (http://www.hse.gov.uk/horizons/nanotech.htm) First bulletin of HSE NanoAlert Service issued December 2006 – included review of literature going back to 2000. Review split into two main areas: a) Measurement, exposure and control and b) Health effects Second bulletin issued May 2007 Mailing list to be created to inform customers when a new bulletin is available
2) An analysis of potential exposures throughout lifecycle of engineered nanoscale materials. Part of NANOSAFE 2 (see RO6/7)	Active - 22-partner EU FP6 IP project work carried out by UCL Overall budget 8.3m	Review of existing Life Cycle Analysis programmes carried out and found to be in need of modification. Work started on modification of programmes with intention of using incorporation of carbon nanotubes into tyres as a practical case. (Consortium has CNT manufacturer but work needs co-operation from tyre company)
3) Addressing potential exposure through developing the techniques for a life-cycle approach	Proposed	
4) Project to quantify the amount of exposure within the life cycle of a nanoparticle	Proposed	
5) Identification of further uses and resources.	Proposed	
6) Identification of environmental emission data and usage scenarios	Proposed	

Objective: RO6 Optimisation and development of technologies that enable the measurement of occupational and environmental exposure to nanoparticles via air and RO7 Understanding of fate and behaviour of nanoparticles in air		
Project Description	**Active/Proposed/Completed (with costs in £s committed, proposed or spent)**	**Progress/Outcome/Next Steps**
1) NOSH (Nanoparticle Occupational Safety & Health) Consortium: Three parts: – nanoparticle generation and behaviour – development of portable instrument for assessing exposure control – measurement of barrier function of RPE and PPE materials (RO8)	Active – Multi-partner "club" project overall budget ~ 400,000, HSE -35,000	Laboratory work for Phase 1 has been completed at DuPont's Experimental Station Laboratories. A second phase is being used to investigate some of the issues looked at in Phase 1, in terms of aerosol synthesis, how the aerosol chamber is used, continued efforts in the development of the portable monitor, and the role of particle chemistry, relative humidity, storage conditions and ambient working conditions on filtration efficiency performance. In Phase 1 methods have been developed for reproducible generation of SiO_2, citric acid and Ag aerosols with median sizes in the range 10 to 60 nm. Polystyrene latex aerosols (100 nm) have been generated from suspension by atomisation. Three processes have been used to generate nano aerosols – the one chosen depends on the starting material: SiO_2 or TiO_2 were generated by pyrolysis; silver aerosol was generated by thermal evaporation; solid citric acid aerosol was generated from solution. The work carried out is useful as a reference method for particle generation. Aerosols generated have been used to characterise performance of range of instruments for nanoparticle aerosols. Aerosols generated have also been used to investigate fate of nanoparticle aerosols. Instrument specification produced and discussions held with various instrument manufacturers. So far there are no agreements in place to take this aspect forward with any particular manufacturer. Work has continued within the project and two concepts have emerged that show promise to form a basis for a commercial device meeting the consortium needs. The work on this will continue in Phase 2. The final Project Advisory Board meeting was held in August 2007 following distribution of the draft final report at the end of July, to the Board members. The purpose of this meeting was to discuss the health and safety implications of the findings. This will contain an executive summary aimed at a non-technical audience as well as the main detailed report. A number of papers for submission to peer-reviewed journals are in preparation. The general principle is that the consortium will publish all significant findings. There was one more presentation in 2007 at the 3rd International Symposium on Nanotechnology Occupational Health Implications (September 2007, Taiwan).
2) NANOSH: Inflammatory and genotoxic effects of engineered nanomaterials. Comprises 5 work packages on: WP1: particle characterisation, WP2: workplace exposure assessment and associated control, WP3: genotoxicity of nanoparticles, WP4: pulmonary inflammation induced by nanoparticles,	Active – Seven-partner EU FP6 STREP project 573,000 from EU/HSE/HSL. Overall budget 2.7m	Particle characterisation parameters of bulk nanomaterials have been agreed taking account of measurement capability as well as desirability. Will be used for toxicology work and to develop database. Outline sampling strategy for work place exposure monitoring including contextual information (sampling instruments, where to sample and for how long, etc) agreed using experience gained in NANOSAFE 2 and other HSL work.

RO6/RO7 contd...		
Project Description	**Active/Proposed/Completed (with costs in £s committed, proposed or spent)**	**Progress/Outcome/Next Steps**
WP5: effects of nanoparticles on microcirculation:		All partners concluded pilot study. For HSL, this was carried out at a university in February 2007. Initial results show rush hour peaks of nanoparticles but no increase over background due to work activities. Difficulties of determining exposure to *engineered* nanoparticles very clear. Developing protocol for elemental mapping by X-Ray analysis / electron microscopy to distinguish between natural and engineered particles collected onto filters or carbon film supported on TEM grid. Second monitoring campaign carried out at second university using improved methodology. Initial results include observation that no particles were detected under clean room conditions – the next site to be studied has been agreed. Other partners are looking at sites elsewhere in Europe. Information on control measures in place and the risk of dermal exposure noted via observation. Programme to assess performance of RPE and protective clothing in working laboratory conditions will be discussed for implementation in second year of project. Will take account of work carried out elsewhere. Discussions have been held about setting up EU-wide database on anonymised measurements and associated contextual information
3) NANOSAFE 2: four main scientific subprojects: SP1: measurement of exposure to and characterisation of airborne nanoparticles; SP2: potential health effects; SP3: procedures for safe production and handling; and SP4: standards, regulations and societal implications.	Active – 22-partner EU FP6 IP project 70,000 from HSE/HSL Overall budget 8.3m	HSL is mainly involved in SP4: standards, regulations and societal implications. HSL has produced a preliminary report for the project consortium on review of regulations (summarising Government reviews which can be found in full at http://www.dti.gov.uk/science/science-in-govt/st_policy_issues/nanotechnology/page20218.html) and on the suitability of current standards for measuring and controlling exposure to nanoparticles, and controlling fire and explosion risks. Report will be updated as more information becomes available. HSL contributed to the drafting of the sampling strategy in SP1 and will visit one industrial workplace as part of SP3 Will use NANOSH/University kit.
4) HSL Investment Research Programme – Nanochallenge: Objectives: 1. Exposure Assessment and Control i) The development of the HSL aerosol generation and measurement capabilities ii) The development of improved methods of collection and characterisation of airborne nanoparticles. iii) The applicability of biological monitoring to nanoparticles.	Active – Approx 900,000 from HSE/HSL	Close links between this project and NOSH, NANOSH and NANOSAFE2 Limited work done so far on nanoparticle generation techniques, and HSL will trial methodologies developed in NOSH (with their permission) in the first instance. For the improved collection/characterisation element a start has been made on assessing collection methods (electrostatic and thermal precipitators made or refurbished for use in collecting nanoparticles in NANOSH exposure study). A new camera for the electron microscope has been installed. In addition, a new Energy-dispersive X-ray analyser (EDAX) for the scanning transmission electron microscope (STEM) has been delivered and installed. It will enable HSL to map the elements of airborne nanoparticles collected on carbon film/TEM grids or filters. This work links to the NANOSH project where HSL and the Finish Institute of Occupational Health (FIOH) will be

RO6/RO7 contd…		
Project Description	**Active/Proposed/Completed (with costs in £s committed, proposed or spent)**	**Progress/Outcome/Next Steps**
iv) The investigation of whether the current method of dustiness testing of solids is suitable for nanomaterials		developing analytical methods for the characterisation of airborne nanoparticles by electron microscopy and carrying out analysis of particles collected onto filters or carbon films/TEM grids. No work done yet on biological monitoring for assessing exposure to nanoparticles. The work to date has been on investigating whether the equipment currently used to assess dustiness of solids is suitable for nanoparticles. Several nanopowders (e.g. carbon black; newly purchased and old TiO_2; CeO_2) have been tested in the conventional dustiness equipment. The health-related fractions were collected onto metal foams and a filter for gravimetric analysis. A P-Trak Condensation Particle Counter (CPC) was connected to a probe introduced in the drum to measure the number of particles generated with time. The powders exhibited different dustiness behaviour from very low to measurable levels. Experiments on a new range of nanopowders (including cerium oxide, aluminium oxide, and carbon nanofibres) have been carried out with NIOSH (USA). NIOSH has been using a compressed air dustiness tester. Very interesting results were obtained showing behavior differences between very 'fluffy' low-density powders and more compact materials as well as between dustiness testers. A way forward was agreed including the measurements of (i) size distribution using a scanning mobility particle sizer (SMPS) and (ii) mass using gravimetric analysis. Progress presented in August 2007 at 3rd International Symposium on OH implications of nanomaterials in Taiwan (http://nano-taiwan.sinica.edu.tw/2007_EHS2007/index.htm).
2. Fire and Explosion Hazard Assessment The development of test vessel for explosive properties of nanoparticles		The literature has been reviewed and the properties for the new vessel for Fire and Explosion testing are being drawn up. Qinetiq have donated a quantity of old nano aluminium that will be used to compare results from the standard and new vessel. A full risk assessment is being completed.
3. *In vitro* Toxicology Assays The project aims to develop a human blood based assay. The endpoints being covered include immunotoxicity, blood coagulation, oxidative stress and cell death.		The protocol for the new *in vitro* toxicology assay is being refined at the moment. Optimising the oxidative stress measure has been a challenge for free blood cells. Therefore, now considering the use of myeloperoxidase. A case study will be conducted in the next few months to compare the toxicity of micro and nano sized particles where existing toxicity is known – could include (new and aged) aluminium.
4. Assessment of the potential use of nanomaterials as food additives or food ingredients in relation to consumer safety and implications for regulatory control.	Active – 40,000 from FSA	A published final report is due Autumn 2007.

