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Specific Advice on Exposure Assessment and Hazard/Risk Characterisation for Nanomaterials under REACH (RIP-oN 3)

Final Project Report

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EXECUTIVE SUMMARY

The REACH Implementation Projects on Nanomaterials (RIP-oNs) seek to provide scientific and technical advice on key aspects of the implementation of REACH with regard to nanomaterials. The objectives of the RIP-oN 3 project were to: 1) develop advice on how to do exposure assessment for nanomaterials within the REACH context to cover i) development of Exposure Scenarios, ii) evaluation of operational conditions and risk management/mitigation measures and iii) exposure estimation, and; 2) to develop ideas for how to conduct hazard and risk characterisation for nanomaterials. The latter will involve threshold/non-threshold considerations.

The approach taken was largely driven by the contract specifications and comprised a step wise, evidence based approach, on which guidance changes were developed. The project was implemented through a series of specified and linked tasks (A, B1-B4, C1 – C3, and D).

The project identified and reviewed relevant information sources (Task A) for carrying out an evaluation of the evidence base to identify the key scientific issues arising that had possible implications for the REACH guidance. In relation to exposure issues, Task B1 comprised case studies to capture practical learning on the development of exposures scenarios (ES), Task B2 evaluated the evidence base on Operational Conditions and Risk Management Measures, and Task B3 considered exposure estimation. In relation to hazard and to risk characterisation, Task C1 developed case studies on how no effect levels could be established and Task C2 evaluated on-going activities in relation to hazard and risk characterisation. Task D comprised an analysis of the needs and options for metrics/parameters in the hazard assessment compatible with the exposure assessment parameters/metrics in order to prepare a meaningful risk characterisation.

The next stage was the identification, from the perspective of the scientific evidence, of where recommendations for guidance changes should be made. This comprised Tasks B4 (in relation to exposure issues) and C3 (in relation to hazard and risk characterisation issues).

The final stage of the project was a section by section analysis of the existing REACH guidance. The assessment considered in detail the optimum set of changes which could be made to the guidance. Based on this analysis, detailed recommendations for

guidance changes were developed along with recommendations for research where this was indicated by the evidence.

Comprehensive discussion of the findings from the project is provided in the individual Task Reports. This Final Project Report summarises the key specific issues related to nanomaterials in a REACH context and a form compatible with the possible future integration into the existing REACH Guidance on Information Requirements and Chemical Safety Assessment, with clear reference to the existing REACH Guidance Part or Chapter and Sub-chapter. For issues that are not currently technically/scientifically mature for developing detailed guidance, the need for further research and development is indicated.

The ES Case-Studies (Task B1) were provided by companies of various sizes and at different stages of the business life, in different industry sectors and at different stages of the nanomaterials supply chain. They delivered detailed exposure information for occupational, consumer and environmental release/exposure scenarios for specific nanomaterials: nano-TiO_2; nano-TiO_2 (Mn-doped); nano-Ag; Multi-walled Carbon Nanotubes (MWCNTs). Some Case-Study providers conducted state-of-the-art detection and measurement approaches using multi-instrument, multi-metric measurement studies. While this resulted in an extensive data set, the complexity of the data collected made this data difficult to interpret for the purposes of exposure scenario development. Some of the Case-Studies used models (e.g. Consexpo, ECETOC TRA) to estimate exposure. These were used without specific modification for nanomaterials. No data was available to test the validity of the model estimates. The reporting template (based on the ES format) was criticised due to lack of clarity, and guidance. A number of specific observations were made, primarily general difficulties with the current REACH guidance, and might benefit any further guidance update. It was considered that down-stream users may lack qualified staff to complete the reporting template. The Case-Studies developed should be considered as nanomaterial product-specific examples only and that no generalisation with regard to practices within an entire nanomaterial type-specific branch could be based on these individual ES Case-Studies.

Task B2 considered Operational Conditions (OC) and Risk Management Measures (RMM). The ‘hierarchy of control’ concept which underpins much of the REACH guidance in this area was considered to be equally valid for nanomaterials as for other

substances. There is evidence that control and risk management methodologies which are already known *can* provide levels of protection for workers from exposure to engineered nanomaterials. It is not indicated that new nano-specific RMMs need to be developed. However, the specific protection provided against specific nanomaterials needs to be evaluated. Evidence indicates that emissions to the workplace are substantially reduced if a process involving engineered nanomaterials is performed in a properly designed enclosure/containment, although this was not universal. The situation is further amplified when considering what happens when containment is opened. Similarly, evidence indicates that worker exposure can be significantly reduced or prevented through the use of correctly designed and implemented extraction ventilation and filtration. Filtration theory indicates that filtration will be effective for particles in the nanometer size range. This also applies to personal protective equipment where several studies clearly demonstrate the potential of respirator filters to capture nanoparticles. As for chemicals in general, further work is required to investigate human factors such as leakage around (rather than through) a face-piece filter. The situation is not as clear with protective suits and gloves, where much less work has been carried out.

Control Banding (CB) may have use in relation to the selection of control approaches. Attempts are being made to develop this approach for nanomaterials, but they are at an early stage. However, given the current level of development, CB cannot be used to demonstrate that the risks are adequately controlled. As an interim measure, users might consider CB approaches to provide initial selection of control measures as a starting point while collecting further information about exposure, toxicity and risk. Although preliminary medical surveillance activities, such as documentation of the presence of engineered nanoparticles and identification of potentially exposed workers, are likely to be beneficial in the long term, no clear guidance can be given at this time as to which specific medical endpoints should be examined. For safety data sheets (SDS), it is important that information provided for a nanomaterial is representative, valid and provides the protection needed for the forms addressed by the SDS.

Other than in the case of filtration, no recommendations for risk management measures in REACH guidance relating to the environment can be made at this time, due to lack of evidence. Almost no work has been done on the effectiveness of consumer risk management measures.

For operational conditions, only limited information was found to be available in the public literature. Information is available on the risk management measures adopted and in some cases the quantity of material produced and used on a daily or batch basis. Information concerning room sizes, ventilation rates, and temperature is almost entirely absent.

Task B3 considered exposure estimation. Key issues identified included discrimination from background nanoparticles, measurement of size distribution, maximum relevant particle size, effect of high spatial and temporal variability, assessment of high aspect ratio nanomaterials, application of exposure models & choice of metric, and instrument & measurement strategy. Alternative approaches in dealing with background particle measurements included a time series approach, near and far field paralleled measurements and off-line analysis to confirm whether peak concentrations observed correspond to an identified nanoparticle, either by composition, morphology or both. Consideration for using size distribution data concluded that recommended methods should be able to account for complex distributions (e.g. bimodal distributions) and that the full size distribution curve should be reported. Particle size issues were concerned with aggregates and agglomerates and the need to identify and characterise these. Nanoparticles of interest may be present as primary particles, larger aggregates/agglomerates, and potentially background particles from which primary particles may subsequently be released. It was suggested that the respirable convention is the appropriate upper size limit. Given the effect of high spatial and temporal variability, measurements of workplace air concentrations are unlikely to represent personal exposure. Therefore strategies which encourage comparison (even limited) between workplace air concentrations and personal exposure are recommended. At this time, it is not possible to make a definitive statement concerning which of the metrics are the most appropriate for nanoparticles. In relation to measuring exposure, the recommended practice at this time is that measurements should encompass assessment of at least mass, but where possible also number and/or surface area concentration. This issue was considered further in Task D.

For high aspect ratio nanomaterials, the application of the WHO approach has not yet been validated. Given an absence of measurement methods or terminology to describe ‘bundles’ or ‘clumps’ of high aspect ratio nanomaterials, no specific guidance can be given at this time for quantitative assessment of these entities. However, their presence should be noted in any assessment. The limited evidence of validation for

occupational exposure indicates that model estimates should not be relied on alone without further confirmation of their validity in individual cases. In any case, model estimates should be used with caution and with further scientific justification.

Detailed implications for these issues in relation to the REACH guidance has been developed in Task B4 and refined through discussions with the Stakeholder Consultation Group (SCG) into proposals for guidance amendments, which have been fully elaborated in this Final Project Report.

Task C1 involved the consideration and evaluation of the REACH approach for deriving no effect levels through the use of case studies for multi-walled carbon nanotubes (MWCNT), nano-TiO_2 and silver nanoparticles. In relation to the case studies, in all cases it was observed that there were some data gaps that could hinder a full evaluation under REACH. Normally, the approach for dealing with deficiencies in data would be to look for other studies using similar materials, which may provide some knowledge of the likely effects of the materials (e.g. long-term effects, systemic effects etc.). However, in relation to many nanomaterials, there is insufficient evidence to apply such an approach.

Where data was available, a Case Study was performed. It emerged that a major question relating to the applicability of the REACH guidance was the applicability of the current assessment factors (AF) in relation to nanomaterials, as these AF have been derived from classical (soluble substance) toxicity in relation to both human and environmental health. Considerations have been made regarding their applicability to (nano)particles and the impact that alternative metrics and other issues such as agglomeration/aggregation state could have on the different AF. However, it was considered that, for the most part, the current guidance in relation to deriving exposure limits provides sufficient flexibility to address areas of uncertainty, data gaps and, if justified, deviations from the default approach/AFs. In relation to agglomeration/aggregation, it was considered that it is unclear whether aggregation/ agglomeration of nanoparticles will result in higher or lower toxicities found in standard tests. However, the aggregation/agglomeration state could affect various parameters such as deposition zone in the lung, or uptake by organisms and thus characterisation of particles both within test systems and the exposure environment is important.

Within Task C2, considerations were made of on-going hazard and risk characterisation approaches, using the case study nanomaterials (MWCNT, TiO_2,

nanosilver). Evaluation of the identified alternative approaches for hazard and risk characterisation under REACH revealed both merits and deficiencies in the derivation of exposure limits. This was very much the case in relation to extrapolating from experimental animals to humans for inhalation exposure (pertaining to both initial starting point modification and interspecies adjustments). Based on the information gathered and considered within the Task C2 report, and the wider particle toxicology literature, an alternative approach for extrapolating from experimental animals to humans for inhalation exposure was suggested for consideration and development in relation to its suitability for possible future incorporation into guidance.

The aim of Task C3 was to evaluate the outcome of Tasks C1 and C2 in relation to the relevant parts of the REACH "Guidance on Information Requirements and Chemical Safety Assessment" for human health and the environment (specifically sections R.8. and R.10 of REACH Guidance). Issues identified within these reports are discussed in relation to the guidance and proposals are made regarding how the current guidance could be adapted or complemented in order to facilitate the hazard and risk characterisation of nanomaterials in the REACH context.

Task D identified the critical items on exposure/dose descriptors and outlined needs for adequate metrics/parameters as appropriate for exposure assessment compatible with those used for hazard assessment. The metrics currently used in risk assessment (both regulatory and otherwise) across the three elements of exposure, toxicology and risk, are based on mass or number. The most prominent emerging alternative or additional metric identified for use in relation to the risk assessment of nanomaterials is surface area. This is based primarily on toxicological evidence relating particle surface area to inflammation, an indicator of toxicity. There are currently no definitive conclusions on the best metric. However, there is consensus that there should be sufficient characterisation of the forms of a substance tested to allow the dose-response to be expressed in the different metrics discussed - number, surface area and mass. It is important to note that there are other parameters which can act as modifiers of the toxicity, including particle size, size distribution, density, surface modification, aggregation/agglomeration state and shape, but these parameters would not generally be considered as scalable quantities and do not appear to conform to the current use of the term "metric" under REACH, and were therefore not considered further in relation to the metric issue.

On the basis of the activities undertaken in each of the Tasks, recommendations have been proposed for guidance updates in relation to: Part D (Exposure Scenario building), Part E (Risk Characterisation), Part F (Chemical Safety Report, including CSR format), Part G (Extending the SDS), Chapter R.12 (Use descriptor system), Chapter R.13 (Risk management measures and operational conditions), Chapters R.14, R.15, R.16, R.17 and R18 (on exposure estimation in different situations) and also considering the RMM library. In each case, for each issue, all of these documents have been reviewed to evaluate the need for guidance changes.

The content of a recommendation for a specific update to guidance is consistent with the focus of current REACH Guidance document, its level, and language, such that:

- where the need is for 'strategic-level' guidance applicable to nanomaterials (i.e. high-level or overarching principles), succinct contextual information and reference(s) to primary sources of information are provided;
- where the need is for updated detailed pragmatic information on, for example methods, a synopsis of specific guidance with appropriate reference(s) are provided;
- where there is simply a need identified to acknowledge an important relevance or limitation in existing guidance to nanomaterials, a simple wording clarification may be proposed.
- wide-scale acknowledgement confirming the general applicability of Guidance to nanomaterials has not been made.

As necessary some of the recommendations for guidance updates make specific reference to nanomaterials. For the avoidance of doubt however, with these changes, *all* clauses of the guidance document, unless explicitly stated otherwise, would be applicable to nanomaterials and should be used for that purpose.

A summary of the proposals for guidance changes are now indicated on a section by section basis.

In Part D, recommendations have been made to indicate the need to consider particle size issues when justifying "generalising" exposure scenarios (4.3.3) and the need to

take account of background concentrations (D.5.2). In appendix D1, a caveat has been added to draw attention to the limitation of models.

In Part E, the only recommendation is the addition of a footnote to remind users that in risk characterisation ratios, exposure estimates and PNEC/DNEL need to have the same relevant metric (E.1.2).

In Part F, a recommendation has been made to add footnotes indicating that other metrics should also be considered with respect to inhalation.

In Part G, a recommendation has been made to indicate the need to consider the properties of the specific (nanomaterial) form when preparing the eSDS.

In R.8, the overall conclusion from the evaluation of the Guidance document was that whilst the REACH guidance for hazard and risk characterisation have not been written primarily for nanomaterials, nonetheless due to their wide applicability and inherent flexibility they are, for the most, considered suitable for nanomaterials. As may also be the case for various more conventional materials, information for nanomaterials on hazard and risk characterisation is often scarce. For 'conventional' materials, due to the existence of a greater wealth of data surrounding analogous materials, other approaches such as read across or categorisation are available for use in the assessment process. The scientific understanding, such as concepts of similarity or drivers of toxicity, is not yet sufficiently mature for a wealth of nanomaterials to allow for such an approach to be taken in the absence of information with any degree of certainty. As such it is suggested that, if these approaches are to be used (such as the use of data on the bulk or other forms of the material in place of nano-specific data) they must be scientifically justified and may be associated with additional uncertainty. It is also suggested that this point be made in relation to the use of a route-to-route extrapolation in determining health hazards for nanomaterials, as the use of this approach has yet to be established for nanomaterials. Therefore, the use of route-to-route extrapolation for nanomaterials must be scientifically justified on a case-by-case basis.

As well as uncertainty surrounding the chronic effects of nanomaterial exposure, the consideration of potential systemic availability, accumulation and effects should be borne in mind and proposed guidance updates to this effect have been made. It is suggested that the availability of chronic data (in particular addressing carcinogenic

endpoints), and data addressing absorption, systemic availability and accumulation would be seen as reducing uncertainty. However this may require further R&D to develop methods of detection and analysis both of the nanomaterial and any associated effects.

Within the extrapolation process from animal data to a human equivalent dose, there is the potential for deviation away from the REACH approach using other approaches such as those suggested within several publications discussed within the Task C1 and C2 reports. Specifically, in deviating from the default assessment factor during the derivation of a Derived No (Minimal) Effect Level (DN(M)EL) for (nano)particles, a calculation of the actual lung dose could be performed. However it has been noted that there are considerable differences in ventilation rates, deposition patterns, and clearance rates between humans and animals, and all of these factors should be taken into account within this calculation. In addition, if performing an extrapolative calculation based upon physiological parameters such as ventilation rates, this should be assessed against other calculations performed in the derivation of a DN(M)EL (i.e. starting point modification for exposure duration, ventilation rates etc.). This is to address potential for duplication of calculations. As part of the proposed Guidance update, text has been suggested covering such issues as lung deposition and clearance rates as well as the suggestion that consideration be given to the use of alternative physiological parameters to body weight, e.g. lung weight, lung surface area. In relation to both deviation from the REACH default approach and the use of alternative parameters etc., these should be scientifically justified. The use of additional exposure metrics such as particle surface area or number concentration (especially for fibres) should be considered when performing analysis. Sufficient characterisation of a material being tested, to allow obtained results to be expressed using several different metrics in addition to the conventional mass metric, should be encouraged and would be seen as a benefit to study design

In R.10, a caveat is recommended indicating a limitation of the use of the equilibrium partitioning method for nanomaterials (R.10.5.2.1, R.10.5.3.1, and R.10.6.1). In addition a recommendation is made to highlight the increased uncertainty when no nanomaterial-specific data are available.

In R.13, a paragraph has been added to indicate that the effectiveness of risk management measures (RMM) for nanomaterials should not be assumed to be the

same as for other substances. Additional changes are proposed to the RMM library in the form of notes concerning the effectiveness of enclosure, Respiratory Protective Equipment (RPE), hand protection and suits, and health surveillance.

In R.14, changes are recommended to provide more information on the technical issues relating to the measurement on nanomaterials, the need to consider other metrics, the applicability of simulation studies, and the limitations of models. An extensive appendix dealing with discrimination from background particles, measurement of size distribution, maximum relevant size, spatial and temporal variability, choice of metric, high aspect ratio nanomaterials, measurement instruments and sampling strategy has been developed. The recommendation is made that this appendix should also be linked to R.7. In R.14.2, a paragraph has been added to recommend consideration of other units, in addition to mass based ones for inhalation. Several recommendations to consider the use of simulation studies have been made (R.14.4.1, R .14.4.4). In R.14.4.7, a caveat has been added to indicate that exposure models have not been validated for nanomaterials and should be used with caution. Caveats in relation to modelling have also been added in several places in several other exposure related chapters (R15.2.3, R.16.5, R.17.2, R.17.4.1, R.17-1 and 18.5.2).

In R.15.2, a paragraph has been added to recommend consideration of other units, rather than only mass based ones for inhalation. In R.15.3.1, reference is made to the relevance of the respirable fraction for nanomaterials.

In addition to these guidance recommendations, a series of recommendations for further research have been made. Specifically,

In R.8:

- Establishing the most appropriate metric(s) upon which to base a derived exposure limit.
- An improved understanding of the drivers of toxicity and the influencing physico-chemical attributes which affect absorption kinetics.
- Generation of quantitative or at least qualitative approaches for addressing respiratory sensitisation.

In R.13:

- Assessment of the effectiveness of a whole range of RMM needs to be established for use with different types of nanomaterials.
- Collection of fundamental information about how RMM and OC are actually implemented through industrial practice.
- More information on the efficacy of any of the consumer RMMs for substances containing nanomaterials.
- More information is required on the effectiveness of prevention of release to air, and to water, and in relation to release to soil.

In R.14:

- There is a need for development of improved measurement tools for assessment of exposure to nanomaterials. These would include tools which give the possibility of multi-metric approaches. Linked to this issue is the need for development of a personal sampler.
- Improved methods and approaches for discrimination of background nanoparticle aerosols are required. These could take the form of measurement or analytical solutions or improved validated strategic approaches (experimental design approaches) which would enable discrimination to be more clearly demonstrated and achieved.
- There is a need for a much improved sampling strategy to be implemented to take account of the multiple needs and the issues which have been identified. In the context of REACH, the development of a strategy specifically for REACH compliance issues is necessary.
- There is also a need to further develop the evidence base about the potential for release from a whole range of types of activities and processes. This would include measurements made in actual industrial scenarios but also laboratory based simulation experiments which would provide the basis for more rapid gathering of data and information.

- Collection of available evidential data concerning release and exposure would enable much more extensive validation of models to be carried out if required and, based on these validation exercises, new model approaches could be developed.

- Most of the published data concerns synthesis/manufacturing processes. There is a clear need for more information to be gathered from other stages of the life cycle of substances. For example, uniform release of nanomaterials during the use of products containing nanomaterials is currently almost completely absent from the literature.

In R.15:

- Substantial additional work is required to be done in order to validate the models for use with nanomaterials. This includes generation of base data for validation including for example through simulations and use of this data to test and adapt the models.

In R.17:

- Much more work is required to assess the potential emissions of articles which contain nanomaterials or are coated with nanomaterials. This would include the use of simulation type studies (in practice simulation studies are probably the only way by which useful data can be obtained). Based on the collection and assembly of such data, the efficacy of the release models could be validated. This should be considered a high priority for research. This applies both to release and exposure for humans and for the environment.

In conclusion, the RIP-oN 3 project has been performed an objective scientific review based on an informed, objective and systematic gathering and consideration of evidence by experts who have used their knowledge and professional judgement when considering the impact and contribution of the scientific evidence towards delivering the project's objectives. A comprehensive synthesis of findings, implications, issues and advice has been developed and integrated through the Task Reports and the Final Project Report. Where considered relevant, feasible and justified, specific advice for updating guidance has been provided. For issues which are not currently technically/scientifically mature for developing detailed guidance, the need for further

research and development has been indicated. The assessment of the scientific evidence and subsequent recommendations are the considered opinion of the authors and are submitted for consideration by the European Commission.

CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AF	Assessment Factor
AC	Article Category
ANSES	French Agency for Food, Environmental and Occupational Health and Safety
ART	Advanced REACH Tool
BAUA	The Federal Institute for Occupational Safety and Health
BEL	Biological Exposure Limit
BET	Brunauer, Emmet and Teller
BMD	Benchmark Dose
BMDL	Benchmark Dose (Lower Confidence Limit)
BOEL	Binding Occupational Exposure Limit
BSI	British Standards Institution
CARACAL	Competent Authorities for REACH and CLP
CASG-Nano	Competent Authorities Sub-group on Nanomaterials
CB	Control Banding
CEFIC	European Chemicals Industry Council
CEN	European Committee for Standardization
CES	Contributing Exposure Scenario
CLP	Classification, Labelling & Packaging
CMR	Carcinogenic, Mutagenic, or Reproductive toxin
CNT	Carbon Nanotube
COSHH	Control of Substances Hazardous to Health
CPC	Condensation Particle Counter
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
D_{ae}	Aerodynamic Diameter
DG	Directorate-General
DIS	Draft International Standard
DMA	Differential Mobility Analyzer
DMEL	Derived Minimal Effect Level
DNA	Deoxyribonucleic acid
DNEL	Derived No Effect Level
EC	European Commission
EC10	Effective Concentration at 10% mortality rate
EC50	Half Maximal Effective Concentration
ECHA	European Chemicals Agency

Abbreviation	Definition
EDAX	Energy-dispersive X-ray Spectroscopy
EFSA	European Food Safety Authority
ELPI	Electrical Low Pressure Impactor
ENRHES	Engineered Nanoparticles – Review of Health & Environmental Safety
EPA	Environmental Protection Agency
ERC	Environmental Release Categories
ES	Exposure Scenario
eSDS	Extended Safety Data Sheet
EU	European Union
FDIS	Final Draft International Standard
FMPS	Fast Mobility Particle Sizer
FP	Framework Programme
HARN	High Aspect Ratio Nanoparticle
HED	Human Equivalent Dose
HEPA	High Efficiency Particulate Air
ICHP	Institute for Health and Consumer Protection
IOEL	Indicative Occupational Exposure Limit
IOM	Institute of Occupational Medicine
IPCS	International Programme on Chemical Safety
IR	Information Requirements
ISO	International Organization for Standardization
JRC	Joint Research Centre
K_{ow}	Octanol-Water Partition Coefficient
Kp	Partition Coefficient
LC50	Half Maximal Lethal Concentration
LEV	Local Exhaust Ventilation
LMS	Linearised Multistage Model
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
MMAD	Mass Median Aerodynamic Diameter
MSDS	Material Safety Data Sheet
MWCNT	Multi-walled Carbon Nanotubes
NEDO	Japanese New Energy and Industrial Technology Development Organisation
NGO	Non-Governmental Organisation
NIA	Nanotechnology Industries Association
NIOSH	National Institute for Occupational Safety and Health
NM	Nanomaterial

Abbreviation	Definition
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NOM	Natural Organic Matter
NP	Nanoparticle
OC	Operational Condition
OECD	Organisation for Economic Co-operation and Development
OECD-WPMN	Organisation for Economic Co-operation and Development Working Party on Manufactured Nanomaterials
OEL	Occupational Exposure Limit
OPC	Optical Particle Counter
PAR	Proximal Alveolar Region
PBPK	Physiologically-Based Pharmacokinetic
PC	Product Category
PEC	Predicted Environmental Concentration
PET	Polyethylene terephthalate
PM	Particulate Matter
PNEC	Predicted No Effect Concentration
PPE	Personal Protective Equipment
PROC	Process Category
PSLT	Poorly Soluble, Low Toxicity
QSAR	Quantitative Structure Activity Relationship
QSPR	Quantitative Structure Property Relationship
R&D	Research and Development
RCR	Risk Characterisation Ratio
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals Regulation
REL	Recommended Exposure Level
RIP-oN	REACH Implementation Projects on Nanomaterials
RIVM	National Institute for Public Health and the Environment
RMM	Risk Management Measure
RMV	Respiratory Minute Volume
RPE	Respiratory Protective Equipment
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCG	Stakeholder Consultation Group
SDS	Safety Data Sheet
SEM	Scanning Electron Microscopy
SI	Substance Identification
S-IN	Solluzioni Informatiche

Abbreviation	Definition
SMPS	Scanning Mobility Particle Sizer
SPE	Skin Protective Equipment
STP	Sewage Treatment Plant
SU	Sector of Use Category
SWA	Safe Work Australia
TEM	Transmission Electron Microscopy
TTC	Threshold of Toxicological Concern
TWA	Time Weighted Average
WEL	Workplace Exposure Limit
WHO	World Health Organization

1 INTRODUCTION

This document constitutes the Final Report provided by the contractor to the Joint Research Centre (JRC) on the project "Specific Advice on Exposure Assessment and Hazard/Risk Characterisation for Nanomaterials under REACH (RIP-oN 3)".

1.1 PREFACE

1.1.1 The implementation of the European Union's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation (EC) No 1907/2006, represents a fundamental shift in the regulation of manufactured and imported chemicals in the European Union. Having entered 'into force' on 1 June 2007 and 'into operation' on 1 June 2008, the new regime's overriding objective is 'to ensure a high level of protection of human health and the environment, including the promotion of alternative methods for assessment of hazards of substances, as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation '. Its provisions are underpinned by the precautionary principle.

1.1.2 As REACH effectively shifts responsibility from authorities to industry to gather information on chemical substances and assess their safety. It has been clarified that the provisions of REACH refer to substances (in whatever size or forms) and also apply to nanomaterials that are considered either as distinct substances or forms of a substance (CA/59/2008rev1). However, a degree of uncertainty exists concerning the adequacy of the regulation and the accompanying guidance for the emerging and rapidly developing nanomaterials industry.

1.1.3 Therefore the Commission launched the REACH Implementation Projects on Nanomaterials (RIP-oNs) with the objective to provide scientific and technical advice on key aspects of the implementation of REACH with regard to nanomaterials, namely:

i) Substance Identification (SI) (RIP-oN 1)
ii) Information Requirements (IR) (RIP-oN 2)
iii) Chemical Safety Assessment (CSA) (RIP-oN 3)

1.1.4 The Institute for Health and Consumer Protection (IHCP) of the JRC was asked to perform and coordinate the activities aimed at developing advice for possible future REACH guidance improvement. The advice should be based on the scientific and technical state of the art information, experience and methodology regarding nanomaterials (NM). It should provide concrete proposals that could be implemented directly, and indicate the possible way forward for any issues and methods that need further work and could be implemented in the short and medium term. The main focus should be on issues and methods that could be included in the REACH guidance and possibly implemented in the short term, after the pertinent further development and consultation process. These recommendations would contain practical proposals for how and based on which information this update could take place. The outputs are to be developed in such a way that the advice on specific issues related to nanomaterials can be integrated into the existing REACH guidance documents and/or propose research and development (R&D) needed for developing such guidance. The actual inclusion of any of the advice into the guidance documents is the responsibility of the European Chemicals Agency (ECHA) and is not part of commissioned projects. The work is performed in close collaboration with Directorate-General (DG) Environment, DG Enterprise and ECHA who constitute the steering group for these activities.

1.1.5 JRC let competitive tenders and commissioned two REACH Implementation Projects on Nanomaterials (RIP-oN 2 and RIP-oN 3), with the purpose of advising how the Information Requirements (IR) and Chemical Safety Assessment (CSA) guidance could be updated to better reflect the REACH requirements for nanomaterials.

1.2 CONSIDERATION OF THE PURPOSE, SCOPE AND FINDINGS OF THE RIP-ON3 PROJECT IN THE CONTEXT OF SUBSTANCE IDENTIFICATION AND REGISTRATIONS ADDRESSING SEVERAL FORMS, INCLUDING NANOFORMS

1.2.1 Assisted by the 'Guidance for identification and naming of substances in REACH'[1], the registrant shall decide whether different forms of a (nano)material shall be registered in their own right or together with other forms, e.g. the micron or bulk (non-nanoscale) form. It should be noted that the ongoing RIP-oN 1 project is addressing how the guidance on identification and naming could be updated to reflect in more detail how to address nanoforms. The results of RIP-oN 1 will eventually be handed over to ECHA and ECHA might in turn decide to update the guidance for identification and naming of substances.

1.2.2 Until a possible update of the identification and naming guidance, the registrant is referred to the document 'Nanomaterials in REACH' (CA/59/2008 rev. 1)[2], specifying, between others:

> "REACH is based on the principle that it is for manufacturers, importers and downstream users to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment (Article 1(3) of REACH). This principle is applicable to substances in whatever size or form and for all their identified uses. Thus, a registration of a nanomaterial has to include all relevant information on the nanomaterial as manufactured or imported, covering the properties, uses, effects and exposure related information as well as the relevant classification and labelling, safety assessment and any relevant exposure scenarios " (p. 6), and;
>
> "For substances at nanoscale that are phase-in substances, the registration can be more complex, especially when the same substance exists in the nanoform as well as in the bulk form. In such a case not only the information of the substance in the bulk form should be included

[1] http://guidance.echa.europa.eu/docs/guidance_document/substance_id_en.htm?time=1301642719

[2] http://ec.europa.eu/environment/chemicals/reach/pdf/nanomaterials.pdf

in the registration dossier, but also any information regarding intrinsic properties where the properties of a substance in the nanoform differs from the bulk form, any different classification and labelling, any different chemicals safety assessment as well as all identified uses (see also Annex VI.3 of REACH) and relevant exposure scenarios for the nanoform of the substance." (p.8).

1.2.3 Until more concrete guidance is provided by ECHA, it is suggested that the registrant follows this line. This has a direct influence on the generation of hazard data, e.g. any read-across from one form to the other (being from a bulk form to a nanoform or between nanoforms) should be scientifically justified. It also has influence on the information in the supply chain, which has to be appropriate to the form(s) passing down the supply chain and the Chemical Safety Assessment should support this. The suggested guidance updates from the RIP-oN 3 project need to be seen in this light.

1.3 PROJECT OBJECTIVES

1.3.1 The objectives of the RIP-oN 3 project were to:

- Develop advice on how to do exposure assessment for nanomaterials within the REACH context. This shall be the main focus of project and shall cover: 1) development of Exposure Scenarios, 2) evaluation of operational conditions and risk management/mitigation measures and 3) exposure estimation;
- Develop ideas for how to conduct hazard and risk characterisation for nanomaterials. The latter will involve threshold/non-threshold considerations.

1.3.2 The results of this project are to be developed in such a way that the advice on specific issues related to nanomaterials can be integrated into the existing REACH guidance documents and/or propose research and development (R&D) needed for developing such guidance.

1.4 THE PROJECT CONSORTIUM

1.4.1 The consortium awarded the tender for RIP-oN 3 comprises the Institute of Occupational Medicine (IOM) through its SAFENANO initiative, the

Nanotechnology Industries association (NIA), the European Chemicals Industry Association (CEFIC) and Solluzioni Informatiche (S-IN).

1.4.2 IOM/SAFENANO, with an established reputation for independent scientific work, led the consortium and carried out the bulk of the technical activities. NIA facilitated and provided a transparent interface between the project and the stakeholder group, as well direct access to industry and industrial knowledge. CEFIC contributed a breadth of experience and expertise on REACH activity as well direct access to industry and industrial knowledge. S-IN contributed primarily to the C1 task.

2 DESCRIPTION OF THE PROJECT

2.1 OVERVIEW

2.1.1 The main overall aim of this project is to develop recommendations for changes to the REACH guidance which take account of specific issues in relation to nanomaterials. This assessment is based on current generation NMs and consequently future generation NMs have not been addressed. The approach taken was largely driven by the contract specifications and comprised a step wise, evidence based approach, on which guidance changes were developed. The approach therefore is based on a number of interlinked tasks which are identified below.

A. Identification & Review of Information Sources

B1. Exposure scenario cases/examples

B2. Operational conditions & Risk Management Measure (RMMs) - harvesting results from on-going activities

B3. Exposure estimation - harvesting results from on-going activities

B4 Advisory report on Operational Condition (OC), RMM, Exposure Scenario (ES) and Exposure estimation with the purpose of conducting Exposure assessment of NM for REACH

C1. Case studies on how no effect levels could be established

C2. Hazard / risk characterisation – harvesting results from on-going activities

C3. Advisory report on hazard and risk characterisation for NM

D. Metrics to compare in risk characterisation

2.1.2 The initial activity was the collection and review of information from a wide range of sources. This comprised the main activity in Task A.

2.1.3 This was followed by an evaluation of the evidence base to identify the key scientific issues arising that had possible implications for the REACH guidance. This included, in relation to exposure and exposure scenarios Tasks B1, B2 and B3, in relation to hazard and to risk characterisation the Tasks C1 and C2, and in relation to metrics the Task D.

2.1.4 The next stage was the identification, from the perspective of the scientific evidence, where changes should be made within the guidance. This comprised Tasks B4 (in relation to exposure issues) and C3 (in relation to hazard and risk issues).

2.1.5 The final stage of the project was a section by section analysis of the existing REACH guidance. Specifically, for the B tasks: Part D (Exposure Scenario building), Part F (Chemical Safety Report (CSR), incl. CSR format), Part G (Extending the Safety Data Sheet (SDS)), Chapter R.12 (Use descriptor system), Chapter R.13 (Risk management measures and operational conditions), including the RMM library and Chapters R.14, R.15, R.16 and R.17 (on exposure estimation in relation to different types of scenario). It also considers the RMM library. For the C tasks: the focus was on Chapters R.8 and R.10.

2.1.6 The assessment considered in detail the optimum set of changes which could be made to the guidance. Based on this analysis, detailed guidance changes were developed along with recommendations for research where this was indicated. This activity forms the main aspect of the final project report (this document).

2.2 DELIVERABLES

2.2.1 A series of reports were developed for the specified tasks, as summarised in the table below.

Task	Deliverable
A	**A short report** containing: 1. A brief description of the approach/methodology used to identify relevant information sources; 2. A list of identified information sources with clear indications of which ones are relevant for the subsequent tasks; 3. For relevant information sources, a brief summary of relevant content and timelines for final outputs (in the case of on-going projects).
B1	**Exposure Scenario Examples for the selected 3-4 cases,** including the process of identifying uses, the process of obtaining the right information from the downstream users, ESs in the iterative CSA and how the ESs can be incorporated into SDSs, as well as a list of types and efficiency of Risk Management Measures (RMM) and operational conditions typically applied within the branch and, where necessary, additional RMMs or refinement of operational conditions needed to adequately control risks. When measurements are applied, advice on available instrumentation and equipments should be specified, as well as how to deal with background exposure.
B2	**A working document** summarising what can be harvested in relation to applicability and efficiency of operational conditions and risk management measures for controlling nanomaterial exposure to workers, consumer, the environment and man via the environment.
B3	**A working document** summarising what can be harvested in relation to exposure estimation (sampling, modelling and measurements) of workers, consumer, the environment and man via the environment to nanomaterials. When measurements are considered, this should address potential background exposure to nanoparticles and choice of instrumentation and equipment for detection of nanoparticles
B4	**An advisory report** with detailed proposals with a view to be considered, if appropriate, for possible future guidance in relation to information requirements and chemical safety assessment, i.e. in relation to operational conditions, Risk Management Measures, Exposure Scenarios and Exposure Estimation (sampling, modelling, measuring and how to deal with background exposure to nanoparticles) and for measurements issues related to monitoring devices and equipments; and where detailed technical proposals are not yet possible, indications of further research and development needs and likely time frame
C1	**3-4 case examples** demonstrating how no-effect levels can be established.
C2	**A working document** summarising what can be harvested from ongoing activities in relation to qualitative and quantitative hazard/risk characterisation for nanomaterials.
C3	**An advisory report** with detailed proposals with a view to be considered, if appropriate, for possible future guidance in relation to information requirements and chemical safety assessment, i.e. in relation to hazard and risk characterisation; and where detailed technical proposals are not yet possible, indications of development needs and possible time frame .
D	**A working document on** identification of critical items on exposure/dose descriptors and related parameters, outlining needs for adequate metrics/parameters as appropriate for exposure assessment compatible with the ones used for hazard assessment as well as for the read-across from bulk substances and from other nanomaterials. This document will be developed in close collaboration with RIP-oN 2.

2.2.2 The present report, as already indicated in the introduction, constitutes the Final Project Report and provides advice for updating the guidance and on R&D needs. This takes the form of specific recommendations or options for consideration by the Commission. For issues which are not currently technically/scientifically mature for developing detailed guidance, the need for further R&D is indicated.

2.2.3 The focus of the RIP-oN 3 project has been on nanomaterial relevant issues. Nevertheless, due to the nature of some NMs, some proposals may have implications for other substances that are not nanomaterials. These would need to be considered if reshaping of the REACH guidance takes place.

2.3 LIST OF TASK REPORTS

2.3.1 The following task reports have been developed during the project and are referred to further in the current document using the names indicated:

- Final Report on Task A: Identification and Review of Information Sources (RNC/RIP-oN3/A/1/FINAL)
- Final Report on Task B1: Exposure Scenario Case Studies (RNC/RIP-oN3/B1/2/FINAL)
- Final Report on Task B2: Operational conditions and risk management measures - harvesting results from on-going activities (RNC/RIP-oN3/B2/2/FINAL)
- Final Report on Task B3: Exposure estimation (modelling and measurements) - harvesting results from on-going activities (RNC/RIP-oN3/B3/2/FINAL)
- Final report on Task B4: Advisory Report on Operational Conditions, Risk Management Measures, Exposure Scenarios and Exposure Estimation (modelling and measurement) with the Purpose of Conducting Exposure Assessment of Nanomaterials for REACH purposes (RNC/RIP-oN3/B4/2/FINAL)
- Final Report on Task C1: Case-studies on how no-effect-levels for health and the environment could be established (RNC/RIP-oN3/C1/2/FINAL)
- Final Report on Task C2: Hazard / risk characterisation harvested from on-going activities (RNC/RIP-oN3/C2/2/FINAL)

- Final Report on Task C3: Advisory Report on Hazard and Risk Characterisation of Nanomaterials (RNC/RIP-oN3/C3/2/FINAL)
- Joint Final Report on RIP-oN2 Task C & RIP-oN3 Task D: Metric(s) to compare in the risk characterisation (RNC/RIP-oN3/D/2/FINAL)

2.4 REVIEW AND CONSULTATION WITH THE EC-APPOINTED STAKEHOLDER CONSULTATION GROUP (SCG)

2.4.1 All Task Reports were subject to review by the project's Steering Group (constituting representatives of JRC, DG Environment, DG Enterprise and ECHA) and a Stakeholder Consultation Group (SCG) consisting of the members of the REACH Competent Authorities Sub-Group on Nanomaterials (CASG-Nano) and other relevant experts from Member States, industry and Non-Governmental Organisation (NGOs) nominated by the REACH and Classification, Labelling & Packaging (CLP) Competent Authorities (CARACAL). The draft Task Reports were opened for consultation with the above mentioned groups, discussed at meetings of the SCG, revised by the Project Consortium and re-opened for comment before being finalised.

2.5 TECHNICAL APPROACH

2.5.1 The project has been performed as an objective review of the existing guidance and available scientific evidence pertinent to the specified tasks.

2.5.2 The conduct of this scientific review is based on an informed, objective and systematic gathering and consideration of evidence by experts who have used their knowledge and professional judgement when considering the impact and contribution of a source document to the task objective. It is important to note the inherent limitations of a review activity. Reviews are conducted at a fixed point in time which precludes the inclusion of information that becomes available after a set cut-off date. Information sourced may be incomplete or, on closer inspection, the content of a source document bears no relevance to the issues being considered. Information may also change in revisions of the sources considered.

2.5.3 Based on the objective and informed assessment of published reports constituting the evidence-base available to call upon, a synthesis of findings, implications and/or issues distilled from the sources has been developed and

integrated into the task reports. The review of source reports has identified and used the methods and materials used (as appropriate), key findings, and remaining gaps in establishing the technical basis facilitating the development of advice pertinent to the project.

2.5.4 **Identification and review of information sources (Task A)**

2.5.5 Relevant information was collected, assessed, categorised and made available for the project team. There is a range of relevant information and information types. The information includes background information from organisations such as CASG Nano, Organisation for Economic Co-operation and Development Working Party on Manufactured Nanomaterials (OECD WPMN), Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Standards organisation such as International Organization for Standardization (ISO) and European Committee for Standardization (CEN), FP6/7 projects, other ongoing national projects, other international regulatory organisations such as National Institute for Occupational Safety and Health NIOSH and Environmental Protection Agency (EPA) and from the peer reviewed literature. Reports and papers were assessed for specific relevance to the project.

2.5.6 The report from Task A comprised a brief description of the approach/methodology used to identify relevant information sources, the list of identified information sources with clear indications of their relevance to the respective tasks and comment of the relevant content.

2.5.7 **Exposure Scenario (ES) case studies (Task B1)**

2.5.8 In this task, Exposure Scenario (ES) case studies for nanomaterials were developed working with industry “Case Study Providers”. They were intended to investigate the process of collating, reporting and processing information required for the building of ES on specific nanomaterials, providing information to downstream users and obtaining the right information from the downstream users in return, as well as providing a list of types and efficiency of Risk Management Measures (RMM) and Operational Conditions (OCs). The Case-Studies furthermore aimed to evaluate the use of ESs in the iterative CSA, including estimating exposure to nanomaterials, the possibility

of incorporating ESs into Safety Data Sheets (SDSs) for the purpose of communication down the supply chain. Specific emphasis was given to reviewing the methodology applied by a Case-Study providing company to estimate the generic exposure, providing details on any assumptions made, models applied or instrumentation and equipment used to conduct static or personal (monitoring) exposure measurements. The review of this methodology allowed for a case-specific evaluation of: a) the clarity of guidance given on generic exposure estimation, and; b) the applicability of modelling tools and measurement equipment to the case-specific nanomaterials, with view to expressing recommendations on potentially necessary additions to the REACH guidance.

2.5.9 The ES Case-Studies were based on the reporting template provided in the ECHA Guidance on information requirements and chemical safety assessment – Part D: Exposure Scenario Building; Part F: CSR Format (Version available January 2010). This was close to, but not identical to, the version subsequently published by ECHA in May 2010.

2.5.10 The tables outlined in this ECHA Guidance were reproduced in an Excel Spreadsheet (with extra columns added for the provision of details on any assumptions made, models applied or instrumentation and equipment used to conduct static or personal (monitoring) exposure measurements).

2.5.11 For each ES Case-Study, the ES reporting templates were completed and discussed in an iterative process involving the case study providers and experts from the RIP-oN 3 team through a series on meetings and telephone discussions. During the iterative discussion process between Case-Study providers and RIP-oN 3 team experts, specific attention was given to obtain feedback from both the Case-Study providers and the RIP-oN 3 team experts.

2.5.12 Case-Study providers were asked to provide feedback with regard to: the technical process of working with the reporting template provided by ECHA Guidance Document Part D & F as a reporting template for ES on nanomaterials; the information required in completing the reporting template for nanomaterials, and the overall experience in building exposure scenarios for nanomaterials. Experts were asked to comment on their opinion on interpreting the data delivered by the Case-Study providers in the reporting

template, with a specific view to: compare the data delivered by the individual Case-Study providers; consider the appropriateness of exposure estimation approaches, with a specific view to highlighting the gaps arise from the non-nano-specific nature of the methods, and; consider the appropriateness of the reporting template for building ES for nanomaterials, highlighting the shortcoming and gaps in the reporting template.

2.5.13 **Operational Conditions and Risk Management Measures - harvesting results from on-going activities (Task B2)**

2.5.14 Task B2 was a review task. The inputs to the task included literature (guidance, reports, standards, peer reviewed) identified in Task A of RIP-oN 3 as well as the information collected from industrial sources in the exposure scenario case studies that make up Task B1. Sources of information include standards from ISO (ISO, 2007; 2008) and the British Standards Institution (BSI, 2007), reports from the Organisation for Economic Co-operation and Development (OECD, 2010) and outputs from European projects such as NanoSafe2 (http://www.nanosafe.org; accessed 4th September 2010), as well as the general scientific literature.

2.5.15 The literature identified in Task A was reviewed to harvest the relevant material relating to operational conditions and risk management measures. The review had a primary focus of identifying and capturing such information as was likely to make a material contribution to the development and guidance of the REACH guidance.

2.5.16 The deliverable foreseen in this task was a working document summarising what can be harvested in relation to applicability and efficiency of operational conditions and risk management measures for controlling nanomaterials exposure to workers, consumer, the environment and man via the environment.

2.5.17 **Exposure estimation (modelling and measurements) - harvesting results from on-going activities (Task B3)**

2.5.18 The technical approach taken in this task mirrored that taken in Task B2 but considered the evidence relating to exposure estimation. In this task all

relevant information pertaining to availability, adequacy and applicability of methods for sampling, modelling and/or measuring exposure of workers, consumers, the environment and man via the environment to nanomaterials was estimated.

2.5.19 The deliverable foreseen in this task was a working document summarising what can be harvested in relation to estimation of exposure to workers, consumer, the environment and man via the environment.

2.5.20 **Advisory report on Operational Conditions, Risk management Measures, Exposure Scenarios and exposure estimation (modelling and measuring) with the purpose of conducting exposure assessment of nanomaterials for REACH purposes (Task B4)**

2.5.21 In this task, Tasks A to B3 were drawn together to prepare an advisory report, in order to cover the exposure assessment of nanomaterials in the REACH context.

2.5.22 It was the intention that the contents of the report would be presented in such a form that the advice on specific issues related to nanomaterials is scientifically justified and written in a form that will facilitate easily the future integration into the existing REACH Guidance on Information Requirements and Chemical Safety Assessment (i.e. guidance text/language) with clear reference to the existing REACH Guidance Part and Chapter and Sub-chapter.

2.5.23 **Case examples on how no-effect-levels for health and the environment could be established (Task C1)**

2.5.24 The aim of sub-task C1 was to examine how no-effect-levels for health and the environment could be established using case examples of four nanomaterials, namely carbon nanotubes, nano-titanium dioxide (nano-TiO_2), nano-particulate silver, and nano-zinc oxide (nano-ZnO) (the latter for ecotoxicology aspects). Our selection of these nanomaterials is based on the relative widespread use of these materials and evidence of differing toxicological profiles. (Note that these cases do not necessarily address the same nanomaterials as those in Task B1).

2.5.25 The task began with a consideration of the publically available literature surrounding these four materials and, from the identified sources, data of particular relevance to the derivation of no-effect-levels for health and the environment was selected. As the concepts of similarity between nanomaterials is ill defined and methods such as grouping or classification is not yet apparent (suggested as a high R&D priority within RNC/RIP-oN2/B5/2/FINAL and RNC/RIP-oN2/FPR/1/FINAL), a case-by-case approach was taken.

