WORKING FOR A HEALTHY FUTURE

Concise Report
March 2009

EMERGNANO: A review of completed and near completed environment, health and safety research on nanomaterials and nanotechnology (concise report)

Defra Project CB0409

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EMERGNANO was carried out by IOM as part of its SAFENANO activities (www.safenano.org). SAFENANO is one of the UK Micro and Nanotechnology (MNT) Centres, and is focussed on collecting, interpreting and disseminating emerging scientific evidence on nanoparticle risks.

Our collaborators in this project were Napier University, the University of Edinburgh, the Central Science Laboratory – all partners in the SnIRC collaboration (www.snirc.org) – plus the University of Leeds, Cranfield University and the Woodrow Wilson International Center for Scholars Project on Emerging Nanotechnologies (PEN).

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EXECUTIVE SUMMARY

In 2004, the Royal Society and the Royal Academy of Engineering published, at the request of the UK Government, a major review of the opportunities and uncertainties of nanotechnologies (RS/RAEng, 2004). This was one of the first reports to highlight the potential risks to health and the environment which may arise from exposure to nanoparticles. Since then, more than 50 national and international reviews carried out by government departments, industry associations, insurance organisations and researchers have considered nanoparticle risk issues. These reviews have provided a consistent view about the nature and the potential risks of nanoparticles, which may be summarised as follows:

- There are potential risks to health and the environment from the manufacture and use of nanoparticles;
- There is a lack of knowledge about what these risks are and how to deal with them;
- As more processes and products containing NP were developed, the potential for exposure of people and the environment will increase;
- More information about the toxicity, exposure and risk is required;
- All of the stakeholders (regulators, companies) need to start to address these risks now.

Since publication of the Royal Society / Royal Academy of Engineering report, there has been a significant increase in research activity in the UK and internationally intended to fill these gaps.

In the UK, the Nanotechnology Research Coordination Group (NRCG) was set up by the Government in 2005 to determine priorities and to coordinate publicly funded research into the potential risks presented by the products and applications of nanotechnologies. The UK Department for Environment, Food and Rural Affairs (Defra) chairs the NRCG and membership includes Government Departments, Regulatory Agencies and the Research Councils. Its first research progress report (Defra, 2006) set out a programme of 19 Research Objectives (ROs), across five main scientific areas, to characterise the potential risks. The five areas were:

- Metrology, Characterisation, standardisation and reference materials;
- Exposures – Sources, pathways and technologies;
- Human health hazard and risk assessment;
- Environmental hazard and risk assessment;
- Social and economic dimensions of nanotechnologies.

The NRCG set up five Task Forces, one for each area, to take forward the 19 objectives outlined in its first research progress report.

In this project we have carried out a detailed review and analysis of research carried out worldwide on Environment, Health and Safety aspects of engineered nanoparticles, (NP) including issues relating to hazard, exposure and risk assessment and regulation, and made an assessment of how far 18 of the ROs have been met and which gaps still remain to be filled (RO01, Nanotechnologies and public engagement, was specifically excluded from the contract). As far as practicable, we have carried out an appraisal of the research results with a view to highlighting any new information that may trigger a consideration for the need for regulation of nanomaterials, assessed the possibility of a qualitative risk assessment and considered whether there is sufficient information to

invoke the precautionary principle for one or more nanomaterials. Finally, we have made recommendations for new research to fill gaps.

The approach used in our review and analysis was to:

- Develop a comprehensive and categorised list of potentially relevant studies, active since 2004, starting with those on the Woodrow Wilson Project on Emerging Technologies database (www.nanotechproject.org), and adding to this through the knowledge and personal contacts of the authors plus information from national and agency contacts, existing project listings compiled at a national or agency level, and a focussed review of the peer-reviewed literature;
- Compile information about status, duration, funding, objectives, methods and output relating to these studies through dialogue with project leaders;
- Based on preliminary review, allocate (map) the studies to the 18 ROs being considered;
- Through a multidisciplinary panel of expert reviewers (the authors of this report), chosen to cover the range of scientific disciplines represented in this activity, carry out an appraisal of the contribution of each study in relation to 18 ROs, the extent to which the RO is likely to be met, and the gaps remaining;
- Undertake a risk assessment appraisal identifying the need for control or management of risk, including an appraisal of whether there is sufficient information to invoke the precautionary principle for one or more nanomaterials;
- And through a workshop and dialogue reach a consensus view about the remaining gaps and future priorities.

Since 2004, work in this area has been funded by both national government activity and research programmes within each country and at an international level, for example within the European Union. Internationally we have identified and assessed more than 650 projects. More than half of the projects identified in the first pass were only of marginal relevance to nanoparticle risk issues, were related to activities such as funding for a conference, or were duplicates. These were eliminated in the preliminary assessment. There was a wide disparity in the information available for the remaining studies, but sufficient to allow a preliminary allocation across the four task force areas and 18 ROs. Study allocation to the ROs was verified as part of the detailed review activity carried out by the expert panel. We found a widespread imbalance in the work being carried out (in terms of numbers of studies) between the four main task force areas and between the eighteen research objectives. The largest number of studies was in the Human Health area, followed by the Exposures area. Numbers in both the Environment and Characterisation areas were substantially lower. The distribution by RO was even more striking. RO14 (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) had 44 studies identified as relevant whereas RO9 (Optimisation, development and application of technologies that enable the measurement of exposure to nanoparticles in soil and water) had only one study.

As might be expected, there are large regional variations in the type of study funded in different countries or economic areas, perhaps reflecting different national priorities or capabilities. The largest number of studies was found in the US, followed by the UK.

It was noted that there was substantial overlap between many of the ROs. This may be quite appropriate from a scientific perspective but made the analysis quite challenging, both in study allocation and in the review activity where individual studies

had to be reassessed several times (or assessed by different assessors) from (slightly) different perspectives.

We were unable to identify useful output from many of the studies involved in the programme, including studies which had already been completed. It is unsatisfactory when publicly funded studies do not result in information being released into the public domain. It also made undertaking of this EMERGNANO project much more challenging.

In Task Force Area (TFA) 1, (Metrology, characterisation, standardisation and reference materials), the reviewers found that none of the studies could be said to be conclusive in providing new approaches or guidelines to characterising and measuring nanomaterials. Nor was the selection and/or development of exposure metric or metrics addressed well. Studies were focussed on addressing mainly the relevance and practicality of using surface area which, whilst important, is unlikely to be relevant for all NP. Progress has been made in identifying candidate materials which may be used to develop characterised reference nanoparticles for toxicology. Candidate lists, along with minimum characterisation specifications, have been developed and some commercial reference materials are beginning to emerge. However, there is little evidence that issues such as storage, distribution or protocols for use are being addressed. Only two studies were identified as addressing potential risk of explosion of NP and only one study was identified as addressing the issue of measurement of exposure to nanoparticles in soil and water. Overall the specific objectives within this RO appear to have been very sparsely addressed. A great deal of work remains to be done.

In TFA2, (Exposures, sources, pathways and technologies), some work has been undertaken on establishing inventories of nanoparticle use and application, and on trying to map out some of the potential exposure pathways. However, there are many complex exposure pathways and only a few have been considered. Little is known about NP in relation to consumer exposure and work in relation to NP in food seems to be entirely missing. Use of a life cycle assessment approach is missing. Little progress has yet been made in relation to development of measurement technologies for nanoparticles in air. Although there is some evidence that ongoing studies may produce devices, such as personal samplers, and approaches for some types of nanoparticles, major questions remain. These include discrimination between NP and the background particles and the evaluation of whether fibre counting methods can be applied to high aspect ratio nanoparticles. It now seems clear that filtration systems will be effective against nanoparticles and several studies have found improving collecting efficiency as particle size decreases. Studies have not thus far specifically addressed the performance of engineering controls as they are implemented in practical settings. Issues of leakage from filtration systems and the effectiveness of skin protective equipment are also under-researched.

In TFA3, (Human health hazard and risk assessment), there is an absence of studies aiming to describe the accumulation of particles in a variety of organs after inhalation. There are no specific studies on whether carbon nanotubes and other high aspect ratio nanoparticles behave like asbestos with respect to whether they translocate to the pleural mesothelium. In general there is no attempt to try to identify potential structure-activity relationships that govern penetration at any of the important boundaries. Many studies are addressing the issue of oxidative stress – inflammation. Several studies are also attempting to address structure- activity relationships in relation to this but, as yet, little progress has been made. There are few *in vivo* studies being carried out, making comparison between *in vitro* and *in vivo* data problematic. Few studies are using NP exposures at or near plausible exposure levels and also few studies are

addressing genotoxicity. Dermal uptake is not being addressed to any great extent and as yet toxicological testing strategies have not evolved to any level of agreement.

In TFA4, (Environmental hazard and risk assessment), studies have improved the understanding of kinetics of nanoparticle uptake in invertebrate and vertebrate models and have related this to toxicity. In addition, there are now a few studies focussing on microbial organisms and these provide information on effect assessment at both individual and community level. However, studies only cover a limited range of species and material types (metal oxide, fullerenes, CNT). There is some effort to relate study design and interpretation to human toxicology of nanoparticles, but there remains much more to be done in this area. Only one project is addressing bioaccumulation and bio-concentration of nanoparticles.

We have identified 260 relevant studies which are either completed or already underway. In projects which are just starting or have just started there is some evidence to support the view that the work in these projects will deliver much more in terms of output than the projects which are currently just closing. At this point in time, based on the evidence we have been able to collect regarding these studies, progress thus far has been disappointing. Whilst many studies are undoubtedly contributing in an incremental way to the advancement of knowledge, few of the key questions have been resolved. We conclude that the programme of research activity has yet to deliver step changes in the knowledge base on these issues.

In assessing quality and completeness for the purpose of carrying out a risk assessment, we did not identify a sufficient body of evidence in any case to make a risk assessment feasible. However, three different nanomaterials have been identified that give rise to sufficient concern from the results presented within the RO reports. There is evidence that carbon nanotubes may have an adverse effect on human health; and that silver nanoparticles and titanium dioxide nanoparticles are detrimental to the environment. In these specific cases, further investigation as to the need to invoke the precautionary principle is required, taking into consideration all available data.

The EMERGNANO project has been a unique attempt to identify and assess *worldwide* progress in relation to nanotechnology risk issues. On an international basis we have identified and assessed more than 260 unique, relevant projects completed, close to completion or in progress. We have observed a wide disparity in quality and quantity of the information available for these studies. We have also mapped these projects against the eighteen ROs set in the UK by the NRGC/DEFRA. This has been achieved over a period of six months. We cannot be certain that we have identified all of the relevant studies or that we have assessed all of these studies using all of the publicly available information. However, we consider that what has been achieved has been successful in identifying the overwhelming majority of important studies and having these studies assessed as to their output and relevance by some of the leading researchers currently working in this area. We have, as part of the project, achieved a comprehensive listing of projects and produced detailed comments and assessment of their outputs. It is our view that EMERGNANO represents the best available picture currently available of current strategic research. As such, EMERGNANO presents an excellent basis for assessing progress of these and other studies in the future.

1 INTRODUCTION

1.1 BACKGROUND

In 2004, the Royal Society and the Royal Academy of Engineering published, at the request of the UK Government, a major review of the opportunities and uncertainties of nanotechnologies (RS/RAEng, 2004). This was one of the first reports to highlight the potential risks to health and the environment which may arise from exposure to nanoparticles. Since then, more than 50 national and international reviews carried out by government departments, industry associations, insurance organisations and researchers have considered nanoparticle risk issues. These reviews have provided a consistent view about the nature and the potential risks of nanoparticles, which may be summarised as follows:

- There are potential risks to health and the environment from the manufacture and use of nanoparticles;
- There is a lack of knowledge about what these risks are and how to deal with them;
- As more processes and products containing NP were developed, the potential for exposure of people and the environment will increase;
- More information about the toxicity, exposure and risk is required;
- All of the stakeholders (regulators, companies) need to start to address these risks now;

Since publication of this report, there has been a significant increase in research activity in the UK and internationally intended to fill these gaps.

In the UK, the Nanotechnology Research Coordination Group (NRCG) was set up by the Government to coordinate publicly funded research into the potential risks presented by the products and applications of nanotechnologies. The UK Department for Environment, Food and Rural Affairs (Defra) chairs the NRCG and membership includes Government Departments, Regulatory Agencies and the Research Councils. The NRCG produced a research progress report (Defra, 2006) setting out a programme of 19 research objectives (ROs), across five main scientific areas, to characterise the potential risks. The five areas are:

- Metrology, Characterisation, standardisation and reference materials;
- Exposures – Sources, pathways and technologies;
- Human health hazard and risk assessment;
- Environmental hazard and risk assessment;
- Social and economic dimensions of nanotechnologies.

The NRCG set up five Task Forces, one for each area, to take forward these ROs. These 5 areas became the Task Force Areas (TFA).

Each Task Force has members from a wide range of stakeholders including academic institutions, independent research organisations, industry, Government departments, their Agencies and the Research Councils. The 19 research objectives and their distribution across the five task forces are shown in Table 1.1.

Table 1.1: Defra Task Forces and NRGC Research Objectives

Defra Task Force	NRCG Research Objective (RO)	
1. Metrology, Characterisation, Standardisation and Reference Materials	RO 02	To identify the most suitable metrics and associated methods for the measurement and characterisation of nanoparticles.
	RO 03	To develop standardised, well-characterised reference nanoparticles.
	RO 04	To understand the properties of nanoparticles in the context of their ignition and explosion potential, and assess/develop methods for evaluating this.
	RO 09	Optimisation, development and application of technologies that enable the measurement of exposure to nanoparticles in soil and water.
2. Exposures – Sources, Pathways, and Technologies	RO 05	Further identification of sources of nanoparticles.
	RO 06	Optimisation and development of technologies that enable the measurement of occupational and environmental exposure to nanoparticles *via* air.
	RO 07	Understanding the fate and behaviour of nanoparticles in air.
	RO 08	Development of exposure control devices.
	RO 10	Research to understand the environmental fate, behaviour and interaction of nanoparticles in soils and water.
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.
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.
5. Social and economic dimensions of nanotechnologies	RO 01	Nanotechnologies and public engagement.

Work to realise these objectives has comprised of both information-gathering activities (such as reviews and workshops), and, increasingly, new research activity intended to address the fundamental questions about the risks. This work has been most recently reported in "Characterising the Potential Risks posed by engineered Nanoparticles – A second UK Government Research Report" (Defra, 2007).

Many national and international organisations have developed similar research strategy documents and have initiated programmes of research in order to achieve the objectives described therein. For example, the European Framework (FP) Programme has funded several projects under the 6th Framework Programme (FP6), e.g. NANOSAFE2, PARTICLE_RISK and has a number of projects starting or under final negotiation resulting from calls in the 7th Framework Programme, under the NMP theme 4.1.3 Health, Safety and Environmental Impacts in FP7. In Europe, several countries including Germany, Denmark and Switzerland have developed their own national programmes. In the US, research has been funded principally by National Institute for Occupational Safety and Health (NIOSH), National Institutes of Health (NIH) and the Environmental Protection Agency (EPA).

While many of these agencies and organisations have developed and published research strategies, and although attempts are being now made to link up, for example through EU/US joint calls in the EU Framework Programme and OECD, until now there has been little effective international co-ordination on research activity. As a result, funded projects are unlikely to provide coherent or comprehensive coverage of the issues.

Many of the funded projects are only at the early stages of their work and as yet have not begun to publish their outputs. Such is the range of ongoing work, it is a significant challenge to track progress (or the promise of progress) in this complex landscape. Attempts have been made to collate information about ongoing studies, for example the Woodrow Wilson Project on Emerging Nanotechnology's Research Inventory, (www.nanotechproject.org) and the recent EU inventory of research and development activity on nanotechnology health and safety (European Commission, 2008). However, these inventories are not necessarily complete and do not provide an interpretation of the value of the work being carried out, or how the findings collectively contribute to resolving the uncertainties.

Research is currently underway across the spectrum of risk management for NP, including hazard, characterisation, exposure and risk assessment. This research is international in nature, multidisciplinary and recognised as a high priority by government and international organisations. In the UK context, NRCG needs to understand the extent to which the research objectives are being met on an international basis, and what gaps remain. To address this need, Defra commissioned the EMERGNANO project. EMERGNANO aims to capture and critically appraise the rapidly emerging evidence through a review of research projects concerning the health and environmental risks of nanomaterials, to inform the future prioritisation of research.

1.2 OBJECTIVES

The proposal for this work was developed in response to an invitation to tender published by Defra. The objectives stated in that tender, on which the current project is based, were as follows:

i) a detailed review and analysis of research carried out worldwide on Environment, Health and Safety aspects of engineered nanomaterials including issues relating to hazard, exposure and risk assessment and regulation;
ii) an evaluation of how far research objectives have been met and to identify which gaps still remain to be filled;
iii) an appraisal of the research results with a view to highlighting any new information on hazards and risks to human health and/or the environment from nanomaterials that may trigger a consideration for the need for regulation of nanomaterials;
iv) come to an interim position regarding the magnitude of risk and associated uncertainty given the evidence to date (and where the largest uncertainties lie), noting that this will almost certainly be a qualitative risk assessment process that is under review with respect to fitness-for-purpose;
v) consider whether there is sufficient information to invoke the precautionary principle for one or more nanomaterials;
vi) to make specific recommendations for new research to fill gaps in the understanding of the potential risks posed by engineered nanomaterials taking into consideration, as far as practicable, work currently in progress.

1.3 STRATEGIC APPROACH

We proposed the following approach, in line with the stated objectives of the call, to review completed and near-completed environment, health and safety research on nanomaterials and nanotechnology.

Our approach was to:

- Develop a comprehensive and categorised list of potentially relevant studies, active since 2004, starting with those on the Woodrow Wilson Project on Emerging Technologies database (www.nanotechproject.org), and adding to this through the knowledge and personal contacts of the authors plus information from national and agency contacts, existing project listings compiled at a national or agency level, and a focussed review of the peer-reviewed literature;
- Compile information about status, duration, funding, objectives, methods and output relating to these studies through dialogue with project leaders;
- Based on preliminary review, allocate (map) the studies to the 18 ROs being considered;
- Through a multidisciplinary panel of expert reviewers (the authors of this report), chosen to cover the range of scientific disciplines represented in this activity, carry out an appraisal of the contribution of each study in relation to 18 ROs, the extent to which the RO is likely to be met, and the gaps remaining;
- Undertake a risk assessment appraisal identifying the need for control or management of risk, including an appraisal of whether there is sufficient information to invoke the precautionary principle for one or more nanomaterials;
- And through a workshop and dialogue reach a consensus view about the remaining gaps and future priorities.

1.4 PROJECT TEAM

The proposal for this work was submitted as a consortium bid by the SnIRC collaboration (www.snirc.org) led, for this study, by the Institute of Occupational Medicine (IOM). SnIRC is uniquely placed to carry out such an extensive and authoritative review of nanomaterials toxicology issues due to its positioning as the leading group undertaking research in this area, our work and links with governments and industry and, our world-wide network of collaborators and experts. Partners in this project have a track-record in review activities and hosting workshops as well as undertaking fundamental research. All of the core participants have previous experience in working together. The capabilities of the core participants are outlined below in Table 1.2.

Table 1.2: The EMERGNANO Project Team

Name	Expertise	Institution
Dr Rob Aitken	Director of Strategic Consulting, IOM. Director of SAFENANO. Principle areas of expertise include exposure assessment, manufacture and use of nanomaterials.	IOM
Dr Lang Tran	Director of Nanotechnology Risk Research. Leading UK quantitative toxicologist.	IOM
Dr Steve Hankin	Consultant Chemical Toxicologist and Director of Operations, SAFENANO. Principle areas of expertise are the characterisation, toxicology and risk assessment of chemical hazards.	IOM
Bryony Ross	Research Scientist. Editor of SAFENANO Website (www.safenano.org).	IOM
Prof Ken Donaldson	Professor of Toxicology. One of Europe's leading particle toxicologists. Editor in Chief of Particle and Fibre Toxicology.	Consultant
Dr Roger Duffin	Particle Toxicologist.	Consultant
Prof Vicki Stone	Professor of Toxicology. Director of Toxicology, SAFENANO. Editor in Chief of Nanotoxicology. Leading UK particle toxicologist and ecotoxicologist.	Napier University
Dr Teresa Fernandes	Reader in ecotoxicology of nanoparticles and environmental chemicals.	Napier University
Dr Andrew Maynard	Chief Science Advisor to the Wilson Center Project on Emerging Nanotechnologies. Leading expert in identifying and addressing potential impacts of nanomaterials.	Woodrow Wilson International Center for Scholars
Prof Terry Wilkins	Professor of Nanomanufacturing. 30 years experience in nanostructured materials manufacturing.	University of Leeds
Dr Simon Wilkins	Enterprise Officer, Keyworth Institute.	University of Leeds
Prof Len Levy	Professor of Environmental Health. Author of occupational and environmental risk assessments on many types of substance.	Cranfield University
Dr Sophie Rocks	Toxicologist with background in materials science.	Cranfield University
Dr Qasim Chaudhry	Senior Environmental Chemist.	Central Science Laboratory

The Steering Group for the project consisted of Defra and the heads of the NRCG Task Forces 1-4.