RO6/RO7 contd...		
Project Description	**Active/Proposed/Completed (with costs in £s committed, proposed or spent)**	**Progress/Outcome/Next Steps**
5. Assessment of current and projected applications of nanotechnology for food contact materials in relation to consumer safety and regulatory implications.	Active – 68,500 from FSA	Project due for completion Spring 2008
6. Modelling: generation of real exposure data and comparison to predictions of existing environmental and human exposure models.	Proposed	Work on improving human exposure models reported in the literature will be monitored via NanoAlert (RO5) and should finish before work on modelling nanoparticle exposure starts.
7. Discrimination between ambient and engineered nanoparticles	Proposed	Strong link to RO2 (Task Force 1), but the direct need is for exposure assessment.
Objective: RO8 Development of exposure control devices		
1) NOSH Consortium (see RO 6/7)	Active Multi-partner "club" project overall budget ~ 400,000, HSE -35,000	Work on respirators proceeds with results showing an unusual pattern of efficiency with an exposure peak when the unit is used after a break in use. The hypothesis is that it might be the loss of static charge that reduces filter efficiency. SiO_2 aerosols used to assess barrier efficiency of a range of filter materials including N95, N100 and P100 RPE material and simple paper filters using aerosols. The majority of this work is now completed and the findings will be included in the final report. Further work is being carried out in Phase 2 of the project. For more information on the report see under R06 and R07.
2) NANOSH (see RO 6/7)	Active Seven-partner EU FP6 STREP project 573,000 from EU/HSE/HSL. Overall budget 2.7m	Workplace exposure assessment (especially in research laboratories in universities) and associated control issues – assessment ongoing. Programme to assess performance of RPE and protective clothing discussed for implementation in second year of project. HSL is involved in WP1: particle characterisation and WP2: workplace exposure assessment (especially in research laboratories in universities) and associated control issues.
3) NANOSAFE 2: four main scientific subprojects: SP1: measurement of exposure to and characterisation of airborne nanoparticles; SP2: potential health effects; SP3: procedures for safe production and handling; and SP4: standards, regulations and societal implications.	Active 22-partner EU FP6 IP project 70,000 from HSE/ HSL Overall budget 8.3m	Range of control measures used in university research laboratories is being noted as part of the Nanosh project HSL is mainly involved in SP4: standards, regulations and societal implications. SP3 has included work on efficiency of RPE and PPE systems carried out by other partners. Also work has been carried out on potential fire and explosive properties of nanoparticles and on suitable designs for packaging of nanoparticles for transportation and storage. Improved designs for total containment of processes have been explored by industrial partners producing nanoparticles.

RO8 contd…		
Project Description	**Active/Proposed/Completed (with costs in £s committed, proposed or spent)**	**Progress/Outcome/Next Steps**
4) NANOCHALLENGEHSL Investment Research Programme – Nanochallenge (see RO6/7)	Active Approx 900,000 from HSE/HSL	Includes work on efficiency of RPE and PPE systems Close links between this project and NOSH, NANOSH and NANOSAFE 2. Limited work done so far on nanoparticle generation techniques, but HSL will trial methodologies developed in NOSH (with their permission) in the first instance. Will provide means to evaluate the performance of RPE and protective clothing in real conditions and evaluate the performance of RPE and protective clothing in working laboratory conditions
5) Effectiveness of current control measures: a review of control measures currently used for the production, handling and end use of nanoparticles	Proposal	Range of control measures used in university research laboratories is being noted as part of the NANOSH project.
6) Control Banding project.	Proposed	Links to ongoing international work.
7) Assessment of the effectiveness of water filtration techniques against nanoparticles.	Proposed	Drinking Water Inspectorate to be contacted.
Objective: RO10 Research to understand the environmental fate, behaviour and interactions of nanoparticles in soils and water		
1) The Environmental Nanoscience Initiative: mechanism to address basic research into fate and behaviour of nanomaterials in the environment.	Active – Approx. 750,000	Set up by NERC, Defra and the Environment Agency. See TF 4 for details
2) Current and Predicted Environmental Exposure to Engineered Nanomaterials.	Active – Approx 50,000 from Defra	Project has used simple models based on pharmaceutical levels in water along with concentration data and usage scenarios of products to come up with predictions of worst case concentrations. Final report[18] published in Autumn 2007.
3) Consideration of the unintentional release of nanoparticles through disposal to landfill or discharge to sewage systems and wastewater treatment plants. Address scale of exposure through disposal routes.	Proposed	
4) Review of the published literature on the range of nanoparticles developed and used for wastewater remediation.	Proposed	

RO10 contd…		
Project Description	**Active/Proposed/Completed (with costs in £s committed, proposed or spent)**	**Progress/Outcome/Next Steps**
5) Laboratory study of nanoiron and bimetallic materials currently available for remediation of soil or water. The study will provide a benchmark for decision-making on which nanoparticles are potentially suitable for small-scale releases to provide information on field-scale fate and transport	Proposed	
6) Field-scale remediation of contaminated groundwater and soil. Comparative assessment of remedial performance using micro- and nano-scale particles, assessment of measurement technologies and investigation of nanoparticle transport	Proposed	
7) Develop an understanding of nanoparticle behaviour and fate in drinking water treatment processes	Proposed	
8) Targeted monitoring	Proposed	

Annex B

In vitro testing of nanoparticles

We have reviewed our thinking on *in vitro* testing of nanoparticles following publication of our report on this topic last year.

Introduction

It is felt that *in vitro* studies have the potential for use as a screening tool to provide information on the relative toxicity of manufactured nanomaterials (MN) compared to the corresponding bulk material. Some *in vivo* data would however be needed before definite conclusions could be drawn for hazard assessment.

Investigations relating to cells/tissues of initial contact (respiratory tract, gastrointestinal tract, skin) together with cells/tissue from potential target organs would be appropriate; ideally the latter would be based on information available from studies on the distribution of absorbed MN.

Metrology aspects

Physicochemical characterisation of the nanoparticle (size, shape, surface area, surface reactivity etc), selection of an appropriate vehicle, and measurement of actual exposures in-situ, allowing for agglomeration/disagglomeration, are fundamental and challenging requirements.

There is a need to reflect the *in vivo* situation as closely as possible. For example if the concern relates to possible local effects on the lower respiratory tract then an appropriate vehicle may be one that simulates the respiratory tract lining fluid (thin liquid layer of surfactant mix applied to the surface of the cells).

There has been much debate about whether nanoparticles will aggregate or disaggregate in aqueous media and whether any generalisations can be drawn. This is probably dependent on the type of MN and the presence of surfactant and needs to be considered on a case-by-case basis. Ideally, insitu measurements in the experiment should be carried out to provide information on this aspect.

A recent paper has argued that use of the physicochemical characteristics of exposure, although critical, are not on their own a surrogate of dose and may even be misleading. Dynamics over time in the cell culture system should be considered, reflecting diffusion, settlement, agglomeration/disagglomeration etc. This was termed 'Particokinetics'. It was recognised in the summary that the techniques such as transmission electron microscopy (TEM) and scanning electron microscopy (SEM) needed to measure cellular dose *in vitro* are difficult and costly and that there cannot be the expectation that cellular dose will be measured directly in most *in vitro* studies. In the future validated computer models for *in vitro* dosimetry may become available, but this is not possible at present. Thus although this paper is critical of current approaches it does not provide any practical alternative. {Ref: Teeguarden JG et al Particokinetics *in vitro*; Dosimetry considerations for *in vitro* nanoparticle toxicity assessments. Toxicological Sciences **95 (2)** 300-312 (2007)}

Annex B

Physicochemical properties and potential toxicity

Nanoparticles can act by reacting with surface receptors or by passing into cells and reacting with intra-cellular receptors; which is more important can only be judged on a case-by-case basis.

A few generalisations can be made regarding physicochemical characteristics and properties of the MN:-

Physical properties, specifically size, are important in governing the inter- and intra-cellular distribution of nanoparticles. As an approximation, nanoparticles above 200-300nm will not penetrate cells, although they can be taken up by cells such as macrophages. Nanoparticles of size 50-80 nm will penetrate cells but not cellular organelles such as the nucleus or mitochondria, and those below 20nm will enter the latter organelles.

Thus any intracellular nanoparticle-receptor interactions will be dependent on size.

Macrophage recognition and uptake is more likely with larger particles and is perhaps more likely if the particles are in an aggregated state.

Surface area is clearly inversely related to size of the MN and the extent of any agglomeration.

Surface reactivity e.g. with cellular contents or extracellular fluids, is dependent on chemical composition as well as surface area.

In the case of metal oxide nanoparticles, physical effects (particle size and surface area) tend to dominate rather than chemistry. For other MN a combination of both may be important.

Agglomeration is a particularly complex issue. Agglomeration in air will lead to deposition in the conducting airways rather than in the gas exchange zone. But once deposited the agglomerates may well break down and individual nanoparticles will be free to react with the cells. How tightly the nanoparticles are stuck together in the agglomerates is thus a key factor.

End-points as indicators of toxicity.

Oxidative stress is considered a good, general endpoint for the relative toxicity of ultrafines and possibly for the effect of MN in general on the respiratory tract.

Useful information on comparative toxicity may also be obtained from studies investigating the inflammatory response, cytotoxicity or genotoxicity. A range of different studies is likely to be appropriate depending on what is known about the mechanism of action of the MN in question.

Further details of the recommended approaches for each endpoint are provided in the Task Force 3 Report on *In vitro* Methods for Assessing the Toxicity of Nanomaterials.[2]

Task Force 3, NRCG

In vivo testing of nanoparticles

We have considered factors likely to be important in the *in vivo* testing of nanoparticles.

A number of recent reports have concluded that current methods used to assess the health effects of chemicals, based largely on experimental studies in animals, are generally appropriate for manufactured nanomaterials (MN). However special attention needs to be given to metrology and dosimetry aspects. Also to certain types of toxic effects that may arise from nanomaterials that would be poorly detected in conventional toxicology studies.

There follows an outline of the key factors to consider in the design of *in vivo* studies to investigate the toxicology of MN.

Metrology aspects

This is a very challenging area.

Clearly the MN must be well characterised with respect to particle size, shape, surface area, surface reactivity etc. with information on homogeneity and stability and whether aging affects these properties. These characteristics could change in the dosing vehicle. Information on the stability in any dosing vehicle is also necessary. This includes air; a high concentration will lead to increased agglomeration and this will affect deposition patterns in the lung.

Ideally the most appropriate dose metric (mass, particle number, surface area, surface reactivity etc.), should be known in advance of the study; this will be dependent on the nature of the MN.

If this is not known (currently this is not known with confidence for any MN) a range of parameters need to be measured to cover various possibilities. Particular attention needs to be paid to any changes in the characteristics of the MN that may occur under local conditions due to agglomeration/disagglomeration etc.

For pragmatic reasons we probably will have to accept less than ideal data sets in this regard in the first instance.

Specific types of toxicity warranting special consideration when testing MN.

There is concern that MN may induce specific types of toxic effects that are not readily detected in the conventional animal studies. It is widely believed that ultrafines are responsible for the well established cardiovascular effects of air pollution, although this hypothesis remains unproven. Nanoparticles have been shown to interfere with the clotting process of the blood and the suggestion has been made that nanoparticles may be a cause of atherothrombosis (disruption of an atherosclerotic plaque, leading to platelet aggregation and thrombus formation). Such effects may not be easily picked up in conventional toxicity studies, at least in the early stages and ApoE -/- transgenic mice have been developed as a model for human atherosclerosis. Single wall carbon nanotubes have been shown to accelerate atheroma formation in this model.