2.5.26 Using the identified data sources, an assessment of the REACH approach for the generation of no-effect-levels for health and the environment was made in the context of the current data, scientific understanding and the approach taken by others.

2.5.27 When considering human health effects of a substance, a level needs to be specified at which no adverse effects will occur or where this is not possible, a level at which only minimal adverse effects may occur. In order to achieve this, REACH introduces a methodology for deriving a derived no effect level (DNEL) or when a threshold can not be determined, a derived minimal effect level (DMEL). Studies identified under Task A were reviewed in regard to deriving a human exposure limit for case-study nanomaterials.

2.5.28 Whilst an increasing volume of data exists surrounding the potential (adverse) health effects of nanomaterials, only a few studies have been performed using acceptable methodologies and study design suitable for DN(M)EL derivation. These studies were identified and used as a starting point in the consideration of whether effects were threshold or not and the reported no/low observed adverse effect level (N(L)OAEL) used in the derivation of an exposure limit.

2.5.29 Within the studies considered, two further approaches to deriving exposure limits were identified within the literature for nanomaterials, specifically that of Pauluhn (2010a) and that of the Japanese New Energy and Industrial Technology Development Organisation (NEDO) project (Hanai et al. 2009; Kobayashi et al. 2009). These approaches were also evaluated for scientific merit and compared to the REACH default approach.

2.5.30 In the case of effects to environmental species, the REACH regulation uses the Predicted No Effect Concentration (PNEC) in order to specify the concentration of the substance below which no adverse effects are expected to occur. Studies identified under Task A were reviewed in regard to deriving a PNEC.

2.5.31 Water and soil were considered as the environmental compartments for the case example nanomaterials - MWCNT, nano-titanium oxides, nano-silver, and nano-zinc oxide. For each environmental compartment, the available concentration-response data (Half Maximal Lethal Concentration (LC50), Lowest Observed Effect Concentration (LOEC) and No Observed Effect Concentration (NOEC)) was obtained from the peer reviewed literature and reports accessible via the information resource constructed under Task A in RIP-oN 3. Notably, the recent Engineered Nanoparticles – Review of Health & Environmental Safety (ENRHES) report (Stone et al., 2009) has been used as a starting point and subsequently updated with further scientific data and information considered to be of specific relevance in the context of the RIP-oN 3 project. The same approach to examining the data as used by Stone et al. (2009) in the FP7 ENRHES project was followed.

2.5.32 A limited number of ecotoxicological studies have explored nanomaterial toxicity towards the base-set organisms used in the REACH risk assessment procedures for chemicals (fish, crustacean and algae). Few studies report the results of these studies in the format required by the REACH risk assessment procedures for chemicals (LC50, EC50, NOEC, and LOEC).

2.5.33 The identified data on MWCNT, nano-titanium oxides, nano-silver, and nano-zinc oxide was evaluated with regard to its adequacy and completeness.

2.5.34 The kind of data available (e.g. one long-term test (NOEC or Effective Concentration at 10% mortality rate (EC10)), one acute freshwater or marine test), according to R.10.3-10.10 on the derivation of PNEC, was determined for:

2.5.35 a) aquatic compartments (freshwater and marine) (table R.10-4 Assessment factors to derive a $PNEC_{aquatic}$ and table R.10-5

Assessment factors proposed for deriving $PNEC_{water}$ for saltwater for different data sets);

2.5.36 b) micro organisms in sewage treatment plants (STP) (table R.10-6 Test systems for derivation of $PNEC_{microorganisms}$);

2.5.37 c) Freshwater and marine sediment (table R.10-7 Assessment factors for derivation of $PNEC_{sed}$, table R.10-8 Assessment factors for derivation of $PNEC_{marine}$ sediment from short-term sediment toxicity tests, table R.10-9 Assessment factors for derivation of $PNEC_{marine\ sediment}$ from long-term sediment toxicity tests);

2.5.38 d) Terrestrial (soil) compartment (table R.10-10 Assessment factors for derivation of $PNEC_{soil}$).

2.5.39 Based on the available data, the appropriate assessment factor was identified and a PNEC was derived and commented on.

2.5.40 **Hazard/risk characterisation - harvesting results from on-going activities (Task C2)**

2.5.41 In this review activity, we harvested relevant information concerning how human and environmental hazards and risks of nanomaterials could be, or have been characterised – quantitatively and/or qualitatively by others. The report investigated aspects of quantitative hazard characterisation relevant to nanomaterials covering particle size and surface area with particular focus on their relevance to toxicology/ ecotoxicology.

2.5.42 In the discussion of the hazard/risk characterisation from on going activities, the approach again focused upon three case examples of nanomaterials (MWCNT, nano-titanium dioxide and nano-particulate silver). Specifically key relevant work already identified was summarised and discussed in its relevance to REACH from sources including NIOSH (on TiO_2), BSI (BSI PD 6699-2: 2007), RIVM (on silver) and outputs by the NEDO covering both TiO_2 and MWCNT.

2.5.43 **Advisory report on hazard and risk characterisation of nanomaterials (Task C3)**

2.5.44 Based on the findings from tasks C1, C2 and gleaned from other sources within the RIP-oN 3 project, a report was prepared advising as to how the "Guidance on Information Requirements and Chemical Safety Assessment" could be adapted or complemented in order to facilitate the hazard and risk characterisation of nanomaterials in the REACH context.

2.5.45 The consideration of guidance in relation to its applicability to nanomaterials and the identification of any deficiencies was performed on a section-by-section basis of the relevant guidance documents.

2.5.46 All identified issues within each guidance sub-section were presented in such a form that the advice on specific issues related to nanomaterials is justified based on the current scientific literature available. In addition, where issues have been identified that are not currently technically/scientifically mature for developing detailed guidance, further research and development has been suggested and where possible these have been prioritised.

2.5.47 **Metric(s) to compare in the risk characterisation (Task D)**

2.5.48 Task D was also primarily an analysis and reporting task. The primary inputs were the information developed in Task A and considerations from Task B. In this task, a working document on identification of critical items on those descriptors and related perimeters, outlining needs of what were adequate metrics was deployed.

2.5.49 Key issues considered are the feasibility of measurement for different relevant metrics and the links between toxicology (including how to express no-effect levels) and exposure assessment. Specifically the relationship between measured exposure parameters (alone or in combination) and existing metrics used for dosages (and vice versa). In addition, the possibility and relevance of 'read-across' from bulk substances and from other nanomaterials and to historical data were considered. As indicated in the call text, this document was developed in close collaboration with the similar task in RIP-oN 2 and with the agreement of the Commission, a single joint report covering

the issue from the hazard side (RIP-oN2) and the exposure side (RIP-oN3) was the final deliverable. This report was prepared by a small team with a multi-disciplinary expertise in exposure, toxicology and eco-toxicology.

3 SUMMARY OF FINDINGS

3.1 PREAMBLE

3.1.1 A comprehensive discussion of the findings is provided in the individual task reports. This Final Project Report compiles findings from the previous deliverables into a single document, summarising the key specific issues related to nanomaterials in a REACH context in a form compatible with eventual future integration into the existing REACH Guidance on Information Requirements and Chemical Safety Assessment. Clear references are provided to the existing REACH Guidance Part and Chapter and Sub-chapter.

3.1.2 The summary of findings is presented, with cross-referencing, according to the key outcomes from each task undertaken.

3.2 TASK A: IDENTIFICATION & REVIEW OF INFORMATION SOURCES

3.2.1 The identification and review of information sources (Task A) in RIP-oN 3 has identified, screened (for relevance) and then categorised as comprehensive a range of sources of information as possible, to compile a resource for use in subsequent tasks of the project.

3.2.2 Key organisations, FP6/7 projects and other national projects of relevance to the scope of the project were identified by the project team and through consultation with the European Commission, via JRC. Publically-available reports and outputs from these sources of relevance to the project were then identified and obtained directly from their associated websites and/or through web-based searching.

3.2.3 In relation to the OECD WPMN, three levels of accessible documents which were used and referenced:

- Published documents available on the public OECD WPMN website;
- Documents approved for declassification but not yet published;
- OECD documents developed by the Steering Groups and presented in meetings of the WPMN.

3.2.4 Documentation at an earlier stage of development (e.g. committee draft) was not considered.

3.2.5 With regard to ISO and CEN publications, only published documents and those classified as being at Final Draft International Standard (FDIS) or Draft International Standard (DIS) stage were assessed and utilised where appropriate. Documents in development but not able to be cited at the time of carrying out the RIP-oN 3 project have been identified and recommendations for them to be considered as soon as they become available have been made.

3.2.6 A substantial resource of peer-reviewed literature references was constructed. Literature from the recently completed FP7 Coordination & Support Action ENRHES (Stone et al., 2009), provided an initial comprehensive listing of literature published up to 31st December 2008. The ENRHES literature search was updated for the period 1st January 2009 - 3rd March 2010 and supplemented with additional literature of specific relevance to the RIP-oN 3 project through a non-date-limited Boolean search strategy similar to that of ENRHES using PubMed and Web of Knowledge. In cases where excessively large numbers of references were obtained, the searches were refined by incorporating material-specific terms (e.g. silver, titanium dioxide, zinc oxide).

3.2.7 This search strategy provided a comprehensive bibliography of references across the topic areas of physico-chemical characterisation, production, use and exposure, toxicology, epidemiology, ecotoxicology, and environmental fate and behaviour.

3.2.8 The criteria upon which judgements were made for tagging a reference as relevant for a task are outlined in the table below:

Task	Task Name	Criterion for Inclusion
B1	Exposure scenario (ES) cases studies	Reports and publications outlining exposure assessment case studies for nanomaterials or other relevant substances.
B2	Operational conditions and risk management measures - harvesting results from on-going activities	Reports and publications which discuss operational conditions and risk management measures for nanomaterials or other relevant substances.
B3	Exposure estimation (modelling and measurements) - harvesting results from on-going activities	Reports and publications which discuss occupational, environmental and consumer exposure for nanomaterials or other relevant substances, including literature relating to fate and behaviour in the environment.
B4	Advisory report on operational conditions, risk management measures, exposure scenarios and exposure estimation (modelling and measuring) with the purpose of conducting exposure assessment of NMs for REACH purposes	N/A. This Task is based on Tasks B1-B3 and the literature discussed therein.
C1	Case-examples on how no-effect-levels for health and the environment could be established	Reports and publications, relevant to nanomaterials, which discuss derivation of no effects levels, approaches, threshold considerations and relevant metrics.
C2	Hazard/risk characterisation - harvesting results from ongoing activities	Reports and publications relating to hazard or risk characterisation for nanomaterials or other relevant substances.
D	Metrics to compare in the risk characterisation	Reports and publications dealing specifically with metrics relevant to risk characterisation.

3.2.9 The number of information sources identified and categorised for RIP-oN 3 are as follows:

- 74 published reports and standards from key organisations;
- 30 reports and standards under development from key organisations;
- 92 reports and publications from EU FP6/7 and other relevant international projects;
- 515 reports and publications reviewed in the ENRHES report;
- 630 additional publications from the peer-reviewed literature.

3.2.10 An appendix in the task report provides the complete listing of the sources of information.

3.3 TASK B1: CASE STUDIES

3.3.1 The Case-Studies were intended to illustrate the development of branch-specific general exposure scenarios that take into account normal practice within these branches, cover several processes and, where relevant, be applicable to ranges of nanomaterials and the challenges related to their sampling, detection, measurement and monitoring.

3.3.2 The industrial Case-Studies presented in this report have been collected in the context of REACH; they deliver detailed exposure information for occupational, consumer and environmental release/exposure scenarios for specific MNMs; available information on three very relevant NMs was collated and reviewed:

- nano-TiO_2
- nano-TiO_2 (Mn-doped)
- nano-Ag
- Multi-walled Carbon Nanotubes (MWCNTs)

3.3.3 The ES Case-Studies were provided by companies of various different sizes and at different stages of the business life, working with nanomaterials in different industry sectors and at different stages of the nanomaterials supply chain. The ES Case-Studies presented and discussed in this report therefore have to be regarded as snapshots of various individual and sometimes independent parts of different nanomaterials supply chains; the Case-Studies do not aim to deliver a complete set of ES that covers the entire life-cycle of a specific nanomaterial.

3.3.4 The case studies developed are summarised in the table below.

Case study	Exposure scenario
nano-TiO_2 (BASF) The TiO2 (BASF) Case-Study encompasses 5 Exposure Scenarios (ES), each with Contributing Exposure Scenarios (CESs), describing the different sequential steps in respective TiO2 downstream use and consumer use processes	**ES1:** ***'Transfer of pure nanomaterial for cosmetic formulation (industrial scale, in compliance with GMP)'*** CES1.1: Contributing exposure scenario (1) controlling environmental exposure for *'Transfer of nanomaterial into formulation vessel'* CES1.2a:Contributing exposure scenario (2) controlling worker exposure for *'Transfer of nanomaterial into formulation vessel – PROC2'* CES1.2b:Contributing exposure scenario (3) controlling worker exposure for *'Transfer of nanomaterial into formulation vessel – PROC8b'*
	ES2: ***'Cosmetic formulation and handling of processed nanomaterial (industrial scale, in compliance with GMP)*** CES2.1:Contributing exposure scenario (1) controlling environmental exposure for *'Formulation of sunscreen (large scale)'* CES2.2:Contributing exposure scenario (2) controlling worker exposure for *'Formulation of nanomaterial in oil in closed process'* CES2.3:Contributing exposure scenario (3) controlling worker exposure for *'Sampling of sunscreen formulation and maintenance of equipment'* CES2.4:Contributing exposure scenario (4) controlling worker exposure for *'Sampling and packaging of sunscreen formulation'*
	ES3: ***'Exploratory cosmetic formulation (on laboratory scale)'*** CES3.1:Contributing exposure scenario (1) controlling environmental exposure for *'Formulation of sunscreen (small scale)'* CES3.2:Contributing exposure scenario (2) controlling worker exposure for *'Use as laboratory agent'*

Case study	Exposure scenario
nano-TiO_2 (UMICORE; Manganese-doped) The TiO_2 (UMICORE) Case-Study encompasses 2 Exposure Scenarios (ES), each with Contributing Exposure Scenarios (CESs), describing the different sequential steps in a the respective Mn-doped-TiO_2 manufacturing process	**ES1:** ***'Production of intermediate TiO_2 nanomaterial':*** CES1.1:Contributing exposure scenario (1) controlling environmental exposure for *'Production of intermediate TiO_2 nanomaterial (reactor room)'* CES1.2:Contributing exposure scenario (2) controlling worker exposure for *'Control of production of intermediate TiO_2'* CES1.3:Contributing exposure scenario (3) controlling worker exposure for *'Cleaning, maintenance of reactor room and control room'*
	ES2: ***'Collection & Treatment of Intermediate TiO_2'*** CES2.1:Contributing exposure scenario (1) controlling environmental exposure for *'Collection & Treatment of Intermediate TiO_2'* CES2.2:Contributing exposure scenario (2) controlling worker exposure for *'Collecting Intermediate TiO_2 into bins'* CES2.3:Contributing exposure scenario (3) controlling worker exposure for *'Transfer (of Intermediate TiO_2) from bins to fluidised bed and treatment'* CES2.4:Contributing exposure scenario (4) controlling worker exposure for *'Bagging / Packing of treated TiO_2 into bags'* CES2.5:Contributing exposure scenario (5) controlling worker exposure for *'Cleaning and maintenance in treatment room'*

Case study	Exposure scenario
NANO-SILVER The Nano-Ag Case-Study encompasses 4 Exposure Scenarios (ES), each with Contributing Exposure Scenarios (CESs), describing the different sequential steps in the Nano-Ag value chain	**ES1: *'Production of aqueous silver dispersion 'AgPURE W10'* '(conducted at RAS Materials):** CES1.1:Contributing exposure scenario (1) controlling environmental exposure for *'Production of aqueous silver dispersion 'AgPURE W10''* CES1.2:Contributing exposure scenario (2) controlling worker exposure for *'Preparation/Synthesis of 'AgPURE W10 'nanomaterial'* CES1.3:Contributing exposure scenario (3) controlling worker exposure for *'Transfer of product dispersion into shipment canisters'* CES1.4:Contributing exposure scenario (4) controlling worker exposure for *'Quality Assurance Process'*
	ES2: *'Nano-Ag - Polyethylene terephthalate (PET) Masterbatch Production'* (conducted at Silanotex or at Silanotex subcontractors) CES2.1: Contributing exposure scenario (1) controlling environmental exposure for *'Nano-Ag - PET Masterbatch Production'* CES2.2: Contributing exposure scenario (2) controlling worker exposure for *'Nano-Ag - PET Masterbatch Production'*
	ES3: *'Use/Processing of Nano-Ag - PET Masterbatch'* (conducted at Silanotex or at Silanotex subcontractors) CES3.1: Contributing exposure scenario (1) controlling environmental exposure for *'Use/Processing of Nano-Ag - PET Masterbatch'* CES3.2: Contributing exposure scenario (2) controlling worker exposure for *'Fibre Production'* CES3.3: Contributing exposure scenario (3) controlling worker exposure for *'Fibre Processing'* CES3.4: Contributing exposure scenario (4) controlling worker exposure for *'Fabric Production'* CES3.5: Contributing exposure scenario (4) controlling worker exposure for *'Garment Tailoring'*
	ES4: *'Consumer use of treated Fabrics/Materials'* (conducted by consumers)

Case study	Exposure scenario
Multi-Walled Carbon Nanotubes (MWCNTs The MWCNT Case-Study encompasses 4 Exposure Scenarios (ES), each with Contributing Exposure Scenarios (CESs), describing the different sequential steps in selected MWCNT value chains, ES1 describes the manufacture of crude MWCNTs, while ES2 and ES3 correspond to down-stream use processes of MWCNT-preparations; these are conducted at NanoCyl and the resulting preparations are sold by NanoCyl, but these processes might also be conducted by downstream users, which purchase MWCNTs from NanoCyl. ES4 does not correspond to a real-life process, but simulates a worse-case heavy-duty occupational service life scenario, using a MWCNT-containing thermoplast preparation	**ES1: *'Nanocyl: Upstream manufacture of MWCNTs'* (conducted at NanoCyl):** CES1.1:Contributing exposure scenario (1) controlling environmental exposure for *'Upstream manufacture of MWCNTs'* CES1.2:Contributing exposure scenario (2) controlling worker exposure for *'Manufacturing and packaging of MWCNTs'* CES1.3:Contributing exposure scenario (3) controlling worker exposure for *'Reactor Maintenance'* CES1.4:Contributing exposure scenario (4) controlling worker exposure for *'Quality Control'*
	ES2: *'Production of Thermoplastic Masterbatches'* (conducted at NanoCyl) CES2.1: Contributing exposure scenario (1) controlling environmental exposure for *'Production of thermoplastic masterbatch'* CES2.2: Contributing exposure scenario (2) controlling worker exposure for *'Production of thermoplastic masterbatches by extrusion'* CES2.3: Contributing exposure scenario (3) controlling worker exposure for *'Cleaning of extruder'* CES2.4:Contributing exposure scenario (4) controlling worker exposure for *'Quality Control'*
	ES3: *'Production of Liquid for Coating'* (conducted at NanoCyl) CES3.1: Contributing exposure scenario (1) controlling environmental exposure for *'Production of preparation for coating'* CES3.2: Contributing exposure scenario (2) controlling worker exposure for *'Production of preparation for coating'* CES3.3: Contributing exposure scenario (3) controlling worker exposure for *'Cleaning of the device'*
	ES4: *'Generic Occupational Service Life Scenario of CNTs (heavy-duty abrasion study simulating a sanding process of CNT-containing Thermoplast)'* CES4.1: Contributing exposure scenario (1) controlling environmental exposure for *'Generic Occupational Service Life Scenario of CNTs (heavy-duty abrasion study simulating a sanding process of CNT-containing Thermoplast)'* CES4.2: Contributing exposure scenario (2) controlling consumer exposure for *'Generic Occupational Service Life Scenario of CNTs (heavy-duty abrasion study simulating a sanding process of CNT-containing Thermoplast)'*

3.3.5 The original aim of RIP-oN 3 Task B1 Exposure scenario (ES) Case-Studies was to develop 'branch-specific general exposure scenarios that take into account normal practice within these branches, cover several processes (i.e. have a good life cycle coverage), and where relevant be applicable to ranges of nanomaterials and the challenges related to their sampling, detection, measurement and monitoring'. During the discussion of the ES Case-Studies, however, it became clear that these Case-Studies could serve as nanomaterial product-specific examples only and that no generalisation with regard to practices within an entire nanomaterial type-specific branch could be based on these individual ES Case-Studies.

3.3.6 The main findings of the case studies are outlined below.

3.3.7 Some of the Case-Studies used models (e.g. Consexpo, ECETOC TRA) to estimate exposure. These were used without specific modification for nanomaterials. No data was available to test the validity of the model estimates.

3.3.8 Some Case-Study providers conducted state-of-the-art detection and measurement approaches using multi instrument, multi-metric measurement studies in their facilities.

3.3.9 While this resulted in an extensive data set, this was largely collected on the basis of investigative type studies, rather than a programme of work to collect data for REACH compliance issues. As a result the complexity of the data collected, the fact that in many cases measurements were taken which spanned more than one identified exposure scenario, the fact that multi metric approaches were taken, the fact that in some cases continuous measurements were taken however only a single number was reported (as compared to guidance in REACH which requires demonstration of, e.g. median and 95th percentile measurements) made all of this data rather difficult to interpret for the purposes of exposure scenario development.

3.3.10 The data measurement approaches taken also included the application of new measurement systems e.g. in the case of NanoCyl, the applied Naneum detector was specifically designed to detect MWCNTs with high selectivity

3.3.11 In the case of detection and measurement data, it would be important to have more than one or two measurement periods available for entering these data into modelling of scenarios.

3.3.12 The reporting template, (based on the ES format) received heavy general criticism from the Case-Studies providers, due to:

- lack of clarity of the information required to be entered in the spreadsheet, combined with a;
- lack of guidance on how to complete the template, and;
- the difficulty of handling the reporting template, as well as the adapted Excel Spreadsheet

3.3.13 A number of specific observations were made. None of these issues are nano-specific, but rather general difficulties with the current REACH guidance and might benefit any further guidance update.

3.3.14 Case study providers considered that it would be good to better “guide” the person filling in the fields in the template, clearly state what information is required (e.g. ‘information required to estimate the exposure of a worker: enter either a) size ventilation protection means etc. PLUS measurement results, or b) enter the description of the facilities [e.g. what size ventilation protection means, etc.] and provide additional information needed to model the exposure with a worst-case first tier model’).

3.3.15 Throughout all Case-Studies, both RIP-oN experts and case-study providers had difficulty in distinguishing ‘Exposure Scenario’ (ES) from ‘Contributing Exposure Scenario’ (CES)., as well as distinguishing ‘Service-Life’ ES from non-Service-Life ES.

3.3.16 The companies had some problems to define PROCs for the individual process steps (cf. cleaning, etc.), but all were resolved.

3.3.17 The companies considered that it is not always clear what constitutes an ‘Exposure Scenario’ (ES) and what constitutes a ‘Contributing Exposure Scenario’ (CES).

3.3.18 Down-stream users may lack qualified staff to complete the reporting template.

3.3.19 The issue of Environmental Release Categories (ERCs) were mentioned by the case study providers, not as much in relation to naming the ESs, but rather in relation to using these as input to as yet unvalidated environmental exposure models. The main question is how to develop relevant environmental release factors/coefficients for nanomaterials where there is limited or no evidence base. The examples of processes and uses for which emission/release data are missing were: i) manufacture of substances (ERC1), ii) formulation in materials (ERC3), iii) industrial use resulting in inclusion into or onto a matrix (ERC5), iv) industrial use of reactive processing aids (ERC6b), v) industrial use resulting in inclusion into a matrix (ERC5), vi) wide dispersive indoor use of long-life articles and materials with high or intended release (including abrasive processing) (ERC11b).

3.3.20 In the absence of good information about environmental release, providers questioned whether it was possible to use occupational exposure measurements in environmental release studies. In general it was questioned how or if one can extrapolate information from a single event (worker exposure) to model release to a work space and subsequent release to natural and technical compartments (such as to waste-water, incineration plants as part of waste flows, or directly to surface waters and air). However, given that this is not normal practice for substances in general, there seems no basis for attempting this approach for nanomaterials.

3.3.21 Additional analysis of the case studies not previously published in RNC/RIP-oN3/B1/2/FINAL is included as Appendix 1 of this report.

3.4 TASK B2: OPERATIONAL CONDITIONS AND RISK MANAGEMENT MEASURES - HARVESTING RESULTS FROM ON-GOING ACTIVITIES

3.4.1 In this task, evidence on the pertinent issues and the effectiveness of workplace controls to prevent or minimise exposure to engineered nanomaterials was collated and evaluated.

3.4.2 Types of literature contributing to this activity included:

- Guidance documents developed by national or international organisations providing information about good practice in relation to exposure control;
- Review documents carried out by national or international organisations examining the evidence relating to the availability and effectiveness of control approaches;
- Other review or guidance documents, either produced by industry associations, individual companies or from the peer-reviewed literature identifying or recommending effective control approaches;
- Studies where management measures have been specifically evaluated to determine their efficacy of use along with nanoparticles;
- Studies in which the performance of management methods may be inferred for measurements of exposure concentration;
- Studies which provide information on operational conditions (process, use, duration, amount used etc) which may drive exposure and release, including simulation studies;
- Studies which provide information on nanoparticle behaviour including dispersion, scavenging etc.

3.4.3 Where available and relevant, reference was made to other authoritative reviews and these were quoted extensively.

3.4.4 Information collected was assessed to identify the key technical issues to be considered in relation to any proposed changes to the REACH guidance, sources and reference documents for these changes as well as the need for further research.

3.4.5 A number of initial (provisional) conclusions were drawn concerning possible implications for aspects of the REACH guidance and these are included below. These were not intended to be a definitive analysis but rather intended to serve as a starting point for discussion with the SCG and the Commission prior to finalisation of the project.

3.4.6 **Hierarchy of control**

3.4.7 Based on the current guidance available from a wide range of organisations, there is a consensus view that the conventional approach to control of hazardous chemicals based on elimination, substitution, engineering control, administrative control and use of PPE, sometimes referred to as the hierarchy of control, can be an effective framework on which to base control approaches also for nanomaterials.

3.4.8 Possible implications for REACH guidance. These approaches are highly consistent with the general measures necessary for safety and health protection of workers (Article 6 of Directive 89/391/EC), the reduce-to-a-minimum principle (Article 6 of Chemical Agents Directive 98/24/EC) and the hierarchy of RMM prescribed in the Chemical Agents Directive and therefore do not in themselves suggest a need to change the guidance.

3.4.9 **Existing methods (general)**

3.4.10 As a general statement, there is evidence that control and risk management methodologies which are already known can provide levels of protection for workers from exposure to engineered nanomaterials in the occupational environment, depending on the specific hazards of the nanomaterial and whether these have been adequately identified. It is not indicated that new nano-specific RMMs need to be developed. Further testing and data are however often needed in each specific workplace situation to understand the levels of protection afforded, and ensure effectiveness.

3.4.11 Possible implications for REACH guidance: (D.4.6.1 Effectiveness of RMMs, R. 13.3 Effectiveness of RMMs, R.13.4.2.5 Estimation and documentation of RMM effectiveness in the library). Available “typical default value” (an estimate of the 50th percentile) and a “maximum achievable” value (best

practice) may not be achievable and should not be assumed. Additional research concerning the effectiveness of control approaches may be necessary in some circumstances. These are explored in more detail below.

3.4.12 **Substitution and modification**

3.4.13 Modification of the hazard potential of certain types on nanomaterials appeared to have some, as yet not fully explored possibilities. There are approaches (surface modification, encapsulation, particle size control, functionalisation and crystalline phase control) which have been shown to have the potential to modify the toxicity of nanoparticles (Section 5.4).

3.4.14 Any substitution or modification process adopted would have the added requirement to maintain the desired functionality.

3.4.15 In the context of REACH such modifications would be done as a prior step before developing the specific ES as the specific ESs should control the risk of what is actually handled – not how it is redesigned.

3.4.16 Possible implications for REACH guidance: No specific implications foreseen.

3.4.17 **Enclosure**

3.4.18 Evidence indicates that emissions to the workplace are substantially reduced if a process involving engineered nanomaterials is performed in a properly designed enclosure/containment. In most of the studies where an enclosed or sealed process was used, containment was effective as long as it was maintained, however this was not universal. In one study, a leak was identified which was not evident from other process parameters. In two others releases were measured but no leakage point was identified. Thus it cannot be said that enclosure of a process is always completely effective. A conclusion to be drawn would be that use of an enclosed system is not sufficient in itself to guarantee that there is no release of nanomaterials into the workplace air. This would imply that such systems should be tested directly to demonstrate effective containment.

3.4.19 The situation is further amplified when considering what happens when containment is opened. In almost all cases, elevated level were measured

associated with opening of the containment for recovery of testing of the product. In a general sense, even for other (non-nano) substances, this is always considered to be a critical point.

3.4.20 In relation to the REACH guidance, relevant areas are D.4.6.1 Effectiveness of RMMs, R. 13.3 Effectiveness of RMMs, R.13.4.2.5 Estimation and documentation of RMM effectiveness in the library. From the RMM library, in relation to process control, RMM W8.01 and W8.02 under the heading Automation and enclosure are most relevant. These have default values of H (High). This is probably still justified but use of appropriate caveats to reflect the requirement for effectiveness to be directly assessed should be considered.

3.4.21 **Ventilation (including LEV)**

3.4.22 Evidence indicates that worker exposure can be significantly reduced or prevented through the use of correctly designed and implemented extraction ventilation and filtration for processes involving engineered nanomaterials that would normally result in the release of airborne particles. The types of systems evaluated here cover a range of designs and operational parameters (e.g. ventilation rates, size, degree of enclosure, process being ventilated). In practice very few of the details on degree of enclosure or ventilation rate are available in the publications. In addition there was almost no quantification of the degree of effectiveness provided i.e. what level of effectiveness was given by the local exhaust ventilation (LEV). Such information requires comparison of a process with LEV and without LEV. These studies in the main were not set up to measure this. What is observed is that in some cases the LEV was effective, in some cases not. Again this could be considered to be similar for substances in general.

3.4.23 In relation to the REACH guidance, relevant areas are D.4.6.1 Effectiveness of RMMs, R.13.3 Effectiveness of RMMs, R.13.4.2.5 Estimation and documentation of RMM effectiveness in the library. Information concerning the effectiveness of RMM is provided in the RMM library. In this document the default efficiency given for Labhoods (W.15 EX4), Extracted booth (W.15 Ex5). Laminar flow booths (W.16 Ex1) and LEV captor hood (W17.Ex1) is 80%, there is no expectation of 100% in the general operation of these

devices. The maximum efficiency values range from 99% to 90%. Based on the information presented above there is no justification for a change to the default values for these types of RMM.

3.4.24 **Filtration**

3.4.25 Filtration is relevant both as an occupational and environmental RMM. The better extraction methods have involved the use of high efficiency particulate air (HEPA) filtration and electrostatic precipitation. HEPA filtration, as theory predicts, appears to be very effective at the nanoscale.

3.4.26 Filtration theory indicates that filtration will be effective for particles in the nm size range. The evidence available appears to support this. Whilst theory would predict that some improvement in filtration efficiency at particle sizes of less than 100 nm there is insufficient evidence to demonstrate such improved performance. In many cases, the challenge aerosol to control will be aggregates or agglomerates on nanoparticles and will therefore be > 100nm and possibly be closer to 300-500 nm normally considered to be the most penetrating size for filters. However this most penetrating size is the one generally used to test these filters.

3.4.27 In relation to the REACH guidance, relevant areas are D.4.6.1 Effectiveness of RMMs, R.13.3 Effectiveness of RMMs, R.13.4.2.5 Estimation and documentation of RMM effectiveness in the library. There is no evidence to support any change to the quantification of the Effectiveness of filtration as a RMM (as indicated in the RMM library).

3.4.28 Electrostatic precipitators also appear to be effective at capturing nanoparticles. Again, no change to the effectiveness is appropriate based on the evidence available.

3.4.29 **Administrative controls**

3.4.30 There are a range of administrative controls that may be implemented for workers involved in handling engineered nanomaterials. These are usually implemented in combination with other control measures e.g. enclosure, extraction and Personal Protective Equipment (PPE).

3.4.31 Summary: There is no specific evidence to suggest that administrative controls which are used for substances in general will not be appropriate or equally effective for nanomaterials.

3.4.32 **Personal protective equipment including respirators and gloves**

3.4.33 Evidence suggests that the performance of respiratory protective equipment (RPE) will be effective against particles in the nanoscale size range. Research on this issue has been largely based on the standard test methods used for respirator filters in which filters are challenged with a NaCl or Dioctyl-pthalate aerosol with a median diameter of 300 nm. Particle theory suggests that the maximum penetrating particle size is of the order of 300 nm and that collection efficiency improves below that particle size due to capture by diffusion. This has been confirmed in several studies evaluating filter penetration although some studies have reported lower maximum penetrating particle sizes (as low as 100 nm) but with capture efficiencies increasing below this size. An implication of this, however, is that aggregates or agglomerates of nanoparticles, which could well be around the maximum penetrating size, are likely to be more penetrating than the primary nanoparticles. Only a limited number of material types have been tested but it is not expected, based on diffusion theory, that the chemical composition would greatly affect filter performance. However, a lack of any testing data for instance for CNT must be considered to be a gap.

3.4.34 As for chemicals in general, further work is required to investigate human factors such as leakage around (rather than through) a face-piece filter.

3.4.35 In relation to dermal exposure the use of gloves and airtight fabric clothing has been examined. It has been suggested that some kinds of skin protective equipment (SPE) might have limited effectiveness. For gloves, manufacturing design and material thickness are major issues in determining whether or not nanoparticles penetrate. In some cases two layers are recommended. More work is required.

3.4.36 The use of PPE should be considered as the last line of defence in the hierarchy of workplace exposure mitigation approaches. PPE should also be worn on a precautionary basis whenever the failure of a single control,

including an engineering control, could entail a significant risk of exposure to workers. PPE will also be needed in situations where the use of engineering controls is impractical.

3.4.37 In relation to the REACH guidance, relevant areas are (D.4.6.1 Effectiveness of RMMs, R.13.3 Effectiveness of RMMs, R.13.4.2.5 Estimation and documentation of RMM effectiveness in the library). Available evidence suggests that current “typical default value” and a “maximum achievable” value for other respiratory protective equipment are likely to be appropriate. Additional information may be necessary for dermal protective equipment.

3.4.38 **Control Banding (CB)**

3.4.39 The use of control banding (CB) has importance in relation to the selection of control approaches for conventional material. However, even for such materials use of control banding still has some limitations. The Nano-tool (Paik et al., 2008) is a potentially important development and brings the same structured approach towards decision-making. However, it is challenging to see how this tool could be used without very critical review of the input parameters and collection of much more information about them in relation to each case of its use or without at least a general knowledge on the risks of particles in the nano form and compared to the bulk (non-nano) form. Such validation of the Nano-tool that has been done is primarily only based on expert judgement. It could be argued that, if all the evidence necessary for proper use of the Nano-tool were collected, it would not be necessary to use the tool at all.

3.4.40 The Nano-tool is the only well documented CB approach currently available. However to use this as a basis for guidance at this time would be problematic. It is not at the current time sufficiently well developed or validated to be recommended. More development of CB approaches are on-going under ISO 229 using the approach developed by Paik et al. (2008), however publication of this guidance is some years away.

3.4.41 In relation to REACH, control banding in its current form, given its current level of development cannot be used to demonstrate that the risks are adequately controlled. However, as an interim measure, users might consider

CB approaches to provide initial selection of control measures as a starting point while collecting further information about exposure, toxicity and risk.

3.4.42 **Occupational Exposure Limits (OELs)**

3.4.43 At present, there are in a practical sense no new OELs specific to nanomaterials that have been adopted or promulgated by authoritative standards and guidance organisations. The vast heterogeneity of existing and potential nanomaterials suggests that a large number of specific OELs may have to be developed in due course. Some OELs could be developed more quickly for some nanomaterials by applying increasingly available dose–response data generated from animal studies across categories of nanomaterials with similar properties and modes of action. Controls must still be applied even before OELs are available. However, in the absence of DNELs/OELs it is difficult to be certain that applied control measures are controlling exposure to levels which are low enough.

3.4.44 In relation to the REACH guidance, it should be made clear that an OEL is not a technical risk management measure. Relevant areas are B, D, E, R.14, R.15, R.16, R.8. It is important that where guidance is given in SDS concerning published OELs, this reflects that these are not based on the nanoform of the material and may therefore not offer adequate protection for the nanoform.

3.4.45 **Medical surveillance**

3.4.46 Although preliminary medical surveillance activities such as documentation of the presence of engineered nanoparticles and identification of potentially exposed workers are likely to be beneficial in the long term, no clear guidance can be given at this time as to specific medical endpoints which should be tested for.

3.4.47 **Safety Data Sheets**

3.4.48 The information provided reflects only one study (SWA, 2010b). This study was carried out in relation to Australian regulation. However the requirements against which appropriateness of the SDSs were judged were generic rather than specific to local regulation. The conclusions are very clear and

summarised as: “Overall [only] 18% (9/50) material safety data sheet (MSDS) were assessed as providing reliable information to appropriately inform an occupational risk assessment”. The authors view that there was an urgent need for improvement is justified on the evidence presented.

3.4.49 As indicated in Annex II of REACH, the Safety Data Sheet provides a mechanism for transmitting appropriate safety information on classified substances and preparations, including information from the relevant Chemical Safety Report(s) down the supply chain to the immediate downstream user(s). The information provided in the Safety Data Sheet shall be consistent with the information in the Chemical Safety Report, where one is required. The information provided by Safety Data Sheets shall also meet the requirements set out in Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work. In particular, the Safety Data Sheet shall enable the employer to determine whether any hazardous chemical agents are present in the workplace, and to assess any risk to the health and safety of workers arising from their use.

3.4.50 It is clearly of concern if SDSs are not providing this fundamental mechanism. It is important that information provided on SDSs for a nanomaterial is representative, valid and provides the protection needed for the forms addressed by the SDSs.

3.4.51 **RMM relating to consumers**

3.4.52 Due to lack of evidence, no recommendation relating to REACH guidance for RMM relating to consumers can be made at this time.

3.4.53 **RMM relating to the environment**

3.4.54 Other than in the case of filtration, due to lack of evidence no recommendation relating to REACH guidance for RMM relating to environment can be made at this time.

3.4.55 **Operational conditions**

3.4.56 Operational conditions include duration and frequency of exposure, the applied amount of chemical, temperature, containment of process, capacity of

surroundings. Only limited information on occupational conditions was found to be available in the public literature. Information is available on the risk management measures adopted and in some cases the quantity of material produced are used on a daily or batch basis. Information concerning room sizes, ventilation rates, and temperature is almost entirely absent.

3.4.57 The possible implications for REACH include a lack of information relating to R.13.2.2 Operational conditions and risk management measures related to workers. There is also likely to be a lack of information in relation to estimation of exposures using Tier 1 models (R. 14. R.15. R.16) and a limited opportunity to validate assumptions in these models.

3.5 TASK B3: EXPOSURE ESTIMATION (MODELLING AND MEASUREMENTS) - HARVESTING RESULTS FROM ON-GOING ACTIVITIES

3.5.1 This is a review task. The inputs to the task included literature identified in Task A of RIP-oN 3 as well as the information collected from industrial sources in the exposure scenario case studies that make up Task B1. In relation to the scientific literature, initial examination of the information collected in Task A indicates that the sources of information include ISO (2007, 2008), BSI (2007), OECD (2010) and European projects such as NanoSafe2 (http://www.nanosafe.org; accessed 6th September 2010) and NANOSH as well as the general scientific literature (e.g. Brouwer et al., 2004, Maynard and Aitken 2007).

3.5.2 Various types of relevant studies were identified. These include: i) studies which have attempted to characterise exposure or release in specific situations; ii) studies focused on the development or evaluation of new measurement methods; iii) guidance documents where measurement methods and approaches have been recommended (based either on evidence or not) and; iv) modelling studies.

3.5.3 In this task, all relevant information pertaining to availability, adequacy and applicability of methods for sampling, modelling and/or measuring exposure of workers, consumers, the environment and man via the environment to nanomaterials will be evaluated.

3.5.4 In developing this report the following were produced:

- An overview and summary of the literature;
- Identification of issues where further adjustment of the guidance may be relevant for nanomaterials in general or for specific categories of nanomaterials;
- Evidence for each issue including examples or approaches or limitations or actions to improve;
- A first look at implications for the guidance and how this could be modified in the light of the information collected.

3.5.5 **Discrimination from background nanoparticles**

3.5.6 Typical urban air contains anywhere between 10,000 to 40,000 particles.cm^{-1} which come from a variety of sources including, industrial pollution, traffic and domestic emissions.

3.5.7 In industrial settings, evidence of measurement problems relating to background aerosols has been reported in several studies (e.g. Kuhlbusch et al., 2004, 2006; Demou et al., 2008; Park et al., 2009). Specifically identified sources include heating units, fork lift trucks and vacuum cleaners.

3.5.8 These background number concentrations are dominated by particles smaller the 1000 nm and much of the distribution is typically in the range 10 to 300 nm. The presence of this ambient particulate creates problems when attempting to measure emissions of engineered nanoparticles from nanomaterials sources.

3.5.9 Three strategies have been reported (including combinations) to address this issue of these with varying success. The first is to take time series, or time differentiated measurements with associated log of events, typically including activities such as pre-operation of reactor, to determine a plausible relationship between events and levels.

3.5.10 A second approach is to take parallel samples with the same instrumentation in an area where it is expected that there is only background aerosol present, i.e. there is no expected contribution from the source (e.g. Kuhlbusch et al. 2004, 2006). This is sometimes called the “far field” and can be outside, or at another point in the production building/laboratory. For this type of approach, care is required that there is no contribution from the sources of interest, or from other background sources in the far field sample.

3.5.11 A third approach is to collect physical samples of the aerosol for off-line analysis to confirm that the peak concentrations observed correspond to an identified NM, either by composition (elemental analysis of the primary material or impurity) or morphology or both, for example by Scanning Electron Microscopy (SEM)/ Transmission Electron Microscopy (TEM) and Energy-

dispersive X-ray Spectroscopy (EDAX) analysis (e.g. Methner et al., 2010; Brouwer et al., 2009).

3.5.12 While all of these approaches have utility, all must be applied with care to ensure that no confounding effects, such as a change in the far field background with time, corrupt the data. Combination approaches have been described and are generally more successful. Brouwer et al. (2009) used a combination of these approaches as the basis of a semi-formal decision logic to determine whether nano-objects were present in the workplace air. This required an exceedance of a predetermined near-field/far field ratio (in the reference ratio 1.05 was used), that changes in concentration or size distribution corresponded to observed activities and that the chemical composition of the sample (in the near and far field) matched that expected. The obvious limitation of the method in the light of the dynamic response, detection limits and the measurement uncertainty of the applied measurements is in its ability to detect statistically significant deviations in the ratio. Currently available sampling and analytical methods might also have insufficient sensitivity to assess very low levels required when in due course OELs/DNELs for nanomaterials may be substantially lower than current OELs/DNELs,(e.g. NIOSH (2005) for TiO_2)).

3.5.13 Conclusions and possible implications for the REACH guidance:

- Background aerosol will be an important contribution towards the total number , mass and surface area concentration;
- Where possible, background should be subtracted. Viable approaches are available on which guidance should be based;
- If it is not possible to remove the background contribution, then the total concentration could be considered to be a worst case. However, this may be considered to be over-precautionary.
- Background particle may also act as carriers for nanomaterials which have aggregated with them.

3.5.14 **Measurement of size distribution**

3.5.15 Measurement of size distribution is clearly an important parameter. The size information may be obtained through a number of instrumental routes. Based

on the evidence available, it seems unlikely that the size distribution of aerosols measured in the workplace is the same as the size distribution of the primary material. There is evidence that distributions are complex, not log normal (as might be expected for laboratory generated samples).

3.5.16 Such irregular or sometimes bimodal distributions are quite typical in the published literature available. Various reasons have been suggested for this. One is that the smaller mode represents primary particles and the larger mode either agglomerates or aggregates of these materials or agglomerates in combination with background particles, following scavenging by these particles.

3.5.17 Thus an important question in relation to the ultimate risk to consider is whether these aggregates/agglomerates could subsequently de-agglomerate e.g. when depositing in the lung lining. This may have implications for the potential risk. Given the irregular nature of the distribution in most cases, it is inappropriate to summarise the distribution by a single set of parameters such as median and diameter and geometric standard deviation.

3.5.18 Devices which measure size distribution such as the Scanning Mobility Particle Sizer (SMPS) and Fast Mobility Particle Sizer (FMPS) provide a particularly data rich output. These devices produce count data in several size bins either collected in parallel (in the case of the FMPS) or in a very close time sequence (in the case of the SMPS). There are several ways in which this data might be used. The simplest approach is to inspect the complete size distribution. This is particularly useful in assessing single events or single changes (e.g. the implementation of a control measure, or the comparison between an aerosol and a background). This type of analysis, however, is difficult to quantify as the data are often multimodal. As such, the distributions cannot be described and compared by unique parameters such as the geometric mean and standard deviation.

3.5.19 An alternative is to sum the total counts to provide a single number. However this approach looses the size information and so it is of limited value. In the reviewed studies, several authors (e.g. Fujitani et al., 2008; Bello 2008, 2009) have grouped (integrated) the size distribution into several discrete size ranges e.g. < 10 nanometres, < 100 nm , < 1000 nm etc. and compared their

respective time series to support the development of the background discrimination strategies or understanding of the particle formation dynamics.

3.5.20 Conclusions and possible implications for the REACH guidance:

- Particle size information is clearly important and the full size distribution curve should be reported;
- The size distribution of aerosols measured in the workplace is unlikely to be the same as the primary material;
- Recommended methods should be able to account for complex form of the distributions (e.g. bimodal distributions).

3.5.21 **Maximum relevant size**

3.5.22 Use of size dependent-health related criteria is common practice in measurement of occupational exposure (ISO, 1995). It has been shown that the size distribution of aerosols that are present in workplaces where nanomaterials are synthesised or used can often have a broad distribution. An important issue to consider is whether it is appropriate to impose an upper size limit of the particles to be collected or measured in order to characterise exposure to NM. One option would be to exclude all particles with physical dimensions greater than 100 nm, providing methods were available. This would allow estimation of people's exposure to "nanoparticles" as formally defined in ISO/TS 27687:2008 (BSI, 2008).

3.5.23 Evidence from the studies reviewed suggests that emissions are rarely in the form of single nanoparticles (this is not to exclude this possibility entirely). In most cases the measurements indicated that, where nanoparticles were present, they were in an aggregated or agglomerated form or were associated with other materials including background particles. In the main studies reviewed, the selected strategies were to maximise the information available by looking at a wide particle size range (and thus not operate with a 100nm cut-off). The implicit assumption in that is that agglomerates, aggregates and other combined particles are at least potentially relevant NM exposures. The relevance of these agglomerated forms, including potential for dissolution, or dissagregation, needs to be considered also from the toxicological perspective in the risk characterisation.

3.5.24 Many devices used do already have a maximum measurable particle size. This can be to protect the instruments' detection system or because of decreasing detection efficiency beyond that size. For example, several of the Condensation Particle Counters (CPCs) have a cut-off (maximum size) of around 1000 nm which is achieved by including an impactor in the inlet. There is an argument to standardise on that size, particularly if emphasis is given to (total) number concentration as a parameter. Otherwise, two instruments, with different maximum sizes will give different results. However, this is not a health based selection criterion.