1.5 REPORT OUTLINE

In this **concise report** we summarise the outcomes of the work of the project. The full report should be consulted for more detail. The concise and full reports comprise the following sections:

Description	Full report	Concise report
A description of the methodology adopted (Chapter 2);	✓	✓
Quantitative assessment of the research including information about the distribution of research projects, in terms of number, value, and status, by RO and by country (Chapter 3);	✓	✓
A synthesis of the key studies, highlighting the contribution considered to be being made to each RO, and the extent to which the RO has been met (Chapter 4);	✓	
A summary of what has been achieved and the remaining gaps (Chapter 5);	✓	✓
An assessment of additional relevant activities which are not within the scope of the ROs (Chapter 6);	✓	
An assessment of the extent, based on the evidence collected, to which it is feasible to undertake a risk assessment and whether the evidence suggests that the precautionary principle should be applied (Chapter 7);	✓	✓
Discussion of the above (Chapter 8);	✓	✓
Conclusions (Chapter 9).	✓	✓

2 METHODOLOGY

To achieve the stated objectives of the Invitation to Tender (ITT), namely "to review completed and near-completed environment, health and safety research on nanomaterials and nanotechnology", the EMERGNANO project adopted a structured approach to identifying, collating and appraising research studies on the basis of the available information. This involved:

- Developing a comprehensive and categorised list, focussing on the emerging evidence of studies conducted or ongoing since 2004. This timeframe is appropriate given the publication of the RS/RAEng report, the typical 3-4 year lifetime of a major research study and recent projects commissioned to review earlier work;
- Identifying the completed and near completed studies (UK, Europe, US, Rest of World) primarily through sponsoring agency contacts and existing lists of studies;
- Collecting and compiling core and evidential information about these studies and outputs through dialogue with Project Leaders;
- Identifying the relevance of each study in relation to the NRCG's 18 Research Objectives;
- Appraising the quality and contribution of each study through expert assessment (using a Weight-of-Evidence approach, discussed below) by internationally renowned scientists;
- Undertaking a risk assessment appraisal identifying the need for control or management of risk, including an appraisal of whether there is sufficient information to invoke the precautionary principle for one or more nanomaterials;
- Presenting the evidence to a workshop of national and international experts;
- Reaching a consensus view about the remaining gaps and future priorities.

A series of tasks was specified by Defra in the published ITT. These are identified in Table 2.1 and have been mapped to the sequence of activities conducted in the EMERGNANO project and described in more detail below.

Table 2.1: EMERGNANO activities enabling the Defra Tasks identified in the ITT

Defra Task No.	Task Description	EMERGNANO Activities
1	Nanotechnology Research Coordination Group (NRCG) and the four relevant task forces, identify environment, health and safety research on nanomaterials and nanotechnologies that supports the appropriate 18 objectives of the NRCG.	i. Identify, list and compile information on completed and near completed studies. ii. Preliminary assessment to identify the relevance of each study in relation to the 18 Research Objectives. iii. Weight-of-Evidence appraisal of the quality and contribution of each study through expert assessment by internationally renowned scientists. iv. Risk assessment appraisal. v. Draft report.
2	Carry out a review and evaluation of completed and near-completed national and international research work and compile a summary of results.	
3	Review all research data within the scope of each Task Force and identify new information on hazards and risks posed by engineered nanomaterials.	
4	Consider whether there is sufficient information to identify and quantify risks to human health and/or the environment from manufactured nanomaterials that might lead to a need for control or management of the risk, including an appraisal as to whether there is sufficient information to invoke the precautionary principle for one or more nanomaterials.	
5	Conduct a workshop of national and international experts to discuss the findings of the project.	vi. Present the evidence to a workshop of national and international experts.
6	Identify and prioritise remaining gaps in EHS research on nanomaterials taking into consideration, as far as possible, ongoing UK and international research programmes.	vii. Reach a consensus concerning about the remaining gaps. viii. Finalise report

2.1 IDENTIFICATION, SELECTION AND COMPILATION OF INFORMATION ON STUDIES

We developed a comprehensive and categorised list, focussing on the emerging evidence, of studies since 2004. Information on projects funded in the UK was requested from the Nanotechnology Research Coordination Group (NRCG) and the four relevant task forces. Information on European studies was obtained from liaison with relevant European Commission Project Officers and the recent publication "EU technology R&D in the field of health and environmental impact of nanomaterials" (European Commission, 2008). Information on US and other international studies was gathered using the Woodrow Wilson Centre's Research Inventory (www.nanotechproject.org/) and selected contacts from agencies including National Institute for Occupational Safety and Health (NIOSH), National Institutes of Health (NIH), and the Environmental Protection Agency (EPA).

Studies for assessment under EMERGNANO were selected in an unbiased manner, in accordance with the following selection criteria:

- Study is relevant to at least one of the 18 NRCG Research Objectives;
- Study commenced or reported in or after 2004 (including "commissioned but not yet started" studies);
- Study was funded by recognised body, or nominated by an EMERGNANO expert assessor;
- Study outcomes are published in English (the project timescale and budget did not allow provision for translation).

From those studies meeting all of the aforementioned criteria and selected, a categorised list was collated and subsequently managed using a tailor-made Microsoft Access database. A list of the studies considered in the EMERGNANO project is contained in Appendix 1.

Core Information gathered for each project included the start date, duration, budget, objectives, and links to project websites as appropriate. We augmented this information, through an email dialogue with the principle investigators with available evidential data including project reports, publications, citations and other relevant outputs, as appropriate.

Information requests were distributed from a dedicated EMERGNANO email account, and their status and response managed from within Microsoft Access.

Where relevant information was received, its type was recorded (abstract, objectives, reports and publications) and then saved into designated project folders. Reminder emails were distributed to those who indicated they would provide information at a later date, those who were previously out of office and those who did not initially respond. Responses to this second batch of emails were monitored and any information received dealt with accordingly.

This compilation was also supplemented by recommendations of additional studies from the expert assessors within EMERGNANO's project team.

2.2 DATA MANAGEMENT

Information collated was managed throughout the project's duration within Microsoft Access. Initially data was recorded into an uncategorised database, where each study

was assigned a unique key by which it could be identified, based on the ISO standard country coding and a sequential three digit number. Additional studies suggested by the Assessors are distinctly coded using an "X" (e.g. UKX01). Subsequently, Core Information about the study was collated. A summary of Core Information fields within this initial dataset is outlined in Table 2.2. In addition, the availability of supplementary evidential information on each study was recorded. This information was held within folders labelled according to study key, and was categorised according to whether it was a Statement of Objectives, Study Abstract, Report or Publication. This key information was then used by the EMERGNANO project team to organise studies according to area of relevance, and assign them to the Research Objective(s) for assessment.

Table 2.2: Fields for storing Core Information on studies

Study ID	Funding Source(s)
Study Title	Funding Sector
Short Name	Funding Body Project Reference
Start Year	Budget (native)
End Year	Budget (£)
Duration	Contact Name
Status	URL
Currency	Summary
Country	

2.3 PRELIMINARY ASSESSMENT TO MAP EACH STUDY TO THE 18 RESEARCH OBJECTIVES

Following collation of all available information, duplicates were removed from the study database. Studies within the final pooled list were assigned a nanomaterial category and area of relevance (summarised in Table 2.3) using the available Core Information.

Table 2.3: Nanomaterial categorisation and area of relevance

Nanomaterial Category	
Engineered Nanomaterials	Generic
Incidental Nanomaterials	Unassigned
Natural Nanomaterials	
Area of relevance	
Exposure	Control
Hazard	Characterisation
Response	Risk Assessment
Generation	Risk Management
Safety	

A preliminary assessment to map the studies and their outputs to the appropriate Research Objective(s) was carried out as a centralised process and recorded in MS Access (Figure 2.1), based on inspection of the study title and objectives.

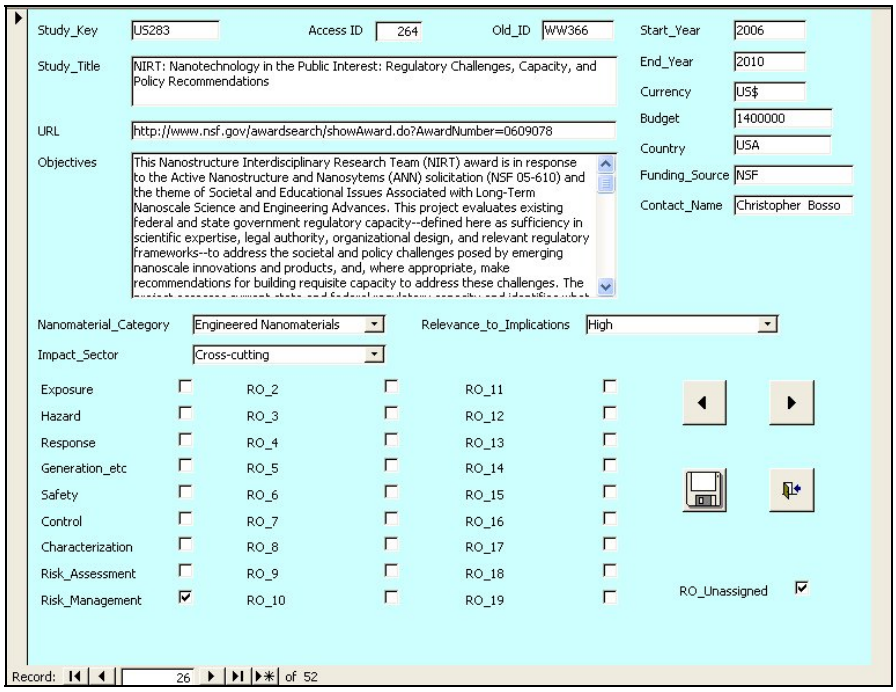

Figure 2.1: Assigning study category and RO

Any errors in the preliminary assignment of studies to the ROs were identified by the expert assessors during their detailed appraisals and corrected. Studies which the project team could not assign to a Research Objective at this time were considered separately, as were studies which were identified to be Enabling Activities, Observatories or Networks. A package of information was then provided to the expert assessor, selected on the basis of their expertise, to appraise studies for the ROs as shown in Table 2.4. This included RO-specific databases of the studies to be assessed, a Weight-of-Evidence appraisal template and the supplementary evidential information.

Table 2.4: Allocation of Research Objectives

Task Force Area	Research Objective	EMERGNANO Assessor	
Metrology, Characterisation, Standardisation and Reference Materials	RO 2	Andrew Maynard	**Lead: Rob Aitken**
	RO 3	Steve Hankin	
	RO 4	Simon Wilkins and Terry Wilkins	
	RO 9	Simon Wilkins and Terry Wilkins	
Exposures – Sources, Pathways, and Technologies	RO 5	Rob Aitken	**Lead: Rob Aitken**
	RO 6	Rob Aitken	
	RO 7	Qasim Chaudhry	
	RO 8	Rob Aitken	
	RO 10	Qasim Chaudhry	

Task Force Area	Research Objective	EMERGNANO Assessor	
Human Health Hazard and Risk Assessment	RO 11	Ken Donaldson and Rodger Duffin	**Lead: Ken Donaldson**
	RO 12	Ken Donaldson and Rodger Duffin	
	RO 13	Ken Donaldson and Rodger Duffin	
	RO 14	Ken Donaldson and Rodger Duffin	
	RO 15	Qasim Chaudhry	
	RO 16	Lang Tran	
Environmental Hazard and Risk Assessment	RO 17	Teresa Fernandes, Vicki Stone and Qasim Chaudhry	**Lead: Vicki Stone**
	RO 18	Teresa Fernandes and Vicki Stone	
	RO 19	Teresa Fernandes and Vicki Stone	

2.4 WEIGHT-OF-EVIDENCE APPRAISAL

An appraisal of the relevance, quality and contribution attributes of each study to its assigned Research Objective(s) was carried out by the designated Assessor using a Weight-of-Evidence (WoE) approach.

Four WoE Frameworks, tailored to the NRCG Task Force areas - Human Health, Environment, Metrology and Exposure, were developed by the EMERGNANO project team with input requested from Defra and the project's Steering Group. The WoE approach was developed to assist the assessors' appraisal of the studies. The purpose was to provide the EMERGNANO Assessors with a standardised and transparent means to appraise and compare studies consistently, within an RO but not across ROs (due to variable weighting), whilst still providing them with a degree of flexibility and latitude to judge the impact and contribution of each study towards the RO.

The WoE criteria and their component categories for the four frameworks are shown in Appendix 2 of the full report. Each of the frameworks was piloted with representative studies and comment was sought from the EMERGNANO project's Steering Group (independent of the partner organisations conducting the project).

To streamline the process of carrying out the WoE assessment and reporting, a Microsoft Access database with a form-based front-end was populated for each of the 18 ROs under consideration (Figure 2.2) and distributed to Assessors on memory sticks along with a set of folders containing any supplementary study information. The WoE appraisal form was designed to present assessors with a standardised set of criteria in a set of drop-down menus. Assessors were provided with guidance on using the database.

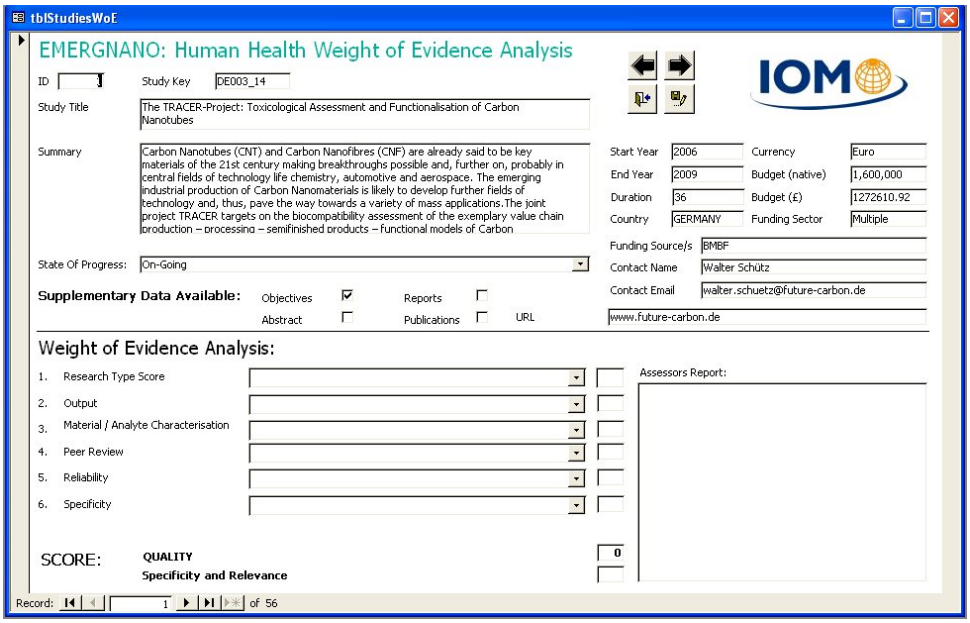

Figure 2.2: Example Weight of Evidence Assessment Form

The most appropriate criterion was selected on the basis of the assessors' expert judgement. In selecting the most appropriate criterion characterising the study, the associated score for the individual category was displayed and summed scores of i) research type, output, material characterisation, peer review and ii) reliability, specicificity, were automatically calculated.

Not all studies could be assessed systematically using the descriptive terms in the WoE frameworks, so the expert assessors used their judgement in a limited number of circumstances to score the study appropriately to reflect its quality and contribution to the RO. A study's WoE score was intended only to be used by the assessor to help rank the studies when considering their impact and contribution to the RO. The tailored design of the four WoE frameworks means that the possible range of scores is a function of the particular framework and therefore the interpretation of WoE scores is not equivalent across all ROs and WoE scores for studies cannot be compared outwith the boundaries of a particular RO. In a limited number of circumstances, not all categories could be assessed for a study, either because the study had just started, there was lack of information, or it was considered that the study did not fit the stated criteria. Thus, on the basis of the available information, some studies may have low WoE scores yet may ultimately contribute substantially to the RO. This is an inherent limitation of any review activity conducted at a fixed point in time.

The WoE form provided space to record comments and remarks on the attributes and contribution of each study considered.

Based upon the WoE score and the commentaries, the Assessors prepared a synthesis report for each of their assigned ROs, using a template provided. Where a large number of studies were to be considered, the assessor used their discretion to introduce a score threshold, to focus their subsequent discussion of studies. Any thresholds introduced are indicated in the histograms of the WoE score distributions for the ROs in Appendix 3 of the full report.

The synthesis report included a summary of the RO, an overview of the relevant studies, comments on the merits of the key studies in meeting the objective of the RO

and the value of their contribution towards the emerging evidence. Specifically, the synthesis report template requested:

- the key features of the studies;
- the types of materials used in the studies;
- the extent to which each of the studies contributes to the RO;
- identification of studies considered to be of highest quality and impact (backed up by the WoE scoring);
- remaining gaps.

Once completed, the WoE data and synthesis report(s) were returned to IOM and the completed WoE databases were concatenated into a single database to enable analysis of the evidence for trends, and preparation of the descriptive statistics on the full dataset.

2.5 RISK ASSESSMENT APPRAISAL

Taking into consideration all the available information and data generated, the project team formed an opinion on whether there was sufficient information to identify and quantify risks to human health and/or the environment from manufactured nanomaterials, that might lead to a need for control or management of the risk. The appraisal is limited to the information collected and presented in the RO synthesis reports and the authors are aware that there may be more information within the published literature that has not been identified within the RO reports. The authors are also aware that there is available published generic advice on the control of exposure to nanomaterials (e.g. BSI, 2007) and also generic advice on health surveillance to workers who may be exposed to nanomaterials (e.g. NIOSH, 2009). In addition to considering the data generated from the Weight-of-Evidence appraisal of the quality and contribution of each study through expert assessment, the risk assessment appraisal also considered whether there is sufficient information to invoke the precautionary principle for one or more of the identified nanomaterials using the information collected in the EMERGNANO project.

It should be noted, however, that the risk assessment appraisal is not a risk assessment per se and the authors have only considered the information and expert opinions within the ROs and not taken into account the wider body of literature that may exist for some of the longer established nanomaterials.

2.6 PRESENTATION OF THE EVIDENCE AT A WORKSHOP

A workshop to present an overview of the project's findings and facilitate a discussion with stakeholders to identify critical issues was held at the Central Science Laboratory in Yorkshire on October 20-21, 2008. Stakeholder representatives invited included key members of the toxicology, regulatory, industry and consumer communities. The workshop participants were provided with a draft collation of the RO synthesis reports. The workshop was structured as follows:

- Introduction to the project's aims, objectives and approach;
- Overview of the studies and gaps from the RO appraisals;
- Chaired discussion and break-out groups to identify critical missing studies and reach a consensus on the extent to which research has met the objectives of the ROs.

Four break-out sessions discussed the findings of the RO appraisals grouped according to the Task Force Area. The relevant RO assessors facilitated the discussion and used the contributions in the preparation of the final version of their synthesis reports.

3 QUANTITATIVE ASSESSMENT

Using data collated on projects included in EMERGNANO, and based on performance of studies within the Weight-of-Evidence appraisals, the following section provides a short quantitative analysis of the studies considered. More detailed information on the distribution of Weight-of-Evidence scores and project financial values as a function of RO, is presented in Appendices 3 and 4 of the full report.

3.1 OVERVIEW OF STUDIES CONSIDERED

In total, 673 studies were identified in an initial data search and collated in a common format into a Microsoft Access based database. Following removal of 315 studies found to be duplicates or which failed to meet the selection criteria, 358 studies remained. Of these, 19 studies were classified as Enabling activities, Networks or Observatories and thus were considered discretely in Chapter 6, and a further 46 did not fall within the scope of any of the 18 ROs and were therefore not included in the assessment. A final count of 293 studies were allocated for expert assessment under RO 2-19; this is represented graphically in Figure 3.1

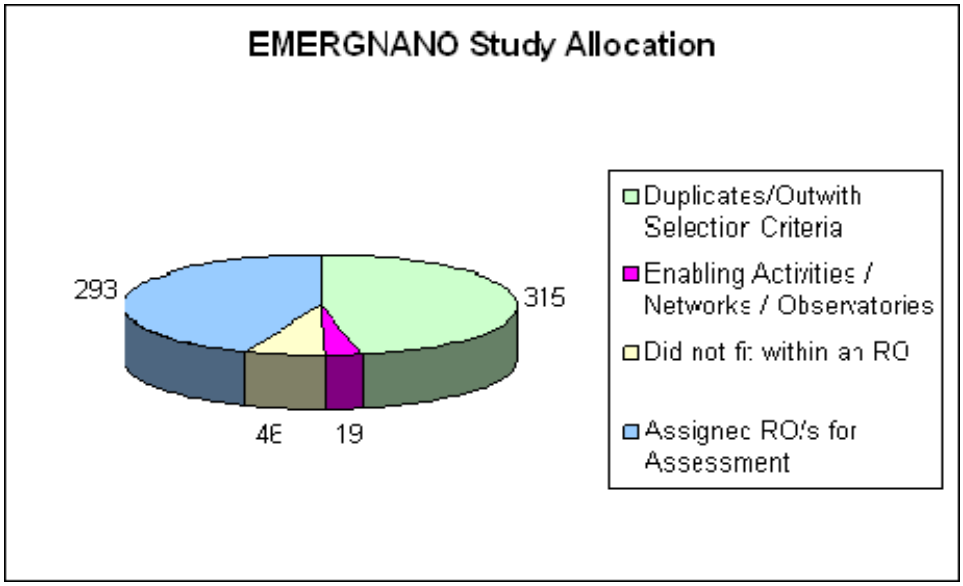

Figure 3.1: Selection and allocation of studies for assessment

Of the initial 293 studies considered, just under one third of these studies were complete (88). Seventy were near completion (i.e. completion was expected to be within 2008), 106 were ongoing and 13 were just commencing. For the remaining 16 studies, a status was not obtainable.