There is some evidence that nanoparticles can translocate from the respiratory tract to the brain via the olfactory nerve suggesting neurotoxicity may be a particular concern. There has been increasing recognition of the importance of adequately investigating the neurotoxicity of chemicals in general, with the more routine animal tests being designed to detect compounds with neurotoxic potential, which may be followed up by more detailed testing to characterise such effects. This has led to the OECD toxicity test guidelines for repeated exposure (28 and 90 days) now giving more emphasis on neurotoxicity (with inclusion of a 'functional observational battery 'and enhanced histopathology of the brain and peripheral nervous system) and there is also a specific guideline for investigating neurotoxicity in more depth, again focussing on the oral route. The inhalation (and also the dermal) exposure guidelines have not been so updated and the need for enhancement to better detect neurological effects needs to be recognised when testing MN by this route.

Route of exposure

For acute studies, routes of exposure may be oral, dermal or inhalation. For repeated exposure, oral or inhalation are likely to be the most appropriate routes (In the chemicals area repeated dose dermal studies are only rarely performed for a number of reasons, with hazard assessment of the systemic toxic effects of repeated dermal exposure being made from oral toxicity data and an estimation of skin absorption. Presumably the same could be true for nanomaterials.)

The question of tracheal instillation as opposed to inhalation needs to be considered as much research work is carried out using instillation, and facilities for inhalation experiments are limited. It is felt that the instillation route can provide useful information on comparative toxicity and on mechanisms, but for definitive information on hazard following exposure by inhalation, studies using this route are necessary; this is particularly the case for effects following repeated exposure.

(We plan to produce a more detailed document on the value and limitations of studies using tracheal instillation rather than inhalation, in June 2008).

Distribution studies

A key consideration when assessing potential toxicity of MN is knowledge of distribution and elimination following absorption. This may allow the identification of any particular tissue where the MN may accumulate, and which could give rise to concerns regarding potential toxicity. Additional information on cellular uptake and subcellular distribution would be helpful. This presents particular problems as it is difficult to track distribution *in vivo* at realistic exposure scenarios. Such studies are dependent on a suitable marker such as radio-labelling being available that does not affect the properties of the MN. These complex studies need be designed on a case-by-case basis.

Task Force 3, NRCG

Summary Status: Progress update and review (Task Force 4)

RO17 Research to establish the uptake, toxicity and effects of nanoparticles on groundwater and soil microorganisms, animals and plants, especially in the context of remediation.

RO 18 Research to establish the mechanisms of toxicity, toxicokinetics and in vivo effects of nanoparticles to key ecological groups (including invertebrates, vertebrates (e.g. fish) and plants). A key aspect of such work should be the facilitating of knowledge transfer from human toxicological studies to inform ecotoxicology.

Project Description	Active/ Proposed/ Completed (with costs in £s committed, proposed or spent)	Progress/Outcome/Next Steps
NERC Responsive Mode Funding	Active 785,791	3 grants awarded since 2005 (Universities of Birmingham, Exeter and Plymouth).
Defra / NERC / EA / EPSRC Environmental Nanoscience Initiative www.nerc.ac.uk/research/programmes/nanoscience	Active 752,938	Directed capacity building programme of research. 1st call for proposals September 2006: 10 grants funded 2nd call for proposals July 2007, evaluation and awards were made in October 2007. 8 additional awards were funded.
NERC/ Defra/ EA/ DH/MOD Environment and Human Health Programme www.nerc.ac.uk/research/programmes/	Active Approx 471,000	2 grants awarded in 2006 on environmental risks of manufactured nanomaterials, 2 on ultrafine particles toxicology
International activity monitoring and co-ordination EU Framework Programmes (FP6, FP7); US Environmental Protection Agency NCER Programme, OECD Working Party on Manufactured Nanomaterials	Active N/A	Monitoring work within USEPA and EU Framework Programmes and engagement with OECD WPMN
Knowledge Transfer	Active N/A Active 128,947	'Environmental Effects of Nanomaterials' – international scientific conference held September 2006 and September 2007, London Nanonet (including International Workshop November 2007: ''Linking ecotoxicology and physico-chemical speciation of nanomaterials".)

RO 19 Define endpoints to be measured in ecotoxicological studies and assess how fit for purpose current standard tests for persistence, bioaccumulation and toxicity (PBT) are when considering nanoparticles. This should lead to the defining of a suite of standard PBT protocols for use in environmental hazard assessment.		
Project Description	**Active/ Proposed/ Completed (with costs in £s committed, proposed or spent)**	**Progress/Outcome/Next Steps**
Hazard and Risk Assessment – ecotoxicological methods Assessment of how fit for purpose current and proposed regulatory ecotoxicological tests are for nanomaterials.	Completed Approx 25,000	Project undertaken by Watts and Crane Associates – Report published and available at: http://randd.defra.gov.uk/Document.aspx?Document=CB01097_6262_FRP.pdf
International activity monitoring and co-ordination SCENIHR Nanomaterials Working Group assessing the Technical Guidance Document (TGD) supporting chemicals regulatory risk assessment. OECD WPMN Steering Group 4: Test Guidelines OECD WPMN Steering Group 6: Risk assessment approaches	Active	Two Opinions published by SCENIHR.[19] Task Force 4 Chair also chairs OECD SG6.

Summary Status: Progress update and review (TF5)		
Objective: R01 To understand the social and ethical implications of nanotechnologies, through a programme of public dialogue and social research.		
Project Description	**2. Active/ Proposed/ Completed (with costs in £s committed, proposed or spent)**	**Progress/Outcome/Next Steps**
Nanodialogues Public engagement experiments discussing applications of nanotechnology	Completed £120K spent	'Nanodialogues: Experiments in public engagement with science', published by Demos on 26/06/07 (http://www.demos.co.uk/files/Nanodialogues%20-%20%20web.pdf)
Small Talk Discussions between scientists and the public	Completed £50K spent	This project has helped organise more than 20 events in the UK, attended by over 1200 participants. Final report published on 9th February 2007 (available at http://www.smalltalk.org.uk/page41g.html)
Sciencehorizons Part of the Wider Impacts of Science and Technology (WIST) programme that considers nanotechnologies as one of eight key emerging science and technology clusters	Completed £330K spent	Sciencehorizons events took place throughout the UK from January to July 2007. Results are due to be presented to Government in Autumn 2007
The Nanotechnology Engagement Group	Completed £90K spent	The NEG has published a number of reports considering various methods of public engagement on nanotechnologies and held a workshop with interested parties
Nanojury UK A citizens' jury heard 'evidence' from expert witnesses on applications, opportunities, challenges and risks of nanotechnologies, then made recommendations on priorities for action to be taken	Sponsored by University of Cambridge, Greenpeace UK, the Guardian and the Policy, Ethics and Life Sciences Research Centre of the University of Newcastle.	20 recommendations were made, attracting various degrees of support. The jury identified the following 4 recommendations which they felt most strongly about: 1. Health - nano-enabled medicines have a societal benefit and should be developed via improved funding mechanisms and made available without discrimination on the National Health Service. 2. The Government should support those nanotechnologies that bring jobs to the UK by investment in education, training and research. 3. Scientists should learn to communicate better. 4. Products containing manufactured nanoparticles should be labelled in plain English. Government is committed to responding to the Nano Jury UK findings.

Some Current Research projects and Proposals outside UK					
Information sources: Woodrow Wilson Inventory of Nanotechnology Environment, Health and Safety research (http://www.nanotechproject.org/18/esh), OECD 2nd WPMN Tour de Table Summary (http://appli1.oecd.org/olis/2007doc.nsf/linkto/env-jm-mono(2007)16), U.S. EPA contact					
Country	**Research Category**				
	1. Metrology, Characterisation, Standardisation and Reference Materials	2. Exposures – Sources, Pathways and Technologies	3. Human Health Hazard and Risk Assessment	4. Environmental Hazard and Risk Assessment	5. Social and Economic Dimensions of Nanotechnologies
Australia Government currently developing response to the paper "Options for a National Nanotechnology Strategy".	National Measurement Institute offers service for calibrating standard reference materials.	Research community has established a network called NanoSafe Australia which is currently preparing position paper on current OH&S best practices.			National Health and Medical Research Council (NHMRC) hosted Roundtable in Dec 2006 and plans future forums and activities.
Belgium		Partnered with NANOSAFE 2 (8 countries involved).	Predominantly human toxicology.		
Canada National Sciences and Engineering Research Council (NSERC) funded.	Recognition and physicochemical characterization of nanomaterial – peptide interactions.		In vitro and in vivo, dynamics and distribution in blood vessels, interactions with: bio membranes and DNA; blood, fate in mammalian cells in relation to different characteristics, transport and association in biological systems.	Effect of size and shape on uptake, degradation and clearance in primary macrophages.	None
China Ministry of Science and Technology funded National Centre for Nanoscience and established the Nanosafety Lab (2006 – 2011) with a remit to consider:		Recognition, identification, quantification of hazards resulting from exposure to NM with focus on characterisation		and, interaction with biological systems, *in vivo* studies.	

Country	Research Category				
Denmark	Technical University of Denmark funded NFA programme – focuses on integrating research on nanoparticles aerosol science and molecular biology.				Standards Association has started network group with various stakeholders in relation to standardisation.
Finland FinNano programme 2005 - 2009. Consists of research and technology development. It is carried out in close co-operation with Academy of Finland's Nanoscience Research Programme which combines nanoscale research in chemistry, physics and biosciences and supports the overall development of the field in Finland.					
France	NANOSAFE 2 and various national institutes including the National Institute for Industrial Environment and Risks (INERIS) and National Institute for Research and Security (INRS) working to develop research programme. Commissariat à l'Energie Atomique (CEA, Atomic Energy Commission) at Grenoble lead NANOSAFE 2.	Partnered with NANOSAFE 2 and other National Programmes.	Partnered with NANOSAFE 2 and other National Programmes, *in vivo, in vitro* and *in silico* modelling.	INERIS cataloguing the environmental hazards. National Research Agency (ANR), CEA, National Centre for Scientific Research (CNRS) funded. Cytotoxicity, genotoxicity and influence of NM on bacteria.	None, but opinions of the CNRS Committee on Ethics for the Sciences (COMETS) and National Consultative Ethics Committee for Health and Life Sciences (CCNE) issued.