3.5.25 One approach could be to use the respirable convention (CEN, 1993) as an upper size limit. This would have the advantage of being biologically relevant and would provide coherence with current practice in occupational exposure assessment. Use of the respirable convention has been recommended by several authors (e.g. Schneider and Jensen, 2008). Respirable concentrations have been measured in several of the reviewed studies (e.g. Peters et al., 2009; Han et al., 2008).

3.5.26 In general however, given the current state of knowledge, the practice adopted in the reviewed scientific studies, assessing multiple parameters with multiple instruments, seems correct. Though the maximum (and indeed minimum) size limits of an instrument and the instrument response function are usually known, they are unfortunately seldom reported.

3.5.27 Conclusions and possible implications for the for the REACH guidance:

- Evidence suggests that nanoparticles of interest may be present as primary particles and larger aggregates/agglomerates potentially including background particles from which primary particles may subsequently be released. Therefore these larger agglomerates, not just primary particles should be measured. Measurement of primary particles alone is not sufficient to fully understand exposure in these situations;
- The use of the respirable fraction, representing the fraction of aerosol capable of entering the alveolar region of the lung is recommended as the default definition of maximum particle size;

- If instruments which have a smaller cut off point than the respirable convention are used, the value of the cut off point should be reported in any document in which this information is given.

3.5.28 **Effect of high spatial and temporal variability**

3.5.29 In occupational settings it is common that airborne concentrations are higher and closer to the source worker (near-field) than at some distance point (far-field). High spatial variability has been reported in the studies reviewed. Demou et al. (2009) reported both high and low spatial variability in different settings. Plitzco (2009) reported “genuine nanoparticles” emitted from a reactor that agglomerated in a very short time and immediately led to a lowering of the number concentration. Seipenbusch et al. (2008), as part of the FP6 project NANOTRANSPORT, investigated the evolution in time of a nanoparticle aerosol released into a particle-free atmosphere and in presence of a pre-existing background aerosol and demonstrated rapid agglomeration and scavenging by the background aerosol.

3.5.30 High spatial and temporal variability emphasises that the need for measurements of exposure in workplaces are based on personal sampling, i.e. by using a sampling device located in the breathing zone of the worker being assessed. Studies with other particles have generally shown that personal exposure is higher compared to exposure as measured in the general environment of a workplace e.g. Stevens (1969). This is partly because the worker is usually closer to the source than static environmental monitors are able to be placed but also from the activities undertaken by the worker himself, and the extent to which these modify the exposure levels. This may be particularly relevant for NM due to high transport, agglomeration and scavenging rates.

3.5.31 Conclusions and possible implications for the for the REACH guidance:

- Measurements of workplace air concentrations may not adequately represent personal exposure;
- A preferred approach is the use of personal sampling devices;
- Given the current lack of such a device, measurements strategies which encourage (even limited) comparison between workplace air concentrations and personal exposure are recommended. However there is no current definitive guidance in this respect which could be implemented at this time.

3.5.32 **Choice of metrics and instruments**

3.5.33 There are three main metrics, all of which could have some utility in measuring exposure to nanoparticles. These are: i) mass concentration (units mg m^{-3}); ii) number concentration (units m^{-3}) and; iii) surface area concentration units (units m^2 m^{-3}). A case may be made for the use of any of these metrics under certain circumstances.

3.5.34 The metric used to assess exposure to nanomaterials should be that which most closely links to any potential health effect. The current evidence suggests that no single metric (or method) for monitoring nano-aerosol exposure will suit all nanomaterials. Rather, there will be occasions where particle number, surface area and mass concentration measurements will play an important role in evaluating potential impact.

3.5.35 Instrumentation is available to measure each of these metrics but there are identified practical issues in the selection, use and analysis of metrics data. For mass, a key issue is a lack of sensitivity towards the particle sizes of interest. Measurement of number concentration is in contrast highly sensitive. In general, analytical methods that measure particle numbers can easily assess much lower levels than analytical methods that measure mass. However, measuring particle number concentration in isolation can be misleading. In all particle number concentration measurements, the integration limits over which a particular instrument operates are critical to the reported results. Real-time measurements of surface area concentration are technically feasible but there is very limited practical experience with these

instruments. The results obtained need to be carefully interpreted and the limitations and boundaries carefully examined. Issues to consider are to include the effect of initial aerosol charge, the composition of the material, how aggregates are dealt with (in particular where both external and internal surfaces are available) and the effect of extreme particle shape.

3.5.36 An ideal approach is to choose a metric which is correlated with the health effect of concern, which can be relatively easily measured and be both measurable and sensitive enough to detect differences in the probable ranges encountered. However, given current knowledge, it is probably not useful to ask "which is the best metric for nanoparticles." Useful preliminary questions might be "what types of particles are we interested in?" and "what is the health effect we are trying to correlate with?".

3.5.37 Conclusions and possible implications for the for the REACH guidance:

- The issues of metrics should not be decided on exposure assessment issues alone, toxicological information needs to be carefully considered;
- At this time it is not possible to make a definitive statement concerning which of the metrics are the most appropriate for nanoparticles. In relation to measuring exposure, the best available guidance at this time is that measurements should encompass assessment of at least mass, but where possible also number and/or surface area concentration;
- Methods which could be recommended in relation to these metrics is provided in this report;
- In addition, measurements of size distribution should also be made as discussed in this report.

3.5.38 **Assessment of high aspect ratio nanomaterials**

3.5.39 Exposure to fibrous aerosols is assessed by measuring the number (concentration) of fibres in the air with a specific shape and composition (WHO, 1997). Critical to the method is definition of a fibre, specifically a respirable fibre. The World Health Organisation (WHO) defines a respirable fibre as an object with length greater than 5×10^{-6} m (5000 nm) a width less

than 3 x 10^{-6} m (3000 nm), and a length to width ratio (aspect ratio) greater than 3:1. It relies on manual counting of fibres by optical microscopy according to a set of counting rules governing size (as above), number of areas (graticules) scanned, number of fibres scanned, number density of fibres on the collection substrate, and how to deal with "bundled" or overlapping fibres. The scope of application of the WHO method is broad, as indicated in the following statement: "The method [..] is applicable to the assessment of concentrations of airborne fibres in workplace atmospheres most commonly personal exposures - for all natural and synthetic fibres, including the asbestos varieties, other naturally occurring mineral fibres and man-made mineral fibres" (WHO, 1997).

3.5.40 Several high aspect ratio nanomaterials (HARN) could fall within this scope. It has been suggested that fibre counting could be an appropriate method to assess exposure to HARN (BSI 6699-2:2007; BSI, 2007). However concerns have been raised regarding the applicability of the WHO criteria for HARN, specifically for carbon nanotubes (CNT). Optical microscopy would not detect individual CNT although it could detect bundles of CNT. The higher magnification needed would require SEM/TEM, which would increase the counting time substantially.

3.5.41 It is known that optical microscopy is less sensitive than SEM/TEM to very fine fibres and therefore underestimates the total number of fibres collected. SEM/TEM will measure these very fine fibres, which would not be observed by optical microscopy, leading to larger counts in what would be an equivalent sample. This would lead to difficulties in making comparison with limit values for fibres set using optical microscopy.

3.5.42 Only one study, Han et al. (2008), used an approach based on the WHO approach and reported fibre concentrations. It is not clear the extent to which WHO counting rules were applied. However it is noted that all the fibres reported were shorter than the WHO definition and so, by strict application of the fibre counting rules, the count would be zero. Bello et al. also collected on to a filter for electron microscopy analysis, but no fibres were identified. Han et al. (2008) made measurements of total carbon using a portable aethalometer. Other investigators used Condensation Particle Counter (CPC),

Optical Particle Counter (OPC) and Scanning Mobilty Particle Sizer (SMPS) to try to detect, although these devices prove no morphological information. A recent review on options for carbon nanotube (CNT) detection and analysis (SWA, 2010a) concluded that the Electrical Low Pressure Impactor (ELPI) spectrometer may have some utility in this respect. Various off-line measurement approaches were reviewed by Tantra et al. (2007) and it was concluded that none were immediately appropriate for measurement of occupational exposure. Currently there is no consensus on the most appropriate approach.

3.5.43 Conclusions and possible implications for the REACH guidance:

- Assessment of fibre concentration is likely to be relevant to some high aspect ratio nanomaterials in terms of their exposure;
- The presence of “fibres” is only likely to be detected by electron microscopy;
- Application of the WHO approach has not yet been validated for any types of high aspect ratio nanomaterials;
- Encouragement should be made in the guidance towards checking of whether fibres are present in exposure assessment samples for all materials which have some potential for the release of fibres;
- Given an absence of measurement methods or terminology to describe bundles or clumps of high aspect ratio nanomaterials, no specific guidance can be given at this time for quantitative assessment of these entities. However their presence should be noted in any assessment.

3.5.44 **Exposure models**

3.5.45 Only limited assessment of the models used in exposure estimation has been carried out so far. The most extensive validation was for occupational exposure by inhalation. Evaluating Stoffenmanager and ECETOC TRA, the conclusion drawn in the FP7 NANEX project (Development of Exposure Scenarios for Manufactured Nanomaterials - NANEX (Grant agreement no.: 247794) was that there was no correlation between the model estimates and measurement data. Neither of the models is tuned to and calibrated for

nanomaterial exposure situations, and hence the actual model estimate will be inaccurate and possibly overestimate the (mass) concentration levels.

3.5.46 For consumer exposure, NANEX evaluated Consexpo, (inhalation, dermal, oral), ECETOC TRA (inhalation, dermal,oral), RiskofDerm (dermal). The authors concluded that dermal modules might be suitable for use for manufactured nanomaterials (MNMs) as the underlying equations do not appear to rely on nano-specific properties. The dermal modules of the models may therefore be applied to nanomaterials, however, they should be used with care as they are not yet validated nor calibrated for MNMs and the output (the exposure estimate) is given in a mass-based metric. There are greater limitations in the currently available inhalation modules in the exposure estimation models. These inhalation modules do not consider the nano-specific properties of the materials that could affect the exposure, e.g. agglomeration effects. Therefore, in the authors view, inhalation modules should be used with even greater care.

3.5.47 In relation to environmental exposure models such as (EUSES), these are often based on QSPR (Quantitative Structure-Property Relationship) calculations using physicochemical properties of the substance, mainly Octanol-Water Partition Coefficient (K_{OW}) and Partition Coefficient (Kp) values. At present, it is highly unlikely that these QSPRs will be applicable for nanomaterials. It is therefore recommended to not use these QSPRs (including read-across approaches) to estimate properties of nanomaterials without relevant scientific justifications, as long as there is no (solid) basis to do so. Instead, measured partition coefficients (i.e. Kp values) should be used to estimate environmental distribution. When sufficient information on the fate and behaviour of nanomaterials becomes available it may either be concluded that the current QSPR estimations are applicable for nanomaterials as well, or new QSPRs for nanomaterials can be developed.

3.5.48 At present, however, there is a need for specific information on nanomaterials, especially on properties that are necessary for (estimating) fate and behaviour and (modelling) hazard characteristics. In addition, information that enables a proper comparison between bulk form and nanoforms is lacking (RNC/RIP-ON3/B3/4/FINAL, (8.4))

3.5.49 While there is information available on models for nanoparticle transportation, aggregation and deposition available in the literature deriving primarily from the colloid literature, this is either theoretical and/or based on idealised relatively simple model systems (e.g. Weisner and Bottero 2007). The models have not been adapted for the large number of components present in natural water which may include salts, clays, micro-organisms, natural organic matter and other colloidal materials (Mylon et al., 2004). At present these are not appropriate for use in a regulatory context without further scientific justification.

3.5.50 Conclusions and possible implications for the REACH guidance:

- Exposure models are a key element of the exposure estimation process;
- The limited evidence of validation for occupational exposure indicates that model estimates should not be relied on alone without further confirmation of their validity in individual cases. In any case, model estimates should be used with caution and with further scientific justification;
- It is not possible to provide reference to models which have been validated for nanomaterials. Therefore, cautionary statements should be added to the relevant parts of the guidance.

3.6 TASK B4: ADVISORY REPORT ON OC, RMM, ES AND EXPOSURE ESTIMATION WITH THE PURPOSE OF CONDUCTING EXPOSURE ASSESSMENT OF NANOMATERIALS FOR REACH

3.6.1 In this task, information collected and analysed in Tasks A to B3 was drawn together to provide an advisory report suggesting how the relevant parts of the REACH "Guidance on Information Requirements and Chemical Safety Assessment" could be adapted or complemented in order to facilitate the exposure assessment of nanomaterials in the REACH context.

3.6.2 The report covers *inter alia* operational conditions, risk management measures, development of exposure scenarios and exposure estimation (via modelling and/or measurements). For measurements, issues related to potential background exposure to nanoparticles, choice of instrumentation and equipments for sampling and detection of nanoparticles have been addressed.

3.6.3 The report provided considerations of where in REACH guidance (highlighting specific sections) there may be implications arising from the issues identified. For each section where a need for change had been identified, key issues relating to what changes are needed were identified as e.g. bullet points. It thus covers where and, in general terms, how the guidance would need to be changed. The need for research and of what type are also discussed where there are significant knowledge gaps.

3.6.4 The primary reference documents for this report are the RIP-oN 3 documents RNC/RIP-ON/B1/2/FINAL, RNC/RIP-ON/B2/2/FINAL and RNC/RIP-ON/B3/2/FINAL in which the available evidence has been gathered together, harvested and analysed, and the current REACH guidance documents.

3.6.5 In these earlier documents a series of key issues relating to nanomaterial properties, which were considered to have possible implications for the REACH guidance, were identified. For each of theses issues, the evidence was drawn together, analysed and conclusions made.

3.6.6 RNC/RIP-ON/B4/2/FINAL builds on these conclusions but does not repeat or reference the evidence base or the analysis in the previous documents. Rather, the report considers, on an issue by issue basis, possible implications

for the REACH guidance and identifies those issues for which a guidance change is recommended. In these cases, an assessment of where and how the guidance could be modified in order to accommodate the specific issue was made. References are made to the specific REACH guidance clause number (e.g. R.13.4).

3.6.7 The analysis is presented in a tabular format in which there is the identified issue, a summary of the key points in the argument (drawn from RNC/RIP-ON3/B1/2/FINAL, RNC/RIP-ON/B2/2/FINAL, RNC/RIP-ON/B3/2/FINAL) and an assessment of the guidance changes. Where specific knowledge gaps have been identified the need for additional research is indicated.

3.6.8 RNC/RIP-oN3/B4/2/FINAL does not cover detailed proposals for modifications of the guidance text. This report was discussed at the SCG meeting on 13th December 2010 and has subsequently been revised, taking into account these comments. The summary tables shown below are from the revised report.

3.6.9 For the avoidance of doubt, the discussion of these elements in this report at this time does not represent a final recommendation with regard to an inclusion or exclusion in the REACH guidance

3.6.10 **Assessment regarding the learning from ES case studies**

3.6.11 Table 4.1 is drawn from and based on the arguments contained in the RNC/RIP-oN3/B1/2/FINAL and summarises the conclusions on the key issues identified and an assessment of possible implications for the REACH guidance.

3.6.12 **Table 4.1 Issues arising from the ES Case studies**

Issue	Possible implications for the REACH guidance	Assessment of guidance changes & research needs
Applicability of Sector of Use Categories (SUs)	Relevant SUs found for all scenarios	The information available suggests that, for this issue, the current guidance works (reasonably) well for nanomaterials. No change to the guidance recommended.
Applicability of Process Categories (PROCs)	Relevant PROC found for all scenarios	The information available suggests that, for this issue, the current guidance works (reasonably) well for nanomaterials. No change to the guidance recommended.
Applicability of ERCs	Relevant ERC found for all scenarios	The information available suggests that, for this issue, the current guidance works (reasonably) well for nanomaterials. No change to the guidance recommended. It should be stressed that this conclusion holds for using the ERC for naming ESs. It does not imply using the ERC in Tier 1 exposure estimation tools.
Complexity of measurement programmes and data	Case study providers used a range of instrument types with differing measurement ranges and metrics as identified in RNC/RIP-oN3/B1/2/FINAL. Measurement programme designs were experimental in nature rather that being specifically designed for REACH compliance. Partly as a result of this, use of the data for ES building was challenging. More information on the issues experienced, along with implications for the guidance are detailed below.	See below.
Discrimination from background particles	In the case study, attempts were made to compare process counts with background based on expert advice. This was not informed by REACH guidance as far as we were aware.	See guidance recommendations in Table 4.3

Issue	Possible implications for the REACH guidance	Assessment of guidance changes & research needs
Maximum particle size	In the case studies instruments with differing maximum particle size were used. Providers had different approaches towards what was the relevant maximum particle size of interest. The importance of the maximum particle size was not really recognised, and was not informed by REACH guidance.	See guidance recommendations in Table 4.3
Metrics	Attempts were made to use different metrics (mass, number, SA concentrations. No definitive guidance within REACH was available	See guidance recommendations in Table 4.3
Use of instruments	Measurements of emissions were made using a range of instruments relevant to the metrics described above. Different instruments with different applicability were used. No definitive guidance within REACH was available	See guidance recommendations in Table 4.3
Data handling - Uncertainty of measurement	Guidance for exposure data recommends the use of the 90th percentile. In the case studies there was difficulty in interpreting data from real time instruments, for the measurement of particle number or size distribution in this way. Typically only single values were recorded which were averaged over unspecified time periods. In other cases time series measurements were made which would provide data from which 90th percentiles (and other summary statistics) could be derived.	More information on the handling of data from real-time instruments should be added to R.14.4.5 (or to Appendix to R.14.4.5) Specifically to include how single value estimates would be derived and used. This could for example include advice on time periods over which data should be added.
Use of exposure models	Exposure models were used to estimate environmental and consumer exposure. Models were used in an unmodified way.	See guidance recommendations in Table 4.3
Applicability of ES	The ES format was assessed through the ES case studies. (Details are provided in Appendix 1 of this report). In the main the assessment showed that the format was generic and equally applicable to nanomaterials as for substances in general. Specific aspects to the relating to the measurement of nanomaterials were identified. In general, these were the same issues which were picked up in the literature review in Task B3.	See guidance recommendations in Table 4.3

3.6.13 Assessment regarding operational conditions and risk management measures

3.6.14 Table 4.2 is drawn from and based on the arguments contained in the RIP-oN 3 Task B2 report (RNC/RIP-ON/B2/2/FINAL) and summarises the conclusions on the key issues identified and an assessment of possible implications for the REACH guidance.

3.6.15 Table 4.2 Issues arising from the RNC/RIP-ON/B2/2/FINAL report on OC and RMM

Issue	Possible implications for the REACH guidance	Assessment of guidance changes & research needs
Hierarchy of control	Based on the current guidance available from a wide range of organisations, there is a consensus view that the conventional approach to control of hazardous chemicals based on elimination, substitution, engineering control, administrative control and use of PPE, sometimes referred to as the hierarchy of control, is likely to be an effective framework on which to base control approaches [RNC/RIP-ON/B2/2/FINAL (5.8.2, 8.2)]. These approaches are highly consistent with the general measures necessary for safety and health protection of workers (Article 6 of Directive 89/391/EC), the reduce-to-a-minimum principle (Article 6 of Chemical Agents Directive 98/24/EC) and the hierarchy of RMM prescribed in the Chemical Agents Directive.	Guidance: The information available suggests that, for this issue, the current guidance works (reasonably) well for nanomaterials. No change to the guidance recommended.

Issue	Possible implications for the REACH guidance	Assessment of guidance changes & research needs
Existing methods (in general)	As a general statement there is evidence that control and risk management methodologies which are already known can provide levels of protection for workers from exposure to engineered nanomaterials in the occupational environment. It is not indicated that new “nano-specific RMMs” need to be developed. Further testing and data is needed on specific workplace situations to understand the levels of protection afforded, and ensure effectiveness. [RNC/RIP-ON/B2/2/FINAL (8.3)], In relation to the REACH guidance, relevant areas are D.4.6.1 Effectiveness of RMMs, R. 13.3 Effectiveness of RMMs, R.13.4.2.5 Estimation and documentation of RMM effectiveness in the library. The information in the library on RMM efficiency is determined by two descriptors: a “typical default value” (an estimate of the 50th percentile) and a “maximum achievable” value (best practice). It is considered that for some RMM, the assumption that the available “typical default value” (an estimate of the 50th percentile) and a “maximum achievable” value (best practice) may not be achievable and should not automatically be assumed. Additional research may be necessary in order to establish the actual effectiveness of any specific RMM. This will be further specified below for specific RMMs like enclosure, filtration PPE, etc. Note that current guidance requires that If M/I assumes a certain effectiveness of a measure, the source of this assumption needs to be documented in the CSR. (D.4.6.1)	Guidance: R.13.4.2.5 Insert caveat to indicate that particle size can affect RMM performance Any other changes would be in relation to the default values in the RMM library. This is not a general indicator of the need for changes of existing methods, rather that the evidence for each should be considered. This is elaborated for each RMM (below).

Issue	Possible implications for the REACH guidance	Assessment of guidance changes & research needs
Modification and substitution	Modification of the hazard potential of certain types on nanomaterials appeared to have some, as yet not fully explored possibilities. There are approaches (surface modification, encapsulation, particle size control, functionalisation and crystalline phase control) which have been shown to have the potential to modify the toxicity of nanoparticles [RNC/RIP-ON/B2/2/FINAL (6.4, 8.4)]. In the context of REACH such modifications would be done as a prior step before developing the specific ES. Therefore the ES would be developed for the modified substance and the modification step would not be a RMM for that modified substance. Possible implications for REACH guidance. No specific implications foreseen.	Guidance: The information available suggests that, for this issue, the current guidance works (reasonably) well for nanomaterials. No change to the guidance recommended.
Enclosure	In relation to NM, enclosure has been mostly observed as an RMM for synthesis processes. Evidence reported in RNC/RIP-ON/B2/2/FINAL indicates that emissions to the workplace are substantially reduced if a process involving engineered nanomaterials is performed in a properly designed enclosure/containment. However this is not always the case. Emissions to the workplace have been reported which were subsequently attributed to a leak in the system. Emissions were also reported during activities such as product recovery and cleaning. Quantification of the effectiveness (e.g. the percentage reduction in emissions associated with use of enclosure) has not been reported. It is acknowledged that these aspects are also relevant to non-nanomaterial process. It is not possible to make an evidence based judgement on whether this reduced performance is more or less likely to occur during nanomaterial processes than non-nanomaterial processes. However it has been suggested that because of their high mobility, nanoparticles are more likely to find leakage paths than larger particles. [RNC/RIP-ON/B2/2/FINAL (6.5, 8.5)]. It is concluded that use of an enclosed system is not sufficient in itself to guarantee that there is no release of nanomaterials into the workplace air. (This is also true for substances in general.)	Guidance: Guidance to be modified to reflect the need to assess the level of containment provided by enclosed systems. Recommended change is the addition of notes or caveats added to the RMM library, in the remarks column.

Issue	Possible implications for the REACH guidance	Assessment of guidance changes & research needs
	In relation to the REACH guidance, relevant areas are D.4.6.1 Effectiveness of RMMs, R. 13.3 Effectiveness of RMMs, R.13.4.2.5 Estimation and documentation of RMM effectiveness in the library which already contain several caveats requiring justification of effectiveness values used. From the RMM library, in relation to process control, RMM W8.01 and W8.02 under the heading Automation and enclosure are most relevant. These have default values of H (High), which, based on R.13.4.2.4 is because "it would be inappropriate to give any figure due to the fact that no quantitative information is available or because these are strongly dependent on the local operational conditions and the skills of the user" Based on the evidence, this assessment (H) is still justified. However, given additional concerns regarding the possibility of leakage it should be recommended that enclosed systems should be tested to demonstrate effective containment.	

Issue	Possible implications for the REACH guidance	Assessment of guidance changes & research needs
Ventilation, LEV, including fume hood, cabinets and other extraction	Evidence reported in RNC/RIP-ON3/B2/2/FINAL indicates that worker exposure can be significantly reduced or prevented through the use of correctly designed and implemented extraction ventilation or processes involving engineered nanomaterials that would normally result in the release of airborne nanoparticles. Some evidence of inadequate control was reported but with no clear pattern. Quantification of the effectiveness (e.g. the percentage reduction in emissions associated with use of LEV) has not been reported [RNC/RIP-ON/B2/2/FINAL (6.6, 8.6)]. It is acknowledged that these aspects are also relevant to non-nanomaterial processes It is not possible to make an evidence based judgement on whether this reduced performance is more or less likely to occur during nanomaterial processes than non-nanomaterial processes. There is no expectation of 100% effectiveness in the general operation of LEV devices in the current guidance. Relevant areas are D.4.6.1 Effectiveness of RMMs, R.13.3 Effectiveness of RMMs, R.13.4.2.5 Estimation and documentation of RMM effectiveness in the library which already contain several caveats requiring justification of effectiveness values used. Information concerning the effectiveness of RMM is provided in the RMM library. In this document the default efficiency given for Lab-hoods (W.15 EX4), Extracted booth (W.15 Ex5). Laminar flow booths (W.16 Ex1) and LEV captor hood (W17.Ex1).Default values appear to be typically 80%. Based on the evidence collected, there is at present no justification for a change to the default values for these types of RMM.	Guidance: The information available suggests that, for this issue, the current guidance works (reasonably) well for nanomaterials. No change to the guidance recommended. Research: More research on the quantification of the performance of LEV systems is recommended.

Issue	Possible implications for the REACH guidance	Assessment of guidance changes & research needs
Filtration	Filtration theory indicates that filtration will be effective for particles in the nm size range. The evidence presented in RNC/RIP-ON3/B2/2/FINAL appears to support this. There is no requirement to develop new types of filters [RNC/RIP-ON/B2/2/FINAL (6.7, 8.7)]. In relation to the REACH guidance, relevant areas are D.4.6.1 Effectiveness of RMMs, R. 13.3 Effectiveness of RMMs, R.13.4.2.5 Estimation and documentation of RMM effectiveness in the library. There is no evidence to support any change to the quantification of the Effectiveness of filtration as a RMM (as indicated in the RMM library). Electrostatic precipitators also appear to be effective at capturing nanoparticles. Again no change to the effectiveness is appropriate based on the evidence available.	Guidance: The information available suggests that, for this issue, the current guidance works (reasonably) well for nanomaterials. No change to the guidance recommended.
Administrative controls	There are a range of administrative controls that may be implemented for workers involved in using engineered nanomaterials. These are usually implemented in combination with other control measures e.g. enclosure, extraction and PPE [RNC/RIP-ON/B2/2/FINAL (6.8, 8.8)]. Summary: There is no evidence to suggest that administrative controls which are used for conventional materials will not be appropriate for nanomaterials. Nor is there any expectation of this.	Guidance: The information available suggests that, for this issue, the current guidance works (reasonably) well for nanomaterials. No change to the guidance recommended.

Issue	Possible implications for the REACH guidance	Assessment of guidance changes & research needs
Respiratory protective equipment - RPE	Evidence reported in RNC/RIP-ON3/B2/2/FINAL generally supports that the performance of respiratory protective equipment (RPE) will be effective against nanomaterials. There is no requirement to develop new types of filters. This is based both on theory and on laboratory test data where measured penetration data has been reported. [RNC/RIP-ON/B2/2/FINAL (6.9, 8.9)]. Typically test evaluations been based evaluation of the highest level of respirator in common use ie P3 (or N95 in the US). In relation to the REACH guidance, relevant areas are (D.4.6.1 Effectiveness of RMMs, R. 13.3 Effectiveness of RMMs, R.13.4.2.5 Estimation and documentation of RMM effectiveness in the library. Default values provided in the RMM library are based on national and international standards against which these devices are tested for the purposes of certification. .Available evidence indicates that current “typical default value” and a “maximum achievable” value already applied in the library are likely to be appropriate and do not require modification.	Guidance: The information available suggests that, for this issue, the current methods and guidance works (reasonably) well for nanomaterials. However, this should be augmented by providing advice that P3 filters should be used. An appropriate place for this advice would be in the RMM library.

Issue	Possible implications for the REACH guidance	Assessment of guidance changes & research needs
Other PPE, gloves suits etc	Some evidence reported by the European project NANOSAFE2 suggests that nanoparticles can penetrate through commercially available gloves and recommends that two layers of gloves (double gloving) are worn. The use of impermeable, non-woven, materials is preferred. For clothing, use of cotton fabrics should be avoided. Glove selection is in general very dependant on several factors including tasks, materials and solvents handled, glove performance [RNC/RIP-ON/B2/2/FINAL (6.9.13, 8.9.3)]. In relation to the REACH guidance, relevant areas are (D.4.6.1 Effectiveness of RMMs, R. 13.3 Effectiveness of RMMs, R.13.4.2.5 Estimation and documentation of RMM effectiveness in the library. No default values are provided for gloves in the RMM library. It is recommended to add a note in the remarks column relating to double gloving.	Guidance: Recommended change is the addition of remarks relating to consideration of double gloving, provided that this in itself does not cause further problems ,e.g. handling issues added to the RMM library. In addition a note recommending that cotton fabrics (for gloves or suits) should be avoided should also be added. Research: More research on the quantification of the performance of gloves and other protective clothing is recommended, building on the research carried out in NANOSAFE2

Issue	Possible implications for the REACH guidance	Assessment of guidance changes & research needs
Control banding	The use of control banding has importance in relation to selection of control approaches for conventional materials. However, even for such materials, use of control banding still has some limitations, in particular in relation to *demonstrating* control of risk as required by REACH. The Nano-tool is a potentially important development and brings the same structured approach towards decision-making. Work is underway in ISO and in the French agency for food, environmental and occupational health and safety (ANSES) based on the same tool. However, it is challenging to see how this tool, which has not been validated, could be used without very critical review of the input parameters and collection of much more information about them in relation to each case of its use. As more refined validated tools become available these may have more utility. [RNC/RIP-ON/B2/2/FINAL (6.10, 8.10)]. In relation to REACH, control banding in it current form, given its current level of development cannot be used to demonstrate that the risks are adequately controlled. However, as an interim measure, users might consider CB approaches to provide initial selection of control measures as a starting point for the collection of more information.	Guidance: No evidential basis for a change to the guidance. No change recommended Research: Further research towards the development and validation of control banding tools is required

Issue	Possible implications for the REACH guidance	Assessment of guidance changes & research needs
Development of OELs	OELs are not in themselves technical RMM nor are they necessarily equivalent to DNELs (without appropriate justification). In that sense discussion of them at this point is perhaps inappropriate. Well validated, justified OELs are however clearly helpful in understanding the relevance of exposure levels and support performant RMM. At present, there are in a practical sense no OELs specific to nanomaterials that have been adopted or promulgated by authoritative standards and guidance organisations [RNC/RIP-ON/B2/2/FINAL (6.11, 8.11)]. It is not appropriate to make guidance recommendations regarding the developments of OELs for the reasons described above.	Guidance: It is not appropriate to make guidance recommendations regarding the developments of OELs for the reasons described and as OELs are developed in support of other legislation. For REACH DNELs are derived. For suggested changes to R.8, see RIP-oN3 Task C3.
Medical surveillance	Although preliminary medical surveillance activities such documentation of the presence of engineered nanoparticles and identification of potentially exposed workers are likely to be beneficial in the long term, no clear guidance at this time can be given at this time as to specific medical endpoints which should be tested for. [RNC/RIP-ON/B2/2/FINAL (6.12, 8.12)], In the absence of this, there is no basis for providing any guidance amendment recommendation.	Guidance: No evidential basis for a change to the guidance. No change recommended
Safety Data Sheets	Limited evidence appears to suggest that “current” (the Australian study primarily reviewed SDS’s produced before 2009) SDS are inadequate as to their coverage of different nano-forms of materials. [RNC/RIP-ON/B2/2/FINAL (6.13, 8.13)]. In any case, it is appropriate to highlight in the guidance that in developing the SDS any data derived for non-nano” form of a material should not be assumed to be relevant to the different nano-forms, unless scientific justification can be provided.	Guidance: Insertion of a clause in G4 to the effect that any data derived for "non-nano” form of a material should not be assumed to be relevant to the *different* nano-forms, unless justification can be provided.

Issue	Possible implications for the REACH guidance	Assessment of guidance changes & research needs
Consumer RMM	There is almost no evidence relating to the effectiveness of consumer RMM. Therefore no recommendation relating to REACH guidance for RMM relating to consumers can be made at this time. [RNC/RIP-ON/B2/2/FINAL (6.15, 8.15)]. Note that R13 advises that it is difficult to estimate the real effectiveness values for consumer RMMs that depend on the action by consumers due to high uncertainty about consumer behaviour. This is also likely to be true for products containing NM	Guidance: Although there is no direct evidence to support it, it is considered that the current guidance will work (reasonably) well for nanomaterials. No change to the guidance recommended. Research: Additional research required to evaluate the effectiveness of this RMM.
Environmental RMM	Other than in the case of filtration, due to lack of evidence no recommendation relating to REACH guidance for RMM relating to environment can be made at this time. [RNC/RIP-ON/B2/2/FINAL (7.1, 8.16)].	Guidance: No evidential basis for a change to the guidance. No change recommended. Research: Additional research required to evaluate the effectiveness of this RMM.
Operational Conditions	Only limited information on occupational conditions was found to be available in the public literature. Possible implications for REACH. Lack of information relating to R.13.2.2 Operational conditions and risk management measures related to workers. Lack of information in relation to estimation of exposures using Tier 1 models (R. 14. R.15. R.16) Limited opportunity to validate assumptions in these models.	No evidential basis for a change to the guidance. No change recommended.

3.6.16 **Assessment regarding exposure estimation**

3.6.17 Table 4.3 is drawn from and based on the arguments contained in RNC/RIP-ON/B3/2/FINAL and summarises the conclusions on the key issues identified and an assessment of possible implications for the REACH guidance.

3.6.18 Table 4.3 Issues arising from the RNC/RIP-ON/B3/2/FINAL report on exposure assessment

Issue	Possible implications for the REACH guidance	Assessment guidance changes & research needs
Discrimination from background nanoparticles	Background aerosol will be an important contribution towards the total number concentration (and possibly mass and surface area concentration also) [RNC/RIP-ON/B3/2/FINAL, (10.1)]. Where possible, this should be subtracted from the measured count. Viable approaches are available on which guidance should be based including a time series approach contrasting periods of activity with periods of no activity [RNC/RIP-ON/B3/2/FINAL (10.1.4)], parallel sampling of background [RNC/RIP-ON/B3/2/FINAL (10.1.5)], or collection of samples for offline analysis [RNC/RIP-ON/B3/2/FINAL (10.1.6)]. Combinations of these approaches have been advocated [RNC/RIP-ON/B3/2/FINAL (10.1.7)]. Background particles may also act as carriers or scavengers for nanomaterials which have aggregated with them [RNC/RIP-ON/B3/2/FINAL (10.1.8)]. If it is not possible to remove the background count contribution, then the total count concentration could be considered to be a worst case. In case studies, attempts were made to compare process counts with background based on expert advice including the 3 approaches described above. None were entirely satisfactory. Approaches chosen were not informed by REACH guidance as far as we were aware.	Guidance: D.5.2 Generalise and apply the “have background concentrations been taken into account” statement. R.14.4.5 Provide a paragraph in the text to indicate the complexity of issues in relation to NM measurement and a link to an annex of additional information An alternative anchor point is R.7.1.14. R.7.1.14 Information on options for discrimination from background nanoparticles to be included in this section. Research: Additional research required on the usefulness of approaches for discrimination from background nanoparticles is required. Research on instruments also appropriate.
Measurement of size distribution	Particle size information is clearly important and should be collected and reported [RNC/RIP-ON/B3/2/FINAL (10.2)]. The size distribution of aerosols measured in the workplace is unlikely to be the same as the primary material. Various methods are available which can be used to measure size distribution.	Guidance: R.7.1.14 Information on options for measurement of particle size information to be included. Include instrument options as indicated in ISO 12885 (2008), ISO 27628 (2008) BSI 6699-3 (2010) and provide advice on their application, limitation and data handling.

Issue	Possible implications for the REACH guidance	Assessment guidance changes & research needs
	These are detailed in ISO 12885 (2008), ISO 27628 (2008) and include instruments such as SMPS, FMPS and off-line methods. [RNC/RIP-ON/B3/2/FINAL (10.2.1)]. Recommended methods should be able to account for complex form of the distributions (e.g. bimodal distributions) and should provide a meaningful and useful parameter(s). Various approaches have been described including direct inspection of the distribution, extraction of median and other statistical parameters and summation number counts into size intervals [RNC/RIP-ON/B3/2/FINAL (10.2.5)], The size interval of interest should include consideration of the maximum relevant particle size (see next issue). In the case studies, there was no unified approach towards the measurement or reporting of size distributions. Various methods were used (as described in the two ISO documents. The methods actually used in the case studies were based on expert advice. This was not informed by REACH guidance.	R.14.4.5 Provide a paragraph in the text to indicate the complexity of issues in relation to NM measurement and a link to an annex of additional information. An alternative anchor point is R.7.1.14.
Maximum relevant size	Evidence suggests that nanoparticles of interest may be present as primary particles and larger aggregates/agglomerates potentially including background particles therefore these larger agglomerates, not just unbound primary particles should be measured. Measurement of unbound primary particles alone is not sufficient to fully understand exposure in these situations [RNC/RIP-ON/B3/2/FINAL (10.3.1)]. For inhalation exposure, measurement of the respirable fraction, representing the fraction of aerosol capable of entering the alveolar region of the lung has been successfully used [RNC/RIP-ON/B3/2/FINAL (10.3.4)], Measurement of the respirable fraction is recommended.	Guidance: R.14.4.5 Provide a paragraph in the text to indicate the complexity of issues in relation to NM measurement and a link to an annex of additional information which includes discussion relating to the relevance of maximum particles size to be included An alternative anchor point is R.7.1.14.

Issue	Possible implications for the REACH guidance	Assessment guidance changes & research needs
	If instruments which have a smaller cut off point than the respirable convention are used, the value of the cut off point should be reported in any document in which this information is given. In the case studies instruments with differing maximum particle size were used. Providers had different approaches towards what was the relevant maximum particle size of interest. This was not informed by REACH guidance.	
Effect of high spatial and temporal variability	Typically, airborne concentrations are higher and closer to the source worker (near-field) than at some distance point (far-field). High spatial variability has been reported in the studies reviewed. Therefore measurements of workplace air concentrations (i.e emissions) will not adequately represent personal exposure [RNC/RIP-ON/B3/2/FINAL (10.4)]. A preferred approach is the use of personal sampling devices [RNC/RIP-ON/B3/2/FINAL (10.4.2)]. There is no current suitably validated device which can be used in this way to collect the range of data of interest. There is activity to develop such devices (for example in the European FP7 project NANODEVICE and elsewhere [RNC/RIP-ON/B3/2/FINAL (6.3)]. Therefore measurement strategies which encourage (even limited) comparison between workplace air concentrations and personal exposure are recommended. Issues related to measurement strategies are discussed below. Only one of the case studies used personal sampling.	Guidance: R.14.4.5 Provide a paragraph in the text to indicate the complexity of issues in relation to NM measurement and a link to an annex of additional information which includes discussion relating to the relevance of personal sampling. An alternative anchor point is R.7.1.14 Research: More research is required to develop appropriate methods for measurement of personal exposure. This includes methodological research and research into new instruments.
Choice of metrics and instruments	There are three main metrics, all of which could have some utility in measuring exposure to nanoparticles. These are: i) mass concentration (units mg m^{-3}); ii) number concentration (units m^{-3}) and; iii) surface area concentration units (m^2 m^{-3}). A case may be made for the use of any of these metrics under certain circumstances [RNC/RIP-ON/B3/2/FINAL (5.1)]. The issues of metrics should not be decided on exposure	Guidance: D.1 Add caveat to indicate that the same relevant metric(s) should be used for DNEL and exposure estimate. F.10 Comment to provide the possibility on using surface area and/or number (*especially* for fibres) as additional metric(s). R.14.2 Indicate the possible use of other metrics

Issue	Possible implications for the REACH guidance	Assessment guidance changes & research needs
	assessment issues alone, toxicological information needs to be carefully considered. In [RNC/RIP-ON/D/2/FINAL(11)], it is recommended that surface area is a potentially useful metric with which to describe the dose (hazard) for inhalation. This implies there is also utility in using surface area as a metric to describe exposure. (It is not suggested that this is the only useful metric for either dose or exposure). It should be recognised that these two metrics are not the same. In relation to dose, SA is usually estimated using a mass dose and applying a specific surface area value for the powdered material as obtained by BET analysis. Surface area concentration of an aerosol in exposure terms can be measured "directly" using the appropriate monitoring instruments. Whilst these two measures should be in related, this has not been demonstrated. Any comparison between the two should be supported with evidence of their equivalence. Further research is required to establish these relationships for different materials under an appropriate set of conditions. Number concentration has also been demonstrated to be a useful metric in detecting emissions. In relation to measuring exposure the best available guidance at this time is that measurements should encompass assessment of mass, number and surface area concentration where possible [RNC/RIP-ON/B3/2/FINAL (10.5.5)],. Measurement methods which could be recommended in relation to these metrics are provided in RNC/RIP-ON/B3/2/FINAL (6.2). In the case studies, instruments a range of metrics and instruments were used. Providers had difficulty in interpreting the data obtained from these instruments. In particular there was understanding the relevance of number concentrations and size distributions and how these could be used in relation to DNELs (derived or assumed) which were based on mass concentrations. There were also differences between measures of the same metric	R.15.2.3 Indicate/recommend where possible the use of complementary metrics. R.14.4.5 Provide a paragraph in the text to indicate the complexity of issues in relation to MN measurement and a link to an annex of additional information Provide the same annex with an anchor point at R7.1.14 Information on options for measurement of particle size information to be included. Include instrument options as indicated in ISO 12885 (2008), ISO 27628 (2008), and provide advice on their application, limitation and data handling. Additional comprehensive information on the applicability and limitations of instruments for exposure assessment has just be been published by BSI 6699-3 (2010), not available and therefore not referred to in previous reports, which could form the basis of guidance. Further information to be provided on the usefulness and applicability of the three metrics. Based on the toxicology, recommendations will be made elsewhere on the applicability of additional metrics such as surface area or number concentration (*especially* for fibres) as a dose metric. Research: Research is required to understand the relationship between mass, surface area and number concentrations for materials of interest Research is also required to establish these relationships between different measures of surface area (e.g. for hazard and for exposure) for different

Issue	Possible implications for the REACH guidance	Assessment guidance changes & research needs
	from different instruments. Resolving these issues is likely to be challenging (and beyond the scope of the current work) in that relationships between these metrics will be highly dependant on the extent to which aerosols are aggregated/agglomerated or not which will in turn depend on the type of process which leads to the emission or release of aerosol. Simple constant relationships will not be routinely available. [RNC/RIP-ON/D/2/FINAL(10)], In addition, guidance for exposure data recommends the use of the 90th percentile. In the case studies there was difficulty in interpreting data from real time instruments, for the measurement of particle number or size distribution in this way. Typically only single values were recorded which were averaged over unspecified time periods. In other cases time series measurements were made which would provide data from which 90th percentiles (and other statistical outputs) could be derived.	materials under an appropriate set of conditions.
Emerging measurement strategy	The issues described above are considerations in relation to what has been described as an emerging measurement strategy. Measurement strategy includes definition of the purpose of sampling, selection of instruments, how they are used, the number and type of samples taken, what data is collected and how this date is used. There is unlikely to be a universal strategy due the many differing purposes for which measurements may be made [RNC/RIP-ON/B3/2/FINAL (6.9)]. Published studies suggest a multi-instrument approach in an attempt to capture all relevant metrics and characteristics [RNC/RIP-ON/B3/2/FINAL (6.9.2)], This could include for example, a multi-instrument approach in which CPCs are used to identify potential sources of emissions (and background sources), an SMPS or ELPI is used to characterise size distribution and how this varies as a function of time or space combined with SEM or	Guidance: R.14.4.5 Provide a paragraph in the text to indicate the complexity of issues in relation to NM measurement and a link to an Annex of additional information. An alternative anchor point is R7.1.14 Research: Research required to investigate the effectiveness of different strategies in particular to measure personal exposure and to assess within the reach context.

Issue	Possible implications for the REACH guidance	Assessment guidance changes & research needs
	TEM analysis of samples collected on filters to characterise the physical or chemical form of the aerosol. Published guidance for example in the document ENV/JM/MONO(2009)16 *Emission Assessment for the Identification of Sources and Release of Airborne Manufactured Nanomaterials in the Workplace: Compilation of Existing Guidance* (OECD 2009) also supports this stepwise approach [RNC/RIP-ON/B3/2/FINAL (6.9.13)] however this in particular requires routine use of Transmission Electron Microscopy. which is unlikely to be routinely available. A similar approach is described in BSI 6699-3 (2010), not available and therefore not referred to in previous reports. Both the published research and the available guidance provide good information of which guidance recommendations can be developed but do not at this stage provide a complete solution. Neither, for example, provides an validated methodology for assessment of personal exposure at this stage.	
Assessment of high aspect ratio nanomaterials	Exposure to fibrous aerosols is assessed by measuring the number (concentration) of fibres in the air with a specific shape and composition (WHO, 1997). Assessment of fibre concentration is likely to be relevant to some high aspect ratio nanomaterials in terms of their exposure [RNC/RIP-ON/B3/2/FINAL (10.6.1)]. The presence of fibres is only likely to be detected by electron microscopy. Application of the WHO approach has not yet been validated for any types of high aspect ratio nanomaterials. Only one study has used an approach based on the WHO method and report fibre concentrations. It is not clear the extent to which WHO counting rules were applied [RNC/RIP-ON/B3/2/FINAL (10.6.4)]. Encouragement should be made in the guidance towards checking of whether fibres (according to the WHO definition) are present in	Guidance: R.14.4.5 Provide a paragraph in the text to indicate the complexity of issues in relation to NM measurement and a link to an annex of additional information An alternative anchor point is R.7.1.14 Research: More research is required to develop validated robust methods for the assessment of HARN. This includes image analysis methods and instrumental approaches. This should have a very high priority.