Taking into consideration a further five additional studies identified and thirty-eight studies rejected subsequently by assessors during WoE assessment, the final number of unique studies considered within the EMERGNANO project was 260. The distribution of studies across the ROs is shown in Table 3.1.

Table 3.1: Summary of studies allocated and analysed per Research Objective

Research Objective	No. studies allocated to RO	Additional studies identified	No. studies excluded by assessor	Total no. studies assessed within RO
2	28	0	0	28
3	6	2	0	8
4	3	2	2	3
5	30	1	6	25
6	25	0	6	19
7	13	0	1	12
8	21	0	5	16
9	1	0	0	1
10	38	0	3	35
11	44	0	18	26
12	48	0	9	39
13	41	0	5	36
14	53	0	9	44
15	8	0	0	8
16	18	0	0	18
17	45	0	2	43
18	26	0	4	22
19	12	0	0	12

3.2 WEIGHT-OF-EVIDENCE SCORE DISTRIBUTIONS

Due to inherent differences in the criteria used to conduct Weight-of-Evidence appraisal for each Research Objective, interpretation of scores awarded and their distributions is not comparable across ROs. With respect to preparation of synthesis reports, the threshold above which studies were deemed to be of the highest scientific value also varied according to the RO analysed; some assessors not electing to set a threshold, and others setting the threshold within the highest quartile of scores awarded. Table 3.2 provides a summary of score distribution per RO. A more detailed graphical representation showing the distribution for each RO is provided in the Figures of Appendix 3.

Table 3.2: Weight-Of-Evidence Score Distribution

Research Objective	No. Studies	Minimum Score	Maximum Score	Threshold	No. Studies over Threshold
2	28	5	23	15	18
3	8	4	20	Not assigned	8
4	3	9	22	Not assigned	3
5	24	7	26	17	16
6	19	7	25	16	16
7	12	3	25	Not assigned	12
8	16	4	26	20	5
9	1	18	18	Not assigned	1
10	35	11	28	16	11
11	26	4	22	12	14
12	39	3	22	11	15
13	36	3	23	18	13
14	44	0	21	13	20
15	8	6	20	18	4
16	18	8	20	14	17
17	43	0	21	11	20
18	22	5	24	11	15
19	12	5	18	11	9

3.3 STUDY FUNDING

Tables 3.3 provides a summary of the total funding value of the studies considered for each RO. A detailed breakdown is provided in Appendix 4 of the full report.

Table 3.3: Summary of Value Study Budget

		State of progress					
		Unknown	**Starting (+/- 3 months)**	**On-Going**	**Near Completed (expected 2008)**	**Completed**	**Total**
RO02	**No. Studies**	4	2	10	5	7	**28**
	Value / £M	-	-	14.06 (6)	4.87 (5)	1.02 (4)	**19.94 (15)**
RO03	**No. Studies**	1	0	1	4	2	**8**
	Value / £M	-	-	-	0.24 (3)	0.17 (1)	**0.41 (4)**
RO04	**No. Studies**	0	0	1	1	1	**3**
	Value / £M	-	-	5.57 (1)	0.31 (1)	0.01 (1)	**5.88 (3)**
RO05	**No. Studies**	1	0	11	4	9	**25**
	Value / £M	-	-	11.57 (8)	1.31 (4)	0.74 (8)	**13.62 (20)**
RO06	**No. Studies**	5	1	5	3	5	**19**
	Value / £M	-	-	5.97 (2)	0.52(3)	4.81 (4)	**6.97 (9)**
RO07	**No. Studies**	0	0	7	3	2	**12**
	Value / £M	-	-	1.23 (5)	1.10 (3)	0.81 (2)	**3.15 (10)**
RO08	**No. Studies**	1	0	7	1	9	**16**
	Value / £M	-	-	5.57 (1)	0.20 (1)	1.16 (6)	**6.93 (8)**
RO09	**No. Studies**	0	0	0	1	0	**1**
	Value / £M	-	-	-	0.06 (1)	-	**0.06 (1)**
RO10	**No. Studies**	0	1	12	14	9	**35**
	Value / £M	-	-	1.51(9)	2.95 (14)	1.46 (9)	**5.92 (32)**
RO11	**No. Studies**	1	1	11	4	9	**26**
	Value / £	-	0.60 (1)	1.9 (9)	0.87 (3)	2.46(7)	**5.83 (20)**
RO12	**No. Studies**	1	2	14	6	11	**34**
	Value / £	-	-	15.97 (13)	2.36 (10)	1.07 (12)	19.41 **(25)**
RO13	**No. Studies**	1	4	14	6	11	**36**
	Value / £	-	-	10.12 (13)	3.80 (6)	1.38 (10)	**15.31 (29)**
RO14	**No. Studies**	5	4	13	9	13	**44**
	Value / £	-	5.96 (1)	16.39 (11)	1.60 (8)	2.99 (12)	**21.58 (32)**
RO15	**No. Studies**	0	0	2	1	5	**8**
	Value / £	-	-	8.15 (2)	0.06 (1)	1.90(4)	**10.11 (7)**
RO16	**No. Studies**	2	3	5	3	5	**18**
	Value / £	-	2.38 (1)	3.94 (3)	0.88 (3)	0.69 (5)	**7.90 (12)**
RO17	**No. Studies**	0	6	14	15	8	**43**
	Value / £	-	0.24 (5)	1.89 (11)	1.99 (15)	1,48(8)	**5.60 (39)**
RO18	**No. Studies**	0	3	4	9	6	**22**
	Value / £	-	0.13 (2)	0.70 (4)	0.70 (9)	0.91 (5)	**2.44 (20)**
RO19	**No. Studies**	0	1	8	1	2	**12**
	Value / £	-	-	4.07 (7)	0.18 (1)	0.51 (2)	**4.75(10)**

3.4 GEOGRAPHIC DISTRIBUTION OF STUDIES ASSESSED

Table 3.4 summarises geographic distribution of studies assessed under the Weight of Evidence appraisal. The majority of studies (56%) were conducted in the USA. The UK presented the second highest number of studies (15%) and Switzerland the third (7%). European Commission EU-wide collaborative projects accounted for 19 of the studies assessed. As it was not possible to obtain a value for every study assessed, the number of studies summed to obtain the total value for each country is in brackets.

Table 3.4: Geographical distribution of studies

Country	Completed	Near Completed	On-Going	Starting	Unknown	Total No. Studies	Value / £
Belgium	0	0	1	0	0	1	7,953,818 (n=1)
Canada	10	0	0	0	0	10	496,914 (n=10)
China	0	0	1	0	0	1	None listed
Czech Republic	0	0	1	0	0	1	None listed
Denmark	0	2	9	0	0	11	7,336,689 (n=11)
EU*	4	3	7	5	0	19	25,914,791 (n=13)
Finland	1	0	1	0	0	2	836,741 (n=2)
France	1	0	12	0	0	13	340,423 (n=1)
Germany	0	0	4	0	0	4	7,397,050 (n=4)
Switzerland	2	8	9	1	0	20	3,120,126 (n=19)
Taiwan	2	0	0	0	0	2	186,917 (n=2)
UK	10	25	5	4	0	44	3,292,976 (n=43)
USA	58	32	56	3	16	165	36,983,288 (n=115)
Total No. Studies	88	70	106	13	16	**293**	**93,859,738 (n=221)**

* Trans-boundary projects funded by the European Commission

Figure 3.2 presents an overview of the state of progress of studies, according to geographical location.

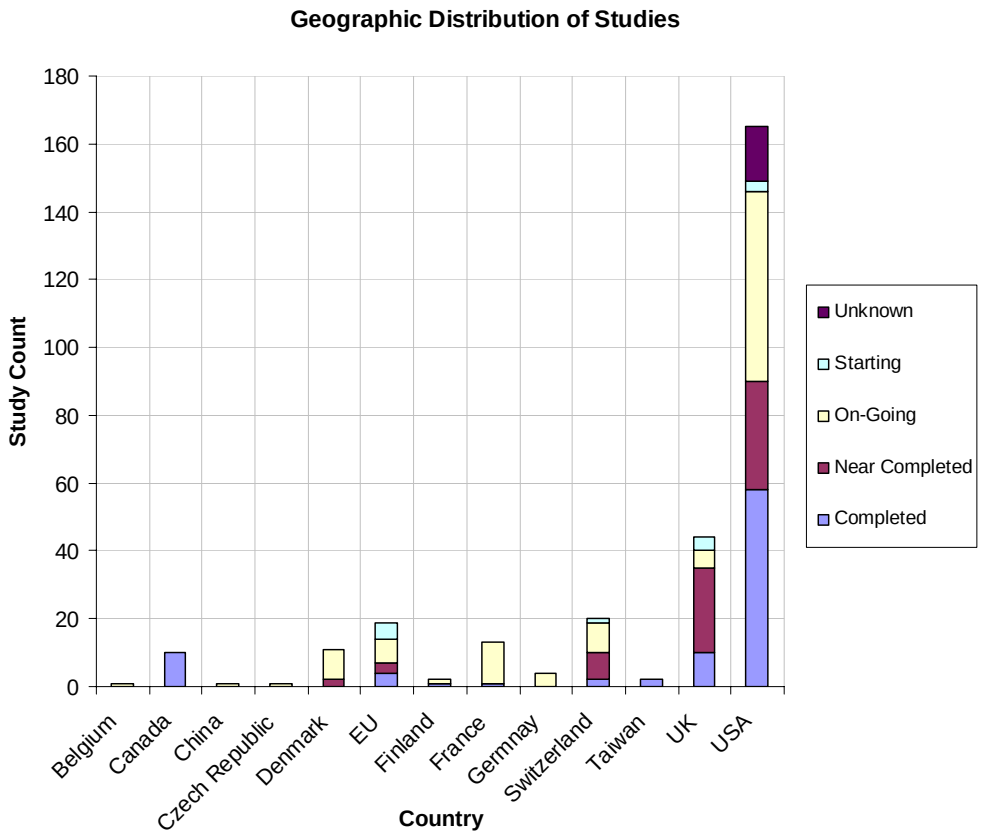

Figure 3.2: Geographic distribution of studies, according to state of progress.

4 ASSESSMENT OF THE RESEARCH OBJECTIVES

4.1 INTRODUCTION

This section of the full report contains the synthesis reviews of the studies relevant to each of the Research Objectives. As discussed in the methodology, each of these *synthesis reports* has the same structure. Firstly the RO is described, including any variation or clarification considered appropriate, followed by an overview of the types of studies found to be relevant to the particular RO. This is followed by a description of the key studies that, in the opinion of the reviewer, contributed substantively towards realising the RO. Studies are identified as complete/near completed and ongoing. The studies are identified by their unique study code which can be tracked back to the study list in Appendix 1. The main elements of each study are described, differentiating between those studies which are complete or on the point of completing and those studies which are ongoing. This is followed by a description of the contribution that these studies make towards the RO, an evaluation of the extent to which the RO has been met and an assessment of the remaining gaps required to complete the RO.

Refer to the full report for the detailed contents of this chapter.

5 PROGRESS AND GAPS

5.1 INTRODUCTION

In this section the outputs from the previous chapter have been summarised to distil out the key issues, progress and gaps in relation to each of the ROs. These have been presented in a tabular format to highlight the important elements. More detail can be found in the previous chapter. These summaries have been arranged in the order presented for each task force area.

5.2 METROLOGY, CHARACTERISATION, STANDARDISATION AND REFERENCE MATERIALS

RO 02 - To identify the most suitable metrics and associated methods for the measurement and characterisation of nanoparticles
Relevant issues • Which physical and chemical characteristics are relevant to the biological behaviour of different nanomaterials? • How do these characteristics vary over time and within different environments (including biological environments)? • With what precision and accuracy do these characteristics need to be measured to investigate the potential impacts of different nanomaterials? • To what extent can existing methods be used to make relevant measurements? • How can current measurement approaches not normally applied to investigating the potential impact of nanomaterials be applied to research in this area? • What are the limitations of current characterisation methods, and how can these limitations be overcome? • Which measurements of nanomaterial characteristics or behaviour best reflect their potential to cause harm? • How do these metrics vary according to whether materials are being measured outside or inside the body? • To what extent can existing exposure measurement instruments and methodologies be used to make relevant exposure measurements for engineered nanomaterials? • What are the limitations of current techniques, and how can these be overcome?
Progress • None of the listed studies can be said to be conclusive in providing new approaches or guidelines to characterising and measuring nanomaterials. However, together they contribute to a growing body of knowledge; • Studies are mainly focussed on addressing the relevance and practicality of using surface area as an exposure metric; • Studies are limited in scope and conclusiveness.
Gaps • Very few of the projects were focussed on systematically developing characterisation or exposure measurement methods for engineered nanomaterials; • There was very little coherence between the identified projects that would lead to significant advances in risk-related measurement and characterisation methods for different classes of nanomaterials; • In most cases, there was insufficient information available to judge whether projects would result in credible and relevant new information; • The predominant materials involved in the projects identified were metal oxides and carbon-based nanomaterials; • There some emphasis on measuring occupational exposures. However, very few projects were designed to provide information useful to measuring exposures outside the workplace; • More specifically, there was a lack of research addressing general measurement methods for characterising nanomaterials and their impact in the environment.

RO 03 - To develop standardised, well-characterised reference nanoparticles
Relevant issues • Very limited number of studies addressing this issue; • Studies were predominantly associated with the development of candidate reference materials for use with exposure or toxicological analyses; • Much of the activity thus far has been on identifying candidate materials – typically with a workshop type approach; • Equally important are the protocols that accompany reference materials, for their storage and use; • In some cases, candidate materials, characterisation techniques and toxicology analyses were stated, but the absence of supporting information on most of the projects precludes verification of progress towards meeting the stated objectives.
Progress • Progress in understanding of reference materials, test materials and how they may be used is developing; • Reasonable level of agreement about the likely candidate materials; • Some commercial materials beginning to emerge, being produced by organisations such as NIST and IRMM.
Gaps • Very few reference nanomaterials are available at this stage; • Little evidence that issues such as storage, distribution are being addressed in the public domain; • No robust process in place by which these materials will be delivered in time.

RO 04 - To understand the properties of nanoparticles in the context of their ignition and explosion potential, and assess/develop methods for evaluating this
Relevant issues • Relevant types of studies would include adaptation of existing methods for assessing ignition and explosion potential for smaller quantities relevant to NP, extending models down into the NP range and collecting data for a range of NP types.
Progress • Little progress has been made, only two studies having been identified. Commercial and military aspects of research on explosive properties of nanoparticles are, however, much more widely reported.
Gaps • It is apparent from the lack of available information that this RO has been largely overlooked by groups working in the general area. Work in this area is very limited in comparison with the vast array of projects addressing nanoparticle toxicology issues. The need for assessment of explosive and flammability properties has been repeatedly highlighted as important (Pritchard, 2004; Knowles, 2006); however the response appears to have been somewhat limited.

RO 09 - Optimisation, development and application of technologies that enable the measurement of exposure to nanoparticles in soil and water
Relevant Issues • This has been interpreted as including analytical techniques and studies on the behaviour of nanoparticles in natural materials.
Progress • Generally little progress has been reported, however approaches considering life cycle reviews of specific nanoparticles may prove useful in determining the extent of exposure in defined environmental areas.
Gaps • It is apparent from the lack of available information that this RO has been largely overlooked by groups working in the general area. The need for new measurement techniques is clearly important, so it would appear that the need has not been met and there are significant knowledge gaps.

5.3 EXPOSURES – SOURCES, PATHWAYS, AND TECHNOLOGIES

RO 05 - Further identification of sources of nanoparticles
Relevant issues • What are the sources of nanoparticles which could potentially cause exposure to humans or the environment? • What sources actually cause exposure? • What are the characteristics of these exposures in terms of intensity, duration, number of people exposed, particle size and composition?
Progress • In terms of identifying the sources, good work has been done which builds on work done by the Royal Society to map out the potential exposure landscape primarily through review and inventory projects; • In terms of describing sources which actually cause exposure, some progress has been made with some scenarios. Occupational exposures have been identified in both synthesis and processing activities; • Studies already identified will make valuable contributions towards characterising exposures. Programmes are underway and these should be encouraged.
Gaps • There are many complex exposure pathways and only a very few have been considered. • Life cycle assessment approach is missing e.g. identify a series of products where nanoparticles are a component and carry out detailed life cycle analysis for each; • Consumer exposures have been postulated but have not been conclusively demonstrated, other than very obvious examples such as the application of skin care products; • Characterisation primarily requires measurement programmes either on real or simulated exposure scenarios using equipment or methods which are established and validated (dealt with under RO6); • The landscape is extremely complex with many materials, products and processes already identified as potentially causing exposure. There is a large programme of work which needs to be carried out in order to quantify and characterise these exposures over the range of important possible exposure scenarios. Studies identified will only cover a small fraction of the potential exposures which are believed to be possible.

RO 06 - Optimisation and development of technologies that enable the measurement of occupational and environmental exposure to nanoparticles *via* the air

Relevant issues

- Which metric is appropriate to use for which scenario (occupational, environmental) or particle type?
- Discrimination of the NP of interest from any background particles;
- Aggregation of nanoparticles and whether or not it is possible to describe an appropriate maximum size;
- For high aspect ratio nanomaterials (HARN) such as CNT or metal nanowires, can variants of existing measurement and counting methods used for fibrous aerosols be used in a meaningful way to determine an appropriate measure of exposure?
- Relevant studies include *instrument development* e.g. development of a new personal sampler, *optimisation studies* including optimisation/adaptation of specific existing methods, combination of different methods, combination of different metrics derive alternate indices of exposure and comparison of methods, including both of real time measurement instruments or offline analysis methods (e.g. image analysis of high aspect ratio nanomaterials using SEM or TEM approaches), *Measurement programmes,* broadly field based activities in which different types of measurement systems are used in order to try to characterise the features of a potential nanoparticle release in a workplace or the environment.

Progress

- Very limited progress in completed or near completed studies. Many studies seem overambitious in their aims;
- New or ongoing studies promise a great deal including:
    - A new personal sampler or samplers for some types of NP;
    - Improved measurement strategies, validated for some types of NP;
    - A method for measuring the surface area of TiO_2, discriminating from background aerosol;
    - A method for estimating total length exposure for CNT;
    - Improved understanding on the range of application of real-time surface area measurement methods.

Gaps

- Even if all of the studies deliver what they promise, many significant gaps will remain. These include:
    - A validated method for real time measurement of HARN;
    - An evaluation of whether fibre counting approaches can be used for HARN;
    - A widely applicable method by which NP of interest can be discriminated from background;
    - A method for assessment of the agglomeration state for NP aerosols;
    - Information about a size selection cut-point for NP.

RO 07 - Fate and Behaviour of Nanoparticles in Air
Relevant issues • Studies could deal with the release of nanoparticles into the air and their subsequent behaviour (e.g. transport, mixing, agglomeration, deposition); • Significant overlaps with RO5, RO6 and RO8.
Progress • The few published articles and reports provide some preliminary information in relation to the determination and characterisation of NPs in the workplace, assessment of potential exposure to NPs in the workplace, and effectiveness of personal protective equipment; • From the aims and objectives of the ongoing studies, it is likely that more relevant scientific evidence to support this RO will emerge in the coming years. It is, nevertheless, reassuring that a few studies carried out so far have indicated the effectiveness of engineering controls and personal protective equipment in preventing or minimising NP exposure in a workplace setting.
Gaps • Studies dealing with transport, mixing agglomeration and deposition were generally not found; • Studies which are available focus primarily on the occupational setting i.e. indoor air; • Most studies, however, relate to one or two types of NPs and it is unclear whether it will be possible to extrapolate the results to other types; • The main elements that so far seem to be scarce or missing in relation to the RO include valid analytical tools that can be used in detection and quantification of different NPs in aerial environments in the workplace, and in other emission scenarios; • There is also a need for systematic studies on different types of air-borne NPs using a range of physicochemical parameters (e.g. size, shape, form, surface area) to generate data on their interactions, fate, behaviour, and dispersal to allow development of reliable models.

RO 08 - Development of exposure control devices
Relevant issues • Can nanoparticles pass through respirator filters? • Can nanoparticles pass around respirator face-pieces (face seal leakage)? • Related to this, can nanoparticles pass through filtration systems used in air cleaning devices? • Can nanoparticles pass through personal protective clothing? • Are workplace engineering control systems (enclosure, ventilation, filtration) effective at reducing or exposure to NP?
Progress • Relatively few studies have been identified which are making a significant contribution towards this RO. All but one of these studies are being carried out in the US. Most of these studies have investigated the penetration of NP through respirator filters and other (HEPA) filters used in air cleaners; • Consistently these studies have found that, as theory predicts, filters are highly efficient collectors of NP and that the efficiency of collection increases as particle size reduces, even down to 4 nm; • For Skin Protective Equipment (SPE), such as gloves and suits, evidence of poor performance has been found in one study, based on laboratory tests, and a recommendation to use double gloves has been made.
Gaps • No information concerning the potential leakage around respirators (face seal leakage), although one ongoing study is addressing this; • For SPE, much more information is required here as to what actually works, in what circumstances and what the limitations are; • None of the studies of personal protective equipment have thus far looked at human factors and how these systems can work in a practical sense. Information on this is needed; • No studies have been carried out which systematically address the performance of engineering controls which have been implemented in practical settings; • This RO could have been extended to the development of exposure control *methods* including the development management systems, control banding and other activities of that type.