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Country	Research Category				
Germany Nanocommission established Nov 2006 3 Working Groups	NANOCARE (13 companies, universities and research institutions) – Primary focus is human toxicology using in vitro and in vivo tests, but will also create new nanoparticles and undertake characterisation studies. TRACER (Federal Ministry of Education and Research, BMBF funded with match funding from industry) – Seeks to answer cytotoxicity of carbon nanomaterials. Characterisation will be undertaken and simulation tools adapted for reception and distribution paths in human organisms INOS (funded by BMBF with 4 research institutions and 1 biotechnology enterprise undertaking research) – developing in vitro methods to evaluate potential. Different nanoparticles will be used and physicochemical dimensions considered.				
Ireland No overall strategic programme			No practical research projects but FP6 funded project NanoInteract "Development of a platform and toolkit for understanding interactions between nanoparticles and the living world".		Nothing following internet consultation undertaken between August and September 2006.
Italy Commission entitled Nanotechnology set up to cover range of risk issues.		National Institute for Occupational, Safety and Prevention (ISPESL) proposal, subject to approval.	Limited number in university, research centres or institutes but poorly coordinated. Partners in FP6 programme "Development of an Integrated Platform for Nanoparticle Analysis" (DIPNA). Cuts across eco-toxicity, particle exposure.		
Japan	Ministry of Economy Trade and Industry (METI) has launched 5 year project named "Evaluation of the Potential Risks of Manufactured Nanomaterials based on Toxicity Tests with Precise Characterisation" Cross cuts with human health and workplace exposure and measurement.	National Institute of Occupational Safety and Health (JNIOSH) started new research on possible health issues in April 2007.	National Institute for Environmental Studies (NIES) programme in vivo and in vitro studies plus chronic inhalation studies over three years.		No formal programmes but Cabinet Office has established committee that coordinates research and development policy which has a remit to consider public acceptance issues.

Country	Research Category				
Korea Inter-ministerial consultation body set up in March 2007 to harmonise policy on safety and will play an important role for effective research			Ministry of Environment (MOE) started project (cross-cutting) on human health and environmental safety within the framework of the project Eco-technopia21 which previously focused on promoting the development of environmental technologies. Ministry of Science and Technology (MOST).		
Netherlands Interdepartmental working group on possible risks established and due to produce an action plan for the Government. National research agenda including a "risks section" is being drafted by the Netherlands Nanotechnology Initiative (NNI) and the National Observatory.					The Dutch Cabinet foresee installation of a so called "broad commission" with stakeholders from both science and public. The SER (Dutch Socio Economic Council comprising business and union representatives and independent academia have been asked to comment on exposure issues in the workplace.
New Zealand	No research programmes but the Foundation for Research Science and Technology has called for research proposals.				

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Country	Research Category				
Norway	A national strategy for nanoscience and nanotechnology has been adopted by the Research Council to build on findings (2005) of the research program NANOMAT in place from 2002. Awaiting consideration by Ministry of Education and Research.				Preceding Research Council adopted national strategy presented at open meeting, draft strategy also put out for public hearing.
Spain	Government launching a National Consortium (regulation) which will include division devoted to EHS issues. Increased funding expected for EHS through the renewal of strategic action on Nanoscience and Nanotechnology (2004 – 2007),under the Ministry of Science and Education (MEC).	Other initiatives include: PHANTOMS Foundation co-funded by the EU and MEC, NANOSPAIN (network of research groups and companies), M'NANO Modelling for Nanotechnology (web-based initiative comprising institutions, universities and the PHANTOM Foundation), NANOMED which integrates industry, hospitals, and experts from the administration. Includes Toxicity and Regulation working party			
Sweden	None but the Government has commissioned the Swedish Chemicals Inspectorate to review available knowledge, identification of data- gaps and proposals for filling gaps.				Ongoing: Swedish Chemicals Inspectorate and Swedish Standards Institute organized Network on Risk assessment, and Standards for Nanomaterials, respectively.

Country	Research Category				
Thailand Government set up National Nanotechnology Centre (NANOTEC, 2004 - 2013) under the umbrella of the National Science and Technology Development Agency (NSTDA) a non-Government public body. The 3rd phase of its strategic plan is aimed to address nanosafety strategy at a national level	Nanosafety/Nanoethics guideline drafting project underway. Nanosafety forum set up in university to share information among researchers and faculty members Some aspects of existing R&D focused NANOTEC programme addresses this, e.g. instrument provision for measurement.		No research programmes addressing these		
U.S.A. Comments from the public being sought on document I"Environmental, Health and Safety Research Needs of Engineered Nanoscale Materials". Gap analysis to develop priority research strategy.	NIOSH, NSF, DOD and EPA funded. Areas covered: characterisation, and characterisation incorporating (i) monitoring and quantification, (ii) cell interactions to test the relationship with physicochemical properties.	Wide range NIOSH and EPA funded. Studies using different materials, a selection of pathways and sources. Targeted studies (e.g. using carbon nanotubes) to consider fate and transformation.	Wide range. NIOSH, EPA, NSF, NIH/NIEHS, NIH/NIEHS/NTP, DOD/AFOSR and industry (DuPont) funded. Dosimetry, inhalation, in vitro, pulmonary toxicity & deposition, cardio-pulmonary inflammation, lung oxidative stress/inflammation, dermal toxicology, etc.	A selection. EPA and NSF funded. Impact on water, soil and subsurface ecosystems, acute and short term toxicity, breakdown kinetics in aqueous systems, NM microbe interactions, acute and developmental toxicity in fish & frogs, bio availability and toxicity.	NIOSH seeking public comments on related documents posted on web-site. Scientific peer consultations on materials characterization and risk management practices scheduled summer and autumn 2007.

DECHEMA-VCI-Working Group "Responsible Production and Use of Nanomaterials"

Roadmap for Safety Research on Nanomaterials Link with the European 7th R&D Framework Programme and national Programmes

July 5th 2007

Details provided with kind permission of DECHEMA-VCI Working Group

Nanotechnology is the technology that characterises, designs, produces and uses structures and systems that require exact control of the size and form on the nanometre scale that is a billionth of a meter. Nanotechnology will enable new developments and novel applications from biomedicine to information technology. Chemistry is the science that delivers basic materials for those technologies by producing so called nanomaterials, mostly defined as <100 nm in at least 1 dimension.

Nanomaterials must be safe for man and the environment. As with any other emerging technology, safety research is necessary to ensure responsible use of nanomaterials. This paper from DECHEMA (Society for Chemical Engineering and Biotechnology) and VCI (German Chemical Industry Association) is directed to provide some recommendations which current research issues might be addressed in the European R&D Framework Programmes especially in the European Technology Platforms for Sustainable Chemistry (SusChem) and for Industrial Safety (ETPIS).

Nanomaterials may exhibit new substance properties, especially due to an increased surface/volume ratio, a higher surface energy and a smaller particle size. These altered substance properties may possibly result in different toxicological and ecotoxicological properties than bulk materials. These possible changes in substance properties currently give rise to the question whether existing exposure measurement technologies and methodologies and toxicological testing strategies are appropriate to assess potential hazards and thus are appropriate to analyse potential risks of nanomaterials. This is currently intensively being studied worldwide by industry and science institutes.

In Germany, DECHEMA and VCI have established a working group "Responsible Production and Use of Nanomaterials" which consists of high-level European scientific and industrial experts and is regularly joined by representatives from the German authorities. The group which was initiated in 2003 shares scientific findings and best practices on safety aspects of the production and use of nanomaterials.

The DECHEMA-VCI working group has already addressed these issues at a very early stage in a roadmap of safety research which is continuously updated and reviewed (Annex "Roadmap of the DECHEMA-VCI Working Group on safety research on nanomaterials"). The DECHEMA-VCI roadmap contributed to the project NanoCare funded by the German Federal Ministry of Research (BMBF).

Overview on the most urgent issues concerning the safety and potential risks of nanomaterials and ongoing research projects

In close co-operation with scientific institutions the chemistry industry works already on almost all of the most urgent research issues:

- The BMBF project "NanoCare" project will
  - Investigate decisive parameters which trigger toxic effects (size, chemical composition, effects of surface, morphology) by end 2007.

- Develop and assess toxicity testing methods with respect to their suitability to detect different specific effects in bodies under practical circumstances, e.g. at the working place by mid 2008.
- Study the toxicology of different materials than Titania and carbon black by end of 2007.
- Develop methods to reproducibly provide inhalable atmospheres of nanomaterials suitable for toxicological studies by end of 2007.
- Investigate the stability of agglomerated nanoparticles in body fluids by mid 2008.

- The project "Nanosafe II" funded by the European Commission
  - Develops and assesses toxicological testing methods with respect to their suitability to detect different specific effects in the body under practical circumstances, e.g. at the working place by end of 2008.
  - Studies the toxicity of other materials than Titania and carbon black by end of 2008.
  - Develops methods to reproducibly provide nanoscaled aerosols for toxicological studies by mid of 2008.
  - Investigates mechanisms to take particles into the lung by end of 2008.
  - Investigates the real morphology (isolated, agglomerated) of nanoparticles and develops methods to detect the kind and concentration at the working place by end of 2008.
- The Centre for Functional Nanostructures of the Deutsche Forschungsge-meinschaft (DFG) (German Research Fundation) has launched a project that
  - Has investigated the transport of nanoparticles into and through cells and the crossing of organic barriers (blood-brain and placenta barrier etc.)
- The research project "Nanoparticle Exposure on Workplaces (NEW)" at the Institute for Environmental Technology and Analytics, IUTA and NanoCare will
  - Investigate the real morphology (isolated, agglomerated) of nanoparticles and develop methods to detect the kind and concentration at the working place by mid 2008.
  - DFG Priority Programme SPP 1313 "Biological Responses to Nanoscale Particles" investigates the manufacturing and characterisation of NPs, the transition of NPs into and interaction with the biological environment, and the impact of NPs on fundamental biological functions.
- "TRACER" is a project of several German companies within one value chain, co-funded by German BMBF, which evaluates cytotoxity and biocompatibility of carbon nanotubes (CNT) and will derive recommendations for safe processing, handling and use of these products.
- "INOS" (UFZ Dresden) will evaluate possible adverse health effects within the process of production, characterisation and processing of nanoscale powders.
- The FP 6 EU project "IMPART" reviews the latest scientific and technological developments related to the risks of nanoparticle exposure on human health and the environment and will end up in producing guidelines and recommendations for the institution of future nanoparticle standards and exposure limits.
- FP 6's "Nanotox" analyses information on the toxicological impact of nanoparticles, by reviewing information on
  - physical and chemical properties of different types of nanoparticles and agglomerated nanocrystals; manufacturing and use; human health effects including side effects; animal toxicology; environmental impacts; mutagenicity/genotoxicity; metabolism/pharmacokinetics; standards for safe use; safe laboratory methods etc.