Issue	Possible implications for the REACH guidance	Assessment guidance changes & research needs
	exposure assessment samples for all materials which have some potential for the release of fibres. No specific guidance can be given at this time towards assessing bundles or clumps of high aspect ratio nanomaterials. One of the case studies (CASE1 Nanocyl) was concerned with nanomaterials which could be considered to be HARN (CNT). Primarily they measured mass concentrations (size differentiated) which they compared with a DNEL which was also expressed in term of mass concentration. This was used in their production scenarios. However they also considered the potential for fibre release in a simulation study (see issue of simulations below) by collection onto a filter for off-line analysis by TEM. They reported that no fibres were observed.	
Exposure modelling	Limited assessment of the models used in exposure estimation has been carried out. The most extensive validation was for occupational exposure. Evaluating Stoffenmanager and ECETOC TRA, the conclusion drawn in the FP7 NANEX project (NANEX 2011) was that there was no correlation between the model estimates and measurement data. Neither of the models is tuned to and calibrated for nanomaterial exposure situations, and hence the actual model estimate will be inaccurate and possibly overestimate the (mass) concentration levels. For consumer exposure NANEX evaluated Consexpo, (inhalation, dermal, oral), ECETOC TRA (inhalation, dermal,oral), RiskofDerm (dermal). The authors concluded that dermal modules might be suitable for use for MNMs as the underlying equations do not appear to rely on nano-specific properties. The dermal modules of	Guidance: Additional commentary relating to the applicability of models to nanomaterials to be added in Appendix D1, "strengths and limitations of available tier 1 exposure estimation tools" R.14.4.7 Caveat to be added indicating the limitations of the models. R.15.3.1. Caveat to be added indicating the limitations of the models. R.16. Caveat to be added indicating the limitations of the models R.17.2. Caveat to be added indicating the limitations of the models. Research Substantial addition research is required to develop and validate exposure models, in in relation to occupational,

Issue	Possible implications for the REACH guidance	Assessment guidance changes & research needs
	the models may therefore be applied to nanomaterials, however, should be used with care as they are not yet validated nor calibrated for MNMs and the output (the exposure estimate) is given in a mass-based metric. There are greater limitations in the currently available inhalation modules in the exposure estimation models. These inhalation modules do not consider the nano-specific properties of the materials that could affect the exposure, e.g. agglomeration effects. Therefore, in the authors view, inhalation modules should be used with even greater care. For environmental models, given the specific properties of nanomaterials it can be concluded that the existing exposure models need to be adapted in order to be ready for use for nanomaterials. Input for environmental exposure models such as EUSES are often based on QSPR (Quantitative Structure-Property Relationship) calculations using physicochemical properties of the substance, mainly KOW and Kp values. At the moment it is highly unlikely that these QSPRs will be applicable for nanomaterials. It is therefore recommended to not use these QSPRs (including read-across approaches) to estimate properties of nanomaterials, as long as there is no (solid) basis to do so. Instead, measured partition coefficients (i.e. Kp values) should be used to estimate environmental distribution [RNC/RIP-ON/B3/2/FINAL (8.4)] While there is information available on models nanoparticle transportation, aggregation and deposition available in the literature deriving primarily from the colloid literature, this is either theoretical and/or based on idealized relatively simple model systems. (e.g. Weisner and Bottero 2007). The models have not been adapted for the large number of components present in natural waster which may include salts, clays, micro-organisms, natural organic matter and other colloidal materials (Mylon et al	consumer, environmental exposure.

Issue	Possible implications for the REACH guidance	Assessment guidance changes & research needs
	2004). At present these are not appropriate for use in a regulatory context. Where models were used in the case studies, these were mostly used without any additional consideration with respect to nanomaterials. Exposure models a key element of the exposure estimation process. The limited evidence of successful validation for occupational exposure indicates that model estimates should not be relied on alone without further confirmation of their validity in individual cases. In any case, model estimates should be used with caution. It is not possible to provide linkage to models which have been validated for nanomaterials. Cautionary statements should be added to the relevant parts of the guidance.	
Utility of exposure simulation studies	Simulation studies provide a useful addition from which additional data on the potential release may be obtained. Typically such studies attempt to simulate, often at worse cases a process which may lead to a release. They provide a basis by which data can be collected relatively quickly under a more controlled set of conditions. This could provide the opportunity very determinants of exposure in a controlled way. There are a number of examples in the literature. For example Hsu and Chein (2007) designed an experimental setup for simulating the abrasive effect of sunlight, wind, and human in a closed chamber to examine the release from TiO2 nanoparticle coatings on wood, polymer and tile. [RNC/RIP-ON/B3/2/FINAL (6.4.6)] Gohler et al. (2010) measured emissions from a sanding simulation using polyurethane coating and architectural paint containing two types of nanoparticles. During the abrasion tests, no significant difference was detected between the number concentrations of released particles of the pure coatings and of the coatings that were dosed with additives [RNC/RIP-ON/B3/2/FINAL (6.4.31)], However, larger particles,	R.14.4.1 Include specific recommendation that simulation studies can be used to provide relevant exposure information Similar statements in R.16. A16-1 and R.17 A17.1

Issue	Possible implications for the REACH guidance	Assessment guidance changes & research needs
	containing nanoparticles were observed. One of the case studies (CASE1 Nanocyl) considered the potential for fibre release in a simulation study from a composite material containing CNT. The method used as described by Gohler et al. (2010). Emissions were assessed by collection onto a filter for off-line analysis by TEM. They reported that no fibres were observed. This study is expected to be published shortly in the scientific literature. Simulation studies of this type can be used to provide relevant exposure information development of the ES and can be used to provide input data to develop and validate exposure models. As with all such simulations sufficient justification of the reality of the simulation should be provided.	

3.7 TASK C1: CASE STUDIES ON HOW NO EFFECT LEVELS COULD BE ESTABLISHED

3.7.1 Human health

3.7.2 In this report we have applied the methods in the REACH guidance to MWCNT, TiO_2 and silver nanoparticles. However only relatively few studies exist which are sufficiently rigorous and exhaustive enough for the REACH approach of deriving a human exposure limit. Therefore, there needs to be further studies conducted at the same robust level as those outlined and analysed. The most robust way in which to establish if the REACH approach is sufficiently robust is the collection of human data, preferably epidemiological evidence based on worker populations. However, such data is rare within risk assessment (for nanomaterials and substances in general) and it is far preferable that negative effects are controlled meaning such data would not become available.

3.7.3 The absence of evidence does not necessarily indicate an absence of an effect and, for nanomaterials, there exists still a great deal of uncertainty in relation to the long-term effects of exposure. Currently the most reliable evidence for effects is studies conducted by researchers such as Pauluhn (2010b) and Ma-Hock (2009) using internationally recognised test methods. However these studies were not intended to look for all effects, such as long term carcinogenicity, and therefore these studies may not fully address the potential hazard of the nanomaterials studied. Indeed it is unrealistic to expect a single study to cover all potential endpoints. Normally the approach would be to look for other studies using similar materials, which may not be suitable for derivation of a DNEL, but which can inform as to the likely effects of the materials (e.g. long-term effects, systemic effects etc.). However in relation to a number of nanomaterials (and other materials) there is insufficient evidence to apply such an approach. Another compounding factor of a weight of evidence approach based on the peer reviewed literature, which is relevant to nano- and non-nano materials, is that negative data is not always reported even though such data may be important in generating a balanced picture of materials toxicity.

3.7.4 A major question relating to the applicability of the REACH guidance is the applicability of the current assessment factors (AF) in relation to nanomaterials which is dealt with in the following section. The default AF used in the REACH guidance have been derived from classical (soluble) toxicity. It is therefore important to investigate whether current scientific knowledge is mature enough to assess applicability and/or suggest deviations from these factors for nanomaterials. In any case, as for substances in general, when deviating from the default, this should be scientifically justified based on substance-specific data.

3.7.5 ***Assessment factors - Interspecies Differences***

3.7.6 The use of interspecies differences is to account for differences between the experimental subjects (such as a rat) to a human. The REACH guidance (R.8) states that the default assumption is that humans are more sensitive than experimental animals. This default assumption may be true for certain chemicals, but as expressed within some of the studies reviewed (Pauluhn 2010a, Kobayshi et al. 2009a/b, Hanai et al. 2009), rats may be far more sensitive to particle effects. This is due to the phenomena of lung overload, to which rats are far more sensitive than humans or indeed other test species such as hamsters. As such it may well be appropriate that the default assessment factor which already takes a conservative position (humans are more sensitive than animals) could be reduced. This was performed within the assessments by Christensen at al. (2010b) that reduced the default AF from the default of 2.5 to 1.5, which appears a valid position based on the use of a the most sensitive species.

3.7.7 Within the study by Pauluhn (2010a) the driver of toxicity was reported as being due to lung overload. As the cell tasked with clearance of particles in the distal lung is the alveolar macrophage, Pauluhn (2010a) accounted for differences in susceptibility by dividing the volume of rat alveolar macrophages by that of human alveolar macrophages. From this it was concluded that, based on alveolar macrophage volume, humans are six times more resistant to lung overload. Within the calculation, considering other differences normalised by the body weight (1/10), this led to an overall

interspecies AF of 2 which appears reasonable based on their overload hypothesis.

3.7.8 ***Assessment factors - Intraspecies Differences***

3.7.9 The use of intraspecies AF takes into account differences within a population, for example the relative sensitivities of the very young compared to the very old in the general population, such that all members of a population should be adequately protected. Within the studies investigated, the use of such factors for a worker population demonstrates the greatest difference to the REACH approach and as such is the source of the greatest variation between derived limits based on similar studies. An example of this is the approach used within the NEDO study (Kobayshi et al. 2009, Hanai et al. 2009). The approach within the NEDO study was to assume a healthy worker population with no sensitivities and as such no AF was applicable. The REACH approach applies a default factor of 5 to account for sensitivities within a healthy worker population as it is unrealistic to assume a population of individuals has completely perfect health and no sensitivities such as asthma. The approach of Pauluhn (2010a) was to use the default factor to scale to workers ventilation ($10/m^3$ working day and adult) and to make no other account for intraspecies differences. This was based upon the lack of systemic bioavailability of Baytubes producing purely local effects and the fact that such an effects was thought to be independent of metabolism. As a hypothesis, there is little to suggest that the approach taken by Pauluhn is incorrect. However it may not take into account systemic effects such as cardiovascular disease which could potentially occur, not through direct translocation, but through other mediators leading to effects.

3.7.10 In relation to MWCNT, and indeed other materials, it is still not yet clear as to the toxico-kinetics of MWCNT (although within the study of Pauluhn (2010b) no systemic effects were detected), specifically, the translocation of these materials into the pleural space. However there are indications appearing in literature that this may be possible for some types of MWCNTs (Mercer et al. 2010; Ryman-Rasmussen et al. 2009). Their persistence in this cavity could lead to pleural inflammation, fibrosis and possibly the generation of mesothelioma. Pauluhn (2010b) showed accumulation of MWCNT in the lung

associated lymph nodes as part of lung clearance routes. However there is currently no evidence that the MWCNT, such as those used by Pauluhn (which tend to exist as loose bundles), will become untangled into individual fibres and translocate into the pleural space where it may be cleared to the outlying lymph nodes or be retained and cause adverse effects. Therefore further studies are needed to clarify this potential route of translocation, target tissue and the potential hazard and for which types of CNTs this may be relevant.

3.7.11 As a precautionary approach, in the absence of better evidence it may be advisable to follow the REACH R.8 guidance approach and use the same intraspecies AF for local effects as it does for systemic effects.

3.7.12 There does not seem sufficient evidence or cause to assume that the application of such an intraspecies AF to nanomaterials would be inappropriate. Indeed within a worker population there are likely to be those which are of increased susceptibility to NM, perhaps due to asthma or sub-clinical cardiovascular disease which would place them at higher risk of adverse effects to nanomaterials.

3.7.13 ***Differences in duration of exposure***

3.7.14 The REACH R.8 Guidance allows for substance specific adjustment of the assessment factors based on factors such as accumulation (which would require an increased AF). This may be very pertinent to certain forms of insoluble nanomaterials and potentially even more so for long straight fibres which may resist clearance and as such, with repeat exposure lead to an accumulation of dose (Donaldson 2009; Muller 2005).

3.7.15 ***Issues related to dose response***

3.7.16 The use of AF to take into account dose response relationships appears equally valid for NM as for other materials. They relate to the nature of the dose response curve obtained, gaps between doses etc. and how these relate to the confidence one can have in the observed effects and limits proposed.

3.7.17 ***Quality of whole database***

3.7.18 In principle, there appears no reason to suggest that guidance is insufficient with regards to addressing issues with the quality of the whole database. However, certain aspects may benefit from clarification. Guidance does stress that increased uncertainty may exist in cases when using a low reliability study or alternative data such as in vitro studies, Quantitative Structure Activity Relationship (QSAR) and read across, which should be accounted for. This is particularly pertinent to the current situation for NM as there is currently little evidence to suggest that (Q)SAR or read-across approaches are applicable. Thus, such approaches should only be applied if scientifically justified on a case-by-case basis. However in the future, through further research, this approach may be appropriate and guidance is adequate to deal with both situations, although a statement in the guidance on the applicability of (Q)SAR and read-across to nanomaterials would be useful.

3.7.19 ***Metric***

3.7.20 The question of which metric is most appropriate for the derivation and application of DN(M)EL is ongoing and is fully discussed in RNC/RIP-oN3/D/2/FINAL. In the examples discussed, the metric of mass has been used in the studies cited to show N(L)OEAC and this has been conserved throughout the derivation of DNELs. This does not propose to suggest that mass is the most appropriate metric, it is simply a practical metric (as reflected in the opinion of NIOSH (2005), further discussed in RNC/RIP-oN3/C2/2/FINAL). Within the conclusions of NIOSH, a surface area metric was identified as the most accurate dose descriptor. The benefit of this as a dose descriptor is that a single limit can be applied irrespective of particle size which is important when considering the role of aggregation. In addition, NIOSH stated that convention and the availability of suitable equipment dictate that mass is still the most practical measurement. NIOSH (2005) suggested two Recommended Exposure Levels (RELs) based on two separate size fractions (fine and ultra fine for TiO_2) in the place of a single surface area metric to account for alterations in particle toxicity based on particle size/ surface area,. The relative considerations of some of the metrics

discussed in RNC/RIP-oN3/D/2/FINAL are discussed below in relation to the studies used.

3.7.21 ***Fibrous nanomaterials***

3.7.22 The question of fibre number concentration may be applicable to CNT but may also be applicable to other nanomaterials. There are various methods available for the formation of nanowires, nanotubes and nanorods from a range of materials and as such these materials may be rendered harmful by virtue of their shape (so long as they reach the minimum length of straight fibres and are biodurable). Indeed in the study by Hamilton et al. (2009), they tested long TiO_2 nanobelts (15-30 μm) against short nanobelts (< 5 μm) and spherical TiO_2 using murine alveolar macrophages and in vivo testing. It was concluded that the long fibre-shaped TiO_2 elicited inflammation in a manner similar to that of asbestos or silica. As such they suggested that any modification of a nanomaterial's shape, resulting in a wire, fibre, belt or tube, be tested for pathogenic potential (Hamilton et al. 2009).

3.7.23 It is impractical to suggest an over-riding single metric for nanomaterials or even within a class of nanomaterials (e.g. CNT), as alterations can occur in the material (such as shape) that potentially alter the mode of toxicity. Instead, an understanding of the physico-chemical characteristics is required to establish potential hazard and tailor the use of the most appropriate exposure metric for setting exposure levels.

3.7.24 Such a link between physico-chemical characteristics and potential hazard with suggested metrics is shown in Task B5 of the RIP-oN 2 project (RNC/RIP-oN2/B5/2/FINAL). Within this scheme, if a nanomaterial satisfies the traditional fibre pathogenicity criteria of being straight, long and biodurable it may act as a pathogenic fibre. As such the correct metric would be fibre number, which is the metric used to measure other pathogenic fibres such as asbestos. This suggestion is also shown in the Safe Work Australia (SWA) document 'Engineered Nanomaterials: Feasibility of establishing exposure standards and using control banding in Australia' (SWA, 2010c). Within this document, the authors discuss the suggestion of benchmark exposure level (BEL) for fibres proposed in the BSI 'Nanotechnologies' document (BSI PD 6699-2:2007). The BSI document proposed a level for fibrous nanomaterials

of 0.01 fibres/ml, in line with the current UK clearance limit in asbestos removal activities. The SWA approach was to suggest a BEL of 0.1 fibres/ml for fibrous nanomaterials, as there is no evidence that fibres are more toxic on a fibre-by-fibre basis. Indeed this is true, and whilst some studies have suggested that CNT can show inflammogenicity over that of asbestos (Poland et al. 2008), these have been performed on a mass basis and the increased inflammogenicity of CNT may simply represent an increased fibre number per unit mass. There are no studies to our knowledge that demonstrate CNT toxicity on a fibre number basis. Such a study would enable the comparison of fibre potency between CNT and other benchmark fibres such as asbestos.

3.7.25 ***Non-fibrous nanomaterials***

3.7.26 The discussion of the relative merits of alternative metrics and their correspondence to toxicity outcomes is fully described in RIP-oN 3 task D report and we will not reproduce such evidence here. Of the studies investigated, mass was the metric reported in the NOAEL and we have conserved this through the derivation of a DNEL. However in relation to non-fibrous nanomaterials, there is strong emphasis that a metric such as surface area may better describe the toxic effects seen with nanomaterials than other metrics such as mass. This has been shown in several studies such as that of Duffin et al. (2007), where materials of a similar surface reactivity but differing sizes, all generate a similar level of inflammation when based on the same surface area.

3.7.27 However, the use of surface area as a metric raises several technical difficulties in measuring exposure, not least that the current convention of workplace exposure monitoring of coarse particles is based on a mass metric. This problem was raised by NIOSH (2005) who noted that surface area was a preferable metric, taking into account increasing particle toxicity with decreasing particle size (increasing surface area) but mass as a metric is more practical. As such, the NIOSH approach was to recommend two recommended exposure limits (REL) based upon size fractions (fine (<10 μm) and ultra-fine (<0.1 μm)) as this was considered most practical in relation to workplace exposure despite surface area being demonstrated to be a more appropriate dose metric than mass.

3.7.28 Using an approach based on this, BSI (BSI PD 6699-2:2007) suggest a BEL of 0.066 x WEL (workplace exposure limit) for a material, which for TiO_2 would correspond to the NIOSH derivation (e.g. 1.5 mg/m^3 x 0.066 = 0.1 mg/m^3). Such an approach appears valid based in the assumption that the increased toxicity of a nanomaterial is related to that of the bulk material (e.g. an inert bulk material gives rise to a similarly inert nanomaterial) based purely on its increase in surface area. This approach would however underestimate the toxicity of a material if there were an additional alteration in the nature of the material in the nano-range over and above that of a simple increase in surface area.

3.7.29 In relation to use of alternative metrics, these may be altered by the aggregation state of the NM which may be reflected in changes in the relative toxicity as discussed in the following section.

3.7.30 ***Agglomeration and Aggregation***

3.7.31 Thermodynamically aggregation and agglomeration are two distinct processes. They have been described by Zhang et al. (1999) although he does not refer directly to the names of the processes. Aggregation is a process that can be described by the fact that material in the nano-phase is converted into material of the bulk phase. The process is irreversible with small forces. Consequently the surface area decreases (mass remains constant). Agglomeration is the process whereby (primary) particles agglomerate. This process can simply be described by an equilibrium reaction. Consequently the total surface area remains constant and the process can be reversed. Unfortunately both processes usually take place simultaneously. Thus, if the toxicity of a particle is dependent on the surface area, the effect will change if the primary particles aggregate. However such is also the case if the toxic effect is based on size since agglomeration is an equilibrium process of which the direction depends on the environment of the particles. As such it can be seen that the aggregation/ agglomeration state of a particle is an important issue when considering its toxicity. This is primarily the case when the driver of toxicity is an attribute that is altered during aggregation/ agglomeration (e.g. surface area, size) rather than conserved (e.g. mass).

3.7.32 Within experimental studies, considerable effort is often placed in gaining as stable and homogenous an aerosol as possible, centred around the primary particle size. However this may not necessarily reflect real life exposure, particularly with regards aggregate/ agglomerate formation (Oller & Oberdörster, 2010). As such, if the driver of toxicity was surface area, it is conceivable that experimental manipulations to decrease aggregation/ agglomeration (and as such increase surface area) may lead to over estimation of the potential hazard of a material if its natural form in the workplace is a much larger, aggregated/ agglomerate particle with a correspondingly lower surface area.

3.7.33 Aggregation/agglomeration of a nanoparticle may also alter its zone of deposition e.g. deposition of larger particles is likely to occur to a greater extent in the upper ciliated airways where clearance is more rapid owing to the mucociliary escalator, whilst smaller (nano)particles may deposit further down the respiratory tract in the proximal-alveolar region. Within this region clearance is macrophage mediated and hence slower. Another interesting aspect is the nature of the aggregate/ agglomerate, such as if its composed of solid spherical nanoparticles forming a larger, denser agglomerate or, for example, if the sample is composed of loose agglomerates of carbon nanotubes which are geometrically large but may still posses a lower density and hence lower aerodynamic diameter and deposit in the distal airways. Based on the discussions by Pauluhn (2010a), low density agglomerates such as that of CNT may lead to volumetric overload of alveolar macrophages at a lower dose of a similar density, but smaller geometric diameter material such as carbon black.

3.7.34 It is impossible to gauge the overall effect aggregation/ agglomeration can have, as this is likely to be different with different forms of nanomaterials and may be dependent on numerous factors such as surface charge, coating or surface forces (e.g. van der Waals forces in the case of CNT). Environmental factors may also influence the degree of agglomeration or separation (e.g. turbulent air flow) and as such the aggregation state is likely to be highly dynamic.

3.7.35 In conclusion, the REACH approach appears to be useful for calculating safe exposure levels for some nanomaterials such as silver and MWCNT. It is currently impossible to evaluate if the assessment factors are sufficiently conservative or overly so without the use of human data based in real exposure situations which is simply not available. The assessment factors used within the risk assessment have been derived for the conventional approach and were not developed with consideration for (nano)particles. Based on current scientific knowledge, it is unknown whether the same factors can be truly applied or not in case of a (nano)particle approach. Within the TiO_2 studies evaluated, the derivation of a lower DNEL (on a mass-metric basis) than that of the bulk, non-nano form of TiO_2 is in line with what the scientific literature shows us. That is, smaller particles have an increased surface area and, as such, a low toxicity (per unit surface area) material may show increased toxicity due to increased surface area. This is in line with what has been derived by NIOSH (2005), as shown in RNC/RIP-oN2/C3/2/FINAL.

3.7.36 The lack of a consensus on nanomaterial non-testing approaches such as QSAR or read-across means that at the current time it may only be practical to conduct risk assessment based on a case-by-case basis for individual nanomaterials. That is, individual sources, production methods etc. rather than individual classes of nanomaterials such as MWCNT. As such, for an experiment which has been conducted with only one type of nanomaterial and for which the dose-response curve has been established by a single metric, such as mass, the derived DNELs may only be valid for the used specific materials. The development of suitable non-testing approaches is important as it may reduce the burden of expensive and ethically challenging in vivo testing. In order to further develop non-testing approaches such as QSAR for nanomaterials to an acceptable level for REACH purposes, comparison of experimental results and physico-chemical characteristics of nanoparticles needs to be performed. Such comparisons are often performed on small panels of selected nanoparticles as part of research projects (e.g. the EU ENPRA project). Whilst these projects are very useful; larger scale comparisons of numerous materials may need to be performed e.g. in high throughput testing systems. Shared information from industry may be an ideal

source of detailed toxicological and physico-chemical data for a wide range of materials which would advance this process greatly.

3.7.37 **Environment**

3.7.38 As shown in RNC/RIP-oN3/C1/2/FINAL and in more detail in the ENRHES review (Stone et al., 2009), it is in principle possible to determine PNEC using the present methodology. However, by doing so the particle behaviour of nanoparticles is neglected and it is inherently assumed that nanoparticles behave like dissolved (organic) chemicals.

3.7.39 In principle, there does not seem to be nano-specific arguments to change the way assessment factors are selected presently, i.e. that more available data from long-term tests can reduce the assessment factor from 1000 to 100, 50, and 10.

3.7.40 However, the assessment factors were originally intended not only to cover the uncertainty related to the amount of available data, but also factors like inter- and intraspecies differences and extrapolations from laboratory to field. The value of the assessment factors are based on regulatory practice and empirical knowledge on ecotoxicological effects of chemicals. Since there is no history for evaluation of nanomaterials, it is at present not possible to claim that the use of the presently available assessment factors will ensure that species will be protected at concentrations below PNEC (RIVM, 2009).

3.7.41 The so-called deterministic approach using species sensitivity distribution modelling would also, in principle, be acceptable for deriving PNEC values for nanoparticles. However, this approach requires at least ten high quality NOECs/EC10-values from different species belonging to eight taxonomic groups. This kind of data is not available for any nanomaterial at present and thus it remains to be shown that the deterministic approach for PNEC determination will actually be applicable to nanomaterials.

3.7.42 A number of factors specific for nanoparticles have been found to influence the responses observed in the standard ecotoxicity tests preferred for determining PNECs. These are mentioned in detail in RNC/RIP-ON/B3/2/FINAL (particle impurities, suspension preparation methods, release

of free metal ions, nanoparticle aggregation, and relevance of dose-response), but not all of these can be claimed to be nano-specific.

3.7.43 Thus, impurities, solvent interaction, and free ion toxicity are issues that have been dealt with for chemicals and procedures/recommendations that may be adapted to nanoparticles are available (see OECD ENV/JM/MONO(2009)20/REV, ENV/JM/MONO(2009)25).

3.7.44 For the more general validity of the present approach to derived PNEC, nanoparticle aggregation/ agglomeration, problems of reproducibility of test results and non-monotonous concentration-response curves are of the highest importance (Hartmann et al., 2010).

3.7.45 The extent that these factors influence the ecotoxicological impact of nanomaterials is unknown. Currently, even the scientific evidence for these factors is contradictory and varies from nanoparticle to nanoparticle (Baun et al., 2009). This impedes the reliability and interpretation of the available ecotoxicity data the direct use of the reported LC50, EC50 and NOEC for PNEC assessment.

3.7.46 It is, at present, unclear whether aggregation/ agglomeration of nanoparticles in test media will result in higher or lower toxicities found in standard tests. It has been argued that the bioavailability of larger particles is lower than for smaller particles and therefore the toxicity could be expected to be lower when aggregation occurs. However, this may not be the case for filter feeders like D. magna that has a preferential filtration of certain particles sizes (generally above 500 nm). For these organisms, aggregation may result in higher uptake and disaggregation may occur during digestion in the daphnids, rendering smaller particles that may cross biological membranes. Biomodification of nanoparticles upon uptake in daphnids has been documented in the literature (Roberts et al, 2008; Baun et al., 2008). It is possible that the Daphnia-test may be sufficiently sensitive to measure possible aquatic toxic effects of nanoparticles also.

3.7.47 It is clear that aggregation/agglomeration strongly affects the reproducibility and also the shape of concentration-response curves obtained in standard tests as shown e.g. by Hartmann et al. (2010). The understanding of the

aggregation process and the determining factors in standardised test media is very scarce at present, making it very difficult to give accurate advice on the best way to test nanoparticles.

3.7.48 It must be expected that the aggregation/ agglomeration behaviour is different from test media to test media (e.g. there are large differences in the medium composition of the M7 media used in OECD Daphnia test and the OECD medium for algal testing). This makes it difficult to conclude on nanoparticle behaviour between different tests.

3.7.49 One way forward may be to strive to test only on stable suspensions, however this may require that the addition of NOM (natural organic matter) is included in standard test protocols for testing nanoparticles. NOM has in many cases been found to stabilise aqueous suspensions of nanoparticles. However, the biological impacts of the interaction between nanoparticles and NOM are not well described at present.

3.7.50 In addition, it has recently been found that aggregation/ agglomeration behaviour in aqueous media might follow a non-linear concentration-aggregation/ agglomeration relationship (Baalousha, 2009; Baun et al., 2009). This implies that traditional test designs in ecotoxicity tests, using a range of different dilutions, will give not only different concentrations (as intended), but also different degree and type of aggregation/ agglomeration (not intended). This may be one of the reasons for the non-monotonous concentration-response curves encountered for some nanoparticles in ecotoxicity tests, since bigger aggregates/ agglomerates formed at high concentrations may be less toxic than smaller aggregates formed at low concentrations.

3.7.51 If this is a general phenomenon, it will severely affect the paradigm of deriving PNEC by extrapolation from standardised tests that usually are carried out in high concentration regimes for hazard identification purposes. It is, at present, not certain whether effects from such tests can be extrapolated “downwards” (i.e. that the application of an assessment factor will in fact be protective).

3.7.52 It seems too early to define the most appropriate metric for concentration-response relationship applicable to all nanomaterials. The present metric used for bulk materials is mass per volume (or per mass in the case of

soil/sediment/sludge). Only very few studies have actually investigated alternative dose metrics at this point in time and correlated these with the observed effects. If another dose metric other than mass is chosen, this also implies that Predicted Environmental Concentration (PEC) estimations should be made in the same units and therefore that the choice of dose metric is not dependent on eco-toxicological considerations alone.

3.8 TASK C2: HAZARD / RISK CHARACTERISATION – HARVESTING RESULTS FROM ON-GOING ACTIVITIES

3.8.1 The objective of Task C2 was that of a review task pertaining to the characterisation of the hazards and risk of nanomaterials to humans and the environment. The information resources from this task were obtained from Task A of RIP-oN 3 and within this task our aim was to use and summarise examples of the analysis of the hazard and risk assessment approach taken by several bodies within different countries.

3.8.2 An example of this, and in common with other studies and reports analysed, the NIOSH report addressing exposure risks associated with TiO_2 (NIOSH, 2005) concluded that particle surface area was the preferred metric for characterisation of particle hazard. However whilst surface area has been identified as the preferred metric, deficiencies exist in sampling technology and meaning it is currently not possible to measure exposure in the environment based on this metric. As such RELs were suggested by mass (assuming a known particle size distribution range) as a surrogate for surface area in two broad groups of fine and ultrafine particle size, with the latter REL being lower than the former REL, reflecting its increased toxicity. The NIOSH derivation reflects our own result in Task C1 and the wider literature, which suggests increased surface area of nano-TiO_2 leads to increased toxicity and as such this should, where practicable, be reflected in the relevant exposure limit.

3.8.3 Another source of information for consideration of hazard/risk characterisation was a nanosilver case study conducted by the National Institute for Public Health and the Environment (RIVM) which simulated a REACH registration for nanosilver. The authors found that, even though information about nanosilver toxicity and even toxicokinetics was available, it was almost impossible to

determine if nanosilver was behaving similarly to its bulk counterpart and only a rough risk assessment could be drawn, highlighting the difficulties faced when producing a risk assessment in with the current limited information. In performing a case-study for nanosilver, the authors have highlighted several problems in using proposed risk assessment framework. For example, the authors noted the need for adequate physico-chemical characterisation and comparative studies of bulk and nano forms of a material which may enable the validation of read-across approaches.

3.8.4 In our evaluations of the NEDO studies addressing occupational exposure limits for TiO_2 (Hanai et al. 2009) and MWCNT (Kobayashi et al. 2009b), a discussion was made of an alternative approach presented within the Hanai et al. paper for hazard characterisation. This approach was termed a bi-axial approach within the study and is suggested as a method by which acceptable levels of human exposure may be predicted for a material for which inhalation data does not exist. The approach uses ranking of a substances toxicity using data not suitable for derivation of a human exposure limit. This is then compared to the relative toxicity of a substance for which inhalation data does exist (and derived human exposure limit) and based on this benchmark inhalation data, an indicative interim human exposure limit established.

3.8.5 As an approach, this raises many questions but is interesting and could be considered for further R&D and assessment for its suitability for REACH regulation.

3.8.6 In reflection and discussion of the approaches for the derivation of exposure limits used by Pauluhn (2010a) and Hanai et al. 2009 (which appears representative of the NEDO approach), an alternative approach for extrapolating from experimental animals to humans for inhalation exposure is suggested, based on current particle toxicology literature. As this approach is a recent addition to the report and as such has not been part of the RIP-oN 3 stakeholder review process, it is presented as an appendix to the report (Appendix 4 herein). The approach however is suggested for consideration and development in relation to its suitability for future incorporation into guidance.

3.9 TASK C3: ADVISORY REPORT ON HAZARD AND RISK CHARACTERISATION FOR NANOMATERIALS

3.9.1 The outcome of the report was that, whilst the REACH guidance for hazard and risk characterisation has been written primarily for soluble substances, nonetheless they seem overall suitable for nanomaterials due to their wide applicability and generality. However the question of what parts of the guidance are also truly suitable for (dispersed) particles like most nanomaterials still needs to be addressed.

3.9.2 However, some major points were emphasised in relation to nanomaterials and hazard and risk characterisation. Firstly, there is a large diversity of nanomaterials and information about the hazard and/or exposure to these materials is often scarce. Such a scarcity of information is not specific to nanomaterials and is often seen with chemicals, but due to the existence of a greater wealth of data surrounding analogous materials, other approaches such as read across or categorisation are available in chemical assessment. However the scientific understanding such as concepts of similarity or drivers of toxicity for a wealth of nanomaterials is not yet sufficiently mature to allow for such an approach to be taken in the absence of information with any degree of certainty. In these conditions, it is difficult to do a proper quantitative risk assessment analysis and the precautionary principle should be applied either via further testing or by taking a very conservative approach in relation to the application of assessment factors.

3.9.3 Secondly, DNEL(s) for an exposure pattern are derived from relevant dose-descriptors firstly by modification if required to a correct starting point followed by the application of assessment factors. These assessment factors whilst not developed specifically for nanomaterials, address numerous aspects of extrapolation and uncertainty that may be both applicable and appropriate for nanomaterials.

3.9.4 The issue of metrics is a difficult one as no single metric can be said to adequately represent all materials. In the case of nanomaterials, whilst mass is commonly used for historical reasons and ease of use, and has been suggested as a driving force behind certain pathogenic process (Pauluhn 2010a), it does not necessarily represent the best metric for all nanomaterials

and all effects. Indeed particle surface area has been suggested to more accurately reflect the particle dose leading to a response and as such in certain circumstances would be the most appropriate choice when deriving a DN(M)EL. In addition derived limits for fibrous nanomaterials, a fibre number metric may be more suitable than either a mass or surface area metric. As no single metric can be established, guidance ideally should reflect the presence of other additional metrics and allow their use by not being overly prescriptive towards a historical mass based metric.

3.9.5 A further important point pertaining to the hazard and risk characterisation of nanomaterials is that the adequacy of exposure patterns should be particularly emphasised. Indeed, it has been stressed that exposure patterns in occupational or consumer settings (e.g. variable particle size distribution) might be different from exposure patterns in experimental settings (e.g. stable particle size-distribution). However, factors such as the size distribution/ agglomeration state of nanomaterials are known to be important in determining the hazard. Therefore, prior to any risk assessment, the relationship between external exposure levels in studied setting and exposure levels in experimental conditions used to derive toxicological reference values is needed. This comparability of the exposure patterns constitutes an additional challenge in the risk assessment of nanomaterials.

3.9.6 The specific issues resulting in specific guidance changes as well as identified R&D priorities are discussed later in this report.

3.10 TASK D: METRIC(S) TO COMPARE IN THE RISK CHARACTERISATION

3.10.1 The objective of Task D was to develop a working document on the identification of critical items on exposure/dose descriptors and related parameters, outlining needs for adequate metrics/parameters as appropriate for exposure assessment compatible with the ones used for hazard assessment. The underlying principal of metrics is the number of molecules expected to participate in the process in question. Most commonly mass is used as a proxy, but particle number or surface areaare increasingly suggested as more scientifically based metrics.

3.10.2 The question of what is the best metric to measure the hazard and exposure of nanoparticles is frequently posed. In practice there are many metrics, all of which include mass or number, which are currently used in the risk assessment (both regulatory and otherwise) across the three elements of exposure, toxicology and risk. The most commonly used are identified in the table below:

Target	Route	Exposure metric (example units)	Toxicology /ecotoxicology dose metric (example units)
Human	inhalation	mass conc in air (mg/m^3)	mass per animal or per body part (m)
	inhalation	fibre number conc in air (f/ml)	fibres per animal or per body part (#f)
	dermal	mass per surface area of skin exposed (mg/cm^2)	mass per animal or surface area (m)
	dermal	mass per kg body wt per day (mg/kg/day)	mass per animal or surface area (m)
	ingestion	mass per kg body wt per day (mg/kg/day)	mass per animal (m)
Environment	air/water/ soil	release rates into compartment (kg/day) or release factors (%)	compartment concentrations (mg/m^3)

3.10.3 The metrics can be units, concentrations, or ratios. They can be measured directly, for example the exposure metric, mass concentration in air or modelled for example risk evaluation metric compartment concentration. Risk characterisation is based on a ratio between the exposures and toxicology metrics and is unit-less.

3.10.4 The most prominent alternative or additional metric identified for use in relation to the risk assessment of non-fibrous nanomaterials, are concentration metrics based on surface area. This is based primarily on toxicological evidence relating particle surface area to inflammation, an indicator of toxicity. The evidence for this has been assessed in the Task report (RNC/RIP-oN3/D/2/FINAL). Other parameters suggested as possible metrics include surface reactivity and charge. Surface reactivity is clearly an important parameter although whether this could be considered as a potential metric or simply a unit to express the toxicological response is a matter for discussion. Its use as a metric (in toxicology) would be as “units of reactivity per body part”. This same is true of charge in which the metric would be coulomb/body part. However, these need further research and it is considered that the basis of these properties becoming “metrics” is not yet sufficiently advanced to a level at which use and guidance for REACH can be recommended.

3.10.5 It is important to note that there are other parameters which can act as modifiers of the toxicity. These include particle size, size distribution, density, aggregation and shape. These parameters would not generally be considered as scalable quantities and do not appear to conform to the current use of the term “metric” under REACH. Therefore they have not been considered further in this discussion.

3.10.6 Metrics in risk assessment need to be scalable quantities which may be used to express the levels of hazard, exposure or risk. To date, conversion between mass, number and surface area has largely been based on simple assumptions, treating (nano)particles as spherical and using mean particle diameters. It is considered advantageous to be able to provide functional conversions between the three metrics based on established and validated relationships. Conversion between the metrics of mass, number and surface area remains challenging both within and between exposure, hazard and dose. Measurement of surface area in relation to dose is still mostly indirect and is typically based on a mass assessment times a measure of specific surface area of the powdered material obtained by Brunauer, Emmet and Teller (BET) analysis or similar. Encouragingly, in relation to inhalation exposure, measurement systems are available to measure mass, number and

surface area concentrations (e.g. ISO 2008). Attempts have been made to assess relationships between these various metrics.

3.10.7 For example, Wake et al. (2001) carried out a laboratory study to compare the performance of Matter LQ1-DC active surface area monitor, a TSI Model 3934 Scanning Mobility Particles Sizer and an R&P Tapered Element Oscillating Microbalance. Using the three instruments described above, experiments were carried out in the laboratory with polydisperse aerosols, containing ultrafine particles, to establish what relationships exist between the three measurement parameters mass, surface area and number as determined by each instrument and how these relationships may be influenced by particle composition and morphology. For each of the five aerosol types investigated, consistent relationships were found for mass and active surface area with increasing particle number concentrations for all the particle sizes investigated. However, these relationships were not consistent with particle size. Amongst Wake's conclusions were that no simple relationship was found for predicting active surface area and mass from the results of measurements made with the benchmark instrument the SMPS. This instrument, therefore, should not be used to calculate surface area and mass unless a detailed knowledge of the aerosol is known. In view of this, the use of all three metrics, measuring in parallel, should continue to the extent feasible despite the difficulty in arranging this in the workplace. Moreover, Wake considered it unwise to make measurements in terms of just one parameter, be it mass, active surface area or number/size, when assessing the potential for engineered nanoparticles to cause ill health when the causal factor has not yet been established.

3.10.8 An advantage of mass over surface area (and virtually all other alternatives) is that the mass in a system is conserved i.e. remains constant (and could be assessed through mass balance), whereas surface area is not. In other words, the actual surface area can change due to aggregation/de-aggregation which may occur following deposition of the nanoparticles and influence the interpretation of data. The same is also true (to an even greater extent) for particle number.

3.10.9 However, there is nevertheless evidence that surface area is an important metric in describing the potential human health hazard of some types of nanoparticles. For low toxicity low solubility materials, surface area of particles administered rather than mass burden of particles may be a more appropriate dose metric for pulmonary toxicity studies. The same type of relationship has also been demonstrated for higher toxicity nanoparticles. For dermal effects, any metric proposed to assess dermal exposure to nanoparticles should be biologically relevant and should relate to health effects. It may be that for local effects, inflammation is the key driver in which it could be speculated that surface area would be the important metric. Further work including workplace studies and in-vivo/vitro assessment of penetration is required. For the environment, it seems too early to tell whether a dose [concentration] - response relationship can be established as well as whether, for instance, number or surface area can be substituted with dose by mass. Too few studies have actually investigated alternative dose metrics at this point in time and correlated these with the observed effects.

3.10.10 In relation to the guidance which can be given now on hazard assessment, it is considered important to continue with mass based measurement. This is the basis of the current risk assessment process and the linkage to past work in both exposure and toxicology. Based on the evidence available, it seems justified to additionally express the data in terms of surface area. In practical terms, this would only require knowledge of BET and density results for the nanomaterial used. For exposure assessment, both surface area and number concentration data are achievable and provide useful information and addition to the standard mass data, and should be collected.

3.10.11 Further consideration of additional issues relating to metrics, as part of an ongoing international dialogue warrant acknowledgement in this final report:

- There is no general rule for the choice of metric as the relevance may depend on the exposure route and even the material itself (e.g. aspect ratio), so it should be decided on a case-by-case basis by the registrant. The mass metric may not always be the most appropriate or relevant metric. However, given the historical and established use of the mass metric, which is the case in most if not all elements of

hazard, exposure and risk characterisation in a Chemical Safety Assessment (CSA) under REACH, it continues to be considered appropriate that even in cases where another metric is relevant and has been used, the mass metric description/data/result should continue to be provided.

- It is clear that one, two or more metrics may be relevant to undertake the best possible CSA for different forms of a materials covered by one registration, including all exposure scenarios etc. This is to be encouraged, albeit with a clear justification and transparency to ensure that the CSA can be understood. The most relevant for determination of the Risk Characterisation Ratio (RCR) should be considered in such cases.

- At present, evidence of the emergence of new metrics is strong in some case (e.g. surface area), but this is acknowledged as an evolving field. It has been made clear in the RIP-oN 2 and 3 projects that there is evidence to recommend surface area as a metric appropriate in inhalation exposure but there is no conclusive evidence with regard to dermal exposure. This has already been reflected in the guidance recommendations. The choice of metrics is rightly left to the registrant, with the expectation that the choice is scientifically justified. As stated above, as exposure scenarios differ, so can the choice of metrics for the related form and the individual scenario.

- It should always be clear how different metrics have been used (in rare cases perhaps even from separate studies) or derived through transformation of final results of the same test etc. It should be ensured that the whole CSA (hazard, exposure, risk characterisation ratio including any required risk management measures) is performed consistently. If the Derived No Effect Level (DNEL) or Predicted No Effect Concentration (PNEC) are determined using one metric, so should the estimation of the Predicted Environmental Concentration (PEC) to characterise the risk ratio. The basis for selecting and assessing the efficiency of RMM employed should be expressed in the same metric. The same applies to the potential application of

models and to the justification of any read-across. If there are transformations of metrics involved, they need to be transparent so the applicability of the data can be justified.

- It is clear that a consideration of Assessment Factors needs to be performed for different metrics, separately, and including the uncertainty potentially arising from the transformation of metrics and from the differences in the tests performed.

- There is more to the conversion between metrics than simply working in one metric and then expressing results in another. Adequate characterisation and the scope of applicability of the test is required, along with consideration of the design of the test (e.g. selected doses, sample preparation to minimise uncertainty/bias) and the selection of the most appropriate instrumentation/method.

- It remains that there are currently no definitive conclusions on the best metric. However, there is growing consensus that if new animal tests on nanoforms are performed, there should be a sufficient characterisation of those forms to allow the dose-response to be expressed in the different metrics discussed - number, surface area and mass.

4 GUIDANCE ASSESSMENT

4.1 RATIONALE

4.1.1 The philosophy adopted for the development of specific recommendations for guidance updates and research & development (R&D) is as follows.

4.1.2 The content of a recommendation for a specific update to guidance is consistent with the focus of current REACH Guidance document, its level, and language, such that:

- where the need is for 'strategic-level' guidance applicable to nanomaterials (i.e. high-level or overarching principles), succinct contextual information and reference(s) to primary sources of information are provided;
- where the need is for updated detailed pragmatic information on, for example methods, a synopsis of specific guidance with appropriate reference(s) are provided;
- where there is simply a need identified to acknowledge an important relevance or limitation in existing guidance to nanomaterials, a simple wording clarification may be proposed.

4.1.3 Recommendations for updates to Guidance are made on the basis of the findings of the RIP-oN 3 task activities, and where there is a recognised case for doing so. Wide-scale acknowledgement confirming the general applicability of Guidance to nanomaterials has not been made. For the avoidance of doubt however, with these changes, all clauses of the guidance document, unless explicitly stated otherwise, are now applicable to nanomaterials and should be used for that purpose.

4.2 GUIDANCE REVIEWED

4.2.1 This report focuses on the following parts of the guidance on Information Requirements and Chemical Safety Assessment: Part D (Exposure Scenario building), Part E (Risk Characterisation), Part F (Chemical Safety Report, incl. CSR format), Part G (Extending the SDS), Chapter R.12 (Use descriptor system), Chapter R.13 (Risk management measures and operational

conditions) and Chapters R.14, R.15, R.16 and R.17 (on exposure estimation in different groups). It also considers the RMM library. In each case, for each issue, all of these documents have been reviewed to evaluate the need for guidance changes.

4.2.2 The mapping between the various guidance documents and the issues identified from exposure assessment aspects (RNC/RIP-oN3/B4/2/FINAL) is shown in Appendix 2. This identifies each of the scientific issues identified in that report and the preceding reports, by reference to the tables in RNC/RIP-ON3/B4/2/FINAL, and maps that to the point in the guidance indicating where they are relevant.

4.2.3 The maps in Appendix 2 represent the intersection between identified scientific issues and a particular section of the guidance. White, unfilled cells indicate where the specific identified scientific issue ***is not relevant*** to that particular section of the Guidance. Therefore no change to that section of the guidance is required because of that specific issue.

4.2.4 Filled blue cells indicate where the specific identified scientific issue ***is relevant*** to that particular section of the guidance but the guidance applies equally well for nanomaterials as for substances in general and therefore, again, no change to the guidance is required.

4.2.5 Filled yellow cells with a plus symbol cells indicate where the specific identified scientific issue ***is relevant*** to that particular section of the guidance but the guidance is not sufficient and needs to be amended to take account of the issue. Guidance recommendations have been made for these cells only.

4.2.6 The matrices are not intended to be part of the guidance, they are merely to illustrate the decision making process which has led to the guidance and/or R&D recommendations.

4.2.7 This same approach has been followed for each of the guidance documents.

4.3 PART D EXPOSURE SCENARIO BUILDING

4.3.1 This part of the guidance explains how to conduct exposure assessment, covering the development of exposure scenarios and exposure estimation. The main focus is on how ES can be developed. It also contains an overview

on exposure estimation however much more detailed guidance on exposure estimation can be found in Chapters R.14 to R.18. The exposure scenario guidance covers both the core content of information to be collected as well as the step-wise procedure to build the final exposure scenarios for a substance, as an integrated part of the iterative CSA.

4.3.2 **Considerations**

4.3.3 Almost all of the issues described in the proceeding tasks of RIP-oN 3 (B1, B2, B3, B4) have some relevance to the exposure scenario building document (Part D). In the main however the document is described at quite a high level and points to other documents for more detailed descriptions and guidance. The version of Part D which was reviewed is version 1.1 (May 2008). In carrying out the work however we also took account of the exposure scenario format document which was being developed in 2010. Version 2 of this document was published in May 2010.

4.3.4 The mapping between Part D and the issues identified from exposure assessment aspects (RNC/RIP-ON3/B4/2/FINAL) is shown Appendix 2. This identifies each of the scientific issues identified in that report and the preceding reports, by reference to the tables in RNC/RIP-ON3/B4/2/FINAL, and maps that to the point in the guidance indicating where they are relevant.