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

Relevant issues

- The research studies are exploring a range of fate and behaviour processes, including aggregation behaviour, transformation reactions, deposition behaviour, leaching behaviour and uptake into different organisms (including soil bacteria, eukaryotes, worms, frogs, aquatic invertebrates) and through food chains;
- Different environmental systems are being explored, including surface waters, soils, air, water-sediment systems, water treatment systems and soil/water-organism systems at different levels of complexity (e.g. tightly controlled experiments with laboratory water *vs* real waters; studies with well characterised porous media *vs* studies with real soils and sediments);
- The effects of environmental variables such as pH, ionic strength, dissolved organic carbon content and light intensity are being investigated;
- In addition, the effects of other anthropogenic substances (e.g. surfactants and detergents), that are likely to occur in the environment alongside nanoparticles, is being investigated;
- Studies are also attempting to develop modelling approaches for the different processes that are being investigated.

Progress

- Significant numbers of projects are now looking at those factors and processes that might affect the fate and behaviour of a wide range of nanoparticles in soils and waters. These studies are likely to provide experimental data and modelling approaches that support the RO.

Gaps

The main elements that so far seem to be scarce or missing in relation to the RO include:

- Valid analytical tools that can be used in detection and quantification of different NPs in complex environmental matrices;
- Systematic studies on different types of NPs using a range of physicochemical parameters (e.g. size, shape, form, surface area) and environmental variables (e.g. pH, ionic concentration) to generate data on fate and behaviour of NPs to allow development of reliable models;
- Assessment of human and environmental exposure in a full lifecycle analysis approach to identify critical stages that can lead to exposure to free NPs and can be targeted for risk management.

5.4 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

Relevant issues

- The types of study were predominantly *in vivo* and *in vitro* studies with a couple of modelling studies.

Progress

- For a limited number of nanoparticles, iridium and carbon, in a very few laboratories, there has been good toxicokinetics following inhalation; these have not related particle characteristics to behaviour, except for limited studies with two different sizes of iridium;
- There have been limited studies tracking the fate of NP of different sizes of gold injected into the blood; the relevance of such studies to lung exposure is not known since passage through the lungs might change the particle surface coating, leading to different toxicokinetics compared to those arising following direct injection into the blood;
- There are piecemeal studies using instillation of suspensions of particles (e.g., on the fate of TiO_2 nanoparticles instilled into the nose of rats and particokinetics after instillation); these can be criticised on the basis of the non-physiological basis of the exposure;
- Very limited studies therefore suggest that some NP can gain access to the blood and the brain after inhalation exposure; the general relevance of this to all NP, structure-relatedness of these findings or the relevance to man (these are only shown in animals), are not yet known.

Gaps

- This review of ongoing studies has failed to demonstrate that there is any comprehensive attempt to gain the toxicokinetic (particokinetic) data required to reach the aims of hazard identification and derivation of plausible dosimetry;
- There is no study that sets out with the aim of simply assessing the accumulation of particles in a wide variety of organs after inhalation exposure to a range of different NP;
- A potential structure activity relationship that governs penetration at each different portal of entry is not being sought;
- No systematic studies on the potential of different kinds of nanoparticles to get into the blood, the lymph or the brain;
- No specific studies on whether carbon nanotubes behave like asbestos, in terms of whether they translocate to the pleural mesothelium and length-relatedness of this effect;
- No studies specifically addressing the interstitialisation of inhaled nanoparticles and the consequences in terms of fibrosis etc;
- Quantum dots have been shown to pass through epidermis to the dermis, albeit in small amounts, raising issues of susceptibility – a recent study by Oberdorster *et al*., has described work where nude mice which were UV irradiated demonstrated a deeper penetration of Quantum dots into the skin;
- Quantitative estimation of translocation to brain is only being seriously addressed in one US laboratory using a limited range of nanoparticles types.

RO 12 - Research to establish a clear understanding of inter and intracellular transport and localisation of NPs and their cellular toxicity
Relevant issues • The types of study were predominantly *in vivo* and *in vitro* studies with a couple of modelling studies.
Progress • Advances in 'between cells and tissue' transport are described in RO11 above; • As regards intercellular transport, there have been studies using a limited number of NP, demonstrating that some nanoparticles can move between different cellular compartments and can cross membranes by free diffusion; • Subsequently, nanoparticles have been described as locating to the mitochondria, nucleus and being found free in the cytoplasm, unlike larger particles; this has clear implications for 'compartment-specific' toxicity.
Gaps • No straightforward study on the intracellular location of a range of different NP with time after exposure; • No studies directly addressing whether nanoparticles are preferentially taken up in the mitochondria or nucleus resulting in concentrated areas of oxidative stress and potential respiratory burst disruption; • No systematic study of structural correlates determining protein particle interactions and transport of important proteins within a cell such as detrimental changes in protein folding and packaging; • No specific studies addressing key generic issues such as whether fluorescent tagging of nanoparticles changes their location in the cell. Lots of studies are utilising quantum dots due to their visibility, but these are not typical nanoparticles; • No addressing of different target cell specific toxicity i.e. brain cells, liver cells (canaliculae formation); • No specific studies addressing carbon nanotubes and the sub-cellular targets of the length-dependent toxicity seen with carbon nanotubes , echoing asbestos (Poland). Translocation from blood into atherosclerotic plaques and their interactions with components of the plaque.

RO13 - Research to establish a clear understanding of whether oxidative stress, inflammatory effects and genotoxicity apply to nanoparticles

Relevant issues

- It would be surprising if oxidative stress, inflammation and genotoxicity were not found to be involved in the pathogenic action of NP, since these processes underlie the pathogenic effects of all other harmful particles so far studied (asbestos, quartz, etc.). They also underlie the toxicity of any number of chemical toxins. It is also true to say that these form the dominant hypothesis for mainstream nanotoxicology.

Progress

- The RO has been met to some extent and many studies are assuming the oxidative stress/inflammation hypothesis;
- More interesting and of importance to nanotoxicology is the relationship between NP structure and these endpoints i.e. the structure function relationship. The predictable heterogeneity in the oxidative stressing and inflammatory effects of NP is a most important aspect of defining the role of oxidative stress and inflammation and could allow predictive toxicology of NP. Subsequently many studies directly contribute to the question of whether oxidative stress and inflammation are involved in the action of NP. However, given the nature of toxicology, whereby doses are increased mostly *in vitro*, until an effect is reached, the relevance of such findings for plausible exposures is questionable. Few studies contribute to the issue of genotoxicity of NP.

Gaps

- Some NP are used a lot (TiO_2, Carbon black and CNT) whilst some are used much less (alumina, ZnO, quantum dots, CeO_2 etc.) and so the generic nature of the findings are questionable;
- Some limited attempts at structure activity relationships (SAR) - there can be little doubt that there will be heterogeneity in the action of NP in causing oxidative stress and inflammation – therefore we are on case-by–case assessment unless some structure function rules can be derived;
- Several studies purport to address the structure activity relationship fully through oxidative stress and inflammation as the activities allied to various structures being measured in a panel of NP;
- Other studies carry out more limited structure activity studies e.g. fixing on limited activities such as role of iron, oxidative stress biopersistence or shape;
- *In vivo* studies are at a premium and where there are *in vivo* studies they are mostly confined to a small subset of NP for proof-of-concept type studies;
- There are few studies addressing genotoxicity – only three were identified;
- Few studies are exposing subjects to NP at or near plausible exposures and then assessing oxidative stress, inflammation and genotoxicity;
- No studies with susceptible models are described except for synergism between CNT and microbial inflammogens *in vitro*, despite the fact that the only data available that may tell us about the effects of (combustion-derived) nanoparticles suggest that a susceptible background of airways inflammation or CV disease is where the main effects of manufactured NP will be found;
- There are few studies addressing the oxidative stress hypothesis for CV effects or the brain so there is a need for *in vivo* exposures to NP then measurement oxidative stress in the vessel wall and in other CV targets or in the brain;
- The focus on oxidative stress and inflammation can be seen as logical but it does stifle other thinking. For example, in one study an alumina with no oxidative stressing activity turned out to be inflammogenic. So there are definitely other mechanisms for inflammation than oxidative stress.

RO14 - 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
Relevant issues • A broad RO. Toxicokinetic study types include deposition, distribution and translocation.
Progress • Deposition is rather poorly addressed, being the focus of only three studies; • Distribution and translocation - several studies directly address the issue of translocation and redistribution from portal of entry; • Pathogenicity - there are a number of studies that superficially address mechanism but this is better covered in other RO; however genotoxicity is addressed in two studies; • Cardiovascular (CV) system - few studies (5) address the CV system as a target, despite the PM10 literature suggesting that this is likely to be a major target for manufactured NP; • Neurological studies - this is addressed in a few studies.
Gaps • Use of a narrow range of particle types - e.g. lots of CNT studies - no mention of e.g. CeO_2; • Piecemeal studies on translocation to brain or CV, but no studies on mass balance toxicokinetics; • Virtually no *in vivo* dosimetry studies marrying up toxicokinetics with studies of response i.e. no information on dose versus response, which is important; • Few studies on the CV impact – a few studies on blood but the real impact of particles is likely to be on atherosclerosis – only one study seriously addressing this issue; • Few studies addressing the issue of deposition and effects on clearance; • Despite numerous CNT studies, no studies addressing the asbestos/HARN paradigm (e.g. translocation to the pleura, role of HARN length or biopersistence etc); • Few studies on brain transfer for common NP; • The important issue of the origin of any CV effects i.e. blood transfer of NP versus indirect effects of pulmonary inflammation- is not directly addressed in any study.

RO15 - 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
Relevant issues • As a result of the consumer products emphasis, it was considered appropriate to expand the scope to take into account ingestion exposure due to the possible presence of NP in food and food contact materials.
Progress • There are only a very few completed studies that provide some relevant information to the RO, but they represent only initial attempts to investigate the potential interactions and effects of NPs on the skin, and through ingestion (gastrointestinal) route; • A few ongoing studies aim to develop well-characterised inhalable welding fumes for dermal exposure studies, and to investigate the link between effects and physicochemical properties of NPs, and the potential role of NPs to carry environmental contaminants. However, detailed results from these studies are not yet available.
Gaps • There is a need for systematic studies to develop the basic understanding of dermal uptake, penetration and toxicity of well-characterised NPs in the skin; • Research also needs to address relevant NPs that are used, or are likely to be used, in dermal products, or those that may come in contact with skin during the whole lifecycle of materials/ products. It is also clear from the two studies on the use of nanomaterials in food and food packaging that very little is known in regard to potential exposure, uptake, toxico- dynamics/ kinetics of NPs through the ingestion route. There is a need for research to address this aspect, and also to assess whether data on uptake, penetration and bioavailability of NPs from one exposure route (e.g. inhalation) can be extrapolated to another routes (e.g. dermal or gastrointestinal routes).

RO16 – Human Health Hazard and Risk Assessment
Relevant Issues • A strategy for assessing the potential hazard of NP, involving both *in vitro* and *in vivo* experiments.
Progress • There are only few completed studies with NP. However, the test protocols remain to be validated; • Ongoing and new studies claim to address the issue and are likely to generate useful data for a future testing strategy.
Gaps • The gaps for a useful testing strategy are: (i) lack of validation of testing protocols; (ii) concordance between *in vitro* and *in vivo* and relevance to human situations. Point (ii) is especially important as it contributes to the 3R (reduction, replacement, refine) principle.

5.5 ENVIRONMENTAL HAZARD AND RISK ASSESSMENT

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
Relevant Issues • Initially, studies included in this RO encompassed microorganisms, invertebrates and vertebrates from both terrestrial and aquatic groups environments; • Studies on fate and modelling were also included within this RO; • Although RO17 mostly included studies that are not specific to remediation, these studies focussed on uptake by, and toxicity of, nanomaterials to microorganisms, animals and plants. Many of these were aquatic rather than terrestrial species, thus not fully fitting within this RO and have been considered under RO18. After discussion at the workshop it was decided that RO17 addresses a very specific objective that is in fact a sub-objective of RO18, therefore ensuring that the need for studies to address specifically remediation nanoparticles is explicit; • Many of the studies initially categorised into RO17 were in fact aquatic species e.g. fish, several aquatic invertebrates and some primary producers, rather than those that might live in groundwater, although of course there are actually very few organisms that do live in groundwaters (which has a specific definition and is distinct from surface waters).
Progress • There is some interesting data emerging relating to the uptake and toxicity of nanoparticles to a range of invertebrates and microorganisms, but relatively little for plants. Most of these studies often provide details of the physicochemical characteristics of nanoparticles that drive uptake and toxicity, which can then potentially be applied to other types of nanoparticles such as those used in remediation.
Gaps • Most of the studies conducted focus on uptake and/or toxicity of nanoparticles, with only very few specifically investigating remediation nanoparticles. There is therefore much work to be done with these particles; • Of the species studied most studies used animals, followed by microorganisms. Only one used plants; • Almost no groundwater or soil exposure scenarios are studied and so there is much work to be done with species in such models.

RO18 - 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
Relevant Issues • A range of nanomaterials and test systems were studied. The focus was on aquatic species and on metal and carbon nanoparticles; • Facilitation of knowledge transfer from human toxicological studies to inform ecotoxicology (and vice versa) is also important.
Progress • The studies assessed have made a useful inroad in the areas listed within this RO in terms of improving the understanding of kinetics of nanoparticle uptake in invertebrate and vertebrate models and relating this to toxicity; • In addition, there are now a few studies focussing on microbial organisms and these provide information on effect assessment at individual level and also at community level, although this may not be so relevant within this RO.
Gaps • The studies only cover a limited range of species and material types; • There is some effort to relate study design and interpretation to human toxicology of nanoparticles, but there is much more to be done.

RO19 - 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
Relevant Issues • A range of nanomaterials and test systems were studied. As for RO17 and RO18, the focus was on aquatic species and on metal and carbon nanoparticles.
Progress • Projects listed use current standard species as well as new models to assess nanomaterial toxicity. While they use standard species it is not clear whether standards protocols are used and assessed for their suitability; • Only one project is addressing bioaccumulation and bioconcentration of nanoparticles.
Gaps • A great deal of work needs to be done, using a range of nanoparticles and a range of species types, to develop standard protocols and to assess persistence, bioaccumulation and toxicity of nanoparticles.

6 ACTIVITIES EXTERNAL TO THE SCOPE OF THE RESEARCH OBJECTIVES

Although they are broad in their scope, the ROs do not describe complete coverage of all the important issues and questions relevant to the health, safety and environmental risks arising from exposure to nanoparticles. In reviewing the studies, more than 50 were identified which were relevant to these issues but did not fit within the scope of any of the ROs. These included:

- Enabling activities;
- Life cycle analysis;
- Effectiveness of risk assessment approaches.

These studies were not formally reviewed according to the WoE appraisal as it was not possible to identify appropriate generic criteria by which they could be assessed. The most important of those in each category are described in the full report.

7 RISK ASSESSMENT

The objective of the risk assessment appraisal was to assess whether there is sufficient information provided in the ROs to determine whether there is a risk associated with manufactured nanomaterials or whether the precautionary principle should be invoked with identified nanomaterials. It should be noted, however, that we have only considered the information and expert opinions within the ROs and not taken into account the wider body of literature that may exist for some of the longer established nanomaterials.

Firstly in this chapter, the Precautionary Principle and its applicability to potential health and environmental risks for application to the manufacture, use and disposal of nanomaterials is considered. Cconsideration is then given to the synthesis reports generated from the ROs in general (detailed in the full report), and then finally the overall impact and concerns related to individual nanomaterials.

7.1 PRECAUTIONARY PRINCIPLE

The Precautionary Principle has been endorsed internationally on many occasions. At the Rio Conference on the Environment and Development in 1992, world leaders agreed on the principles of the Precautionary Principle, stated in the following terms: *'In order to protect the environment, the precautionary approach shall be widely applied by States according to their capability. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation" (Rio Declaration Principle 15).*

In 2000, the European Commission adopted a Communication on the use of the Precautionary Principle providing a general framework for its use in EU policy, and to avoid unwarranted adoption of the precautionary principle as a disguised form of caution (Commission of the European Communities, 2000). The framework to be followed should be that:

- if a preliminary scientific evaluation shows that there are reasonable grounds for concern that a particular activity might lead to damaging effects on the environment, or on human, animal or plant health, which would be inconsistent with the protection normally afforded to these within the European Community, the Precautionary Principle is triggered;
- if the Precautionary Principle is triggered, decision-makers then have to determine what action is necessary, taking into account the potential consequences of taking no action, the uncertainties inherent in the scientific evaluation, and consulting interested parties on the possible ways of managing the risk. The adopted measures should be proportionate to the level of risk and to the desired level of protection. They should be provisional in nature pending the availability of more reliable scientific data;
- action is then undertaken to obtain further information enabling a more objective assessment of the risk. The measures taken to manage the risk should be maintained so long as the scientific information remains inconclusive and the risk unacceptable.

Within this, when action is deemed necessary, then the measures taken should (amongst other things) be *proportional* to the chosen level of protection, *non-discriminatory* in their application, *consistent* with other measures previously taken, based on *examination of benefits and costs* of both the action and inaction,

continuously reviewed taking into account new scientific data, and *assign responsibility* for producing the scientific evidence required to move away from the precautionary response to a more robust risk assessment. Furthermore, the implementation of the precautionary principle should be initiated with a scientific evaluation (as complete as possible), including the evaluation of and degree of uncertainty, ensuring that the decision-makers are aware of the degree of uncertainty attached to the results. The process itself should be transparent and involve all stakeholders in the issue, and the scientific evaluation should be ongoing until it is possible to reasonably determine the risks associated with the substance. It may also be necessary to place the burden of proof onto the manufacturer or importer and assign them the responsibility for producing the scientific evidence necessary for a comprehensive evaluation.

The precautionary principle is, however, only relevant when there is a potential risk, even if this risk cannot be fully quantified or demonstrated due to the insufficiency of the scientific data. It cannot be used to justify the adoption of unsupported decisions. Factors identified by the Commission include the identification of potentially negative effects without further data, a scientific evaluation of the potential adverse effects, and scientific uncertainty in risk assessment. In each case, a scientific examination of the available data must occur and the conclusions drawn must be supported by evidence.

Within this context, we believe that the precautionary principle is directly applicable to emerging nanotechnologies. However, this report can only indicate the opinion of the authors as to whether the precautionary principle should be considered in these cases and cannot be taken as the decision of the regulatory bodies. This report does not indicate what measures should be taken if the precautionary principle is invoked. It is noted that in the UK, the COSHH Regulations 2002 provides an existing framework for protection against hazardous materials in the workplace that will also account for novel substances which might represent an equivalent risk to existing hazardous substances. In addition, the HSE are able to produce specific precautionary guidance where appropriate and, as an example, they are producing specific guidance on potential exposure to carbon nanotubes based of recent experimental findings.

7.2 CONSIDERATION OF RESEARCH OUTPUTS

Refer to the full report for the detailed contents of this section.

7.3 ASSESSMENT OF USE, EXPOSURE AND TOXICITY

Metal nanoparticles (including alumina) are passivated by the introduction of a naturally-occurring oxide layer (RO04) and the agglomeration of nanoparticles reduces their explosive violence (RO04). The aerosol behaviour of a nanoparticle may be affected by the chemical components (RO08).

Physical handling increases the release of fibres and nanoclays. This can be reduced with compaction (nanoclays) but not with particle modification (RO07; only shown with one type of nanoparticle). However, personal protection equipment (PPE), such as local exhaust ventilation and protective suits, has been shown to be effective for preventing exposure to nanoparticles (although the suit material must not be woven). Protective gloves were shown to be less effective, but were suitable if doubled up (RO08).

Certain high aspect ratio (HARN) fibres have been shown to have some similar effects to asbestos fibres in lung tissue (RO14).

Titanium dioxide (TiO_2) particles

Use and exposure - Used in significant quantities in industry (RO05), emission exposure varies with coated substrate (RO05).

Mechanisms of toxicity - There is a possibility of inflammation in the lung after exposure to TiO_2 nanoparticles of different sizes and this increased with particle size, dose based on surface area (RO11). Research is currently ongoing into the cellular toxicity (RO11), but no results are currently available. TiO_2 has been shown to provoke oxidative stress mediated inflammatory responses in macrophages (RO13), and has been demonstrated to cause oxidative stress, as well as activated NF-κB and AP-1 resulting in cytokine gene expression (RO13). The mechanism of toxicity in peripheral vessel dysfunction after inhalation is *via* oxidative stress (RO13).

Inhalation toxicity – Intratracheally-instilled rods, particles and dots produced transient inflammation and cell damage which did not vary with particle size or shape (RO14), however the route of exposure was not considered environmentally relevant. Short-term exposures to high airborne mass concentration of fine particles cause disruption of endothelium-dependent vasodilation. This was thought to be due to polymorphonuclear cells marginated in the blood vessels (RO14).

Dermal toxicity - Nanosized particles were shown to generate hydroxyl radicals in epithelial cells and activated AP-1 through the phosphorylation of MAP kinase signalling pathways (RO15).