  - the potential methods of dispersal, and contamination by, nanoparticles and agglomerated nanocrystals (e.g. sorption, desorption, transport, aggregation, deposition, biological-uptake)
- The "NEST Particle Risk" of the EU Project is devoted to study the health hazards posed by new types of particulates e.g. carbon nanotubes or fullerenes. The partners will also develop methods to detect and quantify the presence of the particulates in living tissues. Mice will be used to assess the uptake and transport of the particulates in living systems. Toxicity testing *in vivo* will use a mouse model, *in vitro* tests will use cultured cells.
- The EU project "Nanoderm" investigated the uptake of Titania and zinc oxide nanoparticles from via the skin. The project has been finalized; the final report is still pending. The interim results confirm the effectiveness of the healthy skin as protective barrier.
- A German company investigated the skin penetration of ZnO and TiO_2 nanoparticles according to OECD guidelines: No skin penetration was found.
- The EU project "NANOTRANSPORT" addresses the behaviour of aerosols released to ambient air from nano-particle manufacturing. The proposed pre-normative study has the objective of bringing into light and to document the need for standardised test aerosols adapted to the scope of nano-toxicology and occupational health studies.

Further issues not mentioned here but identified by the DECHEMA/VCI Working Group (see roadmap in the annex) will be addressed by company projects and projects of the Institute for Environmental Medicine at Heinrich-Heine-University, Duesseldorf.

This shows that almost all of the important issues concerning the safety and potential risks of nanomaterials are already under evaluation. The results will inform the present discussion.

Issues to be addressed within the 7th R&D Framework Programme and to promote European co-operation are described in the following "Recommendations of the DECHEMA-VCI Working Group for 7th R&D FRP".

Recommendations of the DECHEMA-VCI Working Group for 7th R&D FRP

Nanoparticles are mostly produced in closed systems thus avoiding the release of side products and particles to the workplace and the environment. Most applications do not exhibit/use/show isolated free nanoparticles. Characteristically nanoparticles firmly stick together in the formulation processes or are firmly embedded in products. Great efforts have to be made to generate isolated particles for special applications. Thus, to assess potential risks of nanomaterials DECHEMA-VCI recommends focusing on the exposure assessment in the first step.

The DECHEMA-VCI Working Group recommends

- the development of a robust and effective analytic standard method to measure surface and number concentration, morphology and chemical composition of individual particles and agglomerates under real workplace and environmental conditions and to determine the size distribution for high number concentrations, Especially methods for environmental analysis for particles sized between 0.5nm and 20nm and processes to analyze non spherical forms of nanoparticles (tubes, plates etc) are called for.
- The development of new methods to determine the particle number, size, composition and the real morphology (isolated nanoparticles, aggregates, agglomerates, particle/protein or particle/DNA complexes etc) of nanoscale products in liquid media.

- The international harmonization of analytical standards (methods for reproducible particle generation, detection and characterisation of atmospheric nanoparticles and of nanoparticles in biological tissue, reference materials).
- The development of basic toxicology data/test procedures/guidelines for short term testing (genetic toxicity, extra-pulmonary distribution and bioavailability) and long term testing (long-term pulmonary inflammation, and chronic effects).
- The investigation of life cycle aspects of selected articles containing nanomaterials (ecotoxicology esp. accumulation potential and fate at the end of the life cycle).

Annex: Roadmap on safety research on nanmaterials

The roadmap summarizes the most urgent issues for safety research of nanomaterials and for a deepened understanding of biological effects and mechanisms. The issues already undertaken in ongoing projects are marked and scheduled:

Expected results of high priotritized (DECHEMA/VCI) topics									
Priority and description		2005		2006		2007		2008	
		1st	2nd	1st	2nd	1st	2nd	1st	2nd
1	Decisive parameters for toxicity of nanoparticles			INOS NC FZK GSF Nanotox Tracer	INOS NC FZK GSF Nanotox Tracer	INOS NC FZK GSF Nanotox Tracer	INOS GSF Nanotox Tracer	INOS	INOS
2	Development of the validated toxicological methods			NS GSF	NC FZK NS GSF	INOS NC FZK NS GSF	INOS NC FZK NS GSF	INOS NC FZK NS GSF	INOS NS
3	Studies on materials other than TiO_2 and Carbon Black		NC FZK NS Tracer INOS	INOS NC FZK NS GSF PR INOS	NC FZK NS GSF PR INOS	NC FZK NS GSF PR INOS	NC FZK NS GSF PR INOS	NC NS FZK GSF PR INOS	INOS NS
4	Development of methods to reproducibly produce nano-aerosols		NC FZK ASO	NC FZK ASO GSF	NC FZK ASO NS GSF	NC FZK ASO NS GSF	NC FZK ASO NS GSF	NS	
5	Transport mechanisms of particles in/through Cells		CFN	CFN PR NS	CFN PR NS	PR NS INOS	PR DFG NS INOS	DFG INOS	DFG INOS
6	Mechanism to take in particles through skin	BA	ND	ND					
7	Mechanism to take in particles by lung	GSF LS	GSF LS	PDL GSF NS LS	PDL GSF NS LS	PDL GSF NS LS	PDL GSF NS LS	NC LS	NC LS
8	Exposure Assessment (Methods to measure/identify conc., morphology and type of nanoparticles in environment and at the working place)		NEW NS	NEW GSF	NEW GSF	NEW GSF	NEW GSF	DFG NEW	DFG NEW
9	Stability of agglomerates under practical conditions			NC GSF	NC GSF	NC GSF	NC GSF	NC	NC
10	State of particle aggregation/agglomeration in human body			GSF NEW NS	GSF NEW NS	GSF NEW NS	NS NC GSF NEW	NS NC GSF NEW	NS NC GSF NEW
11	Disintegration of agglomerates in body fluids		DE	DE INOS	INOS	INOS	NC INOS	NC INOS	INOS

Annex G

Key: **ASO**: Aerosol synthesis of metal oxides Univ._ Duisburg-Essen, **BA**: BASF; **DE**: Degussa; **DGF**: Deutsche Forschungsgemeinschaft; **CFN**: DFG-Centre for Functional Nanostructures; **FZK**: F&E ITG-TOX; **GSF**: Research Center for Environment and Health; **INOS**: Identification and Assessment on Human & Env. Health, Centre for Env. Res., Leipzig; **LS**: Development of a lung simulator, IUTA, Duisburg: **Nanotox**: Toxicological impact and health & env.; **NC**: NanoCare; **ND**: Nanoderm; **NEW**: Nanoparticle exposure at workplaces, IUTA; **NS**: Nanosafe II, **PR**: Particle Risk project; **Tracer**: Project on CNTs.

Missing: Company projects, projects of the Institute for Environmental Medicine at Heinrich-Heine-University Duesseldorf.

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Annex H

Research Council Spend for Nanotechnology – NRCG research objectives

Biotechnology and Biological Sciences Research Council (BBSRC)

BBSRC is one of the seven UK Research Councils and it is the leading funding agency for academic research and training in the non-clinical life sciences. BBSRC's remit does not cover research on environmental pollution, pathways to exposure and systematic *in vivo* toxicology of nanomaterials (see MRC and NERC annexes) but we recognise the importance of such approaches. We do support research in the wider area of bionanotechnology and recognise that some of this work may contribute indirectly to EHS approaches (see http://oasis.bbsrc.ac.uk/Welcome.html). BBSRC is keen to work collaboratively with other funding partners so basic biological research is incorporated where appropriate. To this end we have co-supported activities funded through the NERC-led Environment & Human Health Initiative.

Engineering and Physical Sciences Research Council (EPSRC)				
EPSRC Project Reference NRCG Research Objectives	**Grant Title/Establishment**	**Total Grant Value in £'s**	**Project Description**	**Period**
EP/D063329/1 RO2	New Tools for Nanometrology Imperial College London	2,746,000	Establishment of a new UK research capacity, based at the London Centre for Nanotechnology, a joint venture between two of the UK's leading universities that will address key challenges in the development of innovative tools for nanoscale characterisation and metrology. The programme will deliver high impact fundamental science and will lead to the development of new techniques capable of quantifying target properties with appropriate spatial and temporal resolution.	2007-2012
EP/D063604/1 RO2	New Tools for Nanometrology University College London	2,803,000	As above. Joint ventures between Imperial College and University College London.	2007-2012
EP/D062861/1 RO2	Nanometrology for Molecular Science, Medicine and Manufacture University of Strathclyde	3,118,000	A Centre for Molecular Nanometrology founded by a UK university in 2005 (considered to be the first by the university), with facilities supported by the Wolfson Foundation and the Science Research Infrastructure Fund. This Centre has the ultimate goal of recording real-time images of dynamical interactions of single molecules *in situ*. This will facilitate the high quality, innovative, multi disciplinary research environment required to nurture and develop the extra capacity needed to make the UK a leader in nanometrology. Also bring together the Centre and medical collaborators, bridging the molecular measurement gap to innovation in emerging areas of strategic importance such as disease pathology, etc. in nanomedicine.	2007-2011
EP/C517555/1 RO6/RO16	Research Network on Nanoparticles at the Science and Engineering/ Medicine Interface University of Birmingham	61,400	This project is to set up a network of people conducting research on both the science and applications of nanoparticles and on the environmental and medical effects so that they benefit from one another's knowledge and expertise. The outcome should be a better knowledge of nanoparticle effects and an improved protection of the public from any ill effects.	2007
EP/C530616/1 RO2	NANOsafeNET (Nanotechnology Safety Network) University of Oxford	61,900	NANOsafeNET will establish a multi-disciplinary network of respected active researchers and observers in their fields from a wide and diverse range of organisations and institutes. The network will establish a knowledge-based and research framework enabling the sharing and dissemination of information pertaining to nanotechnology safety, its usage, health and safety aspects and potential societal and ethical implications. The network will establish groups representing their field of expertise and the results from these will be available via a website interface in addition to hard copy, seminars, symposia which will form the basis for further and future research, policy and standards development.	2005-2007

This is a small portion of EPSRC's funding for nanotechnology, which is currently running at the level of £30-40M pa. It also excludes studentships. Further details of the EPSRC nanotechnology portfolio are given in the EPSRC Nanotechnology Strategy
http://www.epsrc.ac.uk/ResearchFunding/Programmes/Materials/ReviewsAndConsultations/Nanotechnology/NanotechnologyStrategy.htm

Economic and Social Research Council (ESRC) – NRCG research objective 1 (Socio-economic and ethical issues)				
ESRC Project Reference NRCG Research Objectives	**Grant Title/Establishment**	**Total Grant Value in £'s**	**Project Description**	**Period**
RES-000-22-0596	Nanotechnology and News Production: Scientists', Journalists', and Editors' Views University of Plymouth	48,071		2004-2005
RES-338-25-0006	Nanotechnology, Risk and Sustainability: Moving Public Engagement Upstream University of Lancaster	262,403		2004-2006
RES-160-25-0047	Spinning science: The nanotech industry and financial news University of Surrey	45,405		2005-2006
Total		355,879		

ESRC has also funded consultancy studies on 'The Social and Economic Challenges of Nanotechnology' in 2003, and an update entitled 'Nanotechnology: from the science to the social in 2006 by Prof Stephen Wood, Prof Richard Jones and Ms Alison Geldart of Sheffield University.