4.3.5 D.2 describes the contents of exposure scenarios, providing an overview of core information to be taken in to account in ES development (D2.2), examples of determinants of exposure (Table D2.1) a standard format for the final exposure scenario (Table D2.2), subsequently replaced by the May 2010 full document on this issue and an overview of the exposure scenario development steps (D2.3) - information in this section is high level or points to other more detailed guidance. It is considered that this is equally applicable to nanomaterials as for any substance in general. The detail of the revised standard format is considered later. No specific recommendations are made in relation to this section. D.3 describes the overall workflow and dialogues, comprising in tabular format a diagram of the workflow in building exposure scenarios identifying steps in that workflow as well as the output of each step. This is entirely generic and is applicable to any substance including nanomaterials. Also later in that section, *"it will be on the DU to evaluate*

whether in practice the measure is implemented as recommended by the MI e.g. a local exhaust ventilation of a certain effectiveness. The RMM library will aid the transparency of this process." The description of RMMs and their effectiveness in this document is at a generic substance independent level. As such it does not in itself suggest the requirement for changes to be made for nanomaterials. However in the subsequent part of this report we have reviewed in more detail, the individual elements types of RMM etc. and have made recommendations for the document R.13 and for the RMM library itself. These recommendations have not been reproduced here. It is considered that these recommendations will be sufficient to take account of any of the issues in this particular document.

4.3.6 From the analysis of case studies it was considered that "these Case-Studies could serve as nanomaterial product-specific examples only and that no generalisation with regard to practices within an entire nanomaterial type-specific branch could be based on *these individual* ES Case-Studies." This is not to indicate that generalisation of ES for nanomaterials will always be impossible. As with any substance the generalisation of the ES would need to be justified. What would be different for nanomaterials is that this would not just be based on the substance composition but would also need to take account of other parameters such as particle size distribution. Based on this it is recommended that a paragraph is added to D.4.3.3:

4.3.7 *Generalisation of ES for nanomaterials, as with other substances will always need to be justified. For nanomaterials this would not just be based on the substance composition but would also need to take account of other parameters such as particle size distribution.*

4.3.8 D.5 is the section on exposure estimation. Again this is provided largely at a substance independent level and does not go into any detail concerning the exposure measurement methods themselves. The following change is recommended to take account of identified issues related to background discrimination.

4.3.9 Insert into D.5.2 the bullet point:

4.3.10 *Have background concentrations been taken into account for particle measurements.*

4.3.11 Data from measurements (D.5.3.1) is only a single small paragraph, which points to R.14 for more detail. Much of this section is concerned with modelling approaches which are dealt with in more detail in R.14 and other documents. We consider that the changes proposed elsewhere in relation to exposure measurement and estimation are sufficient to take care of the issues which have been identified.

4.3.12 In appendix D.1, the strength and limitations of available Tier 1 exposure estimation tools are indicated. It is recommended that a caveat is added to each of these tools to indicate a limitation in relation to the use for nanomaterials. This limitation will indicate as follows:

4.3.13 *Please note that this tool has not been validated for use with nanomaterials. If the output of the model is used to estimate exposure for NMs, this should preferably be supported by measured data. There should be a clear description in the CSR of the uncertainties associated with the estimated values and the consequences for the risk characterisation.*

4.3.14 This would fall some way short of the statement which is made for some models e.g. for the Control of Substances Hazardous to Health (COSHH)– The Federal Institute for Occupational Safety and Health (BAUA) – tool the statement is made not suited for Carcinogenic, Mutagenic, or Reproductive toxin (CMR) substances. However a requirement for an exclusion of this kind is not justified based on the evidence.

4.3.15 In relation to the ES Format, a detailed analysis of this document was carried out as part of the ES Case studies. A report of the outcomes of this is available as Appendix 1 of the current report. Overall the analysis indicated that most of the document was not substance specific and could be applied to nanomaterials as well as for substances in general.

4.3.16 It should be clear to the user of the ES for which forms (of the substance) the RMMs and OCs given will apply, i.e. protect the one using the materials. This

should be specified under the heading "Product Characteristics", already in the format.

4.3.17 In Appendix D.1, in table D.2.2.3, under the entry “Product Characteristics” in which examples of product characteristics, add the example:

4.3.18 *(Nano)form(s) of the substance*

4.3.19 Issues which were identified related to the use of different measuring systems and the interpretation of the data obtained. There are several aspects to this. One is, for nanomaterials what measurements should be taken with which instruments. It is suggested that it is more appropriate to change the R.14 document in relation to this issue rather than the ES Format document which contains no similar detailed measurement advice. The type of changes indicated (for R.14) are the same as have been proposed based on the evaluation of the other evidence collected in RNC/RIP-ON/B3/2/FINAL. Hence, the case studies support the need for clearer general guidance to be provided.

4.3.20 A second issue relates to the use of real time measurement devices, such as the CPC or SMPS which essentially provide a continuous output of data over a time period which, in most of the devices, can be logged. The current guidance is clearly written from the perspective of multiple single offline measurements and combining these e.g. to develop summary statistics of the data obtained e.g. mean or 95th percentile. There is almost no information on this issue in the guidance documents reviewed. This also illustrates the difficulties in trying to use pre-existing data in order to demonstrate compliance. Again it is suggested that it is more appropriate to change the R.14 document in relation to this rather than the ES Format document which contains no similar measurement advice.

4.3.21 A third issue relates to the use of different metrics. In the data provided by these case studies a range of metrics were used. A number of approaches led to estimates based on number concentration and there was no clear view as to how such measurements could be used for comparison with the DNEL (which was, in all cases expressed in terms of mass concentrations). This cross metric comparison would be possible if there were well established

relationships for conversion between these. However as indicated in the Task D report, such relationships are not available and are unlikely to be stable or generalisable. In the absence of this it is difficult to provide clear guidance on this issue. This may continue to be the case for some time. The key generic message here is that in that, in comparing DNELs with exposure estimate, the metrics used should be relevant and the same in each case. Although this is perhaps obvious, it seems to be worth stating. However, the appropriate place for such a statement to be made would be Part E, Risk Characterisation rather than Part D. These considerations have been carried forward to the next section.

4.4 PART E RISK CHARACTERISATION

4.4.1 Part E describes the risk characterisation and outlines the main steps in the process. Identifying calculation of the risk characterisation ratios, and the need for iteration.

4.4.2 The mapping between Part E and the issues identified from exposure assessment aspects (RNC/RIP-ON3/B4/2/FINAL) is shown Appendix 2. This identifies each of the scientific issues identified in that report and the preceding reports, by reference to the tables in RNC/RIP-ON3/B4/2/FINAL, and maps that to the point in the guidance indicating where they are relevant, where the guidance is adequate for nanomaterials as for substances in general and where it has been necessary to recommend a change.

4.4.3 The document is high level and process orientated. It is generic and therefore most of the provisions apply equally well to nanomaterials as for substances in general. The document emphasises (in E3.1) the need to make the whole process as "*transparent as possible with careful explanation and justification as to assumptions decisions uncertainties and adequacy of the available data set*". The document also acknowledges that the whole risk characterisation process depends heavily on expert judgement. Both of these caveats would tend to give a steer towards expert input in the case of different or unusual substances, such as nanomaterials.

4.4.4 The main section of relevance to exposure issues is E.3.4.3, "*Step wise approach for the qualitative assessment, including development of exposure*

scenarios (ES)". This section points to the need to conduct exposure estimation/assessment according to Part D of the guidance. It also emphasises (in Table E.3-1) suggestions for general risk management measures and operational conditions and PPE to be considered when developing exposure scenarios. Examination of this table indicates that it is based on type of effects and R phrases, rather than substance specific. For example types of effects may include very toxic, respiratory sensitiser, carcinogen, etc. These are characteristics of particular substances rather than substance type groupings. On that basis these provisions are substance generic and apply equally well to nanomaterials as to any substances in general.

4.4.5 As discussed in Section 4.3 (Part D) it is worth emphasising that in comparing DNELs with exposure estimate, the metrics used should be the same in each case. Therefore it is recommended to update the Guidance by inserting the following as a footnote in Section E.1.2:

4.4.6 *In calculating the RCR both the exposure estimate and the PNEC or DNEL should be expressed using the same relevant metric(s).*

4.4.7 Other than for this issue, in relation to exposure issues no specific recommendations for guidance changes are being made.

4.4.8 *Research recommendations*

4.4.9 Mention is made in E.3.5.1 of potential applications of bio-monitoring data. One of the useful challenges for nanomaterials would be to develop effective biomarkers of exposure which could be reliably measured. This would require information on the exposure biomarker response relationship to be developed for a range of different nanomaterials. Where such relationships would be available this would be highly effective and useful in relation to risk assessment of nanomaterials.

4.5 PART F CHEMICAL SAFETY REPORT INCLUDING APPENDIX TO PART F CSR TEMPLATE

4.5.1 The REACH Part F is a high level guidance document which provides notice of general requirements in relation to the chemical safety report (CSR).

Specifically in F2.2 it points the user to the template which is the appendix of the guidance. The CSR template provides further guidance on how to detail and structure the information required in the CSR (based on the standards headings of Annex 1 of REACH). The CSR is intended to document the outcomes of the CSA process.

4.5.2 The template as an appendix to Part F basically provides the structure of this CSR. It is intending to be generic and be applicable to all substances and materials.

4.5.3 The mapping between Part F and the issues identified from exposure assessment aspects (RNC/RIP-ON3/B4/2/FINAL) is shown Appendix 2. This presents each of the scientific issues identified in that report and the preceding reports, by reference to the tables in RNC/RIP-ON3/B4/2/FINAL, and maps that to the point in the guidance indicating where they are relevant, where the guidance is adequate for nanomaterials as for substances in general and where it has been necessary to recommend a change.

4.5.4 The general provisions of this document are considered to be equally applicable to nanomaterials as they are to substances in general.

4.5.5 Units are specified in some of the tables e.g. in the exposure concentration fields of the risk characterisation chapter (chapter 10) inhalation exposure is indicated to be in the units of mg/m^3. Consideration should be given for the inhalation aspects that relevant additional data in relation to number or surface area would be provided. This would also apply to the tables where these units (for inhalation) are recorded. The suggested change would be to add the following footnote at all points in the document where the units of inhalation are provided in terms of mg/m^3:

4.5.6 *For nanomaterials it may be appropriate to also consider other relevant units e.g. in terms of surface area concentration cm^2/m^3 or number concentration n/m^3.*

4.5.7 *Research recommendations*

4.5.8 As this is a high level document which outlines the whole CSR process it does not in itself suggest any new requirements for research.

4.6 PART G EXTENDING THE SDS

4.6.1 This chapter provides guidance to M/I on how to integrate the final exposure scenario for a substance into a safety data sheet (SDS) to make it an extended SDS (eSDS). This includes: i) general guidance on how the exposure scenarios and the main body of the eSDS can be combined in a useful way, and ii) specific guidance on the relationship between the Sections 1.2 (identified uses), 7 (handling and storage), 8 (exposure controls) and 13 (disposal considerations) of the SDS and the exposure scenarios in the annex. The chapter does not provide complete guidance on all sections of the eSDS, and it does not cover safety data sheets for substances for which no CSR is required.

4.6.2 The mapping between Part G and the issues identified from exposure assessment aspects (RNC/RIP-ON3/B4/2/FINAL) is shown Appendix 2. This identifies each of the scientific issues identified in that report and the preceding reports, by reference to the table in RNC/RIP-ON3/B4/2/FINAL, and maps that to the point in the guidance indicating where they are relevant, where the guidance is adequate for nanomaterials as for substances in general and where it has been necessary to recommend a change.

4.6.3 It provides in Table G2 an overview of the relationship between the SDS chapters and standard entries of the exposure scenario. This table and the rest of the document is highly generic and its provisions apply as well to nanomaterials as to substances in general. As discussed in RNC/RIP-oN3/B4/2/FINAL it is appropriate to add in some guidance to ensure that data relevant to the different nanomaterial form is included. It is recommended to insert the following as a bullet point at the end of G3:

4.6.4 *Where (a) particulate form(s) is (are) covered by the Extended Safety Data Sheet (eSDS), the M/I should ensure that the data are relevant to this (these) form(s) in the relevant particle size ranges (e.g. for nanomaterials).*

4.6.5 No further changes to this guidance are recommended.

4.6.6 *Research recommendations*

4.6.7 As this is a high level document it does not in itself suggest any new requirements for research.

4.7 R.8 CHARACTERISATION OF DOSE [CONCENTRATION]-RESPONSE FOR HUMAN HEALTH

4.7.1 The R.8 document provides guidance to enable the generation of no-effect-levels for human health based upon the integration of all available hazard data generated. The approach for generation of derived no effect levels (DNEL(s)) or derived minimum effect levels (DMEL(s)) is outlined within the guidance as follows:

4.7.2 STEP 1: Gather typical dose descriptors and/ or other information on potency

4.7.3 STEP 2: Decide on mode of action (threshold or non-threshold and which next steps(s) to choose

4.7.4 STEP 3: Derivation of effect levels (DNEL (step 3-1) or DMEL (step 3-2) or the use of a qualitative approach (step 3-3).

4.7.5 STEP 4: Select the leading health effect

4.7.6 The approach taken within the recommendations for guidance amendments in this report is the identification of amendments within the introductory section of R.8 followed by an evaluation of each step as outlined above.

4.7.7 **Considerations**

4.7.8 When considering the R.8 guidance document for nanomaterials, for the most part, the guidance provided applies equally well to nanomaterials as for substances in general. However, some issues have been raised within tasks C1 and C2 and these are reflected in discussions and recommendations for alterations for nanomaterials in the following sections.

4.7.9 *Metrics*

4.7.10 One of the major issues with nanomaterials is the determination of the most relevant and most practical dose-metric to study their biological effects. Classically, a mass-based metric is used for dose-response studies with chemicals. However, for nanomaterials, other metrics might be more relevant to assess their hazard. Indeed, particle number or surface area or surface reactivity have been described in some cases as better metrics, to describe dose-response (Duffin et al. 2007, Warheit et al. 2007, Oberdörster 2010). In addition, the best dose metric might depend on the physico-chemical characteristics of each type of nanomaterials, such as its solubility (Oberdörster 2010). Therefore, there are still on going debates about the best dose-metric for nanomaterials.

4.7.11 This uncertainty about the best dose metric to be used for dose-response analysis of nanomaterials leads to uncertainties about the comparability of risk assessment on different nanomaterials. As such it has been suggested within the RNC/RIP-oN3/D/2/FINAL report that for inhalation, in addition to mass, surface area and particle number (especially for fibres) as a metric be recorded and reported also. It should be noted that current assessment factors used within the derivation of exposure levels are typically based on mass based metrics. For the most part, the alteration of metric is not considered to impact on the use of some assessment factors or the suitability of their default values. However for some, such as interspecies factors, there may be some impact on the use of these assessment factors. Therefore where alternative metrics are considered, the impact of the use of an alternative metric factor on the suitability of the assessment factor(s) should be considered and amended, with justification, if necessary.

4.7.12 The R.8 guidance document is from this point on considered by a section by section basis in reflection of guidance.

4.7.13 ***R.8.1 Introduction***

4.7.14 ***R.8.1.1 Overview of legislative requirements***

4.7.15 In our evaluation we considered that the introduction represents a valid overview of the REACH approach which is both equally valid for nanomaterials and non-nanomaterials alike. This is because within section R.8.1.1 (Overview of legislative requirements), it informs that DNEL(s) should reflect likely exposure routes, duration and frequency and in our view this is just as pertinent for nanomaterials as for substances in general and is not overly prescriptive. Indeed the list of factors to be taken into account when establishing a DNEL covers uncertainty, specifically mentioning intra- and inter-species variation, nature and severity of effect and sensitivity of relevant populations. All of these are relevant to nanomaterials and in particular uncertainties arising from variability in data and inter-species variation may also be an issue for nanomaterials and are adequately addressed here in this introductory section.

4.7.16 Under the use of OELs for the derivation of DNELs, the Guidance document refers registrants to Appendix R.8-13. Alterations to this appendix have been suggested (see paragraph 4.7.119), although no changes are required at this point in Guidance.

4.7.17 In addition to introducing the derivation of a DNEL based on threshold effects, the introduction also addresses those situation for which no test data are needed based on exposure arguments, technical impossibility of testing, or the substance being classified as an isolated intermediate. These sections would also be applicable for nanomaterials, should a nanomaterial fall into one of these categories.

4.7.18 The description of the situations whereby the derivation of DNEL is not possible and a qualitative or semi-quantitative approach must be taken, particularly in relation to mutagenic and carcinogenic effects would also be applicable for nanomaterials based on the non-descriptive, introductory nature of the section.

4.7.19 ***R.8.1.2 Overview of aspects to be considered in derivation of DNEL(s)/ DMEL(s)***

4.7.20 Examination of this section indicates that for the most part, the guidance provided applies equally well to nanomaterials as for substances in general. Within the summary introduction of the units (R.8.1.2.7 page 17) it describes how DNELs should be expressed ideally as external values so that they are more easily interpreted in compliance assessment to ascertain if the DNEL is being exceeded. Whilst certainly applicable to nanomaterials, the exposure units are given based upon a mass metric (i.e. mg/m^3). As discussed earlier in this report and in RNC/RIP-oN3/C3/2/FINAL and RNC/RIP-oN3/D/2/FINAL (chapter 11), several other metrics are considered to also be potentially applicable to nanomaterials and indeed may correlate better with observed effects. It is not possible at this stage to identify a single metric that is applicable to all nanomaterials but the incorporation of other metrics in addition to mass, namely surface area should be considered. In relation to fibrous nanomaterials, particle (fibre) number may be a more appropriate metric although the technical feasibility of this has yet to be established. As such this is suggested for further R&D of a high priority. Therefore we would suggest the following amendment to Table R.8-1 footnotes on page 18 of R.8 Guidance (alternations shown underlined):

4.7.21 *[1] Units for systemic exposure are mg/m^3, $\underline{cm^2/m^3}$ (relevant for nanomaterials) and nanoparticle number/m^3* (especially *relevant for fibres)* *for inhalation, and mg/kg bw for oral and dermal exposure. Other metrics may also be used if this is scientifically justified and a comparable exposure metric is available to enable a risk characterisation ratio to be derived. In addition, when expressing metric information it should be stated on what the size distribution is based e.g. as-produced, as-exposed or as-interacted.*

4.7.22 *[2] Units for local effects are mg/m^3, $\underline{cm^2/m^3}$ (relevant for nanomaterials) and number/m^3* (especially *relevant for fibres)* *for inhalation; and for dermal exposure: mg/cm^2, mg/person/day. Other metrics may also be used if this is scientifically justified and a comparable exposure metric is available to enable a risk characterisation ratio to be derived. In addition,*

when expressing metric information it should be stated on what the size distribution is based e.g. as-produced, as-exposed or as-interacted.

4.7.23 ***R.8.2 Step 1: Gather typical dose descriptors and/or other information on potency***

4.7.24 Within this section the issues considering dose-response assessment in the derivation of a no/lowest observable adverse effect level (N(L)OAEL) and benchmark dose (BMD) are discussed. The approach surrounding the generation of N(L)OAEL, its accuracy in relation to a true NAEL and current methodological issues in establishing a BMD using standardised methods are all apparent for nanomaterials and no new information is available for addressing the issues.

4.7.25 The crux of the issues identified relates to the appendices to which the guidance section refers and these are outlined below.

4.7.26 The guidance refers users to Appendix R.8-1 for details on the derivation of different dose descriptors for non-threshold carcinogens and again the units within these tables (R.8-14; R.8-15; and R.8-16) are given based on a purely mass metric which may not be the most appropriate metric for all forms of nanomaterials and other such as surface area or number (especially for fibres) should be considered alongside mass.

4.7.27 Within the dose descriptor for acute toxicity, guidance refers users to appendix R.8-8 which gives a detailed overview of the process of establishing an acute DNEL. Within the process, as summarised by a decision tree for setting an acute inhalation toxicity DNEL, the appendix purports the use of read-across or performing testing in the absence of substance specific data. As discussed the understanding surrounding such a non-testing approach is not yet sufficiently developed for nanomaterials and suggestions for amendments have been made in the relevant section of this report (paragraph 4.7.115).

4.7.28 ***R.8.3. Step 2: mode of action (threshold or non-threshold)***

4.7.29 For non-carcinogenic or non-mutagenic effects, it is assumed that a threshold has to be exceeded before any effects arise. Therefore a threshold is to be

defined and DNEL(s) are set for each threshold endpoint. If a substance exerts its effects at a level at which no threshold can be ascribed, then the substance is to be considered as having a non-threshold mode of action and a qualitative/semi-quantitative risk characterisation should be conducted. A DMEL should be derived if data allow.

4.7.30 As a consequence, it is important to determine if a mutagenic and/or carcinogenic material is acting according to a threshold and/or a non-threshold mechanism. Therefore, as defined in the guidance (R.8.3), step 2 consists of determining if the studied compound is a non-threshold mutagen or a non-threshold carcinogen. For nanomaterials, as with substances in general, this distinction might still be difficult to assess despite the generation of data from a testing approach. The REACH guidance R.8.3 acknowledges that a decision on threshold or non-threshold effects may be difficult to reach and as such, if it is not clear if an effect is threshold or non-threshold in nature "…the assumption of a no-threshold mode of action would be the prudent choice." (R.8.3, page 22, paragraph 4 second sentence). In relation to particles and particularly nanoparticles (due to their large surface area and in certain forms, volume) carcinogenic effects may occur as a result of the threshold phenomena, lung overload in experimental systems. This should be borne in mind when deciding a mode of action and is discussed further in the following section.

4.7.31 *Example of physical process causing secondary carcinogenic effects - Lung overload*

4.7.32 Within this section it may be pertinent to bring attention to carcinogenic effects which may also occur by threshold mechanisms. In relation to (nano)particles, one should consider the generation of lung overload (as described in RNC/RIP-oN2/FPR/1/FINAL) which can lead to tumour formation via indirect mechanisms not attributed to the direct action of the particle itself. Indeed the situation of lung overload and its relation to risk assessment was discussed within the NIOSH TiO_2 study (NIOSH, 2005). The authors of the study concluded after analysing the available evidence that:

4.7.33 "….the tumourgenic effects of TiO_2 exposure in rats did not appear to be chemical specific or acting via a direct action of the chemical but rather as a

consequence of particle size and surface area acting through secondary genotoxic mechanisms."

4.7.34 These route by which secondary genotoxic mechanisms occur is well described within the NIOSH (2005) report and was summarised as such:

4.7.35 "…plausible mechanism of action for TiO_2 in rats can be described as the accumulation of TiO_2 in the lungs, overloading of lung clearance mechanisms, followed by increased pulmonary inflammation and oxidative stress, cellular proliferation, and, at higher doses, tumorigenesis. These effects are better described by particle surface area than mass dose. The observed inflammatory response is consistent with a threshold mechanism."

4.7.36 Exposure to Poorly Soluble, Low Toxicity (PSLT) particles such as TiO_2 at concentrations below the level at which overload occurs is not associated with pathogenic effects. However once this overload threshold has been crossed, approximately 200-300 cm^2 of lung burden as suggest by Tran et al. (2000), there is a sudden increase in lung burden leading to adverse health effects. As such, the phenomenon of lung overload occurs as a threshold effect and pathogenic effects arising from this, such as secondary genotoxicity leading to tumour formation, would naturally also be threshold in nature. Therefore in generating exposure levels based on such data, it would be prudent to derive a DNEL rather than a DMEL which is more commonly used for carcinogenic effects.

4.7.37 It is not the intention here to suggest that as a matter of course a DNEL should be used in replacement of a DMEL for all nanoparticles or that a threshold effect should be presumed. The use of a DNEL based a threshold effect for an observed endpoint such as carcinogenicity should only be done where experimental evidence of overload is apparent or where sufficient weight of evidence indicates overload at the test concentration for the (nano)particle in question. Our suggestion of consideration of lung overload when addressing the question "is the mode of action threshold or non-threshold?", does not supersede the statement already present in guidance that if the mode of action is not clear, then a non-threshold approach would be the prudent choice. As such our placement of a suggested guidance

amendment attempts to reflect this and we suggest the following insertion after the first bullet point of section R.8.3 page 22:

4.7.38 *Substances may exert carcinogenic/ mutagenic effects either via direct mechanisms or by mechanisms secondary to a threshold effect (e.g. threshold induction of chronic inflammation leading to genotoxicity and/ or carcinogenicity). In the case of carcinogenic/mutagenic effects occurring secondary to a threshold stimulus such as inflammation, it could also be considered threshold in nature and as such a DNEL can be derived. A possible example of such a driver is the induction of lung overload in experimental animals exposed to poorly soluble low toxicity (nano)particles leading to chronic inflammation, oxidative stress and culminating in lung tumour formation.*

4.7.39 ***R.8.4 Step 3-1: derivation of DNEL for threshold endpoints***

4.7.40 In the derivation of a DNEL for threshold effects observed, a series of further steps are taken with the data obtained to derive a DNEL. These include:

1) Selection of the relevant dose-descriptor(s) for the endpoint concerned (R.8.4.1)

2) Modification, when necessary, of the relevant dose descriptor(s) per endpoint to the correct starting point (R.8.4.2)

3) The application, when necessary, of assessment factors to the correct starting point (R.8.4.3)

4.7.41 Within section R.8.4.2 there exists a list of occasions where starting point modification may be necessary. Point 2. states:

4.7.42 “if for a given human exposure route there is not a dose descriptor for the same route (in experimental animals or humans)”.

4.7.43 Within the explanatory section for this point (R.8.4.2, Ad2, page 24-25) the guidance suggests that generation of substance-specific data on absorption via different routes are preferred over the use of default values (equally applicable to nanomaterials) and that such information may be generated based on consideration of chemical structure.

4.7.44 This may well be the case for numerous nanomaterials as aspects of its physico-chemical properties such as size, hydrophilicity, shape and solubility could potentially all play vital roles in the materials adsorption and distribution kinetics. There is, however, still a need for further R&D to generate an improved understanding of which physico-chemical attributes affect absorption kinetics, how and to what extent. With this knowledge, generation of substance specific values may be possible based on analogous materials and scientific understanding but this is not yet realisable. We do not feel this requires an amendment to the current guidance text as it is not overly prescriptive but should be acknowledged for further R&D.

4.7.45 Other factors are also addressed within this section including route-to-route extrapolation and the general principles appear appropriate for nanomaterials also. In particular the assumption that, in general, dermal adsorption will not be higher than oral adsorption appears justified as, despite their small size, nanomaterials would not necessarily be expected to penetrate dermal layers more than that of the gastric mucosa. Route-to-route extrapolation is an approach whereby if experimental data for the relevant route of exposure is absent, data from another route may be substituted with appropriate extrapolations. As stated within guidance, this can only be considered for systemic effects, not local effects and not consisting of first past systemic effects and this is certainly also the case for nanomaterials.

4.7.46 Guidance states that where route-to-route extrapolations are made, differences in kinetics and metabolism need to be made but such information may be difficult to obtain. This again is certainly the case for nanomaterials and only limited absorption values exist for a small number of nanoparticles via different routes of exposure.

4.7.47 The current guidance document in its discussion of route-to-route extrapolation is cautionary in its stance and emphasises that obtaining route specific data be considered and the use of substance specific data for extrapolation be used wherever possible. Whilst there is insufficient scientific grounds for challenging the suggested default factors used within route-to-route extrapolation, these have not been developed for nanomaterials. As such the incorporation of the following cautionary statement is suggested for

inclusion at the end of the Ad 2 section on page 25 of the R.8 guidance (section R.8.4.2) and also within appendix R.8-2 appended to the first paragraph:

4.7.48 *The use of a route-to-route extrapolation in determining health hazards for nanomaterials may not be considered suitable at this time as the use of this approach has yet to be established for nanomaterials. Therefore the use of route-to-route extrapolation for nanomaterials must be scientifically justified on a case-by-case basis.*

4.7.49 Further investigation of the effects of certain physico-chemical parameters such as size and surface charge on the absorption and toxicokinetics is needed and should be considered a research and development priority. In particular, sensitive methods of detection are needed. This would be useful not just for informing route to route extrapolations, but also for PBPK modelling and increasing awareness of potential sites of systemic accumulation and/or effects.

4.7.50 The 3rd point in deriving a DNEL relates to the application of assessment factors to areas of uncertainty, variability or deficiencies within a data set which cannot adequately be addressed elsewhere. These consist of assessment factors to address:

- interspecies differences
- intraspecies differences
- differences in duration of exposure
- issues related to dose-response
- quality of the whole database

4.7.51 The outcome of the RNC/RIP-oN3/C3/2/FINAL report and as agreed in the 3rd SCG meeting 15-16 December 2010 in relation to these assessment factors is broadly that they should not be changed for nanomaterials as there exists insufficient evidence to suggest a need for an alteration in the default assessment factors. However, it was agreed that there might be scope for

providing more specific guidance on when and how the defaults factors could be modified for nanomaterials.

4.7.52 *Interspecies differences*

4.7.53 The default assumption within this section is that humans are more sensitive than animals. This, as a starting assumption, is a conservative approach and one would assume is aimed at encompassing all likely modes of action of toxicity, at least for other substances. For the most part the guidance addressing interspecies differences is applicable to nanoparticles and sufficient. Perhaps the most relevant section when considering the current knowledge surrounding particles that would allow the use of substance specific information, is the section surrounding uncertainty in respiratory effects. Within the guidance, it is stated that:

4.7.54 "…there could be significant quantitative differences in deposition, airflow patterns, clearance rates and protective mechanisms between humans and animals and where there is no data…"

4.7.55 Indeed in relation to (nano)particle exposure, there is a great deal of data reporting the differences between humans and various animal species in relation to ventilation rates/ respiratory volumes, airflow patterns and in particular deposition fractions in different respiratory zones based on particle aerodynamic diameter as well as clearance kinetics. Thus, such historical information could be used when addressing interspecies adjustments as, in relation to particle inhalation exposure, the difference in retained dose between two species is the most important parameter when accounting for interspecies differences. A suggested approach for performing an interspecies extrapolation using physiological and experimental parameters commonly reported within high quality studies can be found in Appendix 4 of this report. As this approach is a recent addition to the RIP-oN project and has not been discussed within the stakeholder consultation process, it is presented within the appendix for consideration of further development and assessment for its suitability for incorporation into guidance, potentially within appendix R.8-2 or as a stand alone appendix within the R.8 chapter.

4.7.56 In the interim, the following text is proposed for incorporation into the R.8 Guidance within section R.8.4.3.1, page 33 between the 3rd and 4th paragraphs:

4.7.57 *In deviating from the default assessment factor during the derivation of a DN(M)EL for (nano)particles, a calculation of the actual lung dose could be performed. However as there are considerable differences in ventilation rates, deposition patterns, and clearance rates between humans and animals, all of these factors should be taken into account.*

4.7.58 *If performing an extrapolative calculation based upon physiological parameters such as ventilation rates, this should be assessed against other calculations performed in the derivation of a DN(M)EL. This is to address potential for duplication of calculations. For example in the calculation of the inhaled dose rate, a species respiratory volume and duration of exposure is taken into account and as such, a starting point modification for these parameters would not need to be performed.*

4.7.59 *When considering lung deposition, the aerodynamic diameter not the true (stokes) diameter dictates the fractional deposition of a (nano)particle (see Miller 2000 for further explanation of lung deposition). When calculating the deposited dose, this may also be performed for the zone within the lung showing signs of adverse effects or particle accumulation (e.g. alveolar region) and this could be supported with histopathological findings.*

4.7.60 *When considering the clearance rates it should be noted that clearance half times refer to insoluble particles and as such these values should not be used for soluble particles.*

4.7.61 *Once a calculation of the retained dose within the lung has been made for an experimental animal, this can be normalised to a physiological parameter. Sufficient consideration should be given to the use of alternative physiological parameters to body weight, e.g. lung weight, lung surface area or the surface area of the proximal alveolar region (Donaldson et al. 2008). However the use of alternative parameters should be scientifically justified. In addition the use of additional exposure metrics such as (nano)particle surface area or number*

concentration (especially *for fibres) should be considered when performing analysis which should also be scientifically justified.*

4.7.62 The aim of this inserted section is to inform registrants of issues surrounding extrapolation from experimental animals to humans using inhaled/deposited/retained dose as a parameter. Further guidance based upon Appendix 4 of this report could be considered for further development.

4.7.63 *Intraspecies differences*

4.7.64 Within guidance, assessment factors are used to account for differences within a population, such that the most sensitive member of a population exposure to a substance will be protected. For the general public this considers both those healthy individuals and those with increased sensitivity/ susceptibility such as pregnant women, children, the very old or those with pre-existing disease. In order to account for such differences, a default assessment factor of 10 is applied in the derivation of a DNEL for the general population and there is no evidence to suggest that this would not be an appropriate default for nanomaterials.

4.7.65 When considering a worker population, the range of sub-groups (e.g. children) is reduced and generally consists of 'healthy' adult workers and does not consist of the very old or those with severe disease. However within even a healthy population there may still exist considerable variability. For example the presence of sub-clinical disease (e.g. cardiovascular disease), clinical disease which does not prevent employment (e.g. asthma) or unknown genetic polymorphisms that could result increased sensitivity to a particular substance. As well as physiological differences, other factors may also increase variability such as smoking status, which is known to contribute to the occurrence of certain diseases (e.g. bronchogenic carcinoma).

4.7.66 For these reasons, in deriving a DNEL based on a 'healthy' worker population for substances, including nanomaterials, the use of an assessment factor to take account of this variability is prudent. This approach is not consistently taken by all risk assessors, e.g. the approach taken by Hanai et al. (2009) within the NEDO approach where this factor was not considered necessary. The approach taken for both TiO_2 and carbon nanotubes was to apply no

uncertainty (assessment) factor for their worker population as "this assessment is targeted at workers who are probably in good health and are not sensitive".

4.7.67 In our view such an approach is not supported as within this population there is certainly likely to exist variability in health status and sensitivity (e.g. smokers who due to reduced lung clearance efficiency may be more prone to particle accumulation). As such it is suggested herein that there is not sufficient data available to challenge the use of the default assessment factors for a worker population and where a reduced AF (e.g. 1) has been used within the available literature, this has not been adequately supported.

4.7.68 As such we propose the following appendage to final paragraph of the 'intraspecies differences' section on page 34 of the R.8. Guidance:

4.7.69 *It is to be noted that, as is the case for interspecies assessment factors, relevant substance-specific information on intraspecies variations should always be used to adjust or substitute the default factors (see e.g.* World Health Organization *(WHO)/* International Programme on Chemical Safety *(IPCS), 2005). In the case of (nano)particles, the consideration of lowering the default assessment factor due to perceived sensitivities/ insensitivities within a population must be scientifically justified.*

4.7.70 In order to deviate from the default assessment factors, a greater understanding of the relative sensitivities of certain individuals/ populations and how these may relate to nanoparticle is perhaps required. For example, whilst several studies either assume a local effect or did not detect translocation/ systemic effects after nanoparticle exposure (Hanai et al. 2009, Pauluhn 2010a/b), one may need to take into account other systemic effects (not necessarily occurring as a result of direct particle translocation). An example of this is an increase cardiovascular events (e.g. myocardial infarctions) which have been observed in the wider population during episodes of high particulate matter (PM) concentration in the ambient air. Such R&D is still required to address relative sensitivities.

4.7.71 *Differences in duration of exposure*

4.7.72 Assessment factors to account for differences in experimental exposure duration (typically months to occasionally years) and actual human exposure duration are suggested within guidance and summarised in table R.8-5, page 35 of the R.8 document. There is no current evidence to suggest that the default assessment factors for duration extrapolation would not be equally applicable for nanomaterials. However within this section, there exists guidance on how, with substance-specific data, the defaults may be modified. The lowering of the default assessment factors with evidence of no increase in severity/ incidence of effects with increasing exposure duration is certainly valid for nanomaterials in relation to dermal exposure and due to the reduced sensitivity to lung overload in humans in comparison to rat models, it is also likely to be valid for inhalation exposure.

4.7.73 The guidance also suggests that a higher assessment factor may be appropriate if there is the potential for accumulation of dose. Accumulation may impact on the incidence and severity of an effect by leading to the accumulation of a substance to a critical (threshold) dose leading to an effect and/or through the lack of clearance of a substance. This may result in continual interaction of the substance with the biological environment causing, for example chronic inflammation. This may be especially prudent for exposure routes such as the lung and certain poorly soluble particles/ morphologies associated with reduced clearance, e.g. long straight, biopersistent fibres which are likely to be retained if deposited in the non-ciliated airways leading accumulation of dose with repeated exposure.

4.7.74 The inclusion of this description of situations where it may be appropriate to deviate from the default assessment factors is equally applicable to nanomaterials as to substances in general. We would however suggest that the final sentence of the section be modified to more accurately reflect the situation of lung overload and provide reference to further information within guidance. The sentence found at the end of bullet point 3, page 35 of the R.8 Guidance document could be altered as follows (alterations shown underlined):

4.7.75 *In relation to inhalation of poorly soluble, low toxicity (PSLT) particles, exposure at high doses can lead to accumulation within the alveolar spaces, lung interstitium and lung associated lymph nodes which may result in a further increase in toxicity following long term exposure (Morrow, 1988). For further information see Guidance R.7a.*

4.7.76 *Dose response relationships*

4.7.77 When considering the dose response relationship, guidance provides a great deal of information in relation to the issues surrounding dose descriptors and comments on these and alterations required are given within this report. Within this section there is not sufficient reason or evidence to suggest that the default factors presented would not be sufficient for nanomaterials. Issues surrounding the use of BMD in replacement of a LOAEL and its incompatibility with current testing standards are also addressed within section R.8.2 and no further amendments for nanomaterials are necessary.

4.7.78 *Quality of the whole database*

4.7.79 When looking at the quality of the whole database used to calculate a DNEL, an extra assessment factor can be applied to account for deficiencies within the data set including gaps, inconsistencies between studies, or deficiencies in study design. The application of such extra assessment factors is also applicable to nanomaterials and may be particularly relevant due to the general paucity of information surrounding nanomaterials.

4.7.80 In view of the potential study deficiencies, current R.8 Guidance directs users to evaluating the quality of the testing method, sample size, study design, biological plausibility etc. All of these factors would be equally applicable and measurable for a study of nanomaterial as other materials and there is sufficient scope within the guidance to account for deficiencies within these areas through the use of a more stringent assessment factor. There also appears no evidence to suggest that deficiencies in experimental design, sample number etc. would cause any more or less uncertainty than for substances in general.

4.7.81 However when looking outside a study, across the wider literature and addressing issues such as consistency with other studies and similarity of effects within the body of data, there can be additional uncertainty.

4.7.82 Within the nanotoxicological literature, there appears a spectrum of the depth of toxicological information for nanomaterials. For certain nanomaterials, e.g. very new forms and or commercially less well developed forms, there appears very little toxicological information and as such the overall database would be viewed as possessing additional uncertainty. However for other forms, such as TiO_2 or carbon black nanoparticles, a relatively large amount of data exists with which a registrant could assess their data for reliability and consistency in relation to other studies. Perhaps the largest area of uncertainty is the long-term effects of nanoparticle exposure, especially carcinogenic endpoints. Due to this variation and the constantly evolving nature of the nanotoxicology literature, it would be impractical to suggest a 'one-size-fits-all' approach to dealing with uncertainty within nanomaterials. Indeed, such uncertainty is also prevalent when considering other new materials and the current guidance has been developed with sufficient scope to account for deficiencies when considering a nanomaterial as with any substance. The final sentence of the *Quality of whole database* section (page 37) states that a larger assessment factor can be applied on a case-by-case basis. This should also be considered for nanomaterials, with each derivation assessed on it own merits in relation to the specific study and the wider literature.

4.7.83 It is however suggested that the greater certainty may be achieved where data addressing longer term endpoints, especially carcinogenic endpoints is available. In addition, information on absorption, systemic availability and organ accumulation (including any associated effects) could be seen as reducing uncertainty for nanomaterials and potentially substances in general. As such we suggest the following amendments (underlined) to the fourth paragraph of page 37 of section R.8.4.3.1:

4.7.84 *"……This approach requires a critical evaluation of the entire body of available data for consistency and biological plausibility. <u>In addition the availability of chronic data (in particular addressing carcinogenic endpoints), and data addressing absorption, systemic availability and accumulation would</u>*

be seen as reducing uncertainty. Potentially relevant studies should be judged for quality and studies of high quality given more weight than those of lower quality…."

4.7.85 When considering the entire database of a material, a question raised in relation to nanomaterials is to what extent data on the bulk form can be considered when addressing the quality of whole database for a nanomaterial. This is an important question but also raises many of the issues associated with read-across from bulk materials to nano-forms. The main issue is to what extent are the bulk and nano-forms similar or different. As is the suggested case for read-across approaches, the use of bulk data for informing nano hazard assessment may be associated with more uncertainty than for substances in general and must be scientifically justified. As such it is suggested that as part of R&D into the use of read-across between bulk and nano-forms, that consideration be given to the use of bulk data in assessing the quality of whole database. In addition we propose the following text addition to R.8 Guidance appended to the fourth paragraph of page 37:

4.7.86 *When assessing the consistency and biological plausibility of study data against the wider body of literature for nanomaterials, the use of data on the bulk or other forms of the material in place of nano-specific data must be scientifically justified and may be associated with additional uncertainty.*

4.7.87 *Endpoint-specific issues on AF*

4.7.88 This section refers registrants to appendices R.8-8 to R.8.-12 for further information and any alterations to these appendices is given at the end of this R.8 section.

4.7.89 ***R.8.4.3.2 Use of Physiologically-Based Pharmacokinetic (PBPK) modelling for Engineered Nanoparticles***

4.7.90 Section R.8.4.3.2 describes how physiologically based pharmacokinetic (PBPK) models can be used in the derivation of DNEL/DMEL. The confidence in PBPK modelling is based on a rigorous process of verification; validation, sensitivity testing and model documentation. These are generic steps and are applicable to all PBPK models. A large subset of the model parameters are

identical for (nano)-particles as well as chemicals. They are: (1) Physiological; (2) Anatomical; (3) Physico-chemical parameters. However currently, the rates of translocation of nanoparticles in different anatomical compartments are generally unknown. It is expected that these parameters will vary from particle to particle and will be related to the physico-chemical properties of these nanoparticles. The existing method for extrapolation to other species, as stated in the document (Schneider et al, 2004), may be applicable for nanoparticles but this needs to be verified. For intraspecies variability, the probabilistic techniques such as Monte Carlo sampling are equally applicable to nanoparticle PBPK modelling.

4.7.91 Just as in chemical toxicology, extrapolation from high dose to low dose in order to derive NOAEL is equally important for nanoparticles and will be adopted. Of equal importance is the route to route extrapolation. The step described in guidance is equally valid for nanoparticles.

4.7.92 Finally the application of PBPK models as part of the toolbox for Risk Assessment is equally justified with nanoparticles as it is justified with chemicals in the Guidance. As with chemicals the issues such as extrapolation high to low dose, intra- and inter- animal variation extrapolation are equally of importance to nanomaterials. Currently PBPK models are few and are substance specific. The development of generic models for classes of nm based on their similar physico-chemical structure is an important research need. As such based on the caveats already introduced within guidance (which are equally relevant to nanomaterials), no alterations to guidance are warranted at this time.

4.7.93 ***R.8.4.3.3 Overall assessment factor and its application to the correct starting point***

4.7.94 The summation of the assessment factors used and the application of an overall assessment factor is valid for nanomaterials and as no alterations to default assessment factors are proposed, no alteration to this section of guidance is required either.

4.7.95 ***R.8.5 Step 3-2: derivation of DMEL for non-threshold endpoints***

4.7.96 In the derivation of DMEL for non-threshold effects, a similar approach in many ways to that of deriving a DNEL is taken. Where similarities exist, registrants are generally referred to the appropriate section of guidance instructing the derivation of a DNEL. However certain deviations or alternate approaches are used within the derivation of the DMEL and these are considered in the following sections.

4.7.97 ***R.8.5.1 Deriving a DMEL for a non-threshold carcinogen, with adequate human cancer data.***

4.7.98 This section of the guidance document R.8 has recently been amended and now refers registrants to appendix R.8-15, section B for guidance.

4.7.99 ***R.8.5.2 Deriving a DMEL for a non-threshold carcinogen, with adequate animal cancer data.***

4.7.100 Within guidance, there are two mathematical models suggested for the derivation of the DMEL for a non-threshold carcinogen with adequate animal cancer data. Due to the current paucity of data surrounding the carcinogenic potential of various nanomaterials, it is impossible to state if these approaches would be unsuitable for nanomaterials. However based on the generalised nature of these approaches, taking into account the wide variety of materials to which they are to be applied, there is little reason to suggest that these would not be suitable for nanomaterials.

4.7.101 ***R.8.5.2.1 The 'Linearised' approach***

4.7.102 The linearised approach is based upon the assumption that a linear dose response relationship between tumour formation and exposure exists. The approach, as with the derivation of a DNEL, follows 3 main phases:

4.7.103 a) select the relevant dose descriptor(s)

4.7.104 b) Modify, when necessary, the relevant dose descriptor(s) to the correct starting point

4.7.105 c) derive from this correct starting point a DMEL for each relevant exposure pattern essentially by linear high to low dose extrapolation, and by the application of assessment factors (when necessary).

4.7.106 In the case of modification of the dose descriptor for deriving a DMEL, the modifications are applicable in the same situations as those described for a DNEL with the addition of an extra situation, namely “Differences between occupational and lifetime conditions of exposure.” The Guidance document refers registrants to the relevant section of starting point modification for DNELs and whilst no alteration to these sections has been proposed, R&D requirements are suggested (paragraph 4.7.126).

4.7.107 The additional situation for which a starting modification maybe required is adjusting for differences in occupational and lifetime exposure conditions. Specifically this relates to the fact that within guidance, human environmental exposure (24 hours per day, 7 days a week for 75 years) is considered equivalent to that of a life-time exposure of an experimental animal. Because occupational exposure is for a shorter duration than environmental exposure (8 hours per day, 5 days per week, 48 weeks per year for 40 years), the animal data which is equivalent to environmental exposure needs to be adjusted accordingly.

4.7.108 In the final step of deriving a DMEL, assessment factors are applied when necessary to account for differences between the experimental data and real human exposure situations. These are performed in the same way as for the derivation of a DNEL and registrants are referred to the relevant section of the R.8 guidance covering DNELs for information. As such we refer readers to the relevant part of this report (paragraph 3.7.5) which address these assessment factors in relation to their occurrence in guidance.

4.7.109 The amendments to the application of an interspecies and/or intraspecies factor due to the use of a linear approach also could be considered sufficiently conservative for nanomaterials as it is for substances in general. Also a consideration of issues related to dose-response as discussed in guidance is incorporated into the various dose descriptors used (T25, BMD10 and BMDL10) and is sufficiently prudent for nanomaterials.

4.7.110 The approach taken for extrapolating from high dose levels associated with high cancer risk to low levels associated with a very low risk of human cancer is equally relevant and equally conservative (thought to in some cases lead to an overestimation of risk) for nanomaterials. Indeed the linearised multistage model (LMS) has been in the derivation of a REL by NIOSH for ultra-fine (nano) TiO_2 (NIOSH, 2005).

4.7.111 ***R.8.5.2.2 The 'Large Assessment Factor' approach ("EFSA" approach)***

4.7.112 As described in guidance, the large assessment factor or EFSA approach applies basically the same steps as that of the linearised approach. The steps taken in the selection of the relevant dose descriptor and modifications the correct starting point mirror that of the linearised approach and are equally appropriate.

4.7.113 The application of assessment factors marks the main point of deviation from that of the Linearised approach. The EFSA approach recommends the use of a large assessment factor of 100 to account for differences in interspecies (10) and Intraspecies (10) differences. The factor of 10 for an interspecies assessment factor could be considered conservative for both nanomaterials and substances in general. The use of a factor of 10 for intraspecies differences is based somewhat on the potential impact genetic polymorphisms may have on compound metabolism and cancer susceptibility. It is unknown as to what effect genetic polymorphisms may have on the susceptibility to nanoparticle effects but as removal of nanoparticles is likely to be based on cellular based clearance (e.g. alveolar macrophages, liver kupffer cells) rather than metabolism; one could presume that nanoparticle susceptibility may be less influenced by genetic polymorphisms in drug metabolising enzymes. However insufficient evidence exists to challenge the default assessment factor at this time.