Environmental toxicity – TiO_2 aggregates readily in drinking water (RO17), and the predicted environmental concentration (PEC) is equal to or greater than the predicted no effect concentration (PNEC; no toxic endpoint stated), resulting therefore in a potential scenario that requires further consideration.

Quantum dots

Use and exposure - Used in industry and academia within the UK (RO05).

Mechanisms of toxicity – Quantum dots have been shown to cause more platelet aggregation when coated with PEG compared to uncoated (RO14) and that coating changes the translocation of the particles into the brain (PEG coated quantum dots found in higher concentrations than amine-PEG coated quantum dots; RO14).

Inhalation toxicity – no information supplied in the RO.

Dermal toxicity – no information supplied in the RO.

Environmental toxicity – Functionalised quantum dots did not aggregate readily in drinking water compared to metal oxides (RO17). Nucleobase-conjugated quantum dots (CdSe) were actively taken up by soil and aquatic bacteria and had a toxic effect reducing doubling (RO17).

Carbon nanotubes (CNT) including single walled CNT (SWCNT) multiwalled CNT (MWCNT) – long and short NT

Use and exposure - Used in industry and academia within the UK (RO05). CNTs have similar flammability as compared to carbon black (RO05). Current measuring techniques may only be appropriate for spherical nanoparticles rather than rod or plate-shaped nanoparticles (RO06). Local exhaust ventilation exposure control mechanisms have been shown to be highly effective at reducing exposure (RO05). A case study of CNT exposure has been done, but no results were discussed in the RO (RO05). Some inflammatory effects of CNTs have been attributed to contamination of the test system with iron catalysts (RO14), so the results and methodologies must be carefully considered.

Mechanisms of toxicity – currently under investigation for cellular toxicity (RO12). Mice injected with CNT (location not stated) showed increased atherogenesis, mitochondrial DNA damage, oxidative stress to aorta (RO14). CNT is cytotoxic in muscles after uptake at high mass concentration (RO18).

Inhalation, instillation and intraperitoneal toxicity – CNT inhaled into lungs showed pro-fibrotic effects and iron-mediated free radical generation (RO14). Pharyngeal aspiration and exposure to MWCNT elicited neuroinflammation in discreet brain areas thought to be due to microglial activation (RO14). Long HARN CNT (20 µm length) were shown to be highly inflammogenic following direct exposure of the peritoneal mesothelium in mice by IP injection and caused granulomas to form rapidly on the diaphragm whereas short CNT (< 5 µm) did not provoke similar effects (RO14).
Dermal toxicity – Exposure of human keratinocytes to SWCNT caused oxidative stress and cellular toxicity, as well as ultra-structural and morphological changes in cultured skin cells (RO15).
Environmental toxicity – currently under investigation for ecotoxicological effects (RO19), but the PEC/PNEC ratio has been calculated to be below 1 and is therefore of lesser concern than other nanoparticles (RO17). C_{60} nanoparticles have been shown to be more toxic than CNTs (RO18).

Iron oxide (Fe_xO_x)
Use and exposure - Used in significant quantities in industry (RO05). Used in industry and academia within the UK (RO05).
Mechanisms of toxicity – currently under investigation for cellular toxicity (RO12).
Inhalation toxicity – no information supplied in the RO.
Dermal toxicity – no information supplied in the RO.
Environmental toxicity – currently under investigation for ecotoxicological effects (RO19).

Cerium oxide (CeO_2)
Use and exposure – Identified use as a diesel fuel additive, hence provides the possibility of widespread environmental exposure. However, modelling of exposure indicates very low levels (RO5, **UK074**).
Mechanisms of toxicity – no information supplied in the RO.
Inhalation toxicity – no information supplied in the RO.
Dermal toxicity – no information supplied in the RO.
Environmental toxicity – CeO_2 has been shown to have a reduced toxic effect on aquatic invertebrates when compared with bulk particles and with other nanoparticles (RO18). Further work is currently taking place in the area of ecotoxicology (RO19).

Zinc oxide (ZnO)
Use and exposure - Used in significant quantities in industry (RO05). Used in industry and academia within the UK (RO05).
Mechanisms of toxicity – currently under investigation for cellular toxicity (RO12).
Inhalation toxicity – no information supplied in the RO.
Dermal toxicity – no information supplied in the RO.
Environmental toxicity – currently under investigation for ecotoxicological effects (RO19).

Carbon black (CB)
Use and exposure – Extensively used in the rubber (tyre and rubber-goods) and printing industries, Flammable (RO05).
Mechanisms of toxicity – CB has been shown to provoke oxidative stress-mediated inflammatory responses in macrophages (RO13), and has been demonstrated to cause oxidative stress, as well as activated NF-κB and AP-1 resulting in cytokine gene expression (RO13).
Inhalation toxicity – no information supplied in the RO but we are aware of a wealth of previously published investigations.
Dermal toxicity – no information supplied in the RO.
Environmental toxicity – no information supplied in the RO.

Gold nanoparticles (Au)
Use and exposure – Reference gold nanoparticles (10, 30 and 60 nm in diameter) are being developed for use in experimental tests (RO03).
Mechanisms of toxicity – no information supplied in the RO.
Inhalation toxicity – Gold nanoparticles were found to persist in blood to a greater extent if they were smaller and uncharged (RO14). PEG-coated gold nanoparticles were shown to be present in the brain after installation in the nose, and that smaller particles were more likely to accumulate in the brain, but when installed into the lungs a very small amount showed up in the brain, suggesting that the blood brain barrier prevents movement into the brain from the blood (RO14). RSA-coated gold nanoparticles were taken up in the liver, spleen and bone marrow of rats after injection but PEG-coating enhanced the retention of the nanoparticles in the blood compartment decreasing the amount in the liver (RO14).
Dermal toxicity – no information supplied in the RO.
Environmental toxicity – no information supplied in the RO.

Silver nanoparticles (Ag)
Use and exposure - Used in significant quantities in industry (RO05). Thermal rebound was shown not to occur with filtration devices (RO08).
Mechanisms of toxicity – no information supplied in the RO.
Inhalation toxicity – Penetration of HEPA filters by silver nanoparticles differed significantly (4 – 30 nm diameter, no indication whether a greater or fewer number of particles penetrated the filter) when compared to normal test compound (NaCl) suggesting that the aerosol behaviour differs for different nanoparticles (RO08).
Dermal toxicity – no information supplied in the RO.
Environmental toxicity – The PEC/PNEC ratio was less than 1 (RO17) but silver nanoparticles (no size stated) were shown to have harmful effects on aquatic invertebrates at low concentrations (RO17).

Silica nanoparticles (SiO_2)
Use and exposure - Used in significant quantities in industry (RO05). Reference SiO_2 nanoparticles are currently being manufactured for use in calibrating particle size analysers (40 nm in aqueous solution) (RO03).
Mechanisms of toxicity – currently under investigation for cellular toxicity (RO12).
Inhalation toxicity – whilst mentioned as being studied for inhalation toxicity, no further information was provided (RO14). We are aware that previous studies are available.
Dermal toxicity – no information supplied in the RO.
Environmental toxicity – no information supplied in the RO.

Aluminium oxide (AlO_x)
Use and exposure - Used in significant quantities in industry (RO05). Alumina nanoparticles are passivated by the introduction of a naturally occurring oxide layer (RO04).
Mechanisms of toxicity – currently under investigation for cellular toxicity (RO12). Alumina nanoparticles that had no oxidative stress-related activity have been shown to be inflammogenic suggesting another method of toxicity (RO13).
Inhalation toxicity – whilst mentioned as being studied for inhalation toxicity, no further information was provided (RO14).
Dermal toxicity – no information supplied in the RO.
Environmental toxicity – no information supplied in the RO.

Nickel (Ni)
Use and exposure – no information supplied in the RO.
Mechanisms of toxicity – no information supplied in the RO.

Inhalation toxicity - Inhaled nickel nanoparticles were shown to induce acute and chronic pulmonary inflammation and systemic inflammation with long term exposure resulting in accelerated and exacerbated atherosclerosis (RO14).
Dermal toxicity – no information supplied in the RO.
Environmental toxicity – no information supplied in the RO.

Nanoclays
Use and exposure – Ongoing studies into the dustiness of nanoclays (RO05). Physical handling has been shown to increase the release of nanoclays but is reduced with low pressure compaction (RO07). Present in food packaging as complexes with polymers (RO05).
Mechanisms of toxicity – no information supplied in the RO.
Inhalation toxicity – no information supplied in the RO.
Dermal toxicity – no information supplied in the RO.
Environmental toxicity – no information supplied in the RO.

7.4 CONSIDERATION OF THE APPLICATION OF THE PRECAUTIONARY PRINCIPLE

Titanium dioxide
Titanium dioxide nanoparticles are used in significant amounts (greater than 1000 kg/company/year). They are potentially inflammatory, and have been shown to induce oxidative stress in cell culture which is mediated by the generation of free radicals. They have the potential to be environmentally detrimental as their estimated environmental concentration has been calculated to be greater than their no effect concentration, however the nanoparticle size and type was not further defined, the toxic effect not stated, and the data were based on a modelling study. This must be further investigated and steps taken to ensure the environmental safety of titanium dioxide nanoparticles. The ROs have not identified a sufficient body of evidence to make a risk assessment feasible for this nanomaterial, however there is some evidence to suggest that titanium dioxide nanoparticles may be present in the environment at concentrations greater than the predicted no effect concentration.

Iron oxide
Whilst produced in significant amounts, there was no evidence presented in the ROs to suggest that iron oxide nanoparticles are detrimental or beneficial to human health or the environment, therefore a risk assessment was not possible.

Quantum dots
Quantum dots have been shown to cause platelet aggregation, however there is no information on other toxicological properties. Quantum dots do not readily aggregate in drinking water. Limited exposure as experimental use and normally held in solution or a solid matrix. Quantum dots are a general name given to a range of compounds (including cadmium telluride and cadmium selenide) therefore it will be necessary to consider each chemical compound separately. The ROs have not identified a sufficient body of evidence to make a risk assessment feasible for this group of nanomaterials.

Cerium oxide
Although suggested to have relatively low aquatic invertebrate toxicity, the ecotoxicological properties of cerium oxide nanoparticles is currently under investigation. Data suggests that CeO_2 nanoparticles are not cytotoxic *in vitro* (human hepatic cell line), however this may be cell specific and will require further investigation. However, the ROs have not identified a sufficient body of evidence to make a risk assessment feasible for this nanomaterial.

Zinc oxide
Whilst produced in significant amounts, there is no evidence to suggest that zinc oxide nanoparticles are detrimental or beneficial to human health; or the environment. However, the toxicological effects and ecotoxicological effects of zinc oxide nanoparticles are currently being investigated and the ROs have not identified a sufficient body of evidence to make a risk assessment feasible for this nanomaterial.

Carbon black
Carbon black particles are flammable and have been shown to produce oxidative stress mediated inflammatory responses in cell culture. The ROs have not identified a sufficient body of evidence to make a risk assessment feasible for this nanomaterial.

Carbon black consists of near-spherical colloidal primary particles which exist outside the production chamber as aggregates consisting of a number of fused primary particles. These aggregates may consist of a few or hundreds of particles, or the particles can be bound together by van der Waals forces in more loosely associated agglomerates (IARC; 1996). The average primary particle diameters in several commercially produced carbon blacks range from 10 to 500 nm, while the average aggregate diameters range from 80 to 810 nm (DFG, 1999, IARC, 1996). The particles are likely to be contaminated by chemicals including polycyclic aromatic hydrocarbons (PAHs), elemental sulphur (DFG, 1999; IARC, 1996; McCunney *et al*., 2001). Industrial exposure to carbon black particles has been shown to vary with occupation. Carbon black has been thoroughly reviewed by the International Agency for Research on Cancer (IARC, 1996) who concluded that there was "*inadequate evidence in humans for the carcinogenicity of carbon black*…*sufficient evidence in experimental animals for the carcinogenicity of carbon black* [and its extracts]". It has been classified as "*possibility carcinogenic to humans (Group 2B*)". The risk associated with carbon black particles has previously been characterised.

Nickel
Inhaled nickel nanoparticles have been shown to cause pulmonary inflammation (acute exposure) and systemic inflammation (chronic exposure) which resulted in atherosclerosis in mice models. However, the ROs have not identified a sufficient body of evidence to make a risk assessment feasible for this nanomaterial.

Silicon oxide
Whilst produced in significant quantities, there is no evidence to suggest that amorphous silica nanoparticles are detrimental or beneficial to human health or the environment. Ongoing studies are considering their toxicological behaviour. The ROs have not identified a sufficient body of evidence to make a risk assessment feasible for this nanomaterial.

The inhalation of crystalline silica causes irritation and inflammation in the lungs, with chronic exposure causing the condition silicosis, characterised by unique histological nodules and fibrotic scarring of the lung (Green and Vallvathan, 1996). Animal studies have provided lowest observed adverse effect levels (LOAEL) ranging from 1.0 mg/m^3 (24 month study) to 2 mg/m^3 (6 month study) but it is noted that inhaled silica is much more toxic to humans than rodents (the reported human LOAEL is 0.02 to 0.05 mg/m^3) with the main mechanism of damage being cytokine release and apoptosis produced as a result of receptor-mediated signalling (Hamilton *et al*., 2008). The risk associated with silica particles has previously been characterised.

Aluminium oxide
Whilst produced in significant quantities, there is no evidence to suggest that aluminium oxide nanoparticles are detrimental or beneficial to human health or the environment. However they have been shown to be inflammogenic in cell culture but did not cause oxidative stress. The ROs have not identified a sufficient body of evidence to make a risk assessment feasible for this nanomaterial.

Carbon nanotubes
Carbon nanotubes are increasingly used in industry and research. It has been shown that PPE is effective if used correctly (gloves need to be doubled up). Whilst the cellular toxicity of carbon nanotubes is currently under investigation, they have been shown to cause mitochondrial DNA damage, oxidative stress to the aorta and to be cytotoxic in muscles at high mass concentrations. After installation into the lungs, they have been shown to be pro-fibrotic with some similar effects to asbestos fibres. The inflammatory response has been shown to be *via* iron-mediated free radical generation. CNT have also been shown to cause oxidative stress in keratinocytes and cultured skin cells. The ecotoxicological effect of CNTs is currently under investigation.

The potential of CNTs to cause oxidative stress and cytotoxicity in cell culture, along with the pro-fibrotic response after installation of CNTs into the lungs suggests that caution should be used when handling CNTs. There is currently no indication as to whether CNTs can be released from matrices in products in which they are currently found. Whilst the ROs have not identified a sufficient body of evidence to make a risk assessment feasible for this nanomaterial, there is sufficient evidence to suggest that CNT may be harmful to human health and therefore the use of the precautionary principle should be considered in this case. As noted, we are aware that the UK HSE is in the process of developing specific guidelines for the control of exposure to CNTs.

Nanoclays
Whilst produced and used in food packaging, there is no evidence to suggest that nanoclays are detrimental or beneficial to human health or the environment. The ROs have not identified a sufficient body of evidence to make a risk assessment feasible for this nanomaterial.

Silver
The RO reports present indicative evidence of the harm of silver nanoparticles at low concentrations on aquatic invertebrates, which suggest that the environmental release

of silver nanoparticles will be detrimental for the environment and that any industry/institute using silver nanoparticles should consider taking the necessary steps to reduce or eliminate the potential exposure of the environment to these nanoparticles. The ROs have not identified a sufficient body of evidence to make a risk assessment feasible for this nanomaterial; however there is sufficient evidence to suggest that silver nanoparticles may be harmful to the environment and therefore the use of the precautionary principle should be considered in this case.

Gold
Gold nanoparticles will translocate into the brain after installation in the nose, but this does not occur if the particles are installed into the lungs. As small particles are more likely to travel further into the respiratory system before being removed, it is likely that the exposure to humans will be through the lungs. After injection, coated gold nanoparticles were found in the liver, spleen and bone marrow of rats, although a different coating enhanced the retention of the nanoparticles in the blood compartment. Whilst this suggests that gold nanoparticles translocate within the body, there is no suggestion of toxicity in mammals or in the environment. The ROs have not identified a sufficient body of evidence to make a risk assessment feasible for this nanomaterial.

7.5 SUMMARY

This report draws upon the data identified from the previous activities. Whilst the authors acknowledge that other published studies are available for a number of these NP described above, these do not fall under the remit of this project and have not been considered in the opinions stated above. The authors are aware that some background data has not been included in the RO reports (including reports of ecotoxicological effects of silver and toxicological effects of carbon black nanoparticles). However, the ROs have not identified a sufficient body of evidence to make a risk assessment feasible for any of the NPs described.

The precautionary principle requires that there is a preliminary scientific evaluation showing reasonable grounds for concern that the nanomaterial might lead to damaging effects on the environment, or on human, animal or plant health. For the majority of the identified nanomaterials, the body of evidence identified was not sufficient to suggest that the nanomaterials will cause harm and therefore the precautionary principle should not be considered in these cases. However, three different nanomaterials have been identified that give rise to sufficient concern from the results presented within the RO reports. There is evidence that carbon nanotubes may have an adverse effect on human health; and that silver nanoparticles and titanium dioxide nanoparticles are detrimental to the environment. In these specific cases further investigation as to the need to invoke the precautionary principle is required, taking into consideration all available data.

Further information may be available in the wider literature that was not considered as part of this project. The authors acknowledge that the presented emerging data on nanomaterials described within this project suggest that there is uncertainty, particularly surrounding the ecotoxicological effects of nanomaterials, and that further data should be collected in this area. Whilst certain areas of investigation are extensively covered, for example the pulmonary effects of nanoparticles, other areas require more attention, including the environmental fate of nanomaterials in water and the dermal or ingestion absorption of nanomaterials.

In conclusion, whilst the precautionary principle can be applied to selected nanomaterials as a result of the data investigated within this project, there is an

identified need for further information (which may already be present within the wider literature). Therefore the data presented here must indicate caution over the use of nanomaterials and, if considered alongside the wider literature, there may still be a case for the application of the precautionary principle to certain manufactured nanomaterials.

8 DISCUSSION

8.1 LIMITATIONS OF THE STUDY

The remit undertaken in the EMERGNANO study was an extremely challenging one. It was to identify (recently completed and current) research activities on a worldwide basis, assess the quality and relevance of that activity, to map that against the 18 research objectives published by Defra, and to consider whether, within that emerging data, there was sufficient evidence to justify implementation of the precautionary principle. The plan was to complete the study within a timescale of six months. The constraints of the project, in relation to the timescale for delivery, the resources available and that the focus was on active, rather that published work means that that we cannot be certain to have captured all of these studies, or that we have captured all of the information available on these studies. Nevertheless, the authors consider that EMERGNANO has been successful in identifying and appraising the overwhelming majority of the current work worldwide.

In preparing a proposal to address the remit of this project, we considered, but ultimately rejected, a conventional literature review to identify relevant studies. It was considered likely that many studies ongoing would not yet have information in the literature and so would not be identified by this route. In addition, for those studies which were identifiable, it was not always possible to relate this back to the funding source. Given that an objective here was to evaluate the usefulness and contribution of these planned strategic investments in research, this would not be optimal. Finally the volume of studies now appearing in the literature, particularly in relation to toxicology issues, meant that a review which attempted to cover all dimensions of the risk issue simply could not be done within the allocated timescale or resources. One consequence of this strategy is that important contributions or papers arising from studies which were not funded at a national or strategic level, such as a single PhD study at a university, would not be identified in this approach. For this reason, it was requested that individual reviewers used their own knowledge of the particular area to identify significant and important pieces of work which were otherwise not picked up by our search strategy.

The first limitation concerns study identification. We were fortunate in undertaking this study that we had access to the existing database of research activities held by the Woodrow Wilson Project on Emerging Nanotechnologies. Indeed without access to this database, it is doubtful if the study could have been completed at all. However, the Wilson Center database is a comprehensive, but not exhaustive, catalogue of international nanotechnology risk-related research and, while it provided an essential starting point for this project, it left gaps in the knowledge-base that required further exploration. Our strategy to add to this list was: i) to identify other reviews of existing projects, such as that produced by the European Commission (EC, 2008); ii) identification of resources held on “national” websites or major research programmes in nanotechnology which we were aware of or which were identified through web based searching strategies; and iii) by direct communication with our extensive network of contacts and collaborators. Where possible this was followed up by direct contact with identified persons with responsibilities for the programmes which we found. Whilst this approach could not guarantee identification of all studies, and we cannot exclude that important studies have been missed, we consider that the studies identified represent the overwhelming majority of active or recently active studies which have been funded at a national or strategic level. We consider that the study list identified represents the most comprehensive list available at this point in time.

Having identified the studies, it was necessary to gather together the output from these studies, both published and unpublished. Again, a multiple strategy was adopted here which involved searching for publicly available resources relating to the study and contacting the identified study leader directly by email. Direct contact with study leaders was chosen in preference to going through national contact points since it was considered that this approach would lead to a greater response rate. In practice the response from study leaders was variable. Less than half of those contacted were willing or able to provide additional information. Given the intensity of activity in this area and the demands on researchers, this is perhaps not surprising. However this must also be considered a limitation to the study. Incomplete information about a specific study limits the extent to which the quality and relevance of the study can be assessed.