The ESRC Centre for Business relationships, Accountability, Sustainability and Society is also currently undertaking work in this area.

Other research funded by the ESRC which contain elements of research in nanotechnologies are detailed below

ESRC Project Reference NRCG Research Objectives	**Grant Title/Establishment**	**Total Grant Value in £'s**	**Project Description**	**Period**
L144250037	Public perceptions of Risk, Science and Governance University of Cardiff	40,000		2002-2003

Medical Research Council (MRC)				
MRC Project Reference NRCG Research Objectives	**Grant Title/Establishment**	**Total Grant Value in £'s**	**Project Description**	**Period**
G0502218 RO13	Examining the host response to polymer conetworks University of Sheffield	84,500	The project is to evaluate the host response to series of novel polymeric materials, including nanostructures that are envisaged as the next generation of scaffolds for tissue engineering. The experiments proposed will produce the first *in vivo* data on these materials and will provide a platform for further investigations.	2006-2007
G9901020 RO14	Particulate air pollution mechanisms of action group King's College London – KCL	20,392	Epidemiological studies carried out in several different communities indicate an association between increases in morbidity and mortality and short-term increases in particulate air pollution. Although it is generally believed that fine particles are responsible, lack of information on a number of key aspects of exposure to particles, in particular a plausible biologic mechanism to explain the observed associations, complicates interpreting this research, assessing human risk and designing preventive strategies. The initial principal aim of this Co-operative is to define the basic biological mechanisms underlying particle toxicity.	2001-2006
G9901319 RO14	How is the chemical and physical composition of ambient particles related to their toxicity King's College London – KCL	343,458	Ambient particles vary in composition and physical characteristics depending on their source. As strategies to reduce particle emissions need to target relevant sources we need to understand if particles from different sources have different toxicological potentials. This study will address this specific question through the collection of particulate material from 6 different UK locations and examining them in two models of the human lung.	2001-2004
G9900747 RO14	Factors contributing to susceptibility to cardiopulmonary mortality from particulate air pollution. The University of Manchester	202,392	The purpose of this proposed research is to quantify the extent to which [1] prior cardiopulmonary ill health, [2] social deprivation, and [3] concomitant cold weather and wind-chill, increase the risk of particulate air pollution related mortality. It will also measure [4] any association of shortening of residual lifespan associated with particulate air pollution in people with previous cardiopulmonary emergency hospital admissions.	2001-2004
G9900991 RO13/14	MRC/University of Edinburgh Centre for Inflammation Research University of Edinburgh	1,491,660	The Centre for Inflammation Research includes work on nanoparticle toxicology as well as a range of other research into inflammation	2000-2005
G9900991	MRC/University of Edinburgh Centre for Inflammation Research University of Edinburgh	1,017,824	The Centre for Inflammation Research includes work on nanoparticle toxicology as well as a range of other research into inflammation	2005-2010

MRC Project Reference NRCG Research Objectives	Grant Title/Establishment	Total Grant Value in £'s	Project Description	Period
RO11/13/14	2007 Contribution to proposals under the NERC Environment and Human Health Programme	200,000	Several proposal under the NERC Environment and Human Health Programme involve work on toxicology of nanoparticles (see detail in table of NERC funding)	2007

The MRC issued a Highlight Notice in March 2007.
MRC wishes to encourage innovative, high quality applications in response mode relating to the potential human health hazard of nanoparticles, in particular in areas highlighted by the NRCG. Prior to this we had been disappointed by the uptake of responsive mode funding for research into the health implications of nanotechnologies and so in an attempt to expand the community of researchers, and encourage them to submit proposals for further work, the MRC decided to issue a notice highlighting nanotoxicology as an area of interest. Since the highlight notice was issued, the MRC is pleased to see a substantial increase in the number of proposals that are being received. However, none of these have yet reached the decision stage due to the length of time it takes to process a grant application to the MRC funding Boards.

The contribution towards EHS research in the projects listed ranges from medium to high. The exception is the contribution to proposals under the NERC Environment and Human Health Programme, where the projects support EHS research only.

Natural Environment Research Council (NERC) – Environment and Human Health projects				
NERC Project Reference NRCG Research Objectives	**Grant Title/Establishment**	**Total Grant Value in £'s**	**Project Description**	**Period**
NE/E008860/1 RO13	A proof of concept study for a structure activity model for the toxicity of nanoparticles **University of Edinburgh, Respiratory Medicine**	109,844	A pilot study that aims to relate the physico-chemical characteristics of the particles, such as size and surface chemistry, with the toxicity of the particles in short/term cell toxicology tests. The approach tests the feasibility of using analysis of chemical structure to predict toxicological activity, which has previously been used for chemicals but never been attempted for particles. Oxidative stress is a type of chemical reactivity that has been put forward as an important mechanism for how particles cause toxic effects on cells so there is emphasis on the oxidative stress capacity of the particles in this study.	2007-2008
NE/E00833X/1 RO14	An exploratory study investigating the physiochemical characteristics of ambient air particles responsible for the dysregulation of pulmonary genes **Cardiff University, Division of Community Specialities**	114,452	The investigation will focus on the effects of particles of differing size and chemical constitution sampled from urban and rural environments on human tissue cultured in the laboratory. By combining the expertise of investigators in a number of disciplines from biosciences through to epidemiology, will enable a fuller characterisation of the chemical composition and shape of these particulates, as well as investigating their biological effects through applying the new technologies developed as a result of the genetic revolution.	2007-2008
NE/E008550/1 RO 11	Assessing human exposure, uptake and toxicity of nanoparticles from contaminated environments **Napier University, Life Sciences**	121,078	This study investigates whether nanoparticles released into water can be taken up by water fleas and fish, and to what levels. The study will then investigate whether humans can absorb nanoparticles from food into their bodies by crossing the gut wall, and whether they are toxic to the cells of the gut when eaten. The toxicity of nanoparticles to liver cell will be tested. A dynamic and highly capable team for addressing human and environmental health issues relating to nanoparticles and nanotechnology will be created, adding considerable value to the existing projects.	2007-2009
NE/E008739/1 RO13	Determinants of Oxidative Potential, A Health-Based Metric to Assess Particulate Matter Toxicity **University of Birmingham, School of Geography, Earth & Environmental Sciences**	124,316	The overall aim is to understand which properties of the nanoparticles have the greatest influence on their oxidative potential which could then inform the design of epidemiological studies to investigate the links between those particle properties and effects on human health.	2007-2008

NERC Project Reference NRCG Research Objectives	Grant Title/Establishment	Total Grant Value in £'s	Project Description	Period
NE/E009336/1 RO11	Exploring the link between surface structures and toxicity in mineral particles: Case study of induced and intrinsic toxicity in quartz **University of St Andrews, Geography and Geosciences**	44,198	Experiments will be conducted to test whether additional toxicity can be induced in quartz samples with already high intrinsic toxicity. A proportion of dust that is inhaled consists of particles that are small enough to penetrate deep into the lungs. Most particles are relatively harmless and on being recognised as foreign are removed from the lung by specialised mechanisms. The outcome of the research should be a better understanding of the mechanisms involved and thus better information for regulators and policy makers in the field of environmental and occupational exposure to dusts.	2007-2008
NE/E009166/1 RO11	Hazards of nanoparticles to the environment and human health **The Natural History Museum, Mineralogy**	118,300	An investigation of the behaviour of nanoparticles, following inhalation and possible transition into the blood stream, by investigating the reactivity of multiwall carbon nanotubes and titania nanoparticles, with synthetic lung lining liquid and blood plasma. Following completion of this work, the most and least reactive particles will be tested with primary human lung cells and cell lines to acquire proof-of-concept information as to whether the most reactive particles also tend to cause most harm to lung cells involved in the general defence of lung tissue against particulates.	2007-2009
NE/E009565/1 RO6	Identification and Verification of Ultrafine Particle Affinity Zones in Urban Neighbourhoods / A Proof of Concept Proposal **The University of Manchester, Earth Atmospheric and Environmental Sciences**	78,310	This project focuses upon experimentally comparing concentrations of UFP between different residential zones in Manchester and gradually building up a picture of how and most importantly, why UFP concentrations vary across a large segment of the city. This proposal combines the expertise of three teams within the University of Manchester linking atmospheric measurements with Geographical Information Science (GISc) and environmental health researchers. Once complete, the project will have provided a foundation for subsequent research by allowing researchers to quantify the exposure of urban citizens with much more confidence than at present, and to site more sophisticated monitoring instrumentation at a small number of fixed locations, or a single one, with a much clearer understanding of how measurements at this one location can relate to exposure of citizens across a wide urban area.	2007-2009
NE/E009395/1 RO11	Nanotoxicology of Fine Particle Measurement (PM): The Role of Surfactant and Collections in Short-Term Health Effects of PM Air Pollution **University of Birmingham, Chemical Engineering**	122,070	This exploratory proposal brings together three institutions in a new collaboration to investigate the mechanism by which nanoparticles enter the body and cause damage to lung and circulatory systems. Studies on uptake, lethal and sublethal endpoints, including biochemical biomarkers. The objective is to define a more detailed project which will follow from this exploratory study. The work proposed here stems from a small grant originally awarded by the UK Department of Health (DoH) in 1999. All investigators are regularly invited to participate in international events as invited speakers, reviewers and collaborators, ensuring an international dimension to this project. This enables leveraging of funding from non-UK funding source.	2007-2008
Total	Environment and Human Health Programme	832,572		