4.7.114 The EFSA approach also uses an additional assessment factor of 10 to account for inter-individual variability in cell cycle control and Deoxyribonucleic acid (DNA) repair; two important cellular processes that can affect cancer susceptibility. The use of a second assessment factor to account for differences in inter-individual variability (although based on separate aspects) is also conservative. However the approach of considering

differences in aspects such as DNA repair efficiency between individual of a population (irrespective of health status) is sound and perfectly applicable to nanomaterials. At this time no evidence exists to suggest that a more stringent factor would be required than that applied to substances in general.

4.7.115 It is considered here that guidance allows the scientifically justified alteration (e.g. reduction) of the assessment factors in relation to substance specific information. Therefore for the assessment factors outlined in the guidance document, more stringent default assessment factors are not considered necessary. As such, no alterations to this approach are deemed necessary.

4.7.116 ***R.8.5.2.3 Alternatives to the conventional extrapolation procedures***

4.7.117 This section of guidance simply refers users to the PBPK modelling approach (section R.8.5.2.1 of guidance) which is dealt with in paragraph 4.7.69 of this document.

4.7.118 ***R.8.5.3 Deriving the DMEL for a non-threshold carcinogen/ mutagen, without adequate cancer data***

4.7.119 In the absence of proper data for the derivation of the DMEL, guidance suggests other approaches which may be explored to derive a DMEL including read-across, use of sub-chronic studies or the threshold of toxicological concern (TTC) concept. As previously reported within the RIP-oN projects and extensively in RNC/RIP-oN2/B5/2/FINAL in relation to the R.7a guidance document, the use of read-across needs further R&D for nanomaterials. This is because it is not clear and no consensus exists as to what attributes concepts of similarity should apply to when considering a nanomaterial and its analogue. This is not to say that this not possible, indeed future research may provide grounds for such an approach. However, scientific justification for the use of read-across would need to be provided. As such we propose the following statement for inclusion into Page 51, appended to the final paragraph of the section ‘read across’ section of R.8.5.3 of guidance.

4.7.120 *The use of a read across approach in addressing data gaps for nanomaterials may not be considered suitable at this time as the use of such approaches for*

nanomaterials has yet to be established. Therefore the use of read-across and other non-testing approaches for nanomaterials in deriving an assessment of hazard for humans must be scientifically justified.

4.7.121 The use of the TTC approach is also not appropriate yet for nanomaterials as it is based on a form of read-across from other structural classes for which extensive databases exist. The relevance of these databases or points of comparison/ similarity to nanomaterials has not been established. In addition this approach is only applicable to the oral route and whilst some nanoparticle exposure may occur via the oral route, the predominant route of exposure in the occupational setting (likely to be most relevant when considering high exposure levels) is potentially via the inhalatory route and dermal route. The guidance section on TTC (page 52) currently points out that further development and stakeholder agreement is still required and this is certainly the case for nanomaterials. Due to the uncertainty expressed within guidance addressing use of subchronic studies and TTC approaches, and the requirements of further R&D and expert judgement, further information regarding nanomaterials specifically is not considered warranted.

4.7.122 Due to the difficulties in generating regulatory relevant robust hazard data (incl. carcinogenicity) for many substances, not only nanoparticles, it would be important to consider further R&D into non-testing approaches such as read-across, (Q)SAR etc. Research and development for QSAR, grouping approaches (REACH Guidance R.6.) and *in silico* approaches (general applicability) are also considered within the RNC/RIP-oN2/FPR/2/FINAL as a high priority that should be addressed within the short term. It is recommended that the advice provided be considered for further development of a possible new sub-section on nanomaterials under R.6.2.5 Guidance on specific types of categories.

4.7.123 Within this section, the use of data derived from transgenic animals is also described. The approach suggested is considered appropriate for animal testing using nanomaterials.

4.7.124 ***R.8.6 Step 3-3: qualitative approach***

4.7.125 No changes are considered to be needed although further R&D is required in developing at least qualitative approaches to indentifying respiratory sensitizers as discussed in section 4.7.162.

4.7.126 ***R.8.7. Step 4: Selection of leading health effects***

4.7.127 ***R.8.7.1 Selection of the critical DN(M)EL***

4.7.128 When considering the critical DN(M)EL, the recommendations of guidance appear equally suitable for nanomaterials. In relation to dusts, the section also refers to the general dust limits for nuisance dusts and how, in relation to these limits, a DNEL may need to be lowered. This means that if a DNEL is derived for a particle indicating no effect above that of the general dust limit, then the dust limit would apply rather than the DNEL. Where the DNEL is lower than the dust limit, the DNEL would apply (as one cannot adjust a DNEL upwards). This approach is prudent as if a substance/ nanoparticle shows toxicity below this level, this would result in a DNEL below this level which must be adhered to (and hence any identified health effects should be controlled). If the substance does not show toxicity below this level and a DNEL is derived which is in excess of the dust limit, the dust limit would apply (meaning any identified health effects should still be controlled). Guidance also states that the general dust limit is not to be used as a surrogate DNEL in situations where no substance specific information is available. This is certainly also the case for nanomaterials and there appears no grounds to lower the general dust limit for nanomaterials as any increased toxicity should be detected and reflected in a lower DN(M)EL.

4.7.129 ***R.8.7.2 Endpoints for which no DNEL/DMEL can be derived***

4.7.130 Similarly, the qualitative approach described for risk characterization, when no DN(M)EL value can be derived, seems appropriate for nanomaterials.

4.7.131 ***R.8.7.3 Using DN(M)EL for human exposure patterns***

4.7.132 Guidance considering the use of derived DN(M)ELs to human exposure patterns is considered applicable and appropriate for nanomaterials.

4.7.133 Within the R.8 guidance document appendices, the following alterations are suggested and only those appendices for which an alteration is suggested are shown. For all others these have been assessed as being suitable for nanomaterials with no alterations required.

4.7.134 ***APPENDIX R. 8-8***

4.7.135 This appendix outlines the approach taken in generating a DNEL for acute toxicity and to the most part applies equally to nanomaterials and substances in general. In particular, the appendix under the section 'identification of the typical dose descriptor' outlines that whilst acute toxicity tests traditionally used mortality as an endpoint this may not provide the most rational starting point for deriving a DNEL. This is because toxicity occurs as a continuum to which lethality is the most severe expression and if taken as an endpoint, does not allow the consideration of other, clinical or sub-clinical signs of toxicity. This issue has been raised in the RNC/RIP-oN2/B5/2/FINAL document (paragraph 6.2.5) and the suggestion has been made for further development of current acute toxicity testing guidelines to include further pathological and histological examination to detect more sensitively adverse effects. As such a change is both relevant to all substances tested and relates to further development of test methods, no guidance alteration is considered necessary.

4.7.136 Whilst the guidance appendix provides a detailed overview of the issues and approach to setting an acute DNEL, within box 9 of the decision tree (figure R.8-5 page 111) and in the following discussion of this approach (page 113, paragraph 2) it states that:

4.7.137 "…if acute data are available for a substance(s) with a similar structure and physico-chemical properties (and toxicity profile if such data are available) it can be used for setting the acute toxicity DNEL."

4.7.138 As it is not yet sufficiently understood on what basis a similarity should be established between forms (nano-nano, bulk to nano or some other analogue), we would suggest the insertion of a caveat in the explanatory section in Appendix R.8-8 on page 113 appended to paragraph 2. The suggested inclusion is:

4.7.139 *The use of non-testing data such as read-across, grouping or (Q)SAR approaches in addressing data gaps for nanomaterials is very limited at this time. In addition to this the use of such in silico models for nanomaterials has also yet to be established. Therefore the use of non-testing approaches for nanomaterials in deriving an assessment of hazard for humans must be scientifically justified.*

4.7.140 ***APPENDIX R. 8-13***

4.7.141 This section outlines the approach taken in relation to developing a DNEL in situations where an occupational exposure level already exists, specifically in the case of an EU indicative occupational exposure limit (IOEL), EU binding occupational exposure limit (BOEL) and a nationally adopted occupational exposure limit. Currently, there are no EU occupational exposure limits for nanomaterials and as such the subject of this appendix is not yet apparent for nanomaterials. However, should an EU IOEL or BOEL become available then the contents of this appendix may be required. As such we have felt it prudent to offer proposed amendments where we see deficiencies lie in relation to nanomaterials.

4.7.142 The appendix chapter outlines that for an IOEL, a registrant can use an existing limit in place of a DNEL specifically where:

- The exposure route, duration and exposure population or vulnerable sub-population are the same
- Where no newer scientific information exists, or that which does, supports the IOEL

4.7.143 In situations where an exposure route/ duration, population differs from that of the IOEL or where newer conflicting scientific data exist, then a new DNEL specific to the route(s) etc must be generated. Such an approach is equally applicable to nanomaterials. However in addition, it should be noted that difference in physico-chemical attributes for example size, shape and crystallinity may have an impact on the (adverse) toxicological effects as discussed within the RRNC/RIP-oN3/C2/2/FINAL report (section 2) and RNC/RIP-oN2/B5/2/FINAL report (section 4). As such, an IOEL developed for

a nanomaterial with particular physico chemical characteristics would not automatically be appropriate for another material with the same chemical composition but differing physico-chemical characteristics (e.g. differing shape/ size/ surface functionality). In such a situation, a DNEL should instead be derived for the specific material in question (a case-by-case approach). As such we propose the following insertions into Appendix R.8-13:

4.7.144 Page 142: *Registrants obligations,* paragraph 2, first sentence (insertion shown underlined):

4.7.145 *A registrant is allowed to use to use an IOEL as a DNEL for the same exposure route, duration and (particle) physico-chemical characteristics, such as particle size distribution, shape and surface area unless new scientific information……*

4.7.146 Page 143: *Registrants obligations,* appended to paragraph 1:

4.7.147 *For nanoparticles alterations in physico-chemical attributes such as size, crystallinity, shape (e.g. spherical or fibrous), and surface functionality/ attributes may impact on the relative toxicity of materials of the same chemical composition. As such, the use of an IOEL in place of a DNEL is only suitable where the material physico-chemical attributes are the same as that of the material in question. In situations where such physicochemical characteristics are not the same and read-across is not scientifically justified, a DNEL should be generated for the same form/material that reflects the true physic-chemical properties of the substance.*

4.7.148 The information for using a BOEL in place of DNEL is applicable to nanomaterials with no alterations required (should the use of any future BOEL be made).

4.7.149 The information for using a national OEL in place of DNEL is also applicable to nanomaterials with no alterations required (should the use of any future national OEL be made).

4.7.150 *Research Recommendations*

4.7.151 Within the RNC/RIP-oN3/C3/2/FINAL report several R&D requirements were identified which could either address gaps in the current approach for derivation of exposure limits or provide useful additions to the current understanding of nanomaterials and these are suggested in the following in addition to those already highlighted within the text above.

4.7.152 Metrics

4.7.153 Further research and development is needed in order to establish the most appropriate methods and metric(s) for which to base a derived exposure limit on. This may be different depending on the nature of the material (e.g. reactive surface vs. fibre based toxicity) and should, where possible relate to the biologically effective dose driving an adverse effect. For a number of nanomaterials, surface area is seen as an important metric for measuring inhalation exposure and deriving limits, but other metrics such as fibre number may also be considered. As a component of this R&D suggestion, methodological approaches would need to be developed in order to utilise other metrics in combination with mass. For example current methods to detect fibres in the air are not designed to deal with complex nanofibres such as carbon nanotubes and as such may need further modification or development.

4.7.154 Toxicokinetics

4.7.155 Further R&D is suggested to generate an improved understanding of which physico-chemical attributes effecting absorption kinetics, as well as how and to what extent this occurs. Specifically the generation of such information could allow the use of substance specific values based on analogous materials and scientific understanding. Such information would allow improvements in both addressing the issues of uncertainty in starting point modifications and also for use in PBPK modelling. As an R&D priority, this could be considered a high priority of the short term.

4.7.156 Non-testing Approaches

4.7.157 In tackling the issue of data gaps in establishing hazard and risk characterisation, further R&D is required concerning the drivers of toxicity and how these relate to physico-chemical attributes. This may enable the use of non-testing data based on approaches such as categorisation of nanomaterials, read-across between differing nanomaterials based upon certain physico-chemical similarities and (Q)SAR. The understanding of how nanomaterials behave, how they differ from bulk materials and their drivers of toxicity is crucial in understanding important parameters such as absorption and distribution kinetics as well as establishing rates of translocation which relate to several aspects of hazard and risk characterisation. These include the generation of accurate PBPK modelling and establishing threshold and non-threshold mechanisms of nanomaterials toxicity, which impact on improving data reliability and establishing more accurate exposure limits. As non-testing approaches are potentially of enormous benefit to hazard assessment, a greater understanding to enable their use in relation to nanomaterials is highly desirable. As such, R&D into this area could be considered a high priority of the short/medium term.

4.7.158 Risk Characterisation

4.7.159 An approach for risk characterisation by Hanai et al. (2009) is discussed with the RNC/RIP-oN3/C2/2/FINAL report. This approach uses a bi-axial framework by which acceptable levels of human exposure may be predicted for a material for which inhalation data does not exist. The approach uses data that is not suitable for extrapolation to human exposure limits (e.g. lung instillation data or potentially in vitro data) to rank a materials toxicity in relation to a material for which inhalation data does exists. Based on this ranking, an assessor can judge if a material is more or less toxic than the form for which inhalation data exists and set an interim exposure limit which is higher or lower than limit derived using the inhalation data.

4.7.160 This approach is interesting as, whilst there are many questions surrounding the confidence one may have in the final predicted human exposure level, it opens up a range of data and testing approaches that are unencumbered by issues surrounding read-across based upon physico-chemical characteristics.

As such, this approach could be used to help in the development of an interim approach to using non-inhalation data to address the current situation of a wealth of nanoparticles but few suitable inhalation studies for the derivation of acceptable human exposure levels.

4.7.161 The development and assessment of this approach for its suitability for incorporation into REACH could be considered as an obtainable short term goal if based upon non-inhalation methods which more closely represent inhalation exposure such as instillation methods. The use of other, non-physiological means of assessing toxicity such as *in vitro* methods would require considerably further development and validation as well as greater evaluation before being used in this approach. The bi-axial approach described thus far has been based upon inhalation as a route of exposure. This is because it has been set in the context of the approach taken within the Hanai et al. (2009) paper and also because inhalation is considered one of the foremost routes of exposure to nanoparticles in the occupational setting. However the bi-axial approach may be equally relevant to other exposure routes/target organs such as dermal toxicity based upon extrapolation to human exposure levels using an appropriate testing method, and ranking of another particles based upon other test methods (note this does not suggest that lung instillation could be used to rank nanoparticle toxicity for dermal toxicity or any form of route to route extrapolation).

4.7.162 Qualitative Hazard Characterisation

4.7.163 When considering the hazard/risk characterisation process, REACH Guidance indentifies various tools with which to evaluate hazard/risk and how to use this information to control such identified risks. Whilst substance specific, in depth toxicological evaluation of each substance is most certainly preferable in a hazard characterisation of a material, it is often not available or sometimes not practical. As some form of evaluation still must be performed, a more qualitative characterization of hazard can be used to generate information with which to evaluate a material.

4.7.164 Within RNC/RIP-oN3/C2/2/FINAL, there are several schemes outlined for making a qualitative assessment of hazard. However, none are yet considered to provide a robust framework for incorporation into Guidance on

adopting a qualitative approach for nanomaterials in the absence of quantitative data. They may provide a degree of informative context to elements of the qualitative approach, specifically in Part E Guidance (Section 3.4.3).

4.7.165 Specifically, acknowledging the aforementioned schemes would enhance the guidance's recommendation that the implementation of risk management measures (RMMs) and operational conditions (OCs) needs to be proportional to the degree of concern for the health hazard presented by the substance. In particular, Steps 2 and 4 in the "Step-wise approach for the qualitative assessment, including development of exposure scenarios (ES)" (Guidance Part E, Section E.3.4.3) refer specifically to the use of information on physico-chemical properties.

4.7.166 The particular references to physico-chemical properties in the steps could provide a basis for a recommendation of updating the Part E Risk Characterisation (Section E.3.4.3) guidance with a statement and reference to the availability of qualitative hazard assessment schemes (based on physico-chemical properties) for nanomaterials (RNC/RIP-oN3/C2/2/FINAL).

4.7.167 As such, we can see that as part of a 'tool kit' for hazard characterisation, the development of improved qualitative approaches such as those discussed within RNC/RIP-oN3/C2/2/FINAL report is important. This is not least to reduce the burden of animal testing, but also to provide a rapid interim evaluation of potential hazard so that these may be controlled. However such schemes for nanomaterials have yet to be widely accepted or tested and as such alteration to guidance at this time may be premature. It is therefore considered that the development of such qualitative schemes should be given credence when considering future R&D priorities for hazard evaluation of nanomaterials and could be considered a high priority over the short term. In practical terms, this would provide a more holistic route to the evaluation of nanomaterials for which REACH Guidance is intended, and a route which is already available for some other materials. Indeed when considering the range of nanomaterials and the associated testing burden, the development of accepted qualitative approaches would be a powerful tool for a *rapid* evaluation which is much needed.

4.7.168 Respiratory Sensitisation

4.7.169 Within the R.8 Guidance (Appendix R.8-11) there is a description of respiratory hypersensitivity reactions resulting in allergic airways diseases such as asthma. However in relation to determining the induction or elicitation thresholds with which to establish a DNEL, the guidance currently identifies that there are no validated or widely accepted animal or in vitro test protocols for detecting respiratory sensitisation. Indeed, the current method of hazard identification is based upon the presence of human data and as such is ineffective at preventing adverse human effects in the first place. In relation to nanomaterials, there are some studies which suggest that certain nanomaterials can elicit severe allergic-type inflammation within the lung (Cho et al. 2010).

4.7.170 Whilst certainly nano-relevant, this issue is not nano-specific as methods for addressing potential respiratory sensitisation using quantitative and qualitative approaches does not yet exist for substances in general either. This as an issue impacts on several aspects of REACH guidance including R.7a (and identified as a R&D priority in the RNC/RIP-oN2/FPR/1/FINAL report), guidance part E as well as guidance R.8. Due to the debilitating nature of allergic airways disease and the current lack of methodologies with which to identify respiratory sensitizers for both nanomaterials and other substances, it seems prudent to conduct research and development into methods with which to evaluate respiratory sensitizers. Indeed this may be through the development of quantitative approaches which allow the identification of threshold levels suitable for the evaluation of DNELs or at least allow a qualitative evaluation for hazard characterisation.

4.7.171 Experimental/ Exposure conditions

4.7.172 An issue raised in the paper by Oller and Oberdörster (2010) is the potential impact differences in exposure situations may have on the toxicity of a (nano)particle. Within experimental conditions, a great deal of effort is often placed upon obtaining well dispersed aerosols with fewer large agglomerates. However such dispersions may not accurately reflect real exposure conditions and as parameters such as particle/ agglomerate size can effect the respirability, deposition and clearance of (nano)particles, changes in the size

distribution may impact on the scavenging of nanoparticles and received dose. Further R&D is required to gain a better understating of how representative experimental conditions are of real human exposure conditions, what parameters differ and how these may effect the resultant dose received and observed toxicity.

4.7.173 Assessment Factors

4.7.174 Whilst the assessment factors have been considered in relation to nanomaterials and to the most part there is little scientific evidence to suggest that current default assessment factors are or are not sufficient for nanomaterials. Where deficiencies or alternative approaches lie, these have been discussed and amendments/ further R&D suggested. It would also be prudent to suggest that further R&D is required to further investigate the suitability of the current default assessment factors for nanomaterials as well what substance specific data should be available and what methods used when deviating from defaults. In addition, further research should look into the effect different metrics would have on the application of assessment factors.

4.8 R.10 CHARACTERISATION OF DOSE [CONCENTRATION]-RESPONSE FOR ENVIRONMENT

4.8.1 The R.10 guidance chapter provides guidance on how to characterise the dose (concentration) – response for the different environmental compartments. In other words it is mainly guidance on how to quantitatively assess the effects of a substance on the environment by determining the concentration of the substance below which adverse effects in the environmental compartments of concern are not expected to occur. This concentration is known as Predicted No-Effect Concentrations (PNECs).

4.8.2 When considering the available data and quality of the data both within a study (e.g. statistical power) and between studies, for consistency and biological plausibility, greater certainty and a correspondingly lower assessment factor is gained where greater numbers of data sets are available and experimental data is available for a longer experimental duration (giving a more realistic picture of effects during an organisms life cycle). This approach is succinctly summarised within the R.10 Guidance document (page 17) which states:

4.8.3 "The sparser the available data, the higher is the assessment factor which is applied".

4.8.4 Such an approach may also be suitable for nanomaterials, as when more information is available, greater certainty can be had in a predicted no effect concentration. One issue however that still remains is to what extent data on the bulk form can be considered when addressing the quality of the whole database for a nanomaterial. This raises an important question of to what extent are the bulk and nano-forms similar or different. As such, the use of bulk data for informing nano hazard assessment may be associated with additional uncertainty and should be scientifically justified. It may also be prudent that R&D is undertaken to assess the use of bulk data in assessing the quality of the whole database for nanomaterials. In addition we propose the following text addition to R.10 Guidance after the second sentence of the first paragraph of the section 'Assessment factor methods' (page 17)

4.8.5 *'In relation to nanomaterials where there is uncertainty due to the absence of available data, the use of read-across from available data on bulk or other forms of the material in place of specific data for the nanomaterials being assessed must be scientifically justified and may be associated with additional uncertainty.'*

4.8.6 In addition, the following changes are recommended:

4.8.7 R.10.5.2.1 Calculation of PNEC for freshwater sediment using equilibrium partitioning

4.8.8 The following text is recommended to be added to the first paragraph in R.10.5.2.1 (R.10, pg. 32), following the sentence ending "… coefficient as inputs (OECD, 1992b; Di Toro et al., 1991).":

4.8.9 *For some nanomaterials the Equilibrium Partitioning Method may not be applied provisionally for the calculation of PNEC for freshwater sediment as the method has limited applicability for very adsorptive compounds which do not enter equilibrium.*

4.8.10 R.10.5.3.1 Calculation of PNEC for marine sediment using Equilibrium Partitioning Method

4.8.11 The following text is recommended to be added as to the first paragraph in R. 10.5.3.1 (R.10, pg. 35), following the sentence ending "… provisionally be calculated using the equilibrium partitioning method ":

4.8.12 *For some nanomaterials the Equilibrium Partitioning Method may not be applied provisionally for the calculation of PNEC for marine sediment as the method has limited applicability for very adsorptive compounds which do not enter equilibrium.*

4.8.13 R.10.6.1 Calculations of PNEC for soil using equilibrium partitioning

4.8.14 The following text is recommended to be added as to the second paragraph in R. 10.6.1 (R.10, pg. 39), following the sentence ending "… through food (Van Gestel, 1992)":

4.8.15 *For some nanomaterials the Equilibrium Partitioning Method may not be applied for the calculation of PNEC for soil as the method has limited applicability for very adsorptive compounds which do not enter equilibrium.*

4.9 R.12 USE DESCRIPTOR SYSTEM

4.9.1 This guidance document provides a system of use descriptors to standardise the description of the use of substances. The use descriptor system is based on five separate descriptor-lists which in combination with each other form a brief description of use or an exposure scenario title.

4.9.2 The sector of use category (SU) describes in which sector of the economy the substance is used. The chemical product category (PC) describes in which types of chemical products (= substances as such or in mixtures) the substance is finally contained when it is supplied to end uses (by industrial, professional or consumer users). The process category (PROC) describes the application techniques or process types defined from the occupational perspective. The environmental release category (ERC) describes the broad conditions of use from the environmental perspective.

4.9.3 The article category (AC) describes the type of article into which the substance has eventually been processed.

4.9.4 The use descriptors will help suppliers and users to structure their communication with each other. They are intended to facilitate, the identification of uses to be provided in the registration dossiers, the building of an ES by suppliers, based on communication up and down the supply chain and the building of short titles for exposure scenarios.

4.9.5 **Considerations**

4.9.6 Technical issues described in the case studies under taken as part of Task B1 (further evaluated in task B4) are those which are most relevant to proposals for changes to R12. Specifically the case study providers used this guidance to support development of the exposure scenarios. In this respect they developed/ allocated SUs, PROCs and ERCs based on the guidance. Assessment of these is also based on the review of exposure studies carried out in task B3 (RNC/RIP-oN3/B3/2/FINAL).

4.9.7 The mapping between R.12 and the issues identified from exposure assessment aspects (RNC/RIP-oN3/B4/2/FINAL) is shown Appendix 2. This shows each of the scientific issues identified in that report and the preceding reports, by reference to the table in RNC/RIP-ON3/B4/2/FINAL, and maps that to the point in the guidance indicating i) where they are relevant, ii) where the guidance is adequate for nanomaterials as for substances in general and iii) where it has been considered necessary to recommend a change.

4.9.8 Examination of R12 indicates that for most of the document the guidance provided applies equally well to nanomaterials as for substances in general. As a general statement, the use descriptors can be applied to any substance depending on the physical nature of that substance.

4.9.9 Appendix R.12-1 provides a list of Sectors of Use (SU). All of the case study providers were able to allocate SUs in the development of the ES. No uniquely nano-specific SUs were identified in the case studies or in the review of the literature in task B3 (RNC/RIP-oN3/B3/2/FINAL).

4.9.10 Appendix R.12-2.1 provides a list of product categories (PC). The categories listed are meant to structure the market of a substance according to product types. PCs were not specifically addressed in the case studies. No uniquely

nano-specific PCs were identified the review of the literature in task B3 (RNC/RIP-oN3/B3/2/FINAL).

4.9.11 Appendix R.12-4.1 provides a list of environmental release categories (ERC). All of the case study providers were able to allocate ERCs in the development of the ES. No uniquely nano-specific ERCs were identified in the case studies or in the review of the literature in task B3 (RNC/RIP-oN3/B3/2/FINAL).

4.9.12 Appendix R.12-5.1 provides a list of article categories (AC). The categories listed are meant to structure the market of a substance according to product types. PCs were not specifically addressed in the case studies. No uniquely nano-specific PCs were identified the review of the literature in task B3 (RNC/RIP-oN3/B3/2/FINAL).

4.9.13 Appendix R.12-3.1 provides a list of process categories (PROC). All of the case study providers were able to allocate SUs in the development of the ES. No uniquely nano-specific SUs were identified in the case studies or in the review of the literature in task B3 (RNC/RIP-oN3/B3/2/FINAL).

4.9.14 In any case, the guidance states “This list is not complete with regard to uses potentially to be described under REACH. Describe other uses as appropriate” which allows considerable flexibility for the user to augment these lists as appropriate.

4.9.15 In addition to their description function, some of the descriptor-lists are intended to support identification of the suitable exposure estimation entries in one or more of the available Tier 1 exposure estimation tools (see Section D.5 in Guidance Chapter D). Please note, that this does not automatically mean that those Tier 1 tools can be applied. The efficacy and application of these models for estimating nanomaterials exposure and guidance recommendations arising from that are dealt with in the review and assessment of R.14, R.15, R.16.

4.9.16 This assessment of R.12 indicates that in this document guidance provided applies equally well to nanomaterials as for substances in general. There are therefore no recommendations for guidance amendments in relation to this document.

4.9.17 No additional requirements for change for this part of the guidance, beyond those already indicated, were identified from the evaluation of the hazard assessment (RNC/RIP-oN3/C3/2/FINAL).

4.9.18 *Research recommendations*

4.9.19 As this is a high level document which outlines the whole CSR process it does not in itself suggest any new requirements for research.

4.10 R.13 RISK MANAGEMENT MEASURES AND OPERATIONAL CONDITIONS INCLUDING THE RMM LIBRARY

4.10.1 Chapter R.13 provides supporting guidance on the most common types of use conditions having an impact on exposure. This includes an overview on operational conditions (OC) and risk management measures (RMM) related to exposure of workers (R.13.2.2), to consumers (R.13.2.3) and to the environment (R.13.2.4). Sections R.13.2.5 and R.13.2.6 provide guidance on how to address OC and RMMs related to the life cycle stages subsequent to manufacture and identified downstream and consumer uses: article service life and waste life stage. Each of these sections includes an overview on RMM and OC and guidance on how to use the RMM and the available Tier 1 tools for exposure estimation when carrying out iterations.

4.10.2 Section R.13.3 provides guidance on how the effectiveness of risk control measures can be taken into account. It does not present any information about the effectiveness of risk control measures. These are provided in the RMM library.[3] In Section R.13.4 the set-up of the RMM library is explained in more detail, and how to work with it.

4.10.3 **Considerations**

4.10.4 Technical issues described in RNC/RIP-ON/B2/2/FINAL (further evaluated in RNC/RIP-ON3/B4/2/FINAL) are those which are most relevant to proposals for changes to R13 and in the RMM library. Information obtained from case studies is also relevant.

[3] http://cefic.org/Industry-support/Implementing-reach/Libraries/

4.10.5 The mapping between part R13 and the issues identified from exposure assessment aspects (RNC/RIP-ON3/B4/2/FINAL) is shown Appendix 2. This identifies each of the scientific issues identified in that report and the preceding reports, by reference to the tables in RNC/RIP-ON3/B4/2/FINAL, and maps that to the point in the guidance indicating where they are relevant, where the guidance is adequate for nanomaterials as for substances in general and where it has been necessary to recommend a change.

4.10.6 Examination of R.13 indicates that for most of the document the guidance provided applies equally well to nanomaterials as for substances in general. For workers, general descriptions of the OC (duration and frequency, applied amount, temperature, containment and capacity of the surroundings) and RMM in R.13.2.2 are equally applicable. Similarly for consumers (R.13.2.3) the environment (R.13.2.4), substances and articles (R.13.2.4) and waste life stage (R.13.2.5). The examples in R13 of conversion from risk management library to iteration at tier 1 provided appear to be generally applicable (however the question of the validity of this and other models is described separately in the discussion of R.14). Statements which are already included e.g. *"Solid substances or preparations may be supplied as fine light powders (implies high dustiness)…"* (R.13.2.1) provide emphasis which would highlight the need to take to particular care with nanomaterials.

4.10.7 In R.13.3 general statements concerning the effectiveness of RMMs are applicable and emphasise the need to justify effectiveness values chosen, for example on page *20 "List all known, published RMM effectiveness values for the RMM in question, including specific conditions under which the effectiveness is established"*. The importance of substance properties is emphasised including for example the bullet point *"Influence of substance properties (p21)"*. In R.13.4 the aims, general description and categorisation are all equally applicable and do not require special adaptation. Again statements in these sections draw attention to the user of the need to take particular care about substance properties specifically (R.13.4.2.2).

4.10.8 In R.13.4.2.5, estimation and documentation of RMM effectiveness in the library, the guidance appears to be equally applicable. However there is an opportunity to further strengthen the consideration of nanomaterial properties

by insertion of an additional paragraph as paragraph 4 of this section. The recommended change is as follows;

4.10.9 Inset as paragraph 4 of R.13.4.2.5:

4.10.10 *Specifically in relation to nanomaterials, particle size can affect the performance of RMM and the effectiveness should not be assumed to be the same for nanomaterials as for substances in general, without justification.*

4.10.11 This generic point should be further supported with specific information in the RMM library. This is detailed in the next paragraphs.

4.10.12 The RMM library is an EXCEL spreadsheet that is 'made up' of three parts: The library containing RMMs / OCs and details of their effectiveness lists of information sources for consumers, environment and occupational measures; and a practical guide to use of the library

4.10.13 In terms of structure, the library is organised according to the occupational hygiene concept of 'hierarchy of control' as outlined in the Chemical Agents Directive. The reason for adopting this as the structural basis for the Library is that it allows for one library containing occupational, consumer and environmental measures, as well as also ensuring that occupational RMMs can still be selected according to the priority order governed by the 'hierarchy of control' concept. For consumer and environmental measures, the hierarchy is purely an organisational system for the RMMs.

4.10.14 Effectiveness of individual RMMs is quantified in the library in those cases where technical/scientific evidence is available. The following changes are recommended based on the analysis in RNC/RIP-ON3/B4/2/FINAL.

4.10.15 In relation to the RMM "Enclosure", this has been mostly observed as an RMM for synthesis processes. Evidence reported in RNC/RIP-ON3/B2/2/FINAL indicates that emissions to the workplace are substantially reduced if a process involving engineered nanomaterials is performed in a properly designed enclosure/containment. However this is not always the case. Emissions to the workplace have been reported which were subsequently attributed to a leak in the system and during activities such as product recovery and cleaning. From the RMM library, in relation to process

control, RMM W8.01 and W8.02 under the heading Automation and enclosure are most relevant. These have default values of H (High) which is still justified based on the evidence. The following change is recommended:

4.10.16 RMM library, Sheet Individual Measures, for W8.01 and W8.02 insert:

4.10.17 *For nanomaterials, evidence suggests that this RMM may not always be completely effective. Therefore for nanomaterials the effectiveness of this control approach should be directly assessed.*

4.10.18 In relation to the RMM "Respiratory protective equipment (RPE)", evidence reported in RNC/RIP-ON3/B2/2/FINAL generally supports that the performance of respiratory protective equipment (RPE) will be effective against nanomaterials in that the claimed protection factors are likely to be achieved or exceeded. This applies to both P3 and P2 respirators. There is no requirement to develop new types of filters. However use of a precautionary approach suggests that, to provide added protection, only the higher level respirators (P3) should be used. There are 33 unique RMM measures related to RPE numbered W30.2 to W30.34. The following changes are recommended to be added in the "remarks" column, referring to these devices which offer lower protection than P3:

4.10.19 RMM library, Sheet Individual Measures, for W30.03, W30.04, W30.06, W30.07 insert:

4.10.20 *Not suitable for use with nanomaterials. Respirators of this grade are likely to be technically effective against nanomaterials. However, a precautionary approach would suggest a higher level of protection.*

4.10.21 In relation to the RMMs "Hand Protection" and "Body Protection" Some evidence reported by the European project NANOSAFE2 suggests that nanoparticles can penetrate through cotton fabrics and other commercially available gloves and recommends that two layers of gloves (double gloving) are worn. The following changes are recommended to be added in the "remarks" column;

4.10.22 RMM library, Sheet Individual Measures for CW29.01 insert:

4.10.23 *Users should consider the use of double gloving provided that this in itself does not cause further problems such as manual dexterity issues. Cotton gloves and other woven materials are not suitable for use with nanomaterials.*

4.10.24 In addition, insert reference to the publication NANOSAFE (2008) into RMM library, Sheet Occupational References.

4.10.25 RMM library, Sheet Individual Measures for W28.03, W28.04 insert:

4.10.26 *Suits manufactured from cotton or other woven fabrics are not suitable for use with nanomaterials.*

4.10.27 In addition, insert reference to the publication NANOSAFE (2008) into RMM library, Sheet Occupational References.

4.10.28 In relation to the RMM “Health Surveillance”, there is no specific requirement for this to be used for nanomaterials. To provide the latest information the following change is recommended:

4.10.29 Insert reference to the publication Schulte et al (2008) into RMM library, Sheet Occupational References.

4.10.30 There are a number of other RMM (e.g. ventilation) where there is evidence that the RMM can effectively be used for nanomaterials. One option considered was that in these circumstances a note could be added to specifically identify this. However, this would appear to be a departure from process with other materials since positive affirmations do not generally seem to be used. Therefore, this option is not recommended.

4.10.31 No additional requirements for change in this part of the guidance, beyond those already indicated, were identified from the evaluation of the hazard assessment (RNC/RIP-oN3/C3/2/FINAL).

4.10.32 *Research recommendations*

4.10.33 There are several research needs that have been identified for RMM and OC. Two types of research are envisaged. The first is the assessment of the effectiveness of a whole range of risk management measures needs to be established for use with different types of nanomaterials. In relation to this,

the type of research envisaged includes both development and elaboration of underlying theoretical aspects and the collection of practical measurement data on the effectiveness of RMM as implemented in industrial settings, and on a laboratory or simulation based type of study. In particular more information is required on RMMs such as enclosure, LEV, and the effectiveness of dermal protective equipment. Also in relation to exposure by inhalation (in an industrial setting) tests of the effectiveness of face seal leakage would be appropriate. Secondly, there needs to be collection of fundamental information about how RMM and OC are actually implemented through industrial practice.

4.10.34 For consumer exposure, there is almost no published information on the efficacy of any of the consumer RMMs for substances containing nanomaterials.

4.10.35 In relation to environmental exposure more information is required on the effectiveness of prevention of release to air, and to water, and in relation to release to soil.

4.10.36 From knowledge of the research programmes currently underway very little of it is focussed on to these aspects. It is not anticipated that there is likely to be much in the way of significant publications in the next eighteen months or so.

4.11 R.14 OCCUPATIONAL EXPOSURE ESTIMATION

4.11.1 This chapter provides support for estimating occupational exposures dealing both with measurements and modelling approaches. It describes what information is needed for the assessment at different levels (Tiers) and how to deal with it. The first tier exposure estimations are meant to be conservative and may well be above actual exposure levels.

4.11.2 Information is given to support collection of exposure information for establishing the final exposure scenarios (ES), the information needs for different tiers and estimation or calculation of exposures.

4.11.3 Considerations

4.11.4 Technical issues described in RNC/RIP-ON/B3/2/FINAL (and further evaluated in RNC/RIP-ON3/B4/2/FINAL) are those which are most relevant to

proposals for changes to R14. Information obtained from the case studies (RNC/RIP-ON3/B1/2/FINAL) is also relevant.

4.11.5 The mapping between R.14 and the issues identified from exposure assessment aspects (RNC/RIP-ON3/B4/2/FINAL) is shown Appendix 2. This identifies each of the scientific issues identified in that report and the preceding reports, by reference to the tables in RNC/RIP-ON3/B4/2/FINAL, and maps that to the point in the guidance indicating where they are relevant, where the guidance is adequate for nanomaterials as for substances in general, and where it has been necessary to recommend a change.

4.11.6 Examination of R.14 indicates that much of the guidance that the document provides applies equally well to nanomaterials as for substances in general. However there are opportunities to improve the specificity of the guidance in a number of areas.

4.11.7 In R.14.2 types and routes of exposure are described. Information is provided at a high level. Most of the information provided is equally relevant for nanomaterials as for substances in general. There are three short paragraphs describing inhalation exposure (again at a fairly general level). Metrics are discussed to the extent that an example is provided of the measurement of inhalation exposure as the amount per unit of air volume inhaled with the example given of mg/m^3. The recommended change is as follows:

4.11.8 Insert as the last paragraph of R.14.2 – Inhalation exposure:

4.11.9 *Inhalation exposure can be described by the concentration of the substance in air and the duration and frequency of exposure. It is generally expressed in ppm (parts per million) or amount per unit air volume inhaled, averaged over the duration of the relevant task or shift (e.g. mg/m^3 8hr Time Weighted Average (TWA)). For measurement of exposure to nanomaterials information in relation to number concentration* (especially *for fibres) and surface area concentration are also considered to be of benefit (i.e. n/m^3 or cm^2/m^3).*

4.11.10 The paragraphs on dermal exposure and oral exposure in this section are suitably general and no specific changes are recommended to these.

4.11.11 Section R.14.4 provides more detailed information on exposure estimation for both measurements and modelling approaches. In relation to measurement approaches R.14.4.1 to R.14.4.6 are the sections where most of the information in relation to collection of measurements is provided. However these sections provide little in the way of technical guidance as to how measurements should be made or used. As such it may be questionable as to whether there should be further information of that type included in this chapter. In seeking to make guidance amendments we have tried where possible to make the recommended changes consistent with the style and level of detail provided in the relevant chapters. This has not always been possible however. In these chapters additional recommendations are made which are at a level of detail beyond that which is currently in the guidance. An alternative to making these changes at this point in the guidance would be to make changes in R.7 as originally recommended in RNC/RIP-ON3/B4/2/FINAL. This could be still considered as a separate option.

4.11.12 The first change relates to providing encouragement towards the use of simulations in the estimation of exposure levels as recommended in RNC/RIP-ON3/B4/2/FINAL.

4.11.13 Insert as replacement in R.14.4.1 (page 5):

4.11.14 *For estimation of exposure the following preferential hierarchy should be applied to exposure data for estimation of exposure level:*

- *Measure data including the quantification of key exposure determinants;*
- *Appropriate analogous data, (<u>including data derived from simulations</u>) including the quantification of key exposure determinants;*
- *Modelled estimates.*

4.11.15 In addition, added as a footnote:

4.11.16 *As an example of simulation studies, Gohler et al. (2010) measured emissions from a sanding simulation using polyurethane coating and architectural paint containing two types of nanoparticles. During the abrasion tests, no significant difference was detected between the number concentrations of released particles of the pure*

coatings and of the coatings that were dosed with additives. However, larger particles containing nanoparticles were observed.

4.11.17 A further change in relation to this issue is in Table R.14.1 under the heading Data Characteristics.

4.11.18 Insert in Table R.14.1; workplace exposure assessment rating criteria, in the column data characteristics, in the cell medium quality data an additional bullet point which states:

4.11.19 *Data derived from simulations which mimic the task or activity under controlled conditions.*

4.11.20 Section R.14.4.3 is quite generic.

4.11.21 In Section R.14.4.4 a similar point is recommended to draw the attention to the user of the potential for simulation studies. The recommended change is to insert at R.14.4.4, bottom of page 8 as the third bullet:

4.11.22 *simulation studies replicating the task or activity of concern*

4.11.23 Otherwise this section is applicable. It is noted that the statement is made that particle sizes of produced solid and dustiness and practical use is not very well related. This is consistent with the limited evidence available for nanomaterials.

4.11.24 In Section 14.4.5, selection and interpretation of measured data it is proposed to insert a paragraph drawing attention to the technical issues relating to the measurement of nanomaterials and to provide linkage to further guidance on this issue the recommended change is as follows:

4.11.25 *Measurement of exposure to nanomaterials provides particular challenges. These have been highlighted in several publications (e.g. Brouwer 2009, 2010). They include discrimination from background particles, collection and analysis of size information, effective high spatial and temporal variability, choice of metrics and measurement instruments, and measurement of high aspect ratio nanomaterials. The state of knowledge on these issues is continuing to develop. Further information on current approaches is provided in BSI 6699/3 (2010), OECD (2009) and in Annex R.14.X*

4.11.26 In addition, as indicated above, it is recommended that an appendix is added R.14 which with the title "*Considerations in relation to measurement of exposure to nanomaterials*". Rather than a method statement, this is a discursive document which outlines the main issues to be considered. Technically such an appendix does not fit within the current shape of the guidance at this point. However in relation to the guidance chapters intended to be reviewed and assessed as part of RIP-oN 3, this provides probably the most appropriate place. This document broadly is a digest of the information contained in Chapter 3.5 of this current report. The proposed content of this appendix is added as an appendix to the current report being the same title (Appendix 3).

4.11.27 In order to ensure that this is fully visible to the user, this Appendix should also be added to the guidance document R.7. The rationale for adding it into R.7 is that this is the only guidance document in which any information regarding particle measurement is provided (R.7.1.14). Although R.7.1.14 primarily refers to granulometry it also contains references for example to inhalable and respirable sampling. The issue of whether this appendix should be added and the specific location of where it best fits within the guidance document is a point for discussion with the SCG.

4.11.28 Information provided on dermal data, biological monitoring and uncertainty and statistics in this section are equally applicable to nanomaterials as for other materials. In Section R.14.4.6 the acute exposure is equally applicable to nanomaterials as for substances in general.

4.11.29 Sections R.14.4.7 to R.14.4.9 deal with the use of (first tier) exposure estimation tools as previously discussed in reports RNC/RIP-ON/B3/2/FINAL, RNC/RIP-ON3/B4/2/FINAL. There have been only limited attempts at the validation of models for assessment of exposure to nanomaterials and such attempts at validation have generally not provided confidence in the accuracy of modelled estimates. However, within the current REACH guidance there is already in relation to use of these models, acknowledgement of the limitations in the validation. For example in R.14.4.7 there is a statement *"while limited comparisons of tool predicted exposure with available data show a reasonable correlation for the tools. Nevertheless there is room for*

improvement. This is especially the case for inhalation exposure to particles or aerosols which is more complicated to model and predict. Moreover particulates have not been investigated as much as volatiles, leading to a more uncertain prediction of exposure, including potential underestimation of worst case exposure concentrations for particular activities (or process categories)".

4.11.30 It is appropriate at this point to introduce a further caveat to alert the user to the limitations of the usefulness of exposure estimation tools for nanomaterials. However it is not possible to make a positive statement as to how these could be improved, or how the user should proceed. Therefore the recommended change is as follows:

4.11.31 Insert as paragraph 4 of R14.4.7:

4.11.32 *Please note that this tool has not yet been validated for use with nanomaterials. If the output of the model is used to estimate exposure for NMs, this should preferably be supported by measured data. There should be a clear description in the CSR of the uncertainties associated with the estimated values and the consequences for the risk characterisation.*

4.11.33 No additional requirements for change for this part of the guidance, beyond those already indicated, were identified from the evaluation of the hazard assessment (RNC/RIP-oN3/C3/2/FINAL).

4.11.34 *Research recommendations*

4.11.35 There are a number of potential research needs which have been identified through this review.

4.11.36 There is a need for development of improved measurement tools for assessment of exposure to nanomaterials. These would include tools which give the possibility of multi-metric approaches. Linked to this issue is the need for development of a personal sampler. There are already a number of activities in this direction, including the European project NANODEVICE and a range of commercial initiatives some of which have been identified in RNC/RIP-ON/B3/2/FINAL. There is some evidence to suggest that some

improved methods will be available over the next two year period, however whether they will result in a personal device remains to be seen.

4.11.37 Improved methods and approaches for discrimination from background nano aerosols are required. These could take the form of measurement or analytical solutions or improved validated strategic approaches (experimental design approaches) which would enable discrimination to be more clearly demonstrated and achieved.

4.11.38 Overall there is a need for a much improved sampling strategy to be implemented to take account of the multiple needs and the issues which have been identified. In the context of REACH, the development of a strategy specifically for REACH compliance issues is necessary. Currently available strategies are not focussed on this end point. The strategy would enable (in the absence of personal sampling devices) estimation of personal exposure to nanomaterials to be developed from a range of experimental measurements and techniques by implementing and using the instrumentation already shown to be available and new instrumentation emerging.

4.11.39 There is also a need to collect the evidential base about the potential for release from a whole range of types of activities and processes. This would include measurements made in actual industrial scenarios but also laboratory based simulation experiments would provide the basis for more rapid gathering of data and information. Further development of such simulations should be considered to be a high priority. Within the collection of this data there is also a need to more effectively share this information. This would include the publication of additional contextual data along with actual quantitative measurement data.

4.11.40 Collection of available evidential data concerning release and exposure is necessary. These would include quantification and characterisation of the release in terms of the various metrics discussed, composition, and particle size distribution and how these varied in time and in different environments/media. This data would enable much more extensive validation of models to be carried out if required and, based on these validation exercises, new model approaches could be developed. One promising

approach is that of the Advanced REACH Tool (ART) model, referred to in RNC/RIP-oN3/B3/2/FINAL.

4.11.41 Information on who is exposed to what in which scenarios would also be desirable. This would be an important preliminary activity towards the development of understanding of the links between exposure and health effects, and as a complementary activity to medical surveillance.