Finally, the studies identified differed widely in terms of their relevance, quality and state of completion. To try to assess in a coherent way, a quantitative weight of evidence (WoE) approach was developed and applied in an attempt to introduce more rigor into the review process. In retrospect, we consider this approach to have been necessary but ambitious. Whilst all of the reviewers were involved in the development of approach, feedback from the reviewers was mixed in relation to its viability and overall usefulness. A longer study would have provided the opportunity for this approach to be further developed, evaluated and finally validated before being used throughout such an important study. In practice the evaluation step was truncated and was limited to only two of the reviewers. Overall, the applicability of the approach was compromised by the lack of information available for many of the studies. In some cases reviewers had little more than a study title to go on in completing their evaluation. In these cases the quality of the review cannot be as strong as in situations where more complete information is available. Nevertheless, we consider that the quantitative WoE approach was entirely necessary in order to impose some structure to this review process. As such, we would consider that any future review on this scale should use a weight of evidence approach. What we have provided is a basis on which a more robust approach could be developed.

8.2 QUANTITATIVE OUTPUTS

The quantitative outputs reported earlier may be considered in two parts. Firstly, based on the data gathered, an evaluation has been made regarding the distribution, in terms of both numbers of studies and total value of studies, on issues including:

- Distribution by Task Force Area of work (metrology, exposures, human health and environmental hazard);
- Distribution by relevant RO;
- Distribution by geographic area.

The data on study numbers is more robust then the data on value of the studies. For many studies no information of funding was obtained. For other studies it was not possible to validate whether figures already held were accurate. Finally, we attempted to convert all of the funding to a single currency, so as to facilitate comparison. However, this activity has coincided with unprecedented fluctuations in the world currency markets, with widespread changes on a day to day basis. For this reason, any comparisons based on value of research must be considered indicative only.

There are clear discrepancies between the number of studies (and value) in each of the Task Force Areas. Most of the studies are in the Human Health area (171), followed by exposures (107), environment (77) and characterisation (40).

Given the importance of minimising exposure, particularly of recognising that there are many uncertainties in hazard assessment, this difference is striking. There may be several reasons for this. One is that, at elementary level, the question "how toxic is this material?" is asked much more frequently and apparently with more concern than "which people are exposed to this material?". Second is that broadly toxicity is an intrinsic property of the material whereas exposure is entirely dependant on the scenario i.e. conditions of use and process. The intrinsic nature of toxicity is however somewhat illusory. There are many ways to answer the question of toxicity and an appropriate response to the toxicity question relates to what is the route of exposure, what is the nature of the material to which people are exposed, to which organ is toxicity being investigated, what is the health end point. So, there are many sub-questions to the toxicity question. Thirdly, toxicity questions may be addressed (albeit not completely) with relatively limited resources i.e. these can be carried out in a laboratory, often with staff at a PhD level. In contrast, exposure studies typically need some kind of field work, and access to production or use facilities where nanomaterials are being used. The above are not intended as a complete analysis of the situation, clearly, but are rather suggestions as to why this imbalance may occur.

It is also useful to comment on the relative weight given to the balance between Human Health and Environment. There are some clear regional variations. On a world-wide basis, toxicology studies largely outweigh eco-toxicology studies, by more than two to one. In the UK, however, there seems to be an almost even balance between the number of toxicology studies and the number of eco-toxicology studies. For example, to the best of our knowledge, in the EU framework project there are no ecotoxicological studies funded up to this point in time. It is not clear why this should be, although certainly the emphasis on eco-toxicology within the RO's must be considered to be a factor.

The difference between the numbers of studies in each RO is even more striking with wide disparities even within a Task Force Area Force; for example, in the Metrology TFA, RO02 had 28 identified studies, whereas RO09 had only 1. These disparities may not be problematic and indeed may be appropriate.

8.3 RESEARCH OBJECTIVES - PROGRESS AND GAPS

Progress and gaps are described in detail in Chapter 4 and are summarised for each RO in Chapter 5. These are critical outputs for EMERGNANO and the detail provided there will not be replicated here. Instead the reader is directed to these key sections of the report. In this section, we will discuss the wider, more general issues which we have drawn from our examination of these studies and the information which has been available to us.

For a large number of studies there was almost no information available within the public domain. It would be inappropriate to point to the specific studies for which this was the case but, even for some studies which had apparently completed, it was not possible to find information in the public domain, nor was it possible to get any further information from the project leader. Clearly, for this worldwide effort into understanding the potential risks associated with nanomaterials, it is critical that studies which have been carried out are published, preferably within the peer reviewed literature. A study with no publicly available outputs makes no real contribution to wider public knowledge. We accept that in making this statement some of the studies do in fact have published work which we have been unable to identify trough our search strategy. Funding

organisations should promote and foster publication of the work which they fund and should require (and resource) adequate dissemination of the research outputs.

A second issue relates to what could be described as unrealistic aims of many of the studies which have been funded. Examination of some of these studies has identified very ambitious objectives but with clearly inadequate resources allocated by which these objectives can be addressed. This issue needs to be considered both by researchers, who should be realistic in what they claim to be able to achieve within a programme of work, and by programme funders, who should not expect answers to all questions within modest resources. To some extent this may be due to the emerging nature of the field. It appears that the funding of more recent studies is more proportionate to the promised deliverables.

It was noted that there was substantial overlap between many of the ROs. In the Metrology area, there are four quite distinct ROs, but some overlap with ROs in other areas. RO02, in particular the "associated methods for measurement and characterisation of NP" overlaps substantially with RO06 and RO07. Within the Exposures, ROs 5, 6, and 7 are highly related and contain many of the same studies. For the Human Health TFA, there is substantial overlap between ROs 10, 11, 12, 14. This may be quite appropriate from a scientific perspective but actually made the analysis quite challenging, both in study allocation and in the review activity where individual studies had to be reassessed several times (or assessed by different assessors) from (slightly) different perspectives.

In TFA1, "Metrology, characterisation, standardisation and reference materials", the reviewers found that none of the studies could be said to be conclusive in providing new approaches or guidelines to characterising and measuring nanomaterials. Nor was the selection and/or development of exposure metric or metrics addressed well. Studies were focussed on addressing mainly the relevance and practicality of using surface area, which, whilst important, is unlikely to be relevant for all NP. Progress has been made in identifying candidate materials which may be used to develop characterised reference nanoparticles for toxicology. Candidate lists, along with minimum characterisation specifications have been developed and some commercial reference materials are beginning to emerge, but there is little evidence that issues such as storage, distribution and protocols for use are being addressed. Only two studies were identified as addressing potential risk of explosion of NP and only one study was identified as addressing the issue of measurement of exposure to nanoparticles in soil and water. Overall, the specific objectives within this RO appear to have been very sparsely addressed.

In TFA2, "Exposures, sources, pathways and technologies", some work has been done on establishing inventories of nanoparticle use and application, and on trying to map out some of the potential exposure pathways. However, there are many complex exposure pathways and only a very few have been considered. Little is known about nanoparticles in relation to consumer exposure and work in relation to nanoparticles in food seems to be entirely missing. Use of a life cycle assessment approach is missing. Little progress has yet been made in relation to development of measurement technologies for nanoparticles in air. Although there is some evidence that ongoing studies may produce some devices, such as personal samplers, and approaches for some types of nanoparticles, major questions remain. These include discrimination between NP and the background particles, and the evaluation of whether fibre counting methods can be applied to high aspect ratio nanoparticles. It now seems clear that filtration systems will be effective against nanoparticles and several studies have found improving collecting efficiency as particle size decreases. Studies have not, thus far, specifically addressed the performance of engineering controls as they are

implemented in practical settings. Issues of leakage round filtration systems and the effectiveness of skin protective equipment are also under-researched.

In TFA3, "Human health hazard and risk assessment", there is an absence of studies aiming to describe the accumulation of particles in a variety of organs after inhalation. There are no specific studies on whether carbon nanotubes and other high aspect ratio nanoparticles behave like asbestos in terms or translocation to the pleural mesothelium. In general, there is no attempt to try to identify potential structure activity relationships that govern penetration at any of the important boundaries. Many studies are addressing the issue of oxidative stress – inflammation. Several studies are also attempting to address structural activity relationships in relation to this but, as yet, little progress has been made. There are few *in vivo* studies being carried out, making a comparison between *in vitro* and *in vivo* data problematic. Genotoxicity is only being addressed in a few studies. Few studies are exposing nanoparticles at or near plausible exposure levels and also few studies addressing genotoxicity. Dermal uptake is not being addressed to any great extent and, as yet, toxicological testing strategies have not evolved to any level of agreement.

In TFA4, "Environmental hazard and risk assessment", studies have improved the understanding of kinetics of nanoparticle uptake in invertebrate and vertebrate models and have related this to toxicity. In addition, there are now a few studies focussing on microbial organisms and these provide information on effect assessment at individual level but also at community level. However, studies only cover a limited range of species and material types. There is some effort to relate study design and interpretation to human toxicology of nanoparticles, but there is much more to be done. Only one project is addressing bioaccumulation and bio-concentration of nanoparticles.

We have identified a very large body of work which is either completed or already underway. It is clear from the reviewers' synthesis reports that at present, based on the evidence we have been able to collect regarding these studies, progress has been disappointing. Whilst many studies are undoubtedly contributing in an incremental way to the advancement of knowledge, few of the key questions have been resolved.

8.4 STUDIES AND ISSUES WHICH ARE EXTERNAL TO THE RESEARCH OBJECTIVES

Although they are broad in their scope, ROs do not describe complete coverage of the important issues and questions relevant to the health, safety and environmental risks arising from exposure to nanoparticles. In reviewing the studies underway, more than 50 studies were identified which were relevant to these issues but did not fit within the scope of any of the ROs. These included:

- Enabling activities
- Life cycle analysis
- Effectiveness of risk assessment approaches

These studies were not formally reviewed according to the WoE appraisal as it was not possible to identify appropriate generic criteria by which they could be assessed.

An important category is the enabling activities. A total of 19 of these have been identified. These activities, which include observatories, networking activities and capability building, have played an important role in not only aiding realisation of the benefits nanotechnologies can offer *via* its many applications, but also in bringing together scientists to share understanding of the effects of nanomaterials and NP on

human health and the environment, maintaining public engagement and raising awareness of the need to develop nanotechnologies in a responsible manner in order to ensure its future.

Two studies have been identified which are focussing on life cycle approaches. However, neither has yet provided a significant contribution.

Two studies have been identified which are focussing on development and evaluation of risk assessment approaches. Again, at this point, neither has yet provided a significant contribution.

In addition, there are a number of potentially important topics which currently do not seem to be being investigated to any extent. Three are highlighted below.

The first is development of improved, evidence based, guidance on the control of exposure. While there is generic guidance available, specific evidence-based guidance for control of NP is absent. While some of the studies identified will undoubtedly contribute to this, none of the studies identified have it as a specific objective. Study types which would be helpful here would include studies to investigate the effectiveness of exposure control management approaches, such as control banding, and studies to develop and evaluate exposure models.

A second largely un-researched area is ingestion as a route of exposure. It is widely reported that nanoparticles are available as food supplements (nanosilver is perhaps the best known example) and that other nanoparticles are incorporated into food. Information about which nanoparticles and in what quantities is not available. Nor have we been able to identify any research which is considering the possibility that ingested nanoparticles are able to cross the gut wall, although this has been widely speculated.

Finally, we have been unable to identify studies which are integrating the synthesis of new materials or the development of new products directly with risk assessment of the materials or processes in any meaningful way. Even though at this stage, a great deal of work needs to be done to validate the risk assessment processes for nanoparticles, it would not be premature to begin to incorporate them into development projects.

8.5 RISK ASSESSMENT AND THE PRECAUTIONARY PRINCIPLE

In this study, we were asked to consider whether there is sufficient information to provide a risk assessment for identified nanomaterials or, if not possible, whether there is sufficient information identified to invoke the precautionary principle for one or more of the identified nanomaterials using the information collected during this report.

We therefore considered the information and data generated from the RO assessment activities to form an opinion as to whether there is sufficient information to identify and quantify risks to human health and/or the environment from manufactured nanomaterials that may lead to a requirement for implementation of the precautionary principle. The report is therefore limited by the data collected and presented in the RO reports.

The framework followed was consistent with the Communication on the use of the Precautionary Principle providing a general framework for its use in EU policy, and to avoid unwarranted adoption of the precautionary principle as a disguised form of caution (Commission of the European Communities, 2000). Namely, if a preliminary scientific evaluation shows that there are reasonable grounds for concern that a

particular activity might lead to damaging effects on the environment, or on human, animal or plant health, which would be inconsistent with the protection normally afforded to these within the European Community, the Precautionary Principle is triggered.

Information relevant to the following materials was collated and assessed:

- Titanium dioxide (TiO_2) particles
- Quantum dots
- Carbon nanotubes (CNT) including single walled CNT (SWCNT) multiwalled CNT (MWCNT) – long and short NT
- Iron oxide (Fe_xO_x)
- Cerium oxide (CeO_2)
- Zinc oxide (ZnO)
- Carbon black (CB)
- Gold nanoparticles (Au)
- Silver nanoparticles (Ag)
- Silica nanoparticles (SiO_2)
- Aluminium oxide (AlO_x)
- Nickel (Ni)
- Nanoclays

This list is broadly comparable to the list of substances identified by OECD as their list of representative nanomaterials. Materials on the OECD list not assessed (as there was no specific evidence) were Fullerenes (C60), Polystyrene and Dendrimers

The authors are aware that a proportion of background data has not been included in the RO reports (including, for example, reports of ecotoxicological effects of silver and toxicological effects of carbon black nanoparticles). Identified information on nanomaterial exposure was limited. However, based on the information presented we have not identified a sufficient body of evidence in any case to make a risk assessment feasible for these nanomaterials.

The precautionary principle requires that there is a preliminary scientific evaluation showing reasonable grounds for concern that the nanomaterial might lead to damaging effects on the environment, or on human, animal or plant health. For the majority of the identified nanomaterials, the body of evidence identified was not sufficient to suggest that the nanomaterials will cause harm and therefore the precautionary principle should not be considered in these cases. However, three different nanomaterials have been identified that give rise to sufficient concern from the results presented within the RO reports. There is evidence that carbon nanotubes may have an adverse effect on human health; and that silver nanoparticles and titanium dioxide nanoparticles are detrimental to the environment and, in these specific cases, further investigation as to the need to invoke the precautionary principle is required, taking into consideration all available data.

8.6 LESSONS FOR FUTURE

The EMERGNANO project provides many lessons for the future at both national and international level. In a general sense, funding should be more strategically developed and more focussed on the specific aspects and gaps which have been identified in this and other projects. From a UK perspective it is clear that not all of the gaps can possibly be covered given the likely limitations to funding. However, for the 18 ROs which have been considered, little progress has been made. The implication for this is

that future funding should be much more targeted, much more focussed and much more strategic if the UK wishes to achieve these stated research objectives.

Given the difficulties noted, it would be appropriate to provide more focus on work which enables effective risk assessment and management. For example, this could include, for a single class of NP within a group of applications (e.g. metal oxides in sunscreens) work to assess potential exposures throughout the lifecycle (production, use, disposal), the toxicity within the formulations used and evaluation of the risk management arrangements being applied. The current arrangement in which the research objectives are arranged broadly according to research disciplines does not facilitate multi-disciplinary work of this type. Consideration should be given as to whether this represents the best model for assessing and realising future priorities.

The lack of information available in the public domain from many studies is disappointing. Future research should have as a requirement the need to publish the work, preferably in a peer-reviewed form and to have a commitment (and resource provided) to share the outcome of that work with the wider research community. This could include, for example, active participation in review activities such as EMERGNANO. There is also a requirement for both researchers and funding organisations to be more realistic in the scope of projects relative to the resources and timescale requested. Work in this area is resource intensive and should be recognised and funded as such.

Greater emphasis should also be placed on work which is integrated with existing studies and expertise. The reviews suggest that single stand-alone studies until now do not seem to have contributed significantly to the knowledge base in this area.

All of this implies a much more strategic joined-up funding approach. It is clear that within the UK the multiple routes to funding have yet to deliver this strategic level approach. The same is also true internationally.

The EMERGNANO project has provided a clear benchmark against which progress may be judged both nationally and internationally. This is highly relevant to future UK activity in this area and towards setting and assessing performance against future priorities.

This project has collected and synthesised a wealth of information, and provides a unique snapshot of worldwide research activity. It is recommended that at some future point (12-18 months) the exercise is repeated to determine how much progress has been made.

In the meantime there are a number of activities which we consider would be relevant, but lie outwith the scope of the current project. These include:

- further development of the database which underlies the EMERGNANO, to enhance the quality of data within and to make the database itself more robust and to some extent, more public;
- to publish the report in the form of a peer-reviewed paper, recognising that the challenge of condensing such a wealth of information into such a format is substantial;
- further, more detailed, analysis of the quantitative data collected specifically in relation to national trends, delivery dates and the work currently underway.

9 CONCLUSIONS

EMERGNANO has been a challenging piece of work. Broadly it has been an attempt to identify and evaluate worldwide activity in nanotechnology risk research, specifically those programmes which have been funded at a national or strategic level.

The timescale and resource issues in particular, placed certain constraints on how the work could be carried out, and how robust the outcomes of the work are. We consider that what has been achieved has been close to the specified remit, but cannot exclude that some important studies have been overlooked. However, with this caveat, we feel able to draw conclusions regarding the nature of the work, its relevance and remaining gaps.

Since 2004, there has been an enormous undertaking of activity in this area. Work has been funded by both national government activity and in research programmes within each country and at an international level. We identified 158 studies which had been completed in this period or were about to complete within the next few months, and 119 studies which were scheduled for completion in 2009 and beyond.

We found a widespread imbalance in the work being carried out (in terms of numbers of studies) between the four main thematic areas and between the eighteen research objectives. The largest number of studies were in the Human Health area, followed by the Exposures area. Numbers in both the Environment and Characterisation areas were substantially lower. The distribution by RO was even more striking. RO14 had 44 studies identified as relevant, whereas RO9 had only one study.

There are large regional variations in the type of study funded in different countries or economic areas, perhaps reflecting different national priorities or capabilities.

A disappointing aspect was that we were unable to identify significant output from many of the studies involved in the programme, including studies which had already been completed. We accept, in relation to this, that we have not captured all of the information available on these studies and it is quite likely that there is some information that we have not been able to identify by the various routes through which we attempted to do so.

Our assessment of the available research outputs in the context of the NRCG research objectives, has revealed that some important contributions have been made. These include:

- In terms of characterisation and reference materials, progress has been made in identifying candidate materials which may be used to develop characterised reference nanoparticles for toxicology. Candidate lists, along with minimum characterisation specifications, have been developed and some commercial reference materials are beginning to emerge;
- In terms of exposure assessment and control, it is now clear that filters, such as those used in respiratory protective equipment and in air cleaning systems, are highly effective in removing nanoparticles from the air;
- In toxicology, the lack of mass balance toxicokinetics for any nanoparticle and the patchy nature of the published toxicokinetic data is a severe impediment to identifying extra-pulmonary hazards. This feeds through to problems in utilising plausible doses, for example, in an *in vitro* study with liver cells or blood components. The use of only a very limited number of particle types and sizes makes it impossible to know whether all NP act the same as regards

toxicokinetics, or whether there will be a structure activity relationship that highlights certain sizes and surface chemistries as factors enhancing or limiting potential of any NP to translocate or be toxic, as seems likely;

- In ecotoxicology, studies have improved the understanding of kinetics of nanoparticle uptake in invertebrate and vertebrate models and have related this to toxicity. In addition, there are now a few studies focussing on microbial organisms and these provide information on effect assessment at individual level and also at community level.

In projects which are just starting or have just started, there is some evidence to support the view that the work in these projects will deliver much more in terms of output than the projects which are currently just closing. However, it remains to be seen whether these new projects will in practice deliver their stated objectives. It would be appropriate to review these projects at some future time point, perhaps in 12-18 months.

It is clear nonetheless, that the major gaps in the knowledge base still remain. This was the overall view of the Royal Society report in 2004 (RS/RAEng, 2004), and it remains the view of this review. The major gaps have been identified in Chapter 5 and will not be reproduced in detail here. It is nonetheless the case that, in all of the major thematic areas (characterisation, exposure, toxicology and ecotoxicology), and all of the specific ROs, there is a substantial work remaining to be done. We conclude that the programme of research activity has yet to deliver step changes in the knowledge base on these issues.

In assessing quality and completeness for the purpose of carrying out a risk assessment, we did not identify a sufficient body of evidence in any case to make a risk assessment feasible.

However, from the results presented within the RO reports, three different nanomaterials have been identified that give rise to sufficient concern. There is evidence that carbon nanotubes may have an adverse effect on human health; and that silver nanoparticles and titanium dioxide nanoparticles are detrimental to the environment. In these specific cases, further investigation as to the need to invoke the precautionary principle is required, taking into consideration all available data.

The EMERGNANO project has been a unique attempt to identify and assess worldwide progress in relation to nanotechnology risk issues. On an international basis, we have identified and assessed 673 projects for which there has been a wide disparity in the information available, across four major thematic areas. We have also mapped these projects against the eighteen research objectives set in the UK by the NRGC/DEFRA. This has been achieved over a period of six months. We consider that what has been achieved, has been successful in identifying the overwhelming majority of important studies and having these studies assessed as to their output and relevance by some of the leading researchers currently working in this area. We have, as part of the project, achieved a comprehensive listing of projects and produced detailed comments and assessment on the outputs of those considered to be most relevant. It is our view that EMERGNANO (this report and the accompanying data collected) represents the best available picture of current strategic research. As such, EMERGNANO presents an excellent basis for assessing progress of these and other studies in the future.