Annex H

Natural Environment Research Council (NERC) – Environment Responsive Mode and Knowledge transfer funding				
NERC Project Reference NRCG Research Objectives	**Grant Title/Establishment**	**Total Grant Value in £'s**	**Project Description**	**Period**
NE/F008368/1 RO17	Metal-colloid interactions in freshwaters. **University of Birmingham**	154,838	This project will involve the characterisation (surface area and chemistry; mass and number concentration; solubility; aggregation) of NPs in the presence and absence of natural colloids and attempts to investigate the effects of such interactions on transport processes and ecotoxicology in planktonic and biofilm bacteria.	2005-2008
NE/D007267/1 RO18	Toxicology of Nano Materials to Fish: A Fact Finding Pilot Study. **University of Plymouth**	60,391	A one year pilot study to look at possible effects of nanoparticles on fish. Our objectives are to measure the short and long term effects of two major types of nanoparticles to fish (i) carbon nanotubes (ii) manufactured titanium dioxide nanoparticles.	
NE/D004942/1 RO17	Understanding the environmental behaviour and biological impacts of manufactured nanoparticles in natural aquatic systems **University of Birmingham**	240,614	This project aims to address the interactions between natural and manufactured nanoparticles and assess the impact on manufactured nanoparticle fate and behaviour in natural waters.	2006-2009
NE/D004942/1 RO18	Understanding the environmental behaviour and biological impacts of manufactured nanoparticles in natural aquatic systems **University of Birmingham**	201,001	This project aims to address the interactions between natural and manufactured nanoparticles and assess the impact on manufactured nanoparticle fate and behaviour in natural waters	2006-2010
NER/S/A/2004 /13124 RO18	The Big Issue – The ecotoxicology of nano particles **University of Exeter**	N/A	In the project the uptake and distribution of nanoparticles in fish will be determined (specifically for two manufactured nanoparticles called carbon nanotubes and C60 fullerenes) to identify the major target organs for these nanoparticles.	2005-2008
NE/F009860/1	Trace metal interactions with manufactured and natural nanoparticles **University of Birmingham**	N/A	The aim of this project is thus to understand the flow of trace metals and manufactured nanoparticles at the interface between the surface and subsurface flow regimes.	2006-2009

NERC Project Reference NRCG Research Objectives	Grant Title/Establishment	Total Grant Value in £'s	Project Description	Period
NE/E002889/1 RO17, R018	Engineered nanoparticles in the natural aquatic environment (Nanonet) **University of Birmingham**	128,947	Nanonet is a NERC funded KT Network in the area of manufactured nanomaterials (MN) in the natural aquatic environment. It is involved in KT activities between academia, industry and Government bodies and between established workers in the field and young researchers (at PhD and postdoctoral level). Initial activities and workshops will focus on exchange of ideas between those working in the ecotoxicology of MNs and those involved in the manufacture, characterisation and physico-chemistry of the MNs, meeting one of the key future recommendations of the Task Force. Start date April 2007, PI J.R. Lead www.nanonet.org.uk/	2007-2010
Total	Environment Responsive Mode and Knowledge Transfer	785,791		

Natural Environment Research Council (NERC) – Environment Nanoscience Initiative (ENI) Directed funding				
NERC Project Reference NRCG Research Objectives	**Grant Title/Establishment**	**Total Grant Value in £'s**	**Project Description**	**Period**
First Funding Round:				
NE/E014348/1 RO18	Dietary Exposure to Nanoparticles in Fish: A Pilot Study. **University of Plymouth**	55,383	The objectives are to measure the responses of fish to a dietary exposure to two major types of nanoparticles (i) carbon nanotubes (ii) manufactured titanium dioxide nanoparticles. This information is vital for environmental risk assessments and a pre-requisite to managing potential pollution problems from new nanotechnologies.	2007-2008
NE/E014321/1 RO18	Effects of C-60 fullerenes and carbon nanotubes on marine mussels. **Plymouth Marine Laboratory**	19,849	This study focuses upon the toxicity of C60 and fullerenes, associated with naturally occurring particles (algal cells), to hepatopancreatic digestive cells in the marine mussel.	2007
NE/E014836/1 R018	Genomic and oxidation-related biological responses in fish exposed to fullerenes of different physicochemical characteristics **University of Birmingham**	28,827	This project considers the comparative generic environmental risk of model nanomaterials presented to water in different formats. It aims to establish the biological response of stickleback fish to fullerenes presented to fish in different structural formats and, through pilot studies, to establish organ-specific changes in gene expression as indicators of disturbance of processes in the body associated with oxidative stress or with other (as yet unrecognized) biological processes through analysis of the changes in the genes being expressed.	2007-2008
NE/E015166/1 RO6	Manufactured Nanoparticle Migration in Groundwaters **University of Birmingham**	57,981	If risks from manufactured nanoparticle contamination of groundwaters are to be assessed, it will be necessary to develop methods for prediction of particle movement in pore waters. This is a major goal far beyond the scope of a small project. However, as so little is presently known of transport of manufactured nanoparticles in natural porous media, a pump-priming study, drawing on previous research on other types of colloidal particle, would make some significant progress, paving the way for future, more detailed studies. This is the broad objective of the proposed study.	2007-2008
NE/E01500X/1 RO7	Model nanoparticles for environmental risk studies **The Natural History Museum, London**	56,564	This project will initiate an investigation of the behaviour of nanoparticles, following inhalation and possible transition into the blood stream, by investigating the reactivity of two types of engineered nanomaterials of broad current use and future application potential: multiwall carbon nanotubes and titania nanoparticles, with synthetic lung lining liquid and blood plasma.	2007-2008

NERC Project Reference NRCG Research Objectives	Grant Title/Establishment	Total Grant Value in £'s	Project Description	Period
NE/E01495X/1	Nanoparticle immunotoxicity using an environmental sentinel as a model **NERC Centre for Ecology and Hydrology**	38,993	This project will look in detail at how exposure to metals as nanoparticles, as bulk materials and as the dissolved free metal form impacts on the workings of cells of the immune system of a common UK earthworm species.	2007
NE/E014585/1 RO10	Pharmaceutical and cosmetic silica nanoparticles: towards an understanding of their structure, fate and behaviour in aquatic systems **Kings College London**	63,879	This grant examines the loadings of SiO2 nanoparticles to wastewaters from typical domestic use of cosmetic and pharmaceutical formulations, the efficiency of removal of SiO2 nanoparticles by wastewater chemical treatment (flocculation and sedimentation) and stability, structure and behaviour of SiO2 nanoparticles in natural waters.	2007-2008
NE/E014933/1 RO18	Synthetic polymer nanoparticles: effects of composition and size on uptake, toxicity and interactions with environmental contaminants **University of East Anglia**	61,991	This project aims to make nanoparticles of three different sizes and three different chemical compositions and to determine the toxicity of these particles to a fungus, an aquatic alga and a freshwater invertebrate. It be will determined whether the particles are taken up by these organisms and how particle size and surface chemistry alter uptake and toxicity.	2007-2008
NE/E014496/1 RO10	Understanding the fate and behaviour of manufactured nanoparticles in natural waters **University of Birmingham**	48,327	This work will look at the chemistry of manufactured nanoparticles under realistic environmental conditions and how this relates to aggregation and sedimentation, which are key processes in environmental transport. Their chemical behaviour is also considered key to understanding their ecotoxicological effects.	2007-2008
NE/E015018/1 R017/RO18	Visualisation of Nanoparticles in the Environment **University of Lancaster**	19,668	This study will identify whether a new technology Two-photon excitation microscopy coupled with autofluorescence (TPEM-AF) can be used as a tool to visualise engineered nanoparticles in living systems.	2007
	Total 1st round (ENI Directedfunding)	451,467		

NERC Project Reference NRCG Research Objectives	Grant Title/Establishment	Total Grant Value in £'s	Project Description	Period
Second Funding Round:				
NE/F011784/1 RO10, RO17	Impact of manufactured nanoparticles on the catabolic capabilities and phenotypic structure of soil microbial communities. **University of Cranfield**	56,857	The aim of this project is to determine the effects of manufactured nanoparticles on soil microbial community characteristics, principally phenotypic profiles (by means of phospholipid fatty acid analysis) and community catabolic capability (by means of multiple substrate induced respiratory response), to provide an initial assessment of the likelihood of harm when nanoparticles are introduced into soil systems.	2008
NE/F011830/1 RO10, RO17	Biomembrane interactions in the toxicology of nanoparticles to microorganisms. **University of Leeds**	20,015	The main aim is to initiate an investigation into the mechanisms of biological activity of nanoparticles on relevant in vitro and in vivo models. The work is driven by the hypothesis that the biological membrane is a critical interface in the nanomaterials' toxicology. This study is a pilot study whose purpose is to initiate and integrate the following approaches and obtain some proof of concept results which support the above working hypothesis.	2008
NE/F011881/1 RO10, RO17	Impact and recovery of groundwater microbial communities exposed to manufactured nanomaterials (MNM). **University of Oxford**	53,435	The overall objective of this study is to determine the impact of MNM exposure on the diversity and activities of natural microbial communities in groundwater. In order to address many of the key limitations of previous published exposure studies, we will take a more comprehensive cross-disciplinary (environmental microbiologists and material scientists) and systematic approach to MNM toxicity and impact on microbial communities.	2008
NE/F011911/1 RO10, RO17	A study of the effects of silver surface chemistry on bactericidal properties of silver nanoparticles. **University of Manchester**	20,167	The largest proportion of biomass on the planet is bacteria. These organisms are key to the function of the biosphere and therefore assessing the impact of nanoparticles on these organisms is of paramount importance. This project will study the effect of silver nanoparticles (thought to be toxic to bacteria) and assess the effects of their surface chemistry on their toxicity to single species of bacteria and also communities of bacteria. We will particularly be focusing on the bacteria used to purify waste water.	2008
NE/F01192X/1 RO10, RO17	An investigation into the effects of nanoparticles on the bacterial diversity of freshwater and coastal marine sediments **Plymouth Marine Laboratory**	37,997	The overall aim of the proposed project is to use laboratory-based exposure experiments to test the hypothesis that nanoparticles (NPs) with known antibacterial properties could, upon release into the environment, alter the diversity of the bacterial population in the sediment and the overlying water of freshwater and coastal environments. Specifically, we will investigate the impact of two already widely used NPs, nano-titanium dioxide (TiO2) and nano-silver, which have been shown to have anti-bacterial activities and are being widely used as disinfectants.	2008-2009