4.11.42 Most of the published data reported in RNC/RIP-oN3/B3/2/FINAL was for synthesis/manufacturing processes. There is a clear need for more information to be gathered from other points of the life cycle. For example, uniform release of nanomaterials during the use of products containing nanomaterials (e.g. spraying and subsequent maintenance of paints and coatings, nano-impregnated textiles wear & tear) is currently almost completely absent from the literature. Other examples would include occupational exposure to emissions in waste management in recycling, landfills and incineration.

4.12 R.15 CONSUMER EXPOSURE ESTIMATION

4.12.1 This chapter describes a step-wise and iterative procedure for the estimation of consumer exposure to substances on their own, in preparations or in articles. It consists of the following sections:

- Workflow for consumer exposure assessment (Section R.15.1.2)
- General considerations related to assessment of consumer exposure (Section R.15.2)
- Calculation of consumer exposure at Tier 1 level (Section R.15.3)
- Tools for supporting exposure scenario building at Tier 1 level (Section R.15.4 and Section R.15.5),
- Higher tier models and measured data (Section R.15.6),
- Risk characterisation (Section R.15.7),
- Overview on information sources and available tools (Section R.15.6 and Appendices R.15-3, R.15-4 and R.15-5

4.12.2 The document describes how consumer exposure estimation can be performed by a tiered assessment, beginning with a screening estimation (Tier 1). If the result of the screening is that exposure is below the accepted

thresholds then there is “no concern” and the risks of the product can be considered to be controlled. Most of the document is concerned with the calculation of exposure (R.15.3 onwards). It is noted in the document that “consumer exposure estimation is often difficult due to limited data availability”.

4.12.3 **Considerations**

4.12.4 Technical issues described relating to choice of metrics (RNC/RIP-ON3/B3/2/FINAL, RNC/RIP-ON3/B4/2/FINAL), Exposure modelling (RNC/RIP-ON3/B3/2/FINAL, RNC/RIP-ON3/B4/2/FINAL) and consumer RMM (RNC/RIP-ON3/B2/2/FINAL, RNC/RIP-ON3/B4/2/FINAL) are those which are most relevant to this document.

4.12.5 The mapping between R.15 and the issues identified from exposure assessment aspects (RNC/RIP-ON3/B4/2/FINAL) is shown in Appendix 2. This identifies each of the scientific issues identified in that report and the preceding reports, by reference to the table in RNC/RIP-ON3/B4/2/FINAL, and maps that to the point in the guidance indicating where they are relevant, where the guidance is adequate for nanomaterials as for substances in general and where it has been necessary to recommend a change.

4.12.6 Analysis of R.15 indicates that for most of the document the guidance provided applies equally well to nanomaterials as for substances in general. R.15.1 is a generic introduction and description of the process, which applies equally well to nanomaterials. R.15.2.1 describes the scope of the consumer exposure estimation. This includes both articles that can be purchased from retail outlets by members of the general public and exposure as a result of being near where a substance is being used or has been used. R.15.2.2 describes reasonable worst-case situations. Again these sections are generic and apply equally well to nanomaterials as for other types of substances.

4.12.7 In R.15.2.3 routes of exposure (inhalation, dermal, oral) are described with some inconsistency in the way the metrics (all based on mass) are described. For example mg/m^3 is given as an example in relation to inhalation an stated as an absolute in relation to dermal exposure (mg/cm^2 (or as external dose,

mg/kg body weight/day). To clarify this and to include the possibility the following update to Guidance is recommended:

4.12.8 Insert as the last paragraph of R.15.2.3 – Inhalation exposure:

4.12.9 *Inhalation exposure is expressed in terms of external exposure, as a concentration, usually as mg/m^3. For measurement of exposure to nanomaterials information in relation to number concentration* (especially *for fibres) and surface area concentration are also considered to be of benefit (i.e. n/m^3 or cm^2/m^3).*

4.12.10 In relation to dermal exposure and oral exposure, no clear recommendations about alternative metrics were able to be made in the Task D document. Therefore, current guidance which suggests expressing dermal exposure in terms of mass per surface area or mass per body weight is adequate for dermal exposure to nanomaterials. Similarly for oral exposure mass per body weight per day seems appropriate.

4.12.11 Information provided in R.15.2.4, R.15.2.5 and R.15.2.6 is equally applicable to nanomaterials as to substances in general. In R.15.2.7, reference is made to the potential of the emission by mechanical abrasion, indicating that this should be considered. Also in this section, it is noted that effective risk management measures for consumer are usually product integrated measures. The limitations in relation to consumer instructions and personal protective equipment are noted. In these sections the information provided is equally applicable nanomaterials as for substances in general, no special provisions are required and no recommendations for change are made.

4.12.12 Section 15.3 is concerned with calculation of exposure and refers to the use of Tier 1 tools. This section describes the algorithms used in these tools referring to further discussion regarding the tools in section R.15.4 and R.15.5. The applicability of these tools was assessed as part of the Nanex project and was discussed in RNC/RIP-oN3/B2/2/FINAL and RNC/RIP-ON3/B4/2/FINAL. The conclusions from the Nanex project was that there were limitations in the applicability of these two models for estimation of consumer exposure by inhalation and estimates should only be used with care. Therefore the following guidance update is proposed:

4.12.13 Insert at the end of the first paragraph in R.15.3.1:

4.12.14 *Please note that this tool has not yet been validated for use with nanomaterials. If the output of the model is used to estimate exposure for NMs, this should preferably be supported by measured data. There should be a clear description in the CSR of the uncertainties associated with the estimated values and the consequences for the risk characterisation.*

4.12.15 Modify the paragraph beginning *"When the inhalable and or respirable fraction is known"* as follows:

4.12.16 *When the inhalable and or respirable fraction is known it should be taken into account. If the product contains releasable nanomaterials then the assumption should be made that it is entirely within the respirable fraction if not otherwise known.*

4.12.17 From the Nanex project (NANEX 2011) it is concluded that the models for estimating consumer exposure by the dermal route might be used (if the use pattern can be considered to be the same) as the underlying equations do not appear to rely on nano specific properties and would not need to be changed to address such properties. On this basis no further recommendations in relation to the dermal or oral models are made at this time.

4.12.18 No additional requirements for change for this part of the guidance, beyond those already indicated, were identified from the evaluation of the hazard assessment (RNC/RIP-oN3/C3/2/FINAL).

4.12.19 *Research Recommendations*

4.12.20 Substantial additional work requires to be done in order to validate the models for use with nanomaterials. Therefore research would require to assess, possibly through the use of simulations, actual exposures resulting from a range of types of products, e.g. paints and coatings, textiles, cleaning products etc. for which there may be nanomaterial based applications. Generation of exposure data using these is a priority. Based on the establishment of such a data set, appropriate validation of the models could take place. Based on the outcomes of such validation, the need to develop further more detailed models may be appropriate. On this basis consideration,

particularly for inhalation exposure, should be given to whether or not it is necessary to develop models for which other exposure metrics may be estimated e.g. number concentration or surface area concentration.

4.12.21 The use of modelling approaches particularly in relation to consumer exposure is extensive and therefore full validation of the models used should be considered a priority research need.

4.13 R.16 ENVIRONMENTAL EXPOSURE ESTIMATION

4.13.1 This chapter provides guidance on how to estimate environmental exposure. It deals with estimation of the releases to air, water (either wastewater and/or surface water), and soil at local and regional scale, fate and distribution of the releases in environmental compartments (air, soil, surface water, sediment, biota) and sewage treatment plants and calculation of exposure concentrations in environmental compartments and man via the environment.

4.13.2 Considerations

4.13.3 The mapping between R.16 and the issues identified from exposure assessment aspects (RNC/RIP-ON3/B4/2/FINAL) is shown in Appendix 2. This identifies each of the scientific issues identified in that report and the preceding reports, by reference to the table in RNC/RIP-ON3/B4/2/FINAL, and maps that to the point in the guidance indicating where they are relevant, where the guidance is adequate for nanomaterials as for substances in general and where it has been necessary to recommend a change.

4.13.4 Only a limited number of studies are available in regard to fate and behaviour of nanomaterials such C_{60}, CNT and nano-metals and nano-metal-oxides, but consistent findings are that behaviour of nanomaterials in the environment is dependent on type, form and physico-chemical characteristics of the nanomaterial in question, as well as those of the receiving environment (Stone et al. 2009). Nanomaterial transport and distribution are influenced by a number of factors, such as Brownian diffusion, inertia effects, gravitational influences, thermal influences, pH, ionisation, and presence/absence of Natural Organic Matter (NOM). These interactions ultimately affect the processes the nanomaterial consequently undergoes in its transport and subsequent fate (Stone et al. 2009).

4.13.5 As noted by Stone et al. (2009) traditional predictions of fate and transport are based on inherent properties such as phase transfer properties (e.g. boiling point, vapour pressure, partition coefficients), reactivity (e.g. photo-reactivity and hydrolysis) and biological degradation behaviour (Mackay and Hendry, 2009).

4.13.6 Many of these inherent properties are reported on for regular chemicals under REACH or can be derived via information about the octanol-water partition coefficient and vapour pressure of the substances. However, we know at this point that these properties are not adequate to understand and predict the fate and behaviour of nanomaterials (Stone et al, 2009). This is further complicated by our current lack of understanding of the novel physico-chemical properties exhibited by many nanomaterials and the effect these have on particle behaviour. In addition, it is most likely that those nanomaterials released into the environment will also exist as modified forms of their primary counterpart (SCENIHR, 2009).

4.13.7 While there is information available on models nanoparticle transportation, aggregation and deposition available in the literature deriving primarily from the colloid literature, this is either theoretical and/or based on idealised relatively simple model systems (e.g. Weisner and Bottero 2007). The models have not been adapted for the large number of components present in natural water which may include salts, clays, micro-organisms, natural organic matter and other colloidal materials (Mylon et al 2004). At present these are not appropriate for use in a regulatory context.

4.13.8 It is clearly conceivable that fugitive emission from processes in which nanomaterials are produced, could potentially lead to increased air concentration of these nanomaterials. As well as environmental exposure in these circumstances, it is possible that the general public, as well as the environment, would become exposed.

4.13.9 Some attempts at modelling environmental exposure have been carried out, most notably by Boxall et al. (2007) and by Mueller and Nowack (2008), based on a substance flow analysis from products to air, soil, and water using model inputs such as: estimated worldwide production volume, allocation of

the production volume to product categories, particle release from products, and flow coefficients within the environmental compartments.

4.13.10 In relation to the guidance it follows that the partitioning and degradation behaviour which are based on models which rely on molecular weight, water solubility, vapour pressure, octanol-water partition coefficient and information on ready biodegradability for the substance cannot be relied on. These models include the use of a number of partitioning coefficients (air-water, soil-water, water-sediment, suspended matter-water, etc.), Henry's laws constant, vapour pressure and water solubility of the substances (R.16.5). Based on current understanding, it is not possible to provide validated adaptations or alternative to these models for nanomaterials. The following change is recommended.

4.13.11 Insert at R.16.5 as a last paragraph in the introductory section:

4.13.12 *There are significant limitations in the applicability of any of the environmental fate models (e.g. fugacity models for various compartments and overarching models like EUSES) which depend on LogKow and Henry's law for use with insoluble nanomaterials (and other insoluble particles or substances). As no broadly accepted and scientifically valid models are available for estimating environmental fate of nanomaterials, M/Is are advised to collect measurement information on environmental release and content in the environment where possible.*

4.13.13 Other than for these aspects it seems that the provisions of R.16 apply as well for nanomaterials as for substances in general assuming that mass (kg/day) is the proper metric to describe the release rate (kg/day) to the environmental compartments (R.16.3.2.1).

4.13.14 *Research recommendations - environment*

4.13.15 Much more work is required to assess the potential emissions to the environment relevant to nanomaterials. This would include the development of methods for measuring the release of nanomaterials in waste streams on the emissions from various processes as well as quantifications of these releases for a wide range of material and process types. As part of this,

"characterisation" of *what* is released is of key importance. This should be considered a high priority for research. This applies both to release and exposure for humans and for the environment. Based on the collection and assembly of such data the efficacy of the various models could be assessed and where appropriate, further adjusted.

4.13.16 There is a fundamental need for an analytical method capable of verifying the actual exposure concentration in the soil and over time. There is also a need to develop an analytical method to verify nanomaterial concentrations, aggregations/agglomeration behaviour and stability of nanomaterials in soil.

4.14 R.17 EXPOSURE ASSESSMENT OF SUBSTANCES IN ARTICLES

4.14.1 R.17 describes how to assess exposure to man and the environment from substances in articles. Substances in articles can be assessed as part of the life cycle stage of a substance, as part of a registration for substances in case where substances in the articles are intended to be released further details are available in the document guidance for articles. In general the applicable life cycle stages are “use” and “service life” e.g. wear and tear and maintenance of textiles. The document provides general considerations for exposure estimation and information relating to developing estimates for inhalation dermal ingestion and migration based primarily on tier one models. There is some encouragement towards the use of measured data if available in R.17.2.

4.14.2 Considerations

4.14.3 Technical issues described relating to choice of metrics (RNC/RIP-ON3/B3/2/FINAL, RNC/RIP-ON3/B4/2/FINAL) exposure modelling (RNC/RIP-ON3/B3/2/FINAL, RNC/RIP-ON3/B4/2/FINAL) are those which are most relevant to this document.

4.14.4 The mapping between R.17 and the issues identified from exposure assessment aspects (RNC/RIP-ON3/B4/2/FINAL) is shown Appendix 2. This identifies each of the scientific issues identified in that report and the preceding reports, by reference to the tables in RNC/RIP-ON3/B4/2/FINAL, and maps that to the point in the guidance indicating where they are relevant,

where the guidance is adequate for nanomaterials as for substances in general and where it has been necessary to recommend a change.

4.14.5 For most of the document the guidance provided applies equally well to nanomaterials as for substances in general. The main concern however would be the limited applicability of the models used (or rather limited validation of the models used) particularly in relation to inhalation. As noted in previous sections a statement should be added indicating this to the guidance. The following is recommended:

4.14.6 Insert at the end of paragraph 1 of R.17.2:

4.14.7 *Please note that this tool has not been validated for use with nanomaterials. If the output of the model is used to estimate exposure for NMs, this should preferably be supported by measured data. There should be a clear description in the CSR of the uncertainties associated with the estimated values and the consequences for the risk characterisation.*

4.14.8 Section R.17.4 considers release and exposure estimation for the environment. Provisions in this section appear to be equally applicable to nanomaterials or articles containing nanomaterials as for other types of substances. Almost no data is available by which the models for estimation of emissions can be tested. Although a few studies have been reported the results are not yet generalisable. It may be useful to give some encouragement to users to measure actual emissions by providing some indicators to these studies. However the current state of development of these studies does not provide the basis for guidance recommendations. In any case there is no indication from these studies that the worst case assumptions provided by the model would be insufficiently conservative. All of the models consider only release in mass terms. It is appropriate therefore to add a cautionary caveat:

4.14.9 Insert in Section R.17.4.1 and R.17-1:

4.14.10 *Please note that this tool has not been validated for use with nanomaterials. As such any estimates obtained from these models should be scientifically justified. Consideration should be given to the use of simulation studies to*

generate additional data on emissions. If the output of the model is used to estimate exposure for NMs, this should preferably be supported by measured data. There should be a clear description in the CSR of the uncertainties associated with the estimated values and the consequences for the risk characterisation.

4.14.11 No additional requirements for change for this part of the guidance, beyond those already indicated, were identified from the evaluation of the hazard assessment (RNC/RIP-oN3/C3/2/FINAL).

4.14.12 *Research Recommendations*

4.14.13 Much more work is required to assess the potential emissions from articles which contain nanomaterials or are coated with nanomaterials. This would include the use of simulation type studies (in practice simulation studies are probably the only way by which useful data can be obtained). Based on the collection and assembly of such data the efficacy of the release models could be validated. As part of this, "characterisation" of *what* is released is of key importance. This should be considered a high priority for research. This applies both to release and exposure for humans and for the environment.

4.15 R.18 EXPOSURE ASSESSMENT FOR THE WASTE LIFE STAGE

4.15.1 R.18 aims to illustrate and exemplify how exposure scenarios for the waste life stage may be defined. Based on that, the chapter outlines the basic workflow and methodology how Tier 1 emission estimates can be derived. It also explains the basic approach of how to handle the interface between the REACH regime and the waste regime in practical terms. Guidance on the legal status of substances in recycling streams is not provided.

4.15.2 Considerations

4.15.3 Technical issues described in RNC/RIP-ON/B3/2/FINAL (and further evaluated in RNC/RIP-ON3/B4/2/FINAL) are those which are most relevant to proposals for changes to R.18. Information obtained from the case studies (RNC/RIP-ON3/B1/2/FINAL) is also relevant.

4.15.4 The mapping between R.18 and the issues identified from exposure assessment aspects (RNC/RIP-ON3/B4/2/FINAL) is shown Appendix 2. This

identifies each of the scientific issues identified in that report and the preceding reports, by reference to the tables in RNC/RIP-ON3/B4/2/FINAL, and maps that to the point in the guidance indicating where they are relevant, where the guidance is adequate for nanomaterials as for substances in general and where it has been necessary to recommend a change.

4.15.5 Examination of R.18 indicates that much of the guidance which the document provides applies equally well to nanomaterials as for substances in general.

4.15.6 R.18.2 describes the types waste streams may be generated at each stage in the supply chain, and indicates the type of information the M/I is required to collect on operational conditions of waste generation and existing/suitable waste management routes

4.15.7 These are quite generic and may be applied to any substance. Units are not discussed but the assumption is that they will usually be expected to be expressed in mass terms.

4.15.8 R.18.3 describes the waste operations recovery and disposal. R.18.4 describes the general workflow in M/I's assessment related to waste stage. R.18.5 describes Tier 1 emission estimation and includes discussion on pre-sets for the emission pattern in time and space, examples for treatment pre-sets and other waste operations. Assumptions made appear to be quite conservative.

4.15.9 Sources of possible information for environmental release for 14 widely applied waste treatment techniques.

4.15.10 Everything is considered in mass terms.

4.15.11 There is very little information in the public domain regarding environmental release. There is certainly not enough which could be used to provide better estimates of release or to challenge the assumptions.

4.15.12 The following caveat is recommended at the end of section 18.5.2 similar to the approach taken with other modelling.

4.15.13 *Please note that this approach has not been validated for use with nanomaterials. As such any estimates obtained from this approach should be*

scientifically justified. Consideration should be given to the use of simulation studies to generate additional data on emissions. If the output is used to estimate exposure for NMs, this should preferably be supported by measured data, including the consideration of the most appropriate metric. There should be a clear description in the CSR of the uncertainties associated with the estimated values and the consequences for the risk characterisation.

4.15.14 *Research recommendations*

4.15.15 Much more work is required to assess the potential emissions from waste disposal processes relevant to nanomaterials. This would include the development of methods for measuring the release of nanomaterials in waste streams on the emissions from various treatment processes as well as quantifications of these releases for a wide range of material types. This would include the use of simulation type studies (in practice simulation studies are probably the only way by which useful data can be obtained). Based on the collection and assembly of such data the efficacy of the Tier 1 models cold be assessed could be validated. As part of this, "characterisation" of *what* is released is of key importance. This should be considered a high priority for research.

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6 APPENDIX 1 – ADDITIONAL ANALYSIS OF THE ES CASE STUDIES

6.1 The case studies were intended to provide an assessment of the effectiveness of the ES guidance, including the ES format. The studies were planned and developed prior to the publication of the Version 2 document in May 2010. However the study team had access to an earlier draft of that document and it was that which was used as the basis of the ES case study work. The case studies are described in detail in RNC/RIP-oN3/B1/2/FINAL. In this section the general learnings from the case study in relation to the ES format have been assessed. Exposure scenarios were built by the volunteer companies with support of experts and with greater knowledge of nanomaterials issues. The assessment of the exposure scenario format is now presented. The scenarios which were built related almost exclusively to uses of substance by workers and it is to that aspect that most of the comments are addressed. The ES template used was almost identical to that provided on page 8 of the May 2010 document Exposure Scenario Format. For ease of understanding in relation to the current version, comments are arranged according to that format rather than to the format which was used to collect the comments. Comments are arranged according to the main headings in that scenario format.

6.2 *Title of exposure scenario No. x*

6.3 No problems were identified with this section. All of the case studies identified appropriate ERCs, PROCs and SUs as required. Additional comments were used in some of the case studies to further expand the descriptions. No significant issues identified. No recommendations for change.

6.4 *Exposure Scenario*

6.5 *Contributing Scenario (1) Controlling Environmental Exposure For*

6.6 Initially there was some confusion in relation to the naming of this but it became clear that the name here needed to refer to the whole process that

was being considered. This is not particularly clear from the guidance, however but it is certainly not a nano issue.

6.7 *Product Characteristics*

6.8 Most of the products were identified as some form of powder. Information was also provided in this stage for example about packaging or the composition of the material. No difficulties were experienced, guidance applies equally to nanomaterials as for substances in general. However, it is important that the ES should relate to the specific nanoform and this should be explicitly mentioned in the ES. This should be reflected in the guidance..

6.9 *Amounts Used*

6.10 The providers were able to provide information on the amounts used on both a daily or annual basis. Amounts used ranged from a few kilograms to hundreds of tonnes per year. No difficulties were experienced, guidance applies equally to nanomaterials as for substances in general, no recommendations on this issue.

6.11 *Frequency and Duration of Use*

6.12 Case study providers were all able to provide this information. No difficulties were experienced, guidance applies equally to nanomaterials as for substances in general, no recommendations on this issue.

6.13 *Environmental Factors not Influenced by Risk Management*

6.14 Here the sub information is “flow rate of receiving surface water”. Only two of the case studies completed this, the other two considered it was not relevant since no water was used in relation to the process, and there was no discharge. No difficulties were experienced, guidance applies equally to nanomaterials as for substances in general, no recommendations on this issue.

6.15 *Other given Operational Conditions affecting Environmental Exposure*

6.16 The case study providers gave a variety of responses to this ranging from a simple statement of “indoor use”, “closed and dry process” to statements

which gave much more detailed information about the actual process. Although there was some confusion initially about what needed to be stated here, this was not related to any aspect of the nanomaterial. No specific issues relating to the nanomaterials were identified, and no recommendations are being made in relation to this.

6.17 *Technical Conditions and Measures at Process Level (a source to prevent release)*

6.18 Providers did not produce a great deal on information here. Statements ranged from "full containment" to more detailed explanations of why containment was considered to be effective. One of the cases provided statements regarding a sewage treatment plant, plus additional exposure estimates generated in relation to fresh water, sediment, soil, marine water etc. These were developed using Ecetoc TRA. The guidance here appears to work as well for nanomaterials as for substances in general, no specific guidance recommendations are being made.

6.19 *Technical On-site Conditions and the Measures to Reduce or Limit Discharges, Air Emissions and Releases to Soil*

6.20 Case studies provided a range of information relating for example, to filtration, waste treatment, how waste was collected and taken off site and how it was subsequently disposed off. Other providers simply stated closed process, packaging designed to limit exposure. No difficulties were identified, the guidance works as well for nanomaterials as for substances in general, no recommendations for change being made.

6.21 *Organisational Measures to Prevent / Limit Release from Site*

6.22 There was some differences in the response between the providers in this case. Two of the providers gave information relating to the fact that it was a closed gas phase process adding that it was a requirement for system operation that the process was closed. Additional information about the cooling system being a closed process was also provided. In another case they simply stated that there was a valve system to prevent emission. It is clear that there were different expectations in the level of detail required in the

response on this particular question however again this was not in any way related to the use of nanomaterials but more simply a need to generally provide more information. The guidance appears to work as well for nanomaterials as for substances in general, no changes are proposed in relation to this.

6.23 *Conditions and Measures related to Municipal Sewage Treatment Plant*

6.24 This was not relevant for all cases and was described as such. In the case where this was used the default value was given (2000 m^3/d) was used. The guidance appears to work as well for nanomaterials as for substances in general, no changes are proposed in relation to this.

6.25 *Conditions and Measures related to External Treatment of Waste for Disposal*

6.26 Provider responses ranged from “contract with specialist waste treatment company, with a requirement for incineration of waste” to “not relevant”. It’s not clear why not relevant was considered an appropriate response in relation to that particular scenario. The guidance applies equally well for nanomaterials as for substances in general, no changes to the guidance are proposed.

6.27 *Conditions and Measures related to External Recovery of Waste*

6.28 Two of the providers stated that this was not relevant the other two providers provided information relating to recycling of the material. The guidance applies equally well for nanomaterials as for substances in general, no changes to the guidance are proposed.

6.29 *Additional Good Practice Advice (for environment) beyond the REACH CSA*

6.30 Two of the providers gave additional information to this question. The additional information was towards specific good practice activities, training activities or standardisation / quality control activities. No nano specific issues were identified, the guidance appears to work as well for nanomaterials as for substances in general, no recommendations are being made.

6.31 The preceding sections refer to the information required for the environmental exposure contributing scenario. As a general statement although there were

some difficulties and misunderstanding as to where and at what level of detail information was required to be produced in general, these entries did not create any issues which were considered to be specific for nanomaterials. Therefore no recommendations are being made to the guidance based on the experience of the case study providers for these elements.

6.32 *Contributing Exposure Scenario (to controlling worker exposure)*

6.33 Appropriate names for the exposure scenarios were identified in all cases. Further specification was also provided describing this scenario. No difficulties were identified, the guidance appears to work as well for nanomaterials as for substances in general, no recommendations for guidance changes are being made.

6.34 *Product Characteristics*

6.35 Cases provided information about the product characteristic. This included that the product was in one case a solid powder, in another case a liquid preparation in another pure solid nanomaterial, with high dustiness. Another of the cases provided information in this box in relation to aspects of the measurement programme which was useful information but not appropriate at that point although the guidance appears to be clear enough on this issue. It appears to apply as well to nanomaterials as for substances in general, However, it is important that the ES should relate to the specific form (nanoform) of the material and this should be reflected in the guidance.

6.36 *Amounts Used*

6.37 All cases were able to provide information in relation to this. The guidance appears to work as well for nanomaterials as for substances in general, no guidance changes are proposed.

6.38 *Frequency and Duration of Use / Exposure*

6.39 The information provided in relation to this task includes the request for duration per task / activity and frequency of exposure. In practice the case providers had some difficulty in identifying what comprised a specific task or activity. This was compounded somewhat by the fact that at least in some

cases the providers were trying to fit their tasks around exposure measurements which had been taken prior to this ES building activity and had not been specifically collected in relation to REACH. The providers were supported by occupational hygiene experts both externally and within the project team who helped to resolve these issues. It is clear that this is an issue but not one that is related specifically to nanomaterials. Although the guidance could be improved, this is a very generic need. The guidance applies equally well for nanomaterials as for substances in general, no changes to the guidance are proposed

6.40 *Human Factors not Influenced by Risk Management*

6.41 Responses received ranged from “not relevant (detailed personal protective measures are prescribed)” to descriptions of PPE used. Also there was some confusion over exactly what was required as an entry here. Although the guidance could be improved, this is a very generic need. The guidance applies equally well for nanomaterials as for substances in general, no changes to the guidance are proposed

6.42 *Other given Operational Conditions affecting Workers Exposure*

6.43 Responses range from processes conducted in a fully closed reactor to description of the work room etc. No specific difficulties were encountered, the guidance works as well for nanomaterials as for substances in general, no guidance changes are proposed.

6.44 *Technical Conditions and Measures to Control Dispersion from Source towards the Worker*

6.45 Extensive descriptions of the types of measures used were provided. These included descriptions of specific types of valves which were used to permit emission, separation of control rooms from sources, description of the system as being an enclosed process, details were often provided in an annexe. The guidance applies equally well for nanomaterials as for substances in general, no changes to the guidance are proposed.

6.46 *Organisational measures to prevent limit releases, dispersion on exposure.*

6.47 Respondents most often referred to issues to do with work organisation activities such as those enclosed in an operational handbook e.g. training, and use of PPE in one case the response of not relevant was received. Other different types of responses were received no particular difficulties were identified. The guidance appears to work as well for nanomaterials as for substances in general, no guidance changes are proposed.

6.48 *Conditions and Measures related to Personal Protection, Hygiene and Health Evaluation*

6.49 Respondents provided a range of information about PPE how it was used, how it was disposed and provided linkages to operational handbooks and programmes. Detailed information about the PPE was not typically provided (although in some cases it was available in the company literature. Also the sub question on advice about how long the protective equipment can be used before replacement was not answered. In general more detail would have been useful on this point. However guidance appears to be as appropriate for nanomaterials as for substances in general, no changes to guidance are proposed.

6.50 The preceding paragraphs are concerned with occupational exposures. Two of the case study providers also developed exposure scenarios based on the standard exposure scenario format for uses by consumers. Again in relation to these the guidance appears to work as well for nanomaterials as for substances in general, no specific guidance recommendations relating that are proposed.

6.51 The final stages of development of the overall exposure estimate bring together the various contributing scenarios. Here there was a range of approaches taken. These have been detailed more extensively in the B4 report and will not be reproduced here. Generally, the issues identified related to the use of measurement systems and how data which they generated could be interpreted. Broadly a range of measurement approaches were taken including almost all of the measurement methods described in the current RNC/RIP-ON/B3/2/FINAL report. This included measurement of mass concentration, number concentration, size distribution, analysis of different size fractions and employing a wide range of different methods including

CPC, SMPS and cascade impactors. In most of the cases the providers used some external support or consultancy. In many cases the programme had more of an investigative flavour rather than development of measurement data for the purposes of compliance. In other cases new techniques were being developed which have subsequently appeared in the public domain. They therefore did not in any case really represent a provider going out carrying out a measurement programme specifically with the purpose of compliance. This, coupled with the fact that at the current time there is no clear single route or protocol agreed as to how such nanomaterials can be measured contributed to the diversity of approaches and data taken.

6.52 In relation to this there does seem to be a clear need to provide additional information in relation to this. There are several aspects to this. One is, for nanomaterials what measurements need to be taken. To some extent these issues should be addressed by changes to the R14 document as well as other parts of the guidance (potentially). The type of changes indicated are the same as have been proposed based on the evaluation of the other evidence collected in the RNC/RIP-ON/B3/2/FINAL report. Hence, the case studies support the need for clearer guidance to be provided.

6.53 A second issue relates to the use of real time measurement devices, such as the CPC or SMPS which essentially provide a continuous output of data over a time period. The current guidance is clearly written from the perspective of multiple single offline measurements and combining these e.g. to develop statistical indices of the data obtained e.g. mean or 95th percentile. There is almost no information on this issue the guidance document reviewed. This also illustrates the difficulties in trying to use pre existing data in order to demonstrate compliance.

6.54 A third issue relates to the use of different metrics. In the data provided by these case studies a range of metrics were used. A number of approaches led to estimates based on number concentration and there was no clear view as to how such measurements could be used for comparison with the DNEL (which was, in all cases expressed in terms on mass concentrations). This cross metric comparison would be possible if there were well established relationships for conversion between these, However as indicated in the Task

D report, such relationships are not available and are unlikely to be stable or generalisable. In the absence of this it is difficult to provide clear guidance on this issue. This may continue to be the case for some time.

6.55 A final issue identified was the selection of the DNEL against which the exposure estimate could be compared. Two of the case study providers compared their exposure assessments with research derived potential DNELs for different materials (TiO_2 and CNT), therefore trying to go beyond current information. In these cases derived exposure values where below the (research based) DNEL. This did not provide any additional information as to how DNELs could be derived but such recommendations will arise from the Task C reports of RIP-oN 3.

6.56 Overall in relation to the case studies it was considered that "these Case-Studies could serve as nanomaterial product-specific examples only and that no generalisation with regard to practices within an entire nanomaterial type-specific branch could be based on *these individual* ES Case-Studies." This is not to indicate that generalisation of ES for nanomaterials will always be impossible. As with any substance the generalisation of the ES would need to be justified. What would be different for nanomaterials is that this would not just be based on the substance composition but would also need to take account of other parameters such as particle size distribution.

7 APPENDIX 2 - MAPPING OF EXPOSURE ISSUES TO GUIDANCE

7.1 Introduction

7.1.1 The maps in this appendix represent the intersection between identified scientific issues (arranged vertically on the left of the matrix) and a particular section of the guidance (arranged horizontally across the top of the matrix). White, unfilled cells indicate where the specific identified scientific issue ***is not relevant*** to that particular section of the Guidance. Therefore no change to that section of the guidance is required because of that specific issue.

7.1.2 Filled blue cells indicate where the specific identified scientific issue ***is relevant*** to that particular section of the guidance but the guidance applies equally well for nanomaterials as for substances in general and therefore, again, no change to the guidance is required.

7.1.3 Filled yellow cells with a plus symbol cells indicate where the specific identified scientific issue ***is relevant*** to that particular section of the guidance but the guidance is not sufficient and needs to be amended to take account of the issue. Guidance and/or R&D recommendations have been made for these cells only.

7.1.4 The matrices are not intended to be part of the guidance, they are merely to illustrate the decision making process which has led to the guidance recommendations.

7.2 Part D Exposure Scenario building

Part D	Issue	D.1 Introduction	D.2 Contents of Exposure Scenarios	D.3 Overall Workflow and Dialogues	D.4 Developing the Content of an Exposure Scenario	D.5 Exposure Assessment	D.6 Refining the Hazard Assessment	D.7 Risk Characterisation	D.8 Derive the Final ES	D.9 Use of the Final ES in the Supply Chain	Appendix D1	Appendices D2, D3, D4, D5
Table 4.1	Applicability of SUs											
	Applicability of PROCs											
	Applicability of ERCs											
	Complexity of measurement programmes and data											
	Discrimination from background particles											
	Maximum particle size											
	Metrics											
	Use of instruments											
	Data handling -Uncertainty of measurement											
	Use of exposure models											
	Applicability of REACH ES											
Table 4.2	Hierarchy of control											
	Existing methods (in general)											
	Modification and substitution											
	Enclosure											
	Ventilation, LEV, including fume hood, cabinets											
	Filtration											
	Administrative controls											
	Respiratory protective equipment - RPE											
	Other PPE, gloves suits etc											
	Control banding											
	Development of OELs											
	Medical surveillance											
	Safety Data Sheets											
	Consumer RMM											
	Environmental RMM											
	Operational Conditions											
Table 4.3	Discrimination from background nanoparticles					x						
	Measurement of size distribution					x						
	Maximum relevant size					x						
	Effect of high spatial and temporal variability					x						
	Choice of metrics and instruments					x						
	Emerging measurement strategy					x						
	Assessment of high aspect ratio nanomaterials											
	Exposure modelling										x	
	Utility of exposure simulation studies											

Clause relevant to the issue but applies to NM as for other substances

Clause relevant to the issue and change required — x

Clause not relevant to the issue

7.3 Part D ES Format

D-ES Format	Issue	D.2.2.2 Exposure scenario format	D.2.2.3 Four standard formats	D.2.2.4 Sections of the standard format	D.2.2.5 Information for the downstream use	D.2.2.6 Information structure
Table 4.1	Applicability of SUs					
	Applicability of PROCs					
	Applicability of ERCs					
	Complexity of measurement programmes and data					
	Discrimination from background particles					
	Maximum particle size					
	Metrics					
	Use of instruments					
	Data handling -Uncertainty of measurement					
	Use of exposure models					
	Applicability of REACH ES					
Table 4.2	Hierarchy of control					
	Existing methods (in general)					
	Modification and substitution					
	Enclosure					
	Ventilation, LEV, including fume hood, cabinets					
	Filtration					
	Administrative controls					
	Respiratory protective equipment - RPE					
	Other PPE, gloves suits etc					
	Control banding					
	Development of OELs					
	Medical surveillance					
	Safety Data Sheets					
	Consumer RMM					
	Environmental RMM					
	Operational Conditions					
Table 4.3	Discrimination from background nanoparticles					
	Measurement of size distribution					
	Maximum relevant size					
	Effect of high spatial and temporal variability					
	Choice of metrics and instruments					
	Emerging measurement strategy					
	Assessment of high aspect ratio nanomaterials					
	Exposure modelling					
	Utility of exposure simulation studies					

Clause relevant to the issue but applies to NM as for other substances	
Clause relevant to the issue and change required	x
Clause not relevant to the issue	

7.4 Part E Risk Characterisation

Part E	Issue	E.1 Introduction	E.2 Risk Characterisation PC Properties	E.3 Risk Characterisation Human Health	E.4 Risk Characterisation Environment
Table 4.1	Applicability of SUs				
	Applicability of PROCs				
	Applicability of ERCs				
	Complexity of measurement programmes and data				
	Discrimination from background particles				
	Maximum particle size				
	Metrics	x			
	Use of instruments				
	Data handling -Uncertainty of measurement				
	Use of exposure models				
	Applicability of REACH ES				
Table 4.2	Hierarchy of control				
	Existing methods (in general)				
	Modification and substitution				
	Enclosure				
	Ventilation, LEV, including fume hood, cabinets				
	Filtration				
	Administrative controls				
	Respiratory protective equipment - RPE				
	Other PPE, gloves suits etc				
	Control banding				
	Development of OELs				
	Medical surveillance				
	Safety Data Sheets				
	Consumer RMM				
	Environmental RMM				
	Operational Conditions				
Table 4.3	Discrimination from background nanoparticles				
	Measurement of size distribution				
	Maximum relevant size				
	Effect of high spatial and temporal variability				
	Choice of metrics and instruments	x			
	Emerging measurement strategy				
	Assessment of high aspect ratio nanomaterials				
	Exposure modelling				
	Utility of exposure simulation studies				

Clause relevant to the issue but applies to NM as for other substances

Clause relevant to the issue and change required x

Clause not relevant to the issue

7.5 Part F Chemical safety report including appendix to part F CSR template

Part F	Issue	F.1 Introduction	F.2 Writing the CSR
Table 4.1	Applicability of SUs		
	Applicability of PROCs		
	Applicability of ERCs		
	Complexity of measurement programmes and data		
	Discrimination from background particles		
	Maximum particle size		
	Metrics		
	Use of instruments		
	Data handling -Uncertainty of measurement		
	Use of exposure models		
	Applicability of REACH ES		
Table 4.2	Hierarchy of control		
	Existing methods (in general)		
	Modification and substitution		
	Enclosure		
	Ventilation, LEV, including fume hood, cabinets		
	Filtration		
	Administrative controls		
	Respiratory protective equipment - RPE		
	Other PPE, gloves suits etc		
	Control banding		
	Development of OELs		
	Medical surveillance		
	Safety Data Sheets		
	Consumer RMM		
	Environmental RMM		
	Operational Conditions		
Table 4.3	Discrimination from background nanoparticles		
	Measurement of size distribution		
	Maximum relevant size		
	Effect of high spatial and temporal variability		
	Choice of metrics and instruments		
	Emerging measurement strategy		
	Assessment of high aspect ratio nanomaterials		
	Exposure modelling		
	Utility of exposure simulation studies		

Clause relevant to the issue but applies to NM as for other substances
Clause relevant to the issue and change required (x)

Clause not relevant to the issue

7.6 **Part F-Annex**

F-Annex	Issue	A1 Summary of risk Management Measures	A2 Declaration that RMM are Implemented	A3 Declaration that RMM are Communicated	1 Identity of the Substance and PC Properties	2 Manufacture and Uses	3 Classification and Labelling	4 Environmental Fate Properties	5 Human Health Hazard Assessment	6 Human Health Hazard Assessment of PC Properties	7 Environmental Hazard Assessment	8 PBT and VPVB Assessment	9 Exposure Assessment	10 Risk Characterisation
Table 4.1	Applicability of SUs													
	Applicability of PROCs													
	Applicability of ERCs													
	Complexity of measurement programmes and data													
	Discrimination from background particles													
	Maximum particle size													
	Metrics													x
	Use of instruments													
	Data handling -Uncertainty of measurement													
	Use of exposure models													
	Applicability of REACH ES													
Table 4.2	Hierarchy of control													
	Existing methods (in general)													
	Modification and substitution													
	Enclosure													
	Ventilation, LEV, including fume hood, cabinets													
	Filtration													
	Administrative controls													
	Respiratory protective equipment - RPE													
	Other PPE, gloves suits etc													
	Control banding													
	Development of OELs													
	Medical surveillance													
	Safety Data Sheets													
	Consumer RMM													
	Environmental RMM													
	Operational Conditions													
Table 4.3	Discrimination from background nanoparticles													
	Measurement of size distribution													
	Maximum relevant size													
	Effect of high spatial and temporal variability													
	Choice of metrics and instruments													x
	Emerging measurement strategy													
	Assessment of high aspect ratio nanomaterials													
	Exposure modelling													
	Utility of exposure simulation studies													

Clause relevant to the issue but applies to NM as for other substances

Clause relevant to the issue and change required — x

Clause not relevant to the issue

7.7 Part G Extending the SDS

Part G	Issue	G.1 Aim of this Chapter	G.2 Transmission of Infomraiton down the Chai	G.3 REACH Requirements on Extended SDS	G.4 Guidance to Connect the SDS with ES	A1 Methodology on Scaling	A2 Examples for preparation
Table 4.1	Applicability of SUs						
	Applicability of PROCs						
	Applicability of ERCs						
	Complexity of measurement programmes and data						
	Discrimination from background particles						
	Maximum particle size						
	Metrics						
	Use of instruments						
	Data handling -Uncertainty of measurement						
	Use of exposure models						
	Applicability of REACH ES						
Table 4.2	Hierarchy of control						
	Existing methods (in general)						
	Modification and substitution						
	Enclosure						
	Ventilation, LEV, including fume hood, cabinets						
	Filtration						
	Administrative controls						
	Respiratory protective equipment - RPE						
	Other PPE, gloves suits etc						
	Control banding						
	Development of OELs						
	Medical surveillance						
	Safety Data Sheets						
	Consumer RMM						
	Environmental RMM						
	Operational Conditions						
Table 4.3	Discrimination from background nanoparticles						
	Measurement of size distribution						
	Maximum relevant size						
	Effect of high spatial and temporal variability						
	Choice of metrics and instruments						
	Emerging measurement strategy						
	Assessment of high aspect ratio nanomaterials						
	Exposure modelling						
	Utility of exposure simulation studies						

Clause relevant to the issue but applies to NM as for other substances	
Clause relevant to the issue and change required	x
Clause not relevant to the issue	

7.8 R.12 Use Descriptor system

R12	Issue	R.12.1. Aim of this module	R.12.2. The use description system	R.12.3. Definition of the five descriptor-lists	R.12.4. Exemplification	R.12.5 Describing identified uses, forming ES titles	R.12-1. Descriptor-list for sectors of use (SU)	R.12-2.1. Descriptor-list for PC	R.12-3. Descriptor-list for process cats (PROC)	R.12-4.1. Description for ERC	R.12-6. List of functional categories
Table 4.1	Applicability of SUs										
	Applicability of PROCs										
	Applicability of ERCs										
	Complexity of measurement programmes and data										
	Discrimination from background particles										
	Maximum particle size										
	Metrics										
	Use of instruments										
	Data handling -Uncertainty of measurement										
	Use of exposure models										
	Applicability of REACH ES										
Table 4.2	Hierarchy of control										
	Existing methods (in general)										
	Modification and substitution										
	Enclosure										
	Ventilation, LEV, including fume hood, cabinets										
	Filtration										
	Administrative controls										
	Respiratory protective equipment - RPE										
	Other PPE, gloves suits etc										
	Control banding										
	Development of OELs										
	Medical surveillance										
	Safety Data Sheets										
	Consumer RMM										
	Environmental RMM										
	Operational Conditions										
Table 4.3	Discrimination from background nanoparticles										
	Measurement of size distribution										
	Maximum relevant size										
	Effect of high spatial and temporal variability										
	Choice of metrics and instruments										
	Emerging measurement strategy										
	Assessment of high aspect ratio nanomaterials										
	Exposure modelling										
	Utility of exposure simulation studies										

Clause relevant to the issue but applies to NM as for other substances	
Clause relevant to the issue and change required	x
Clause not relevant to the issue	

7.9 R.13 Risk management measures and operational conditions including the RMM library

R13	Issue	R.13.1. Aim of section	OC and RMM	R.13.3. Effectiveness of RMMs	R.13.4. RMM library	RMM library
Table 4.1	Applicability of SUs					
	Applicability of PROCs					
	Applicability of ERCs					
	Complexity of measurement programmes and data					
	Discrimination from background particles					
	Maximum particle size					
	Metrics					
	Use of instruments					
	Data handling -Uncertainty of measurement					
	Use of exposure models					
	Applicability of REACH ES					
Table 4.2	Hierarchy of control					
	Existing methods (in general)				x	
	Modification and substitution					
	Enclosure					x
	Ventilation, LEV, including fume hood, cabinets					
	Filtration					
	Administrative controls					
	Respiratory protective equipment - RPE					x
	Other PPE, gloves suits etc					x
	Control banding					
	Development of OELs					
	Medical surveillance					x
	Safety Data Sheets					
	Consumer RMM					
	Environmental RMM					
	Operational Conditions					
Table 4.3	Discrimination from background nanoparticles					
	Measurement of size distribution					
	Maximum relevant size					
	Effect of high spatial and temporal variability					
	Choice of metrics and instruments					
	Emerging measurement strategy					
	Assessment of high aspect ratio nanomaterials					
	Exposure modelling					
	Utility of exposure simulation studies					

Clause relevant to the issue but applies to NM as for other substances

Clause relevant to the issue and change required — x

Clause not relevant to the issue

7.10 **R.14 Occupational exposure estimation**

R.14	Issue	R.14.1. Introduciton	R.14.2 Types and routes of exposure	R.14.3. Determinants of occupational exposure and RMMs	R.14.4. Exposure estimation measruements / modelling	R.14.5. Higher tier exposure assessment	R.14.6. References	A R.14-1. Evaporation rate	A R.14-2. Derivation of short term inhalation exposure	A R.14-3. Control guidance sheet numbering system
	Applicability of SUs									
	Applicability of PROCs									
	Applicability of ERCs									
	Complexity of measurement programmes and data									
	Discrimination from background particles									
Table 4.1	Maximum particle size				x					
	Metrics									
	Use of instruments				x					
	Data handling -Uncertainty of measurement									
	Use of exposure models				x	x				
	Applicability of REACH ES									
	Hierarchy of control									
	Existing methods (in general)									
	Modification and substitution									
	Enclosure									
	Ventilation, LEV, including fume hood, cabinets									
	Filtration									
	Administrative controls									
Table 4.3	Respiratory protective equipment - RPE									
	Other PPE, gloves suits etc									
	Control banding									
	Development of OELs									
	Medical surveillance									
	Safety Data Sheets									
	Consumer RMM									
	Environmental RMM									
	Operational Conditions									
	Discrimination from background nanoparticles		x							
	Measurement of size distribution				x					
	Maximum relevant size				x					
	Effect of high spatial and temporal variability									
Table 4.3	Choice of metrics and instruments		x		x					
	Emerging measurement strategy									
	Assessment of high aspect ratio nanomaterials									
	Exposure modelling				x	x				
	Utility of exposure simulation studies				x					

Clause relevant to the issue but applies to NM as for other substances
Clause relevant to the issue and change required (x)

Clause not relevant to the issue

7.11 **R.15 Consumer exposure estimation**

R15	Issue	R.15.1. Introduction	R.15.2. General exposure considerations for consumers	R.15.3. Calculation of exposure	R.15.4. ECETOC TRA for exposure estimation - Tier 1	R.15.5. ConsExpo lower tier models	R.15.6. Advanced refinements, higher tier models	R.15.7. Risk characterisation	R.15.8. References
Table 4.1	Applicability of SUs								
	Applicability of PROCs								
	Applicability of ERCs								
	Complexity of measurement programmes and data								
	Discrimination from background particles								
	Maximum particle size								
	Metrics		x	x					
	Use of instruments								
	Data handling -Uncertainty of measurement								
	Use of exposure models			x					
	Applicability of REACH ES								
Table 4.2	Hierarchy of control								
	Existing methods (in general)								
	Modification and substitution								
	Enclosure								
	Ventilation, LEV, including fume hood, cabinets								
	Filtration								
	Administrative controls								
	Respiratory protective equipment - RPE								
	Other PPE, gloves suits etc								
	Control banding								
	Development of OELs								
	Medical surveillance								
	Safety Data Sheets								
	Consumer RMM								
	Environmental RMM								
	Operational Conditions								
Table 4.3	Discrimination from background nanoparticles								
	Measurement of size distribution								
	Maximum relevant size								
	Effect of high spatial and temporal variability								
	Choice of metrics and instruments		x	x					
	Emerging measurement strategy								
	Assessment of high aspect ratio nanomaterials								
	Exposure modelling			x					
	Utility of exposure simulation studies								

Clause relevant to the issue but applies to NM as for other substances

Clause relevant to the issue and change required (x)

Clause not relevant to the issue

7.12 **R.16 Environmental exposure Estimation**

R16	Issue	R.16.1. Introduction	R.16.2. Exposure assessment principles	R.16.3. Release estimation	R.16.4. Measured data	R.16.5. Partitioning and degradation	R.16.6. Exposure and intake estimation	R.16.7. tools based on models presented in section R16.6.	R.16.8. Refinement of exposure estimation	R.16.9. Summary of default and refined assessment	A.16-1. Envirnomental release categories	A.16-2. Overview of emission scenario documents (ESDs)	A.16-3. Fate of chemicals in a wastewater treatment plant	A.16-4. Connection to Sewage Treatment Plants in Europe
Table 4.1	Applicability of SUs													
	Applicability of PROCs													
	Applicability of ERCs										x			
	Complexity of measurement programmes and data													
	Discrimination from background particles													
	Maximum particle size													
	Metrics													
	Use of instruments													
	Data handling -Uncertainty of measurement													
	Use of exposure models					x	x	x	x					
	Applicability of REACH ES													
Table 4.2	Hierarchy of control													
	Existing methods (in general)													
	Modification and substitution													
	Enclosure													
	Ventilation, LEV, including fume hood, cabinets													
	Filtration													
	Administrative controls													
	Respiratory protective equipment - RPE													
	Other PPE, gloves suits etc													
	Control banding													
	Development of OELs													
	Medical surveillance													
	Safety Data Sheets													
	Consumer RMM													
	Environmental RMM													
	Operational Conditions													
Table 4.3	Discrimination from background nanoparticles													
	Measurement of size distribution													
	Maximum relevant size													
	Effect of high spatial and temporal variability													
	Choice of metrics and instruments													
	Emerging measurement strategy													
	Assessment of high aspect ratio nanomaterials													
	Exposure modelling					x	x	x	x					
	Utility of exposure simulation studies										x			

Clause relevant to the issue but applies to NM as for other substances

Clause relevant to the issue and change required (x)

Clause not relevant to the issue

7.13 **R.17 Exposure Assessment of Substances in Articles**

R17	Issue	R.17.1. Introduction	R.17.2. General considerations for exposure estimation	R.17.3. Release and exposure estimation for humans	R.17.4. Release and exposure estimation environment	R.17.5. Refined exposure estimation	R.17.6. Control of risks	A17-1. Information on release rates from articles
Table 4.1	Applicability of SUs							
	Applicability of PROCs							
	Applicability of ERCs							
	Complexity of measurement programmes and data							
	Discrimination from background particles							
	Maximum particle size							
	Metrics							
	Use of instruments							
	Data handling -Uncertainty of measurement							
	Use of exposure models			x	x			x
	Applicability of REACH ES							
Table 4.2	Hierarchy of control							
	Existing methods (in general)							
	Modification and substitution							
	Enclosure							
	Ventilation, LEV, including fume hood, cabinets							
	Filtration							
	Administrative controls							
	Respiratory protective equipment - RPE							
	Other PPE, gloves suits etc							
	Control banding							
	Development of OELs							
	Medical surveillance							
	Safety Data Sheets							
	Consumer RMM							
	Environmental RMM							
	Operational Conditions							
Table 4.3	Discrimination from background nanoparticles							
	Measurement of size distribution							
	Maximum relevant size							
	Effect of high spatial and temporal variability							
	Choice of metrics and instruments							
	Emerging measurement strategy							
	Assessment of high aspect ratio nanomaterials							
	Exposure modelling			x	x			x
	Utility of exposure simulation studies			x	x			x

Clause relevant to the issue but applies to NM as for other substances

Clause relevant to the issue and change required (x)

Clause not relevant to the issue

7.14 R.18 Exposure Assessment for the Waste Life Stage

R17	Issue	R.18.1 Aim of this chapter	R.18.2 Characterising the waste streams	R.18.3 Waste operations: Recovery or disposal of waste	R.18.4 General Workflow in M/I's assessment related to waste stage	R.18.5 Tier 1 Emission estimation	A R.18-1 Environmental release info for 14 waste treatment technique	A. R18-2A Waste related info in the ES for an identified use	A R.18-2B Waste related info in the ES for spray painting	A. R18-2C ES format for a waste operation
Table 4.1	Applicability of SUs									
	Applicability of PROCs									
	Applicability of ERCs									
	Complexity of measurement programmes and data									
	Discrimination from background particles									
	Maximum particle size									
	Metrics									
	Use of instruments									
	Data handling -Uncertainty of measurement									
	Use of exposure models					x				
	Applicability of REACH ES									
Table 4.2	Hierarchy of control									
	Existing methods (in general)									
	Modification and substitution									
	Enclosure									
	Ventilation, LEV, including fume hood, cabinets									
	Filtration									
	Administrative controls									
	Respiratory protective equipment - RPE									
	Other PPE, gloves suits etc									
	Control banding									
	Development of OELs									
	Medical surveillance									
	Safety Data Sheets									
	Consumer RMM									
	Environmental RMM									
	Operational Conditions									
Table 4.3	Discrimination from background nanoparticles									
	Measurement of size distribution									
	Maximum relevant size									
	Effect of high spatial and temporal variability									
	Choice of metrics and instruments									
	Emerging measurement strategy									
	Assessment of high aspect ratio nanomaterials									
	Exposure modelling					x				
	Utility of exposure simulation studies					x				

Clause relevant to the issue but applies to NM as for other substances
Clause relevant to the issue and change required (x)

Clause not relevant to the issue

8 APPENDIX 3 – CONSIDERATION IN RELATION TO MEASUREMENT OF INHALATION EXPOSURE TO NANOMATERIALS

8.1 Preamble

8.1.1 Measurement of exposure to nanomaterials provides particular challenges. These have been highlighted in several publications (e.g. Brouwer 2009, 2010). They include discrimination from background particles, collection and analysis of size information, effective high spatial and temporal variability, choice of metrics and measurement instruments, and measurement of high aspect ratio nanomaterials. The state of knowledge on these issues is continuing to develop. Further information on current approaches is provided in BSI 6699/3 (2010), OECD (2009).