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10.2 SELECTED WEB LINKS

SAFENANO: www.safenano.org

ObservatoryNANO: http://www.observatory-nano.eu/

KIRnano: http://www.rivm.nl/rvs/075_nanotechnologie/KIR_nano/

NanoImpactNet: www.nanoimpactnet.eu

HSE Horizon Scanning: http://www.hse.gov.uk/horizons/nanotech.htm

WWICS Project on Emerging Nanotechnologies: http://www.nanotechproject.org/

International Council On Nanotechnology: http://www.icon.rice.edu/index.cfm

OMNT: http://www.omnt.fr/index.php?lang=eng&page=accueil

IMPART: http://www.impart-nanotox.org/impart_summary.html

NANOTOX: http://www.impart-nanotox.org/nanotox_summary.html

NOSH: http://www.hse.gov.uk/horizons/nanotech/consortiumsummary.pdf

ENRHES: http://nmi.jrc.ec.europa.eu/project/ENRHES.htm

APPENDIX 1 - LIST OF STUDIES

Study Key	State Of Progress	Country	Study Title	Funding Source/s	Budget (£)	Assessed under Research Objective/s
BE001	On-Going	Belgium	Risk assessment of nanoparticules on human health using in vitro and in vivo models	FP5/Walloon Region of Belgium	7953818	11,14,15
CA001	Completed	Canada	Interactions between semiconductor nanoparticles and biomembranes and DNA	NSERC	49691	12
CA003	Completed	Canada	Understanding Transport and Association of Nanoparticles in Biological Systems	NSERC	49691	12
CA004	Completed	Canada	Interactions Between Nanoscale Materials and Blood	NSERC	49691	11,14
CA006	Completed	Canada	Mechanisms of cellular interactions of functionalized rosette nanotubes	NSERC	49691	12
CA007	Completed	Canada	Recognition and Physicochemical Characterisation of Nanomaterial-Peptide Interactions	NSERC	49691	12
CA008	Completed	Canada	Dynamics, distribution and photochemistry of quantum dots in blood vessels	NSERC	49691	14
CA009	Completed	Canada	Understanding the light-induced cytotoxicity of quantum dots: a cellular, phototophysical and analytical mechanistic approach	NSERC	49691	12
CA010	Completed	Canada	Fate of nanoparticles in mammalian cells: effect of composition, shape, size and surface charge	NSERC	49691	12
CA011	Completed	Canada	Effect of a nanostructure's size and shape on uptake, degradation, & clearance in primary macrophages	NSERC	49691	12,13
CA012	Completed	Canada	Nanoparticles in Phospholipid Membrane Environments	NSERC	49691	12
CH001	Near Completed	Switzerland	Development of a particle exposure system to investigate the inflammation and toxicity potential of nanoparticles in an epithelial airway barrier model	Doerenkamp-Zbinden Foundation, FFVFF Foundation	28845	13
CH002	On-Going	Switzerland	Protein - carbon nanotubes interaction, uptake and the influence on oxidative stress and inflammation as key factors in nanoparticles - cell interaction		191371	13
CH003	On-Going	Switzerland	Quantitative risk assessment of nanoparticles in the environment: Exposure modelling and ecotoxicological considerations	EMPA	146659	17
CH005	Near Completed	Switzerland	Centre for toxicology and fine dust research. Electron microscope tomography for the study of the distribution of nano-tissue and cells	Schenkung von Dr. Alfred Bretscher	1201741	02
CH006	Near Completed	Switzerland	Nanoinventory: manufactured nanoparticles in Swiss industries and the potential for human exposures	Multiple	144223	05
CH007	Near Completed	Switzerland	Particle-lung interaction: mechanisms and effects on lung cell function	Swiss National Science Foundation	124989	14
CH009	Starting	Switzerland	Ecotoxicology of Nanoparticles: Biota-Nanoparticle-Pollutant Interactions in aqueous systems - Comparison of Black Carbon and Carbon Nanotubes	Swiss National Science Foundation	76696	17,18
CH010	On-Going	Switzerland	How to assess the adequacy of safety measures for manufactured nanoparticles	Financed by the participating institutes		05,08
CH011	On-Going	Switzerland	Use of nanoparticles in industry: safety aspects	Other	86530	05
CH012	On-Going	Switzerland	Solubilisation of carbon nanotubes and fullerenes in natural waters under environmental conditions	Swiss National Science Foundation	68291	10
CH013	Completed	Switzerland	Nanorisk: Safety and Risks of Carbon Nanotubes	CTI (Swiss Innovation Promotion Agency), BAG (Federal Office of Public Health), BAFU (Federal Office for the environment), EMPA (Materials science and technology research institution)	267248	11
CH014	Near Completed	Switzerland	Behaviour of ultrafine Particles in tissue and cells of the lung –Importance for our health	Swiss Federal Office for Environment	28845	14
CH015	Near Completed	Switzerland	Health effects of manufactured nanoparticles_ molecular and cellular biology and toxicology	DFG (SPP 1313)	95446	12,13
CH016	On-Going	Switzerland	Interplay of lung cells and their cellular responses upon exposure to combustion-generated ultrafine particles and manufactured nanoparticles	Swiss National Science Foundation	94470	12,14
CH017	Near Completed	Switzerland	Comparison of the effect of asbestos fibres and Carbon-Nanotubes	Swiss Federal Office for Environment	36055	11
CH019	On-Going	Switzerland	Analysis of nanomaterials exposure on humans in Switzerland – Identification of frequent situations for exposure situations with today's and possible future use of consumer products on the basis of nanomaterials	BAG (Federal Office of Public Health)	86542	05,07
CH020	Completed	Switzerland	NeuroCNTox - Neurotoxicity of Carbon Nanotubes	EMPA (Materials science and technology research institution)	113945	14
CH021	Near Completed	Switzerland	Interaction of ultrafine particles with the internal surface of the lung	Bangerter-Stiftung	72109	14
CH023	On-Going	Switzerland	In vitro reactivity of fine and ultrafine particles	French AFSSET and Institut universitaire romand de	169416	06
CH024	On-Going	Switzerland	Fate of hydrophilic nanoparticles in biological environment	Swiss National Science Foundation	86707	10
CN001	On-Going	CHINA	Health and Safety Impacts of Nanotechnology: Exploring Solutions	Ministry of Science and Technology, China		11

Study Key	State Of Progress	Country	Study Title	Funding Source/s	Budget (£)	Assessed under Research Objective/s
CZ001	On-Going	Czech Republic	Study of transport of inhaled nano-sized particles (Ag, Pb, Cd) and their allocation in organs			05,11
DE001	On-Going	Germany	Identification and assessment of the effects of engineered nanoparticles on human and environmental health	BMBF	874920	16,19
DE003	On-Going	Germany	The TRACER-Project: Toxicological Assessment and Functionalisation of Carbon Nanotubes	BMBF	1272611	05,11,14
DE004	On-Going	Germany	Toxicological assessment and functionalisation of carbon nanotubes	BMBF and industrial project partner	1193073	11
DE005	On-Going	Germany	NANOCARE: Development of Inhalation Toxicity Model for Testing of Nanomaterials	BMBF	4056447	11,13,14
DK001	On-Going	Denmark	NANOPLAST: Nano-technological materials and products in the plastics industry: Exposure assessment and toxicological properties	Danish Working Environment Research Fund	540860	05,07,11
DK002	Near Completed	Denmark	Risk analysis and governance of nanomaterials	Technical University of Denmark	190892	16
DK003	On-Going	Denmark	Biopolymer Nanocomposite Films for use in Food Packaging Applications	Government	839942	05
DK006	On-Going	Denmark	Translocation of Nanoparticles and Ultrafine Particles across Tissue Barriers in Mice.	Danish Ministry of Interior and Health, Research Centre for Environmental Health's Fund, and The Danish Medical Research Council	238615	12
DK007	On-Going	Denmark	Environmental Effects of Engineered Nanoparticles	Technical University of Denmark	190892	17,19
DK008	On-Going	Denmark	NanoKem: Nanoparticles in the paint- and lacquer industry. Exposure and toxic properties.	The Danish Working Environment Research Fund and National Research Centre for the Working Environment (DK)	1069062	05,11,12
DK009	On-Going	Denmark	Cardiovascular and Genotoxic Effects of Nanoparticles	University of Copenhagen (DK) and the Research Centre for Environment and Health (Ministry for Interior and Health)	267248	13,14
DK010	On-Going	Denmark	Engineered Nanoparticles and Development of Airway Allergy	National Research Centre for the Working Environment	198845	13
DK011	On-Going	Denmark	Characterisation and toxicological evaluation of nanoparticles from liquid-based nanofilm products	Nanocover Scandinavia A/S	288452	05,07,11,14
DK012	On-Going	Denmark	SUNANO - Risk assessment of free nanoparticles	The Danish Strategic Research Council, Programme Commission on Nanoscience, Biotechnology and IT (NABIIT)	846286	11,16
DK013	Near Completed	Denmark	Air Pollution in a Life Time Health Perspective	DRA	2665596	02,11
EU003	On-Going	EU	Development of an integrated platform for nanoparticle analysis to verify their possible toxicity and the eco-toxicity	DG Research	2221688	12,16,19
EU004	Near Completed	EU	Nano-particle characterization and toxicity	DG Research	143275	13
EU006	On-Going	EU	Cellnanotox: cellular interaction and toxicology with engineered nanoparticles	DG Research	2067993	02,11,12
EU007	Completed	EU	Quality of skin as a barrier to ultra-fine particles	DG Research	873324	15
EU008	On-Going	EU	Nanointeract: development of a platform and toolkit for understanding interactions between nanoparticles and the living world	DG Research	2624760	12
EU009	On-Going	EU	Nanosafe 2: safe production and use of nanomaterials	DG Research	5567543	02,04,06
EU011	On-Going	EU	Nanosh: inflammatory and genotoxic effects of engineered nanomaterials	DG Research	1908916	05,13
EU012	Completed	EU	Nanotransport: the behaviour of aerosols released to ambient air from nanoparticle manufacturing - a pre-normative study	DG Research	357922	08,16
EU015	Completed	EU	MAAPHRI: Multidisciplinary Approach to Airborne Pollutant Health Related Issues: Modelization with Combustion Engine Exhausts	EU	1307441	11,14
EU017	Completed	EU	NANOSAFE: Risk Assessment in Production and use of Nanoparticles with Development of Preventive Measures and Practice Codes	EU	256739	05,08,
EU019	Starting	EU	NeuroNano	FP7		13,14
EU022	Starting	EU	The reactivity and toxicity of engineered nanoparticles: Risks to the environment and human health	FP7		10,11,12,13, 14,16,17,18, 19
EU023	Starting	EU	Comprehensive assessment of hazardous effects of engineered nanomaterials on the immune system	FP7		02,11,12,13, 14,16
EU024	Starting	EU	Nanodevice: Novel concepts, methods and technologies for the production of portable, easy to use devices for the measurement and analysis of airborne engineered nanoparticles in workplace air	FP7		02,06

Study Key	State Of Progress	Country	Study Title	Funding Source/s	Budget (£)	Assessed under Research Objective/s
EU025	Starting	EU	NANOTEST: Development of methodology for alternative testing strategies for the assessment of the toxicological profile of nanoparticles used in medical diagnostics	FP7		16
EU028	On-Going	EU	Safe Production and Use of Nanomaterials	FP6	5567543	02,04,05,06, 08,14
EU030	Near Completed	EU	PARTICLE RISK: Risk Assessment for Particle Exposure	FP6	635968	02,11,12,14, 16
EUX01	On-Going	EU	VI-RM - A European Virtual Institute on Reference Materials	EC		03
EUX02	Near Completed	EU	Nanostrand - Standardization related to Research and Development for Nanotechnologies	EC		03
FI002	Completed	Finland	Inflammatory and genotoxic effects of engineered nanoparticles	Finnish Work Environment Fund, Finnish Institute of Occupational Health	214753	12
FI003	On-Going	Finland	Nanohealth	Finnish academy of sciences	621989	12
FR001	Completed	France	Analyse multi-échelle des interactions physico-chimiques et biologiques entre des nanoparticules manufacturées et des bactéries	ANR, CEA, CNRS	340423	18,19
FR002	On-Going	France	Impact sur cellules rénales des nanoparticules manufacturées : Etude In Vitro des effets cellulaires et moléculaires après exposition aiguë et chronique Impact on renal cells by engineered nanoparticles. in vitro study on cellular and molecular effect	AFSSET		11,12
FR003	On-Going	France	Devenir des nanoparticules minérales manufacturées dans les milieux aquatiques et les sols Institut de Physique du Globe de Paris Fate of engineered mineral nanoparticles in aquatic and soil environment. Institute of global physics (PARIS)	AFSSET		10,17
FR004	On-Going	France	NANOP : niveaux, déterminants et variabilités des nanoparticules dans l'environnement intérieur Level, determinant and variability of nanoparticles in the internal environment	AFSSET		11,12
FR005	On-Going	France	Evaluation in vitro de la réactivité des particules fines et ultrafines In vitro evaluation of the reactivity of fine and ultrafine particles	AFSSET		12,13
FR006	On-Going	France	Toxicité respiratoire des nanotubes de carbone: Université Caholique de Louvain Respiratory toxicity of carbon nanotubes: Catholics University of Louvain	AFSSET		14
FR007	On-Going	France	Signatures toxicologiques de nanoobjets manufacturés sur des cellules humaines après inhalation ou ingestion Toxicological signs of engineered nanoobjects in human cells after inhalation and ingestion	ANR		12,13,14
FR008	On-Going	France	Tests parallélisés sur puce à cellule de cytotoxicité aigue de nanoparticules à morphologie contrôlée Parallel tests on cellular chips of acute cytotoxicity of nanoparticles of controlled morphologies.	ANR		13,16
FR009	On-Going	France	Effets des nanotubes de carbone sur l'appareil respiratoire. Rôle de leurs caractéristiques physico-chimiques Effects of carbon nanotubes on the respiratory tracts. The role of physico-chemical characteristics.	ANR		11
FR010	On-Going	France	Evaluation de l'Influence de la Nature des Nanotubes de Carbone sur la Santé Humaine et l'Environnement Evaluation of the influence of the nature of carbon nanotubes on human health and the environment.	ANR		14,18
FR011	On-Going	France	Synthèse, détection et toxicologie de nanoparticules métalliques (Au, Ag, Pt). Synthesis, detection and toxicology of metallic nanoparticles	ANR		02,11
FR012	On-Going	France	Toxicologie des Nanoparticules : Influence de la taille, de la composition chimique et de la réactivité de surface sur leurs effets pulmonaires et rénaux Toxicology of nanoparticles: Influence of size, chemical composition and surface reactivity	ANR		11,14
FR013	On-Going	France	Caractérisation in situ de la surface des aérosols fins et ultrafins Characterisation in situ of the fine and ultrafine aerosols.	ANR		02
TW001	Completed	TAIWAN	Promoting responsible R&D and manufacturing environment of nanotechnology	Taiwan EPA	69071	05,08
TW002	Completed	TAIWAN	Study in Applying Nanotechnology for Environmental Protection	Government	117846	05
UK005	Completed	UK	Nanoparticles: An occupational hygiene review	Government	15000	05
UK010	On-Going	UK	Nanochallenge	HSL/HSE	400000	06

Study Key	State Of Progress	Country	Study Title	Funding Source/s	Budget (£)	Assessed under Research Objective/s
UK012	Completed	UK	A scoping study to identify hazard data needs for addressing the risks presented by nanoparticles and nanotubes	DEFRA	34500	11,13
UK017	Near Completed	UK	The potential routes of nanoparticle uptake by cells and their impacts on antigen processing	Napier University	45000	12
UK025	Completed	UK	Cellular and molecular responses to oxidative stress	Colt Foundation	150000	13
UK026	Near Completed	UK	Effects of nanoparticles on liver cells	EU	150000	12
UK027	Near Completed	UK	Ecotoxicology of nanoparticles	DEFRA/CSL	48000	18
UK030	Near Completed	UK	Mechanisms of nanoparticle and nanotube-induced pulmonary toxicity	Colt Foundation	176267	02,11,12,13
UK031	Completed	UK	The Assessment of Different Metrics of the Concentration of Nano (Ultrafine) Particles in Existing and New Industries	HSE	97073	02
UK047	Completed	UK	Blood and cardiovascular effects of nanoparticles	EU	76000	14
UK051	Near Completed	UK	Nanotube toxicity (PhD studentship University of Edinburgh Medical Faculty)	University of Edinburgh Medical Faculty	50000	13
UK057	Near Completed	UK	Evaluation of Risk Assessment Approaches for Manufactured Nanomaterials	DEFRA	51765	16
UK071	Near Completed	UK	An outline scoping study to determine whether high aspect ratio nanopartcles (HARN) should raise the same concerns as do asbestos fibres	DEFRA	57349	11,13
UK073	Near Completed	UK	Reference materials for engineered nanoparticle toxicology and metrology	DEFRA	124795	03
UK074	Completed	UK	Current and Predicted Environmental Exposure arising from Engineered Nanomaterials	Government	47731	05
UK075	Completed	UK	An Assessment of Regulatory Testing Strategies and Methods for Characterising the Ecotoxicological Hazards of Nanomaterials	DEFRA	24560	16
UK086	Near Completed	UK	Genomic and oxidation-related biological responses in fish exposed to fullerenes of different physicochemical characteristics	NERC	28828	17,18
UK088	Near Completed	UK	Nanotoxicology of Fine PM: The Role of Surfactant and Collectins in Short-Term Health Effects of PM Air Pollution	NERC	122070	12
UK089	On-Going	UK	Hazards of nanoparticles to the environment and human health	NERC	118300	14
UK090	On-Going	UK	Determinants of Oxidative Potential, A Health-Based Metric to Assess Particulate Matter Toxicity	NERC	62126	13
UK091	On-Going	UK	Assessing human exposure, uptake and toxicity of nanoparticles from contaminated environments	NERC	103327	17,18
UK092	Near Completed	UK	An exploratory study investigating the physiochemical characteristics of ambient air particles responsible for the dysregulation of pulmonary genes	NERC	114452	14
UK093	On-Going	UK	A proof of concept study for a structure activity model for the toxicity of nanoparticles	NERC	48273	13
UK094	Near Completed	UK	Visualisation of Nanoparticles in the Environment	NERC	19668	04
UK095	Near Completed	UK	Understanding the fate and behaviour of manufactured nanoparticles in natural waters	NERC	48327	10
UK096	Near Completed	UK	Synthetic polymer nanoparticles: effects of composition and size on uptake, toxicity and interactions with environmental contaminants.	NERC	61991	03,17
UK097	Near Completed	UK	Pharmaceutical and cosmetic silica nanoparticles: towards an understanding of their structure, fate and behaviour in aquatic systems	NERC	63880	10,17,18
UK098	Near Completed	UK	Nanoparticle immunotoxicity using an environmental sentinel as a model	NERC	38994	17,18
UK100	Near Completed	UK	Manufactured Nanoparticle Migration in Groundwaters	NERC	57982	10
UK101	Near Completed	UK	Dietary Exposure to Nanoparticles in Fish: A Pilot Study.	NERC	55384	17,18
UK102	Near Completed	UK	Effects of C-60 fullerenes and carbon nanotubes on marine mussels.	NERC	19850	17,18
UK103	Near Completed	UK	Nanoscale zerovalent iron (nZVI) impact on soil microbial communities	NERC	64682	17,18
UK104	Starting	UK	Interaction of Nanoparticles with Microbial Populations during Particle Transport	NERC	48316	17,18
UK105	Starting	UK	Impact of manufactured nanoparticles on the catabolic capabilities and phenotypic structure of soil microbial communities	NERC	56857	17,18
UK106	Near Completed	UK	Impact and recovery of groundwater microbial communities exposed to manufactured nanomaterials (MNM).	NERC	53435	17,18
UK107	Near Completed	UK	Biomembrane interactions in the toxicology of nanoparticles to microorganisms	NERC	20016	17,18
UK108	Starting	UK	An investigation into the effects of nanoparticles on the bacterial diversity of freshwater and coastal marine sediments	NERC	37997	17
UK109	Starting	UK	A study of the effects of silver surface chemistry on bactericidal properties of silver nanoparticles.	NERC	20167	17
UK110	Completed	UK	Assessment of the current and projected applications of nanotechnology in the food sector	FSA		05,11,15