NERC Project Reference NRCG Research Objectives	Grant Title/Establishment	Total Grant Value in £'s	Project Description	Period
NE/F011938/1 RO10, RO17	Interaction of Nanoparticles with Microbial Populations during Particle Transport. **University of Sheffield**	48,316	This project aims to investigate new and innovative methods that will allow the *in vitro* and *in vivo* application of Raman microspectroscopy to study the impact of nanoparticles on microbial community. It will make an initial attempt at answering some of the fundamental questions posed within the Environmental Nanoscience Initiative, concerning interfacial and intercellular interaction, cell transport and particulate accumulation. Testing the hypothesis that 'surface chemical properties of manufactured nanoparticles are critical to transport, bioavailability, uptake and toxicity mechanisms for microorganisms' is at the centre of the project.	2008
NE/F011946/1 RO10, RO17	Nanoscale zerovalent iron (nZVI) impact on soil microbial communities. **University of Reading**	64,682	The overall aim of the proposed research is to advance understanding of nanoscale zerovalent iron (nZVI) impacts on microbial communities important for bioremediation, stabilisation and improvement of soils contaminated with chlorinated aromatic compounds.	2008
	Total 2nd round (ENI Directed funding)	301,471		
	Total (ENI Directed funding)	752,938		
	Total (Directed funding and Responsive Mode)	2,371,301		

Annex I

Acronyms	
Acronym	**Definition**
ACHS	Advisory Committee on Hazardous Substances (UK)
ADME	Adsorption, distribution, metabolism and elimination
AFOSR	Air Force Office of Scientific Research, USA
ANF	Asia Nano Forum (non-government network organisation, Asia Pacific region)
BBSRC	Biotechnology and Biological Sciences Research Council (UK)
BMBF	German Federal Ministry for Education and Research
BRASS	Centre for Business Relationships Accountability Sustainability and Society (UK)
BSI	British Standards Institute
BTWG	Technical Board Working Group (BTWG, CEN) 166
CEA	Commissariat à l'Energie Atomique (Atomic Energy Commission), France
CEMMNT	The Centre of Excellence in Metrology for Micro and Nanotechnologies (UK)
CEN	European Committee for Standardisation
CINR	Centre for Interdisciplinary Nano-Research (UK)
CNS	Central Nervous System
CNTs	Carbon Nanotubes
CST	Council for Science and Technology (UK)
DECHEMA	Society for Chemical Engineering and Biotechnology, Germany
Defra	Department for Environment, Food and Rural Affairs (UK)
DH	Department of Health (UK)
DIPNA	Development of an Integrated Platform for Nanoparticle Analysis (Italy)
DIUS	Department for Innovation University and Skills (UK)
DoD	Department of Defence, USA
DSTL	Defence Science and Technology Laboratory (UK)
DTA	Doctoral Training Account
DTI	Department for Trade and Industry (UK)
EA	Environment Agency (England and Wales)
EDAX	Energy-dispersive X-ray analyser
EDXA	Energy-dispersive X-ray analysis
EGA-GCMS	Evolved Gas Analysis-Gas Chromatograph Mass Spectrometry
EHS	Environment Health and Safety
ENI	Environmental Nanoscience Initiative (UK)
ENP	Engineered Nanoparticles
EPSRC	Engineering and Physical Sciences Research Council (UK)
ESRC	Economic and Social Research Council (UK)
EU	European Union
FDA	Food and Drug Administration, USA
FinNano	Nanotechnology programme, Finland
FOEN	Swiss Federal Office for the Environment
FSA	Food Standards Agency (UK)
HARN	High aspect ratio nanoparticles
HMT	Her Majesty's Treasury
HPU	High Production Volume

Acronyms cont…	
Acronym	**Definition**
HSE	Health and Safety Executive (UK)
HSL	Health and Safety Laboratory (UK)
IEC	International Electrotechnical Commission
INERIS	National Institute for Industrial Environment and Risks, France
INRS	National Research and Safety Institute, France
IOM	Institute of Occupational Medicine (UK)
IRC	(Nanotechnology) Interdisciplinary Research Centres (UK)
ISO	International Standards Organisation
JRC	The European Commission's Joint Research Centre
JWG	Joint Working Groups (with ISO/TC 229)
KT	Knowledge Transfer
LCA	Life Cycle Analysis
MET	Measurements for Emerging Technologies programme (UK)
MN	Manufactured Nanomaterials
MNT	Micro and Nanotechnologies (Network)
MoD	Ministry of Defence, UK
MRC	Medical Research Council (UK)
MWCNTs	Multi-Walled Carbon Nanotubes
NANOSAFE2	EU Framework 6 Programme project for Nanotechnology
NANOSH	Nanotechnologies Occupational Safety and Health programme
NCER	National Center for Environmental Research, USA
NEG	Nanotechnology Engagement Group (UK)
NERC	Natural Environment Research Council (UK)
NFA	National Research Centre for the Working Environment, Denmark
NGO	Non Governmental Organisation
NIDG	Nanotechnology Issues Dialogue Group
NIEHS	National Institute for Environmental Health and Safety, USA
NIH	National Institute of Health, USA
NIOSH	National Institute of Occupational Health and Safety, USA
NIR-PL	Near-Infrared Photoluminescence
NMS	National Measurement System, DIUS (UK)
N-NIRC	National Nanotoxicology Inhalation Research Centre (UK)
NOSH	Nanoparticle Occupational Safety & Health (consortium of international stakeholders led by DuPont)
NP	nanoparticle(s)
NPL	National Physical Laboratories (UK)
NRCG	Nanotechnology Research Coordination Group (UK)
NSERC	National Sciences and Engineering Research Council, Canada
NSET	National Science, Engineering and Technology Committee, USA
NSF	High aspect ratio nanoparticles
NTI/1	BSI Committee for Nanotechnologies

Annex I

Acronyms cont…	
Acronym	**Definition**
OECD	Organisation for Economic Co-operation and Development
OHSA	Occupational Health and Safety Administration, USA
PAS	Publicly Available Specification
PD	Published Document
PEN	Project on Emerging Nanotechnologies (Woodrow Wilson International Center for Scholars, USA)
PPE	Personnel Protective Equipment
QCM	Quartz Crystal Microbalance
RAEng	Royal Academy of Engineering
RCs	Research Councils
RCUK	Research Councils UK
REACH	Registration, Evaluation and Authorisation of Chemicals
REFNANO	Reference Materials for Nanotechnology project
RPE	Respiratory Protective Equipment
RS	Royal Society (UK)
SCENIHR	Scientific Committee on Newly Identified and Emerging Health Risks (European Commission)
SEM	Scanning Electron Microscopy
SETAC	Society of Environmental Toxicology and Chemistry
SFOPH	Swiss Federal Office of Public Health
SMPS	Scanning Mobility Particle Sizer
STEM	Scanning Transmission Electron Microscope
SWCNTs	Single Walled Carbon Nanotubes
TEM	Transmission Electron Microscope
TGA	Thermo Gravimetric Analysis
TSB	TSB Technology Strategy Board (UK)
UFP	Ultra Fine Particles
UNESCO	United Nations Educational Scientific and Cultural Organization
US EPA	Environment Protection Agency, USA
VAM	Valid Analytical Measurement (Programme)
VCI	German Chemical Industry Association
WPMN	Working Party on Manufactured Nanomaterials (of the Organisation for Economic Co-operation and Development (OECD))

Annex J

Breakdown of Research Objectives by Task Force

Task Force 1 – Metrology, Characterisation, Standardisation and Reference Materials

RO 2 To identify the most suitable metrics and associated methods for the measurement and characterisation of nanoparticles.

RO 3 To develop standardised, well-characterised reference nanoparticles.

RO 4 To understand the properties of nanoparticles in the context of their ignition and explosion potential, and assess/develop methods for evaluating this.

RO 9 Optimisation, development and application of technologies that enable the measurement of exposure to nanoparticles in soil and water.

Task Force 2 - Exposures – Sources, Pathways, and Technologies

RO 5 Further identification of sources of nanoparticles.

RO 6 Optimisation and development of technologies that enable the measurement of occupational and environmental exposure to nanoparticles via air.

RO 7 Understanding the fate and behaviour of nanoparticles in air.

RO 8 Development of exposure control devices.

RO 10 Research to understand the environmental fate, behaviour and interaction of nanoparticles in soils and water.

Task Force 3: Human Health Hazard and Risk Assessment

RO 11 Research to establish a clear understanding of the adsorption of nanoparticles via the lung, skin and gut and their distribution in the body (i.e. toxicokinetics), identifying potential target organs/tissues for toxicity assessment.

RO 12 Research to establish a clear understanding of inter and intracellular transport and localisation of nanoparticles and their cellular toxicity.

RO 13 To establish a clear understanding of whether oxidative stress, inflammatory effects and genotoxicity apply to nanoparticles.

RO 14 Research to establish a clear understanding of the deposition, distribution, toxicity, pathogenicity and translocation potential and pathways for nanoparticles in the airways and lung and their potential impacts on the cardiovascular system and brain.

RO 15 Given the current use of nanoparticles in consumer products there is a need to further our understanding of dermal uptake, penetration and toxicity in the skin.

RO 16 To develop testing strategies for human health hazard assessment and assess how fit for purpose current test methods are as applied to nanoparticles.

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Task Force 4: Environmental Hazard and Risk Assessment

RO 17 Research to establish the uptake, toxicity and effects of nanoparticles on groundwater and soil microorganisms, animals and plants, especially in the context of remediation.

RO 18 Research to establish the mechanisms of toxicity, toxicokinetics and in vivo effects of nanoparticles to key ecological groups (including invertebrates, vertebrates (e.g. fish) and plants). A key aspect of such work should be the facilitating of knowledge transfer from human toxicological studies to inform ecotoxicology.

RO 19 Define endpoints to be measured in ecotoxicological studies and assess how fit for purpose current standard tests for persistence, bioaccumulation and toxicity are when considering nanoparticles. This should lead to the defining of a suite of standard PBT protocols for use in environmental hazard assessment.

Task Force 5: Social and Economic Dimensions of Nanotechnologies

RO 1 Understand the social and ethical implications of nanotechnologies, through a programme of public dialogue and social research.

Annex K

Membership – Nanotechnology Research Coordination Group (NRCG) Task Forces

NRCG Chair – Dr John Garrod, Department for Environment, Food and Rural Affairs (Defra)

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Dr Ian Berkshire, Oxford Instruments
Dr Steffi Friedrichs, Nanotechnology Industry Association (NIA)
Dr John Garrod, Defra
Dr Peter Hatto, Ionbond Ltd (Chair of ISO TC229 on Nanotechnologies)
Prof Graham Leggett, University of Sheffield
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Task Force 5

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PB12901, December 2007

Published by the Department for Environment, Food and Rural Affairs.

Printed on material that contains a minimum of 100% recycled fibre for uncoated paper and 75% recycled for coated fibre.

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