Study Key	State Of Progress	Country	Study Title	Funding Source/s	Budget (£)	Assessed under Research Objective/s
UK111	Near Completed	UK	Assessment of current and projected applications of nanotechnology for food contact materials in relation to consumer safety and regulatory implications.	FSA	68500	05,15
UK113	Near Completed	UK	Model nanoparticles for environmental risk studies	NERC	56564	03,08,17
UKX01	Completed	UK	A scoping study into the manufacture and use of nanomaterials in the UK	DEFRA	39329	05
UKX04	Near Completed	UK	HSL - Fire and Explosion Properties of Nanopowders	HSE	305621	04
UKX05	Completed	UK	Explosion Properties of Nanometric Aluminium Powder and Nickel Powder	HSE	10000	04
US001	On-Going	USA	Carbon Nanotubes: Environmental Dispersion States, Transport, Fate, and Bioavailability	EPA	184958	10,19
US002	Near Completed	USA	Structure-function Relationships in Engineered Nanomaterial Toxicity	EPA	186507	02,12
US003	On-Going	USA	Photochemical Fate of Manufactured Carbon Nanomaterials in the Aquatic Environment	EPA	99421	10
US005	On-Going	USA	Bioavailability and Fates of CdSe and TiO_2 Nanoparticles in Eukaryotes and Bacteria	EPA	198934	10,12,17
US015	Completed	USA	CRAEMS: Fundamental Studies of Nanoparticle Formation in Air Pollution	NSF	611002	07
US021	On-Going	USA	Development of Bench and Mist Protocols for Particulate Measurements of Protective Clothing and Ensembles	NIOSH		08
US023	On-Going	USA	Systemic Implications of Total Joint Replacement	NIH	2874289	12
US029	Completed	USA	Role of CNTs in Cardiovascular Inflammation & COPD Related Diseases	NIOSH	447617	14
US030	Completed	USA	Review of Best Practices for Nanotechnology Safety	ICON	27354	08
US034	Completed	USA	Mechanistic Dosimetry Models of Nanomaterial Deposition in the Respiratory Tract	EPA	186507	14
US035	Unknown	USA	Direct Reading Instrument Metrology	NIOSH		06
US038	On-Going	USA	Respirator Testing and Certification	NIOSH		08
US041	On-Going	USA	Bypass Leakage and Recirculation of Workplace Aerosols	NIOSH		08
US045	On-Going	USA	Nanoparticle Disruption of Cell Function	NIH	182461	12
US046	Near Completed	USA	Monitoring and Characterizing Airborne Carbon Nanotube Particles	NIOSH	198941	06
US047	Completed	USA	Cytotoxicity of Nanoparticles	NSF	45756	12
US048	On-Going	USA	Neurotoxicity after Pulmonary Exposure to Welding Fumes Containing Manganese	NIOSH		06,11,13,14
US055	On-Going	USA	Development of methods and models for nanoparticle toxicity screening: Applications	NIH	179209	13
US056	On-Going	USA	The Effect of Surface Coatings on the Environmental and Microbial Fate of Nano iron and Fe oxide Nanoparticles	EPA	198941	10,17
US057	On-Going	USA	Impact of Physiochemical Properties on Skin Absorption of Manufactured Nanomaterials	EPA	194772	11,15
US058	Near Completed	USA	Comparative Life Cycle Analysis of Nano – and Bulk-materials in Photovoltaic Energy Generation	EPA	99470	07
US059	On-Going	USA	Biological Fate & Electron Microscopy Detection of Nanoparticles During Wastewater Treatment	EPA	198443	10,17
US060	Completed	USA	Olfactory transport of inhaled nanoparticles	American Chemistry Council	188994	11,14
US065	On-Going	USA	An Ultrafine Particle Intervention Study in Automotive Production Plants	NIOSH		05,07,08,14
US066	On-Going	USA	NIR Absorbing Nanoparticles For Cancer Therapy	NIH	227674	11
US068	Unknown	USA	Pulmonary Toxicity Screening Studies with Nano vs. Fine-Sized Particles in Rats.	DuPont		14
US072	On-Going	USA	Nanoparticles: Dosimetry and Risk Assessment	NIOSH		11
US079	On-Going	USA	Lung Deposition of Highly Agglomerated Nanoparticles	NSF	198941	14
US083	Completed	USA	Filter Efficiency of Typical Respirator Filters for Nanoscale Particles	NIOSH		08
US086	On-Going	USA	Generation and Characterization of Occupationally Relevant Airborne Nanoparticles	NIOSH		02
US088	On-Going	USA	The chemical and physical nature of particulate matter affecting air, water, and soil quality.	USDA		07,10
US090	Completed	USA	SGER: Aquatic Nanotoxicology of Nanomaterials and Their Biomolecular Derivatives	NSF	14921	18
US091	Completed	USA	New Instruments for Real-Time, High-Resolution Characterization of Nanoparticles in the Environment	NSF	52719	06
US092	Completed	USA	Fullerene, carbon nanotube, and reactive nano iron particle toxicity in aquatic species.	Lonestar Nanotechnology fund		18
US093	Completed	USA	Dermal Effects of Nanoparticles	NIOSH	348147	13,15
US095	Completed	USA	Biological Interactions of Nanomaterials	DOD	149206	11,12,13
US096	Completed	USA	Systematic Microvascular Dysfunction Effects of Ultrafine Versus Fine Particles	NIOSH	298411	13,14
US098	On-Going	USA	Near-Infrared Fluorescence Nanoparticles for Targeted O*	NIH	1439640	11

Study Key	State Of Progress	Country	Study Title	Funding Source/s	Budget (£)	Assessed under Research Objective/s
US099	Near Completed	USA	Nanoparticles for efficient delivery to solid tumors	NIH	165660	12
US101	Near Completed	USA	IMR: Development of an Analyzer for Size and Charge Characterization of Nanoparticles in Research and Training	NSF	124849	06,08
US102	On-Going	USA	Sorption and availability of metals and radionuclides in soils	USDA		17
US104	On-Going	USA	Reactivity, aggregation and transport of nanocrystalline sesquioxides in the soil system	USDA	61409	17
US107	Near Completed	USA	Colloid interfacial reactions in open microchannel representing unsaturated soil capillaries	USDA	47746	10
US108	On-Going	USA	Cellular and materials-based studies of marine invertebrates to advance biomineralization, antifouling and nanotechnology fields	USDA		19
US110	On-Going	USA	Methodology Development for Manufactured Nanomaterial Bioaccumulation Test	EPA	198825	19
US111	On-Going	USA	A Rapid In Vivo System for Determining Toxicity of Manufactured Nanomaterials	EPA	198941	18,19
US112	On-Going	USA	Ecotoxicology of Underivatized Fullerenes (C60) in Fish	EPA	197353	17,18,19
US113	On-Going	USA	Effects of Ingested Nanoparticles on Gene Regulation in the Colon	EPA	99470	12,13
US114	Completed	USA	Absorption and Release of Contaminants onto Engineered Nanoparticles	EPA	166015	10
US115	Completed	USA	Impacts of Manufactured Nanomaterials on Human Health and the Environment - A Focus on Nanoparticulate Aerosol and Atmospherically Processed Nanoparticulate Aerosol	EPA	166613	11
US118	Completed	USA	Transformations of Biologically-Conjugated CdSe Quantum Dots Released Into Water and Biofilms	EPA	165170	17
US119	Completed	USA	Chemical and Biological Behaviour of Carbon Nanotubes in Estuarine Sedimentary Systems	EPA	166489	17,18,19
US120	Completed	USA	Iron Oxide Nanoparticle-Induced Oxidative Stress and Inflammation	EPA	166613	12,13
US121	Near Completed	USA	The Bioavailability, Toxicity, and Trophic Transfer of Manufactured ZnO Nanoparticles: A View from the Bottom	EPA	180877	19
US122	Completed	USA	Health Effects of Inhaled Nanomaterials	EPA	166612	13,14
US123	On-Going	USA	Agglomeration, Retention, and Transport Behaviour of Manufactured Nanoparticles in Variably-Saturated Porous Media	EPA	198461	10
US124	Completed	USA	Responses of Lung Cells to Metals in Manufactured Nanoparticles	EPA	165597	10,11
US125	Near Completed	USA	Internalization and Fate of Individual Manufactured Nanomaterial within Living Cells	EPA	99470	12
US126	Completed	USA	The Fate, Transport, Transformation and Toxicity of Manufactured Nanomaterials in Drinking Water	EPA	226295	10,17,18
US127	Near Completed	USA	Hysteretic Accumulation and Release of Nanomaterials in the Vadose Zone	EPA	186507	10
US128	On-Going	USA	Aquatic Toxicity of Carbon-Based Nanomaterials at Sediment-Water Interfaces	EPA	198695	17,18
US129	Near Completed	USA	Chemical Fate, Biopersistance, and Toxicology of Inhaled Metal Oxide Nanoscale Materials	EPA	186507	11,12,13,14
US130	Near Completed	USA	Effects of Nanomaterials on Human Blood Coagulation	EPA	186507	14
US131	Near Completed	USA	Assessing the Environmental Impacts of Nanotechnology on Organisms and Ecosystems	EPA	186507	10,17,18
US132	Near Completed	USA	Acute and Developmental Toxicity of Metal Oxide Nanoparticles to Fish and Frogs	EPA	186507	17
US133	On-Going	USA	Nanoparticle Stability in Natural Waters and its Implication for Metal Toxicity to Water Column and Benthic Organisms	EPA		10,17
US134	On-Going	USA	Nanoparticle Toxicity in Zebrafish	EPA	198094	17
US135	Near Completed	USA	Evaluating the Impacts of Nanomanufacturing via Thermodynamic and Life Cycle Analysis	Government	186507	05
US136	Near Completed	USA	Fate and Transport of Carbon Nanomaterials in Unsaturated and Saturated Soils	EPA	196603	10
US137	Completed	USA	Implications of Nanomaterials Manufacture and Use: Development of a Methodology for Screening Sustainability	Government	49606	05
US139	Completed	USA	Evaluated Nanoparticle Interactions with Skin	EPA	163615	15
US140	On-Going	USA	Aquatic Toxicity of Waste Stream Nanoparticles	EPA	198855	17
US144	Near Completed	USA	Assessment Methods for Nanoparticles in the Workplace	NIOSH	198941	06,08
US147	On-Going	USA	Carbon Nanoparticles in Combustion: A Multiscale Perspective	NSF	119365	07
US151	Completed	USA	Chemical Characterization of Ultrafine Aerosol Particles	NSF	180539	06
US154	Near Completed	USA	Microbial Impacts of Engineered Nanoparticles	EPA	186507	10,17
US155	Near Completed	USA	NIRT: Nanoparticle-Environment Interfaces: Interactions in Natural Systems	NSF	745903	10

Study Key	State Of Progress	Country	Study Title	Funding Source/s	Budget (£)	Assessed under Research Objective/s
US156	Completed	USA	Pulmonary Deposition and Translocation of Nanomaterials	NIOSH	447617	11,14
US158	On-Going	USA	Investigating the Surface Structure and Reactivity of Bulk and Nanosized Manganese Oxides	NSF	163913	10
US159	Near Completed	USA	Nanotox: Cross-Media Environmental Transport, Transformation, and Fate of Manufactured Carbonaceous Nanomaterials	NSF	174073	07,10
US163	On-Going	USA	Lung Oxidative Stress/Inflammation by Carbon Nanotubes	NIOSH	746028	13
US168	Near Completed	USA	Nanoparticles for siRNA delivery to mammalian neurons	NIH	248739	14
US170	Completed	USA	The Role of Nano-Scale Colloids in Particle Aggregation and Trace Metal Scavenging in Aquatic Systems	NSF	258760	10
US176	On-Going	USA	The Measurement and Control of Workplace Nanomaterials	NIOSH		05,06,07,08
US179	Near Completed	USA	CNS Gene Delivery and Imaging in brain Tumor Therapy	NIH	3299013	13
US181	Near Completed	USA	Fate and Transformation of C60 Nanoparticles in Water Treatment Processes	EPA	186507	10
US182	Near Completed	USA	NIRT: Investigating Nano-carbon Particles in the Atmosphere: Formation and Transformation	Government	917176	05
US183	Completed	USA	Reverse Engineering Cellular Pathways from Human Cells Exposed to Nanomaterials-Development of Novel Risk Assessment Methods	NSF	99470	16
US188	Near Completed	USA	NIRT: Nanoparticle Fe as a Reactive Constituent in Air, Water, and Soil	NSF	696293	10
US190	Unknown	USA	Development of Computer-Aided Face Fit Evaluation Methods	NIOSH		08
US191	Completed	USA	Rapid Environmental Impact Screening for Engineered Nanomaterials: A Case Study Using Microarray Technology	Project on Emerging Nanotechnologies	14921	17
US192	On-Going	USA	Performance Test of High APF Respirators	NIOSH		08
US193	Completed	USA	Pulmonary, Immune, and Dermal Effects of Welding Fumes	NIOSH		11,14,15
US197	On-Going	USA	Innate Immune Response of an Aquatic Vertebrate Model to Manufactured Nanoparticles Assessed Using Genomic Markers	EPA	198349	17
US204	Completed	USA	Elemental Composition of Freshly Nucleated Particles	EPA	193967	06
US211	On-Going	USA	Genomics-based Determination of Nanoparticle Toxicity: Structure-function Analysis	EPA	99467	02,12
US215	Completed	USA	Pulmonary Toxicity of Diesel Exhaust Particles	NIOSH		13
US216	Completed	USA	Penetration of Nanoparticles Through Respirator Filter Media	NIOSH	248676	08
US220	On-Going	USA	Long Term Cardiovascular Effects of Inhaled Nanoparticles	NIH	176975	14
US222	Completed	USA	Role of Surface Chemistry in the Toxicological Properties of Manufactured Nanoparticles	NIOSH	198941	02,13
US225	Near Completed	USA	NIRT: Response of aquatic and terrestrial microorganisms to carbon-based manufactured nanoparticles.	NSF	795763	17
US227	Completed	USA	Short-Term Chronic Toxicity of Photocatalytic Nanoparticles to Bacteria, Algae, and Zooplankton	EPA	166554	17
US228	On-Going	USA	Aggregation and Deposition Behaviour of Carbon Nanotubes in Aquatic Environments	NSF	198941	10
US229	Completed	USA	From Nanoparticles to Novel Protective Garments	NIOSH	49735	08
US238	Completed	USA	NIRT: Nanoscale Processes in the Environment: Nanobiogeochemistry of Microbe/Mineral Interactions	NSF	497352	17
US241	Completed	USA	The Role of Nano-Scale Colloids in Particle Aggregation and Trace Metal Scavenging in Aquatic Systems	NSF	159275	10
US242	Completed	USA	The Role of Nano-Scale Colloids in Particle Aggregation and Trace Metal Scavenging in Aquatic Systems	NSF	120966	10
US243	Completed	USA	The Role of Nano-Scale Colloids in Particle Aggregation and Trace Metal Scavenging in Aquatic Systems	NSF	136602	10
US244	Near Completed	USA	Nanotox: Biochemical, Molecular and Cellular Responses of Zebrafish Exposed to Metallic Nanoparticles	NSF	174073	17,18
US247	On-Going	USA	NIRT: Design of Biocompatible Nanoparticles for Probing Living Cellular Functions and Their Potential Environmental Impacts	NSF	658370	12
US248	Completed	USA	ADVANCE Fellow: Microscopy of Nanomaterials	NSF	223228	02
US249	Near Completed	USA	Pulmonary Effects of Exposure to Various Nanoparticles	NIOSH		11,14
US250	Completed	USA	Portable Monitors for Airborne Metals at Mining Sites	NIOSH		06
US251	Completed	USA	Nanoparticle in the Workplace	NIOSH	198941	05,06,07,08
US253	Unknown	USA	Development of Alternative In Vitro Methods to Assess Pulmonary Toxicity of Inhaled Fine and Nano-sized Particles	DuPont		16
US254	On-Going	USA	Experimental and Numerical Simulation of the Fate of Airborne Nanoparticles from a Leak in a Manufacturing Process to Assess Worker Exposure	NSF	198941	07

Study Key	State Of Progress	Country	Study Title	Funding Source/s	Budget (£)	Assessed under Research Objective/s
US259	Completed	USA	Repercussion of Carbon Based Manufactured Nanoparticles on Microbial Processes in Environmental Systems	EPA	166613	10,17,18
US262	Completed	USA	Size Dependent Neuronal Translocation of Nanoparticles	NSF	99469	14
US263	Completed	USA	Nanotox: Gene Expression Profiling of Single-Walled Carbon Nanotubes: A Unique Safety Assessment Approach	NSF	149206	12,16
US264	Completed	USA	Generation and Characterization of Ultrafine Particles	NIOSH		02,03
US271	Near Completed	USA	Collaborative Research: Fullerene Aggregation in Aquatic Systems	NSF	115548	10
US272	Completed	USA	Collaborative Research: Fullerene Aggregation in Aquatic Systems	NSF	58066	10
US273	Completed	USA	NIOSH Current Intelligence Bulletin: Welders and Parkinsonism	NIOSH		08
US274	Near Completed	USA	NIOSH Current Intelligence Bulletin: Evaluation of Health Hazard and Recommendations on Occupational Exposure to Titanium Dioxide	NIOSH		11,14
US285	Completed	USA	Submicron Particles and Fibers for Toxicological Studies	NIH	167999	03
US286	On-Going	USA	NIRT: Micropatterned Nanotopography Chips for Probing the Cellular Basis of Biocompatibility and Toxicity	NSF	917387	13
US288	Completed	USA	Physical Characteristics of Ultrafine Particles	NIOSH		02
US291	Completed	USA	Development of fine particle characterization and monitoring methods	NIOSH		02,06
US293	On-Going	USA	Characterization and Communication of Chemical Hazards	NIOSH		06
US294	On-Going	USA	Emerging Issues for Occupational Respiratory Disease	Government		05
US295	Near Completed	USA	Environmental Biogeochemistry and Nanoscience: Applications to Toxic Metal Transport in the Environment	NSF	59682	10
US296	On-Going	USA	Longitudinal Surveillance/Beryllium Disease Prevention	NIOSH		02
US303	Completed	USA	Particle Surface Area As a Dose Metric	NIOSH	497352	02,14
US306	Completed	USA	Pulmonary Toxicity of Carbon Nanotube Particles	NIOSH	447617	14
US307	On-Going	USA	Ultrafine Aerosols from Diesel-Powered Equipment	NIOSH		08
US309	On-Going	USA	The Fate and Effects of Nanosized Metal Particles along a Simulated Terrestrial Food Chain Investigated Using Genomic and Microscopic Techniques	EPA		10,17
US313	Near Completed	USA	Multifunctional Nanoparticles for Intracellular Delivery	NIH	673985	12
US316	Near Completed	USA	NIRT: Nanoscale Processes in the Environment: Atmospheric Nanoparticles	NSF	830221	07
US318	Completed	USA	Identifying and Regulating Environmental Impacts of Nanomaterials	NSF	64656	16
US320	On-Going	USA	NIRT: Understanding Robust Large Scale Manufacturing of Nanoparticles and Their Toxicology	NSF	696293	02,11,12,13, 14
US326	On-Going	USA	Multidisciplinary University Research Initiative: Effects of Nanoscale Materials on Biological Systems: Relationship between Physiochemical Properties and Toxicological Properties	DOD	2735437	12,13
US331	Completed	USA	Ultrafine Particles in Heavy Vehicle Assembly and Components Manufacturing Plants	UAW, International Truck and Engine Corporation	54709	05,06
US334	Completed	USA	Titanium Dioxide (TiO_2) Nanoparticle Exposure Study	Government	198941	05
US337	Completed	USA	Physical and Chemical Determinants of Nanofiber/Nanotube Toxicity	EPA	166613	13
US339	Completed	USA	NER: Fullerene-Microbe Interactions: Implications for Disinfection and Risk Assessment	NSF	74603	17
US411	On-Going	USA	The Interaction of Polycationic Organic Polymers with Biological Membranes	NIH	553393	12
US421	On-Going	USA	Modulation of Qdot nanoparticle toxicity by glutathione in GCL transgenic mice	NIEHS		12
US422	Unknown	USA	Investigations of Multi-Walled Carbon Nanotube Toxicity	NIOSH		12,14
US425	Starting	USA	Project 5: Nanotechnology-Based Environmental Sensing	NIEHS		6
US426	On-Going	USA	Chemical, structural and superstructural determinants of nanocarbon toxicity	NIEHS		16
US427	Unknown	USA	Determination of diameter distribution of carbon nanotubes by Raman Spectroscopy	NIOSH		02,06
US428	Starting	USA	An Integrated Approach Toward Understanding the Tox of Inhaled Nanomaterials	NIOSH; NIEHS; RFA; ES	596823	11,14
US429	Unknown	USA	Exposure Assessment in Tungsten Refining and Manufacturing	Government		05
US430	Unknown	USA	Specific biomarkers for unusual toxicity of nanomaterials	NIOSH		14
US432	Unknown	USA	Potential Aneuploidy Following Exposure to Carbon Nanotubes	NIOSH		14
US433	Unknown	USA	Ultrafine TiO_2 Surface and Mass Concentration Analysis	NIOSH		02,06
US434	On-Going	USA	Personal Exposure to Engineered Nanoparticles	NIOSH Career Development Grant	159582	06
US435	Unknown	USA	Mutagenicity assessment of carbonaceous nanomaterials	NIOSH		14

Study Key	State Of Progress	Country	Study Title	Funding Source/s	Budget (£)	Assessed under Research Objective/s
US436	Unknown	USA	Cell-based assessment for iron nanoparticles induced health effects	NIOSH		13,16
US437	Unknown	USA	Occupational exposures and potential neurological risks	NIOSH		14
US438	Starting	USA	Nano-Biological Interactions and Toxicity of Engineered Metal Oxide Particles	NIEHS		13
US439	Unknown	USA	Measurement of Nanoscale Carbonaceous Materials	NIOSH		02,06
US452	On-Going	USA	Remote Microvascular Dysfunction after particulate matter exposure	NIEHS		14
US453	Unknown	USA	Nanoscale Reference Materials for Respiratory Disease Prevention	NIOSH		03
US458	Unknown	USA	Nanoaerosol Surface Area Measurement Methods	NIOSH		02,06

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