8.2 Discrimination from background nanoparticles

8.2.1 Typical urban air contains anywhere between 10,000 to 40,000 particles.cm^{-1} which come from a variety of sources including, industrial pollution, traffic and domestic emissions.

8.2.2 In industrial settings, evidence of measurement problems relating to background aerosols has been reported in several studies (e.g. Kuhlbusch et al., 2004, 2006; Demou et al., 2008; Park et al., 2009). Specifically identified sources include heating units, fork lift trucks and vacuum cleaners.

8.2.3 These background number concentrations are dominated by particles smaller the 1000 nm and much of the distribution is typically in the range 10 to 300 nm. The presence of this ambient particulate creates problems when attempting to measure emissions of engineered nanoparticles from nanomaterials sources.

8.2.4 Three strategies have been reported (including combinations) to address this issue of these with varying success. The first is to take time series, or time differentiated measurements with associated log of events, typically including activities such as pre-operation of reactor, to determine a plausible relationship between events and levels.

8.2.5 A second approach is to take parallel samples with the same instrumentation in an area where it is expected that there is only background aerosol present, i.e. there is no expected contribution from the source (e.g. Kuhlbusch et al. 2004, 2006). This is sometimes called the “far field” and can be outside, or at another point in the production building/laboratory. For this type of approach, care is required that there is no contribution from the sources of interest, or from other background sources in the far field sample.

8.2.6 A third approach is to collect physical samples of the aerosol for off-line analysis to confirm the that peak concentrations observed correspond to an identified NM, either by composition (elemental analysis of the primary material or impurity) or morphology or both, for example by Scanning Electron Microscopy (SEM)/ Transmission Electron Microscopy (TEM) and Energy-dispersive X-ray Spectroscopy (EDAX) analysis (e.g. Methner et al., 2010; Brouwer et al., 2009).

8.2.7 While all of these approaches have utility, all must be applied with care to ensure that no confounding effects, such as a change in the far field background with time, corrupt the data. Combination approaches have been described and are generally more successful. Brouwer et al. (2009) used a combination of these approaches as the basis of a semi-formal decision logic to determine whether nano-objects were present in the workplace air. This required an exceedance of a predetermined near-field/far field ratio (in the reference ratio 1.05 was used), that changes in concentration or size distribution corresponded to observed activities and that the chemical composition of the sample (in the near and far field) matched that expected. The obvious limitation of the method in the light of the dynamic response, detection limits and the measurement uncertainty of the applied measurements is in its ability to detect statistically significant deviations in the ratio. Currently available sampling and analytical methods might also have insufficient sensitivity to assess very low levels required when in due course in many cases OELs/DNELs for nanomaterials may be substantially lower than current OELS/DNELS,(e.g. NIOSH (2005) for TiO_2)).

8.3 Measurement of size distribution

8.3.1 Measurement of size distribution is clearly an important parameter. The size information may me obtained through a number of instrumental routes. It is unlikely that the size distribution of aerosols measured in the workplace is the same as the size distribution of the primary material. Evidence is that distributions are not log normal (as might be expected for laboratory generated samples) but more complex, sometimes but not always bi-modal.

8.3.2 Various reasons have been suggested for this. One is that the smaller mode represents primary particles and the larger mode either agglomerates or aggregates of these materials or agglomerates in combination with background particles, following scavenging by these particles. Given the irregular nature of the distribution in most cases, it is inappropriate to summarise the distribution by a single set of parameters such as median and diameter and geometric standard deviation.

8.3.3 Devices which measure size distribution such as the SMPS and FMPS provide a particularly data rich output. These devices produce count data in several size bins either collected in parallel (in the case of the FMPS) or in a very close time sequence (in the case of the SMPS). There are several ways in which this data might be used. The simplest approach in to inspect the complete size distribution. This is particularly useful in assessing single events or single changes (e.g. the implementation of a control measure, or the comparison between an aerosol and a background). However, this type of analysis is difficult to quantify as multimodal distributions cannot be easily be described and compared by summary statistics such as the geometric mean and standard deviation.

8.3.4 An alternative is to sum the total counts to provide a single number. However this approach looses the size information and so it is of limited value. In the reviewed studies, several authors (e.g. Fujitani et al., 2008; Bello 2008, 2009) have grouped (integrated) the size distribution into several discrete size ranges e.g. < 10 nanometres, < 100 nm , < 1000 nm etc. and examining the examiningcompared their respective time series to support the development of the background discrimination strategies or understanding of the particle

formation dynamics. for each. This can be highly effective in looking at how different parts of aerosol distribution change with time.

8.4 Maximum relevant size

8.4.1 Use of size dependent-health related criteria is common practice in measurement of occupational exposure (ISO, 1995). From the preceding section it is clear that the size distribution of aerosols which are present in workplaces where nanomaterials are synthesised or used typically have a broad distribution. An important issue to consider is whether it is appropriate to impose an upper size limit of the particles to be collected or measured in order to characterise exposure to NM. One option would be to exclude all particles with physical dimensions greater than 100 nm, providing methods were available. This would allow estimation of people's exposure to "nanoparticles" as formally defined in ISO/TS 27687:2008 (BSI, 2008).

8.4.2 Evidence from the studies reviewed suggests that emissions are rarely in the form of single nanoparticles (this is not to exclude this possibility entirely). In most cases the measurements indicated that where nanoparticles were present, they were in an aggregated or agglomerated form or were associated with other materials including background particles. In the main studies reviewed, the selected strategies were to maximise the information available by looking at a wide particle size range (and thus not operate with a 100nm cut-off). The implicit assumption in that is that agglomerates, aggregates and other combined particles are at least potentially relevant NM exposures. The relevance of these agglomerated forms, including potential for dissolution, or dissagregation, needs to be considered also from the toxicological perspective in the risk characterisation.

8.4.3 Many devices used do already have a maximum measurable particle size. For example several of the CPCs have a cut-off (maximum size) of 1000 nm which is achieved by including an impactor in the inlet. This can be to protect the instruments' detection system or because of decreasing detection efficiency beyond that size. There is a rationale to standardise that, particularly if emphasis is given to (total) number concentration as a parameter. Otherwise, two instruments, with different maximum sizes will give different results. However, this is not a health based selection criterion.

8.4.4 One approach could be to use the respirable convention as an upper size limit (ISO, 1993). This would have the advantage of being biologically relevant and would provide coherence with current practice in occupational exposure assessment. Use of the respirable convention has been recommended by several authors (e.g. Schneider and Jensen, 2008). Respirable concentrations have been measured in several of the reviewed studies (e.g. Peters et al., 2009; Han et al., 2008).

8.4.5 In general however, given the current state of knowledge, the practice adopted in the reviewed studies, assessing multiple parameters with multiple instruments, seems correct. Where the maximum (and indeed minimum) size limits of an instrument are known, and the instrument response function, this should be clearly stated.

8.5 **Effect of high spatial and temporal variability**

8.5.1 In occupational settings it is common that airborne concentrations are higher and closer to the source worker (near-field) than at some distance point (far-field). High spatial variability has been reported in the studies reviewed. Demou et al. (2009) reported both high and low spatial variability in different settings. Plitzco (2009) reported “genuine nanoparticles” emitted from a reactor that agglomerated in a very short time and immediately led to a lowering of the number concentration. Seipenbusch et al. (2008), as part of the FP6 project NANOTRANSPORT, investigated the evolution in time of a nanoparticle (NP) aerosol released into a particle-free atmosphere and in presence of a pre-existing background aerosol and demonstrated rapid agglomeration and scavenging by the background aerosol.

8.5.2 High spatial and temporal variability emphasis the need for measurements of exposure in workplaces are based on personal sampling, i.e. by using a sampling device located in the breathing zone of the worker being assessed. Studies have generally shown that personal exposure is higher compared to exposure as measured in the general environment of a workplace. This is partly because the worker is usually closer to the source than static environmental monitors are able to be placed but also from the activities undertaken by the worker himself, and the extent to which these modify the

exposure levels. This may be particularly relevant for NM due to high transport, agglomeration and scavenging rates.

8.5.3 Measurements of workplace air concentrations will not adequately represent personal exposure. Therefore a preferred approach is the use of personal sampling devices. However given the current lack of such a device, measurements strategies which encourage (even limited) comparison between workplace air concentrations and personal exposure are recommended.

8.6 **Metrics**

8.6.1 There are three main metrics, all of which could have some utility in measuring exposure to nanoparticles. These are: i) mass concentration (units mg m^{-3}); ii) number concentration (units m^{-3}) and; iii) surface area concentration units (m^2 m^{-3}). A case may be made for the use of any of these metrics under certain circumstances.

8.6.2 The metric used to assess exposure to nanomaterials should be that which most closely links to any potential health effect. Analysis that no single metric (or method) for monitoring nano-aerosol exposure will suit all nanomaterials. Rather, there will be occasions where particle number, surface area and mass concentration measurements or their combination will play an important role in evaluating potential impact.

8.6.3 Instrumentation is available to measure each of these metrics but there are identified practical issues in the selection and use of metrics. For mass, a key issue is a lack of sensitivity towards the nanoparticles of interest. Measurement of number concentration is in contrast highly sensitive. However, measuring particle number concentration in isolation can be misleading. In all particle number concentration measurements, the integration limits over which a particular instrument operates are critical to the reported results. Real-time measurements of surface area concentration are technically feasible but there is very limited practical experience with these instruments. The results obtained need to be carefully interpreted and the limitations and boundaries carefully examined. Issues to consider include the effect of initial aerosol charge, the composition of the material, how

aggregates are dealt with (in particular where both external and internal surfaces are available) and the effect of extreme particle shape.

8.6.4 An ideal approach is to choose a metric which is correlated with the health effect of concern, can be relatively easily measured and be both measurable and sensitive enough to detect differences in the probable ranges encountered. Which then, is the best metric for nanoparticles and is this even a sensible question to ask? Useful preliminary questions might be “what types of nanoparticles are we interested in?” and “what is the health effect we are trying to correlate with?”

8.7 Assessment of high aspect ratio nanomaterials

8.7.1 Exposure to fibrous aerosols is assessed by measuring the number (concentration) of fibres in the air with a specific shape and composition (WHO, 1997). Critical to the method is definition of a fibre, specifically a respirable fibre. WHO defines a respirable fibre as an object with length greater than 5×10^{-6} m (5000 nm) a width less than 3×10^{-6} m (3000 nm), and a length to width ratio (aspect ratio) greater than 3:1. It relies on manual counting of fibres by optical microscopy according to a set of counting rules governing size (as above), number of areas (graticules) scanned, number of fibres scanned, number density of fibres on the collection substrate, and how to deal with “bundled” or overlapping fibres. The scope of application of the WHO method is broad, as indicated in the following statement: “The method [..] is applicable to the assessment of concentrations of airborne fibres in workplace atmospheres most commonly personal exposures-for all natural and synthetic fibres, including the asbestos varieties, other naturally occurring mineral fibres and man-made mineral fibres” (WHO, 1997).

8.7.2 Several high aspect ratio nanomaterials (HARN) could fall within this scope. It has been suggested that fibre counting could be an appropriate method to assess exposure to HARN (BSI 6699-2:2007; BSI, 2007). However concerns have been raised regarding the applicability of the WHO for HARN, specifically for CNT. Optical microscopy would not detect individual CNT although it could detect bundles of CNT. The higher magnification required would require SEM/TEM which would increase the counting time substantially.

8.7.3 It is known that optical microscopy is less sensitive than SEM/TEM to very fine fibres and therefore underestimates the total number of fibres collected. SEM/TEM will measure these very fine fibres which would not be observed by optical microscopy leading to larger counts in what would be an equivalent sample. This would lead to difficulties in making comparison with limit values for fibres set using optical microscopy.

8.7.4 Han et al. (2008), used an approach based on the WHO method and report fibre concentrations. It is not clear the extent to which WHO counting rules were applied. However it is noted that all the fibres reported were shorter than the WHO definition and so by strict application of the fibre counting rules the count would be zero. Bello et al. also collected on to a filter for EM analysis, but no fibres were identified. Han et al. made measurements of total carbon using a portable aethalometer. Other investigators used CPC, OPC and SMPS to try to detect although these devices prove no morphological information. A recent review on options for CNT detection and analysis (SWA, 2010a) concluded that the ELPI spectrometer may have some utility in this respect. Various off line measurement approaches reviewed by Tantra et al. (2007) concluded that none were immediately appropriate for measurement of occupational exposure. Currently there is no consensus on the most appropriate approach.

8.7.5 Assessment of fibre concentration is likely to be relevant to some high aspect ratio nanomaterials in terms of their exposure. The presence of fibres is only likely to be detected by electron microscopy. Application of the WHO approach has not yet been validated for any types of high aspect ratio nanomaterials. No specific guidance can be given at this time towards quantitative assessment of bundles or clumps of high aspect ratio nanomaterials. However, their presence should be noted in any assessment.

8.8 Available instruments

8.8.1 There are a number of instruments available which measure the metrics discussed. The instruments have been described in a number of publications. Table 8.1 overleaf is taken from ISO/TR 27628:2007 (ISO, 2007) and describes the main types of instruments which are currently available along with the metric which they are most often used to measure. This table is not

inclusive of all of the commercial instruments which are available but nonetheless provide good general description of the instrument types and purpose. Similar tables can be found in other publications (eg BSI 2007, ISO 2008) where further descriptions of these instruments can be found.

8.8.2 Table 8.1 Main instruments available for exposure assessment and metric measured (reproduced from ISO, 2007).

Metric	Devices	Remarks
Mass	Size-selective personal sampler	No current devices offer a cut point of 100 nm. Off-line gravimetric or chemical detection is necessary. Mass may also be derived from size distribution measurements (see below).
	Size-selective static sampler	The only devices offering a cut point around 100 nm are cascade impactors.
	TEOM®1)	Sensitive real-time monitors such as the Tapered Element Oscillating Microbalance (TEOM®) may be useable to measure nanoaerosol mass concentration on-line with a suitable size-selective inlet.
	SMPS	Real-time size-selective (mobility diameter) detection of number concentration. Data may be interpreted in terms of aerosol mass concentration, only if particle shape and density are known or assumed.
	ELPI	Real-time size-selective (aerodynamic diameter) detection of active surface-area concentration. Data may be interpreted in terms of mass concentration if particle charge and density are assumed or known. Size-selected samples may be further analysed off-line.
Number	CPC	CPCs provide real-time number concentration measurements between their particle diameter detection limits. Without a nanoparticle pre-separator, they are not specific to the nanometre size range (no suitable pre-separators are currently available).
	SMPS	Real-time size-selective (mobility diameter) detection of number concentration.
	ELPI	Real-time size-selective (aerodynamic diameter) detection of active surface-area concentration. Data may be interpreted in terms of number concentration. Size-selected samples may be further analysed off-line.
	Optical Particle Counter	These are insensitive to particles smaller than approximately 100 nm to 300 nm in diameter and therefore unsuitable for nanoparticle monitoring.
	Electron Microscopy	Off-line analysis of electron microscope samples can provide information on size-specific aerosol number concentration.
Surface area	SMPS	Real-time size-selective (mobility diameter) detection of number concentration. Data may be interpreted in terms of aerosol surface area under certain circumstances. For instance, the mobility diameter of open agglomerates has been shown to correlate well with projected surface area [3].
	ELPI	Real-time size-selective (aerodynamic diameter) detection of active surface-area concentration. Active surface area does not scale directly with geometric surface area above 100 nm. Size-selected samples may be further analysed off-line.
	SMPS and ELPI used in parallel	Differences in measured aerodynamics and mobility diameters can be used to infer particle fractal dimension, which can be further used to estimate surface area.
	Diffusion Charger	Real-time measurement of aerosol active surface area. Active surface area does not scale directly with geometric surface area above 100 nm. Note that not all commercially available diffusion chargers have a response that scales with the particle active surface area below 100 nm. Diffusion chargers are only specific to nanoparticles if used with an appropriate inlet pre-separator.
	Electron Microscopy	Off-line analysis of electron microscope samples can provide information on particle surface area with respect to size. TEM analysis provides direct information on the projected area of collected particles, which may be related to the geometric area for some particle shapes.

8.9 Data analysis

8.9.1 Guidance for exposure data requires the use of summary statistics such as the mean and the 90th percentile. Many of the instruments suggested for use are real time devices which can either provide an instantaneous spot measurement or can be used to average over a set period. In some cases, summary statistics can be derived directly from the device. If this is not feasible then multiple measurements should be taken over appropriate fixed sampling periods to enable these statistics to be calculated. In these cases, the duration of the averaging period should be recorded.

8.10 Strategy

8.10.1 In this context, measurement strategy includes selection of instruments, how they are used and what samples are taken (incl. where and when/timing). Currently, there is no single consensus view on the most appropriate method for assessing exposure to nanomaterials. As indicated earlier in this report, there's is unlikely to be a universal strategy due the many differing purposes for which measurements may be made. In studies published thus far, the purpose seems to have been to have been primarily for identification of emission sources, quantification of same, or for the evaluation of the effectiveness of control approaches.

8.10.2 Initial approaches, for example that described by Brouwer et al. (2004), suggest a multi-instrument approach in an attempt to capture all relevant metrics and characteristics. In this study, based on the assessment of ultra-fine welding fumes, the authors suggest a multi-instrument approach in which CPCs are used to identify potential sources of emissions (and background sources), an SMPS or ELPI is used to characterise size distribution and how this varies as a function of time or space combined with SEM or TEM analysis of samples collected on filters to characterise the physical or chemical form of the aerosol.

8.10.3 The authors recognise that each of the measurement methods has its drawbacks, but when used in combination they "may give full insight into the presence of ultrafine particle aerosols in the workplace". They recommend however that the use of static samplers at fixed locations hampers the

interpretation of the results for personal exposure of ambulatory workers and, even for workers who are positioned at fixed workstations, the interpretation will be “very inaccurate”.

8.10.4 BSI 6699-2 describes a three step process (BSI, 2007). The first step would involve identifying the source of nanoparticle emissions using a CPC provides acceptable capability for this purpose, taking due consideration of any background. In the second stage aerosol surface area measurements should be conducted with a portable diffusion charger and aerosol size distributions should be determined with an SMPS or ELPI using static (area) monitoring. Lastly, personal sampling using filters or grids suitable for analysis by electron microscopy or chemical identification should be employed, particularly if measuring exposures to specific nanoparticles is of interest. Electron microscopy can be used to identify the particles, and can provide an estimate of the size distribution of the particle of interest.

8.10.5 In the US, the National Institute for Occupational Safety and Health (NIOSH) has developed a multi-stage strategy (NEAT) with an initial assessment by CPC and OPC, plus electron microscopy and elemental identification (Methner et al. 2010). The document was developed by the NIOSH team to provide specific advice on how to use the many available techniques in a coherent way. The approach described by these authors comprises three main steps. These are:

8.10.6 ***1. Identify potential sources of emissions.*** The recommendations are that this initial assessment should involve reviewing processes, work flow etc. to gain an understanding of where engineered nanomaterials may be used and including physical chemical properties such as size, shape, composition etc. Once the potential sources of the emissions have been identified the teams should conduct a walkthrough survey, determine the frequency and duration of each operation, determine the presence and absence of local exhaust ventilation and determine the process points where the containment is deliberately breached e.g. opening the system for product retrieval or for cleaning.

8.10.7 ***2. Conduct particle number concentration sampling.*** Critical to this is determining the influence of background particle concentration, e.g. by

making measurements with CPC or OPC before processing or handling of nanomaterial begins. Potential incidental nanoparticles sources identified included heat sources, vacuum pumps, gas heating units, fork lift trucks etc. The authors also carried out measurements of background particle number concentration after the active processing or manufacturing took place. The average of the background number concentration before and after the task is then subtracted from the measurements made during the task. The authors identified a number of problems with their approach which could include e.g. the background particle number concentrations could remain elevated after a particular task indicating that release had occurred. Once background particle number concentrations had been determined process or task specific measurements are made with the CPC and OPC simultaneously at locations near to the suspected emissions source. Airborne particle number concentrations are then determined and compared to background to determine if an emission of nanomaterials occurred.

8.10.8 ***3. Collect filter based samples.*** A pair of filter based air samples (in this case 37mm open face cassettes) were collected at the process task locations and or from workers engaged in the process. (Note that these open faced cassettes would not be size selective in nature). The authors comment that analysis of these samples by electron microscopy allows the determination of particle size range and degree of agglomeration of the aerosol collected. The authors indicate that one of the samples is analysed for airborne mass concentration and the other sample analysed by electron microscopy. For particle characterisation (e.g. size, shape, morphology etc.) by TEM or SEM using measurements specified in NIOSH methods 4702, 4704 or other equivalent methods. The analysis of the air samples using TEM with energy dispersive x-ray spectrometry can provide information on elemental composition.

8.10.9 If measurements obtained with CPC and OPC indicate that engineered nanomaterial is emitted and workers are present then personal (breathing zone) samples should be collected using the two filter strategy. One further option is to use size selection in the collection of filter based samples, e.g. the use of a cyclone to collect the respirable fraction.

8.10.10 The approach described is the basis of the programme of work which is reported in Methner et al. (2010).

8.10.11 One noticeable difference between this approach and that suggested by other authors is the lack of any real time collection of size information, e. g. with an SMPS or similar device. Rather the approach is dependent on collection of samples for off line analysis to determine particle size.

8.10.12 The approached described by Methner et al. (2010) is very similar and has clearly influenced the approach suggested in guidance by OECD in their document ENV/JM/MONO(2009)16 *Emission Assessment for the Identification of Sources and Release of Airborne Manufactured Nanomaterials in the Workplace: Compilation of Existing Guidance (OECD 2009).* Currently available guidance is reviewed in this document. Also it is clear that the apparent lack of use of sophisticated real time size information gathering equipment provides a "relatively simple" approach towards assessing exposure to engineered nanomaterials. It is maybe less challenging both in terms of timescales between collection of the sample and subsequent analysis and also the usability of this method by e.g. small to medium enterprises without access to sophisticated TEM equipment.

8.10.13 Brouwer et al. (2009) describe a strategy which has been developed within the EU sponsored NANOSH (EU FP6 contract NMP4/CT/2006/032777) project. This is a harmonised approach for measurement strategy, data analysis and reporting. In addition to time activity concentration profiles this approach enables a first step to estimate the potential for exposure to manufactured nano objects more quantitatively.

8.10.14 The sampling strategy developed for the NANOSH field studies was based on a mixture of scientific desirability and practical feasibility for all the partners. With respect to the instrumentation, size distributive particles concentration devices, e.g., SMPS model 3080 (TSI, USA) with a differential mobility analyzer (DMA) and a CPC model 3025 (TSI, USA) or ELPI (Dekati, Finland) formed the basis for workplace air measurements. In addition, near-real- time active surface area concentration was measured by either of the two different types of DCs i.e., LQ1 (Matter Engineering, Switzerland), or an Aerotrak 9000 (TSI, USA). The former device measures the active surface area

concentration, whereas the latter one mimics the active surface area of the lung- deposited particles (Asbach et al., 2009B). In addition, particle number concentrations were measured by CPC (TSI, model 3025). The measurement devices were located next to the work station with instrument inlets (tubing) in the workers' breathing zone.

8.10.15 For characterization, samples on TEM grids were collected by (electrostatic) precipitators, e.g., the Nanometer Aerosol Sampler 3089 (TSI, USA).

8.10.16 Key element of this study was the development of a "decision logic" to estimate the likelihood of exposure to manufactured nanomaterials. A preliminary ''decision logic'' was developed to take advantage of the array of measurement results and to assist the evaluation of the results with respect to exposure to manufactured nano objects. First, for a case-by-case comparison, the average concentration during a defined period of activity should be statistically different ($p<0.05$) from either a period of non-activity (''near-field background''), or from a concentration at a ''far-field'' background position during the activity. In addition, the difference should be equal to or larger than 5%, i.e., a ratio of activity–non-activity >=1.05. Second, the characterization of the samples during the activity should indicate the presence of primary particles<100 nm or agglomerates, and the EDX elemental analysis should confirm the (elemental) identity of the objects or agglomerates similar to the MNO. Ideally, there should be a confirmation, that the particle size distribution (or the mode) as determined by SMPS or ELPI, is different from the background. Finally, the observations during the measurements should be evaluated, especially with respect to other sources that might generate nano- sized aerosols.

8.10.17 The issue of determination of background concentration was addressed in two ways, by comparison between near and far field and between periods of activity and non activity.

8.10.18 The decision logic as presented in this article offers guidance as regards how to proceed with data analysis. The NANOSH approach formulates decision criteria explicitly e.g. statistical significance and substantiality of difference and gives a framework to combine the difference types of results. In the case that an application of decision logic shows evidence that the increment of

concentration during the activity is associated with manufactured nano objects is still unclear what the relevance of this observation might be in view of a risk assessment. The authors conclude that it can be stated that workplace air measurements still are not able to generate data for the quantitative assessment of exposure. However these studies can contribute to a better understanding of the potential for the exposure for different types of exposure situations. This contribution can be more effective and powerful if the design of measurement strategies, the data analysis and reporting are compatible.

9 APPENDIX 4 – POSSIBLE FUTURE APPROACH FOR PERFORMING ANIMAL TO HUMAN EXTRAPOLATION FOR NANOMATERIALS

9.1 Preamble

9.1.1 The following appendix describes an approach to the derivation of a human equivalent dose (HED) from animal experimental data. The approach takes into account interspecies differences and exposure duration to derive a corrected HED for further derivation to an acceptable human exposure limit.

9.1.2 The information discussed herein has been developed after the standard RIP-oN 3 consultation process in response to comments and as such has not been reviewed by the European Commission appointed Stakeholder Consultation Group (SCG). Therefore the information should not be seen as a reflection of the RIP-oN consultation process and is for information purposes only, but could be followed up as R&D and/or considered for future updates of the guidance.

9.1.3 It should be noted that the approach outlined here refers to the mass metric.

9.2 Alternative approach to deriving a human no effect level

9.2.1 When considering the data obtained from an animal inhalation study, the value of greatest interest for deriving safe exposure limits is the no observable adverse effect level (NOAEL). This value provides the basis for deriving a level at which no adverse effects would be seen within humans exposed to the same substance. As there are numerous differences between humans and the experimental animal model as well as the exposure conditions, it is inappropriate to directly use the animal NOAEL for humans without making adjustments for these variables. There are several ways in which such an extrapolation from animal to humans can be made for inhalation exposure and these are discussed within the RNC/RIP-oN3/C1/2/FINAL and RNC/RIP-oN3/C2/2/FINAL. The REACH default approach for making and extrapolation from animal to HED begins with an adjustment to the calculated experimental external exposure value to account for certain experimental parameters such as differences in exposure duration. Once these modifications to the starting NOAEL are made, an assessment factor is applied to account for interspecies

differences. This figure, corrected for differences in experimental attributes and interspecies differences, is then subject to additional assessment factors to account for other areas of variability and uncertainty such as intraspecies differences and the data quality.

9.2.2 However, this approach is an extrapolation based upon on the external concentration resulting in no adverse effects. This external concentration is however not the concentration that drives the effect; it is the dose within the lung which drives the effect. In order to establish the internal dose, several pieces of information are required and these are summarised below and in figure 2:

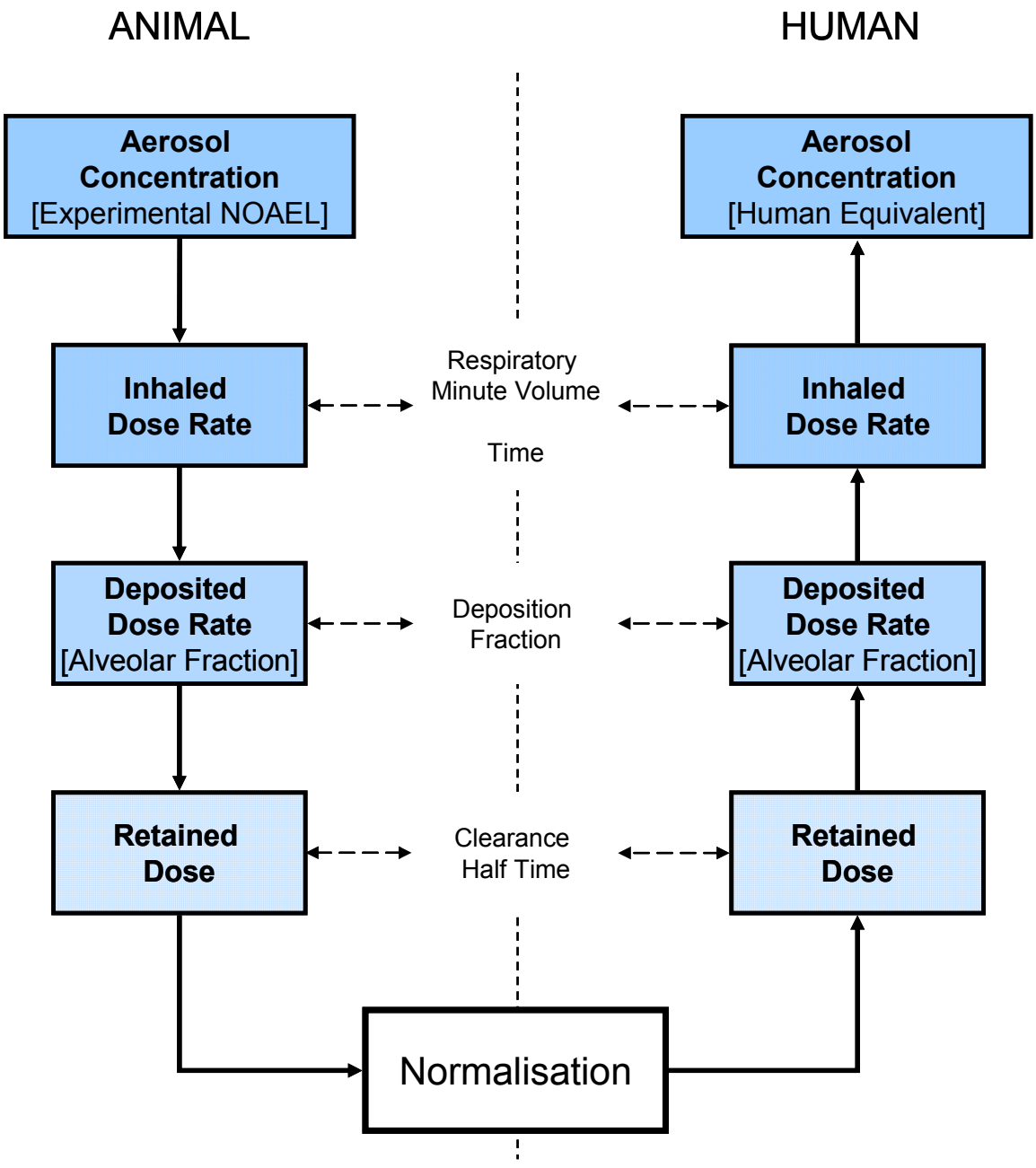
- Respiratory minute volume (RMV)
- Exposure duration
- Deposition fraction
- Clearance rate

9.2.3 The first piece of information required is the inhaled dose which is the proportion of the external aerosol concentration drawn into the body via the airways. To calculate this, one needs to know the respiratory minute volume (RMV) which is simply the volume of air moved in and out of the lung over a period of 1 minute and the time over which exposure occurred (in minutes). Whilst not commonly reported (although it is calculated in both the Pauluhn 2010 and NEDO 2009 reports), the RMV can be calculated using the equation of Bide, Armour and Yee (2000) which is as follows:

$$RMV = 0.499 \times \text{Body weight}^{0.809}$$

9.2.4 Using this calculation, the RMV of a typical 70kg human is 15.5 l/min^{-1} and the RMV of a rat weighing 0.35 kg is 0.2 l/min^{-1}. These values are in keeping with those within REACH guidance which reports default values of 14 l/min^{-1} for a standard human respiratory rate and 20.8 l/min^{-1} for a person undertaking light activity (worker). When calculating the RMV for an experimental animal, the body weight can be based upon a standard convention which normally reports a rat weight as between 250g and 350g or may be subject specific as a

record of the individual animal weight is required for compliance to OECD test guidelines.



9.2.5 **Figure 2: Route of extrapolation from experimental NOAEL derived from animal exposure to human equivalent aerosol concentration taking into account species specific factors.** ***Adapted from Oller and Oberdörster (2010)***

9.2.6 The next step is calculating the inhaled dose over an average time period which for a worker is considered 8 hrs/ day and for the general population this is considered to be 24 hrs (continuous exposure). A typical exposure duration for a rodent in a non-acute exposure scenario is 6hrs/day (e.g. OECD TG 412). The inhaled dose is calculated by multiplying the RMV by the exposure duration (in minutes) to derive the total volume of air inhaled per exposure day.

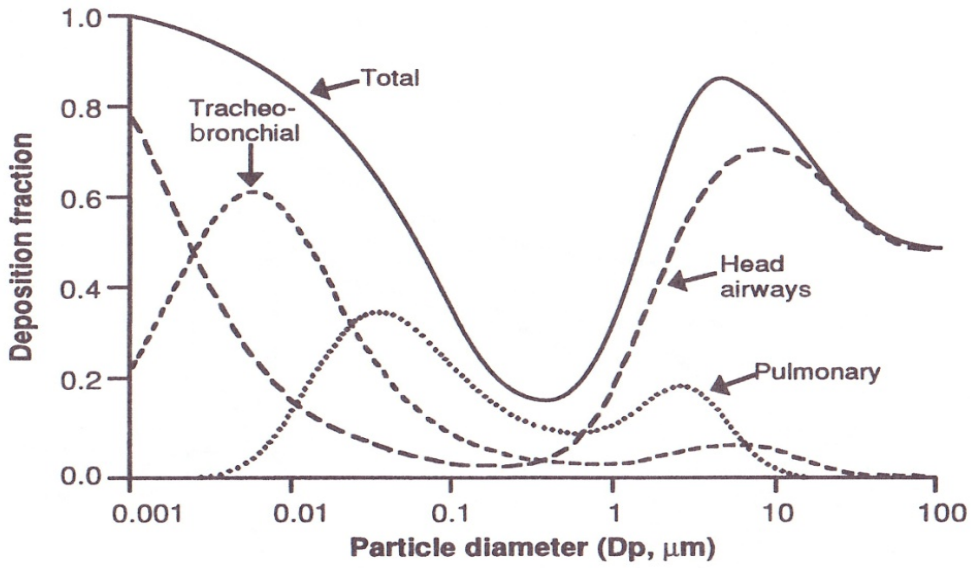
9.2.7 Taking firstly the animal, based on an exposure duration of 360 minutes (6hrs), the inhaled volume of a rat would be 0.072 m^3/day. Within the study of Pauluhn (2010), the aerosol concentration resulting in a NOAEL was 0.1 mg/m^3 and as such, the rodents within the study inhaled a dose of 0.0072 mg of CNT during an average 6hr day.

9.2.8 As figure 2 shows, the D_{ae} of a particle influences what proportion or fraction of the inhaled dose deposits in the different zones of the respiratory tract. The graph shows that with larger particles (~10 µm) the majority of deposition occurs within the pharyngeal region of the respiratory system without penetrating the conducting airways. As particle size reduces into the respirable range (<3 µm), deposition in pulmonary region increases. The largest level of deposition is at the smaller sub-micron size range, with particles able to penetrate the trachea-bronchial and alveolar regions. When particle size decreases further (<0.2 µm), deposition by Brownian diffusion increases and a larger proportion of particles deposit in the upper respiratory tract. Deposition of particles in the range > 0.5 µm is related to aerodynamic diameter whilst smaller particles of less than 0.5 µm deposition is related to its diffusion equivalent diameter (Gehr, Brand, & Heyder 2000). This metric relates to the displacement sustained by a particle due to air molecules causing these smaller particles can behave more like a gas.

9.2.9 Whilst figure 3 shows the fractional deposition by particle D_{ae} in humans, data also exists showing fractional deposition in experimental animals, for example see Miller et al. 2000. Another approach is the use of modelling software such as the Multiple-Path Particle Dosimetry Model (MMPD; Applied Research Associates, Inc.). The D_{ae} may be reported for the primary particle in the case of mono-dispersed non-agglomerated particles or the diameter and density of

an agglomerate/ aggregate. When calculating the deposition fraction, it is the aerosol form of the particle/ agglomerate which dictates the particle deposition. As such, if a primary particle size is reported yet the aerosol form is a large agglomerate, then this will invalidate the deposition fraction. When performing inhalation exposure, OECD test guidelines require experimenters to record and report a range of inhalation data such as particle distribution, mass median aerodynamic diameter (MMAD) and geometric standard deviation as well as primary particle size analysis.

9.2.10 Within the NEDO sponsored studies (Hanai et al 2009; Kobayashi et al. 2009), the deposition fraction in rats was established from Miller at al. 2000 at a value of 10% based on a particle mass mean aerodynamic diameter (MMAD) of 1.44 µm. The Pauluhn study in contrast used the MPPD model and estimated a deposition fraction for a particle with a 3 µm MMAD of 5.7% in rats and 11.8% in humans in the pulmonary region. With these values it is possible to calculate what proportion of the inhaled dose depositing within the lung. Using the Pauluhn value of 5.7 %, the deposited fraction of the 0.0072 mg inhaled dose rate is 0.0004 mg.



9.2.11

9.2.12 **Figure 2: Deposition of particles in the human respiratory tract.** The fractional particle deposition in the different regions of human respiratory tract based on particle size is shown. Reproduced from (Snipes 1994).

9.2.13 Particles depositing within the lung are cleared and the rate of this clearance is dependent on the zone of deposition. Particles depositing in the upper airways are cleared far more rapidly (24-48 hrs; Geiser and Kreyling 2010) as the particles are trapped by mucus and rapidly moved up the respiratory tract by the beating action of cilia present on the cell surface of these larger, ciliated airways. Particle clearance in the proximal alveolar region is much slower (Donaldson et al. 2008) as it mediated by alveolar macrophages which engulf the deposited particles and move them up to the mucocilary escalator. As a result, particles depositing within this region are retained for a greater length of time and as such exposure of the lung to the particles is greater. As particles are cleared, there is obviously a reduction in dose and as such in order to establish the true driving dose behind an effect (or lack of), one must factor in particle clearance to give a retained dose. Experimentally derived clearance half-times ($t½$) are available and have been suggested as ~ 60 days for rats within the Pauluhn study based on the observations of Donaldson et al. (2008), Stober and McClellan (1997) and Brown et al. (2005). The clearance half time for humans is suggested to be approximately

320 days in humans (Bailey, Fry and James 1982) and suggested as 1 year in the Pauluhn paper.

9.2.14 In order to calculate the retained dose one has to take into account the clearance rate (*k*). For a rat, based on a clearance half time of 60 days the clearance rate is 0.0116 using the following equation:

$$k = \ln(2)/ t½$$

9.2.15 The deposited dose rate is divided by the clearance rate to give the retained dose of 0.035 mg in the rat lung (0.0072/0.0116 = 0.035). This steady state occurs as a result of equilibrium between the incoming deposited dose rate and the outgoing clearance rate. As such, at any point after this steady state has developed, the rat lung would contain a total retained dose of 0.035 mg. This equilibrium occurs as a result of continued deposited dose over a long period, e.g. chronic exposure. In the case of acute exposure, a steady state would not have time to occur and as such a different value would be required to calculate the specific retained dose.

9.2.16 As the derived value is the retained dose within a rat based, this value needs to be normalised in such a way to enable accurate extrapolation to a retained human dose. The approach taken by many, including both Pauluhn and NEDO is to normalise based on body weight, often at the initial calculation of inhaled dose rate (to give a value per m^3/kg/day). The approach discussed herein calculates an inhaled and deposited dose rate and retained dose per rat, not per kg. At this stage, once a retained dose has been calculated, the dose can be normalised using a range of parameters including body weight but as the whole body is not the target organ, this may be somewhat inaccurate. As the target tissue is the lung, it would perhaps be more prudent to normalise and scale based on the lung as this in the organ receiving the dose.

9.2.17 Many lung parameters could be used to normalise such as lung weight, lung volume, lung surface area or perhaps a component of the lung such as lung alveolar macrophage volume. A further degree of accuracy could be obtained by normalising based on the specific region of deposition/ interest, such as the proximal alveolar region (PAR) which has been suggested to be a key site

for the retention of respirable particles, as it receives high deposition but has slow clearance compared to the larger airways (Donaldson et al. 2008). The choice of normalisation parameter could be open to expert judgement depending one the nature of the effect of interest and the driving component.

9.2.18 Using the approach of Pauluhn and NEDO, we shall normalise our retained dose on surface area based on a rat weighing 0.35 kg (which would correspond to a RMV of 2 l/min^{-1}). This results in a normalised retained dose of 0.1 mg of CNT per kg body weight resulting in no observable effects. If we extrapolate this to a human we can see that the human equivalent retained dose is 7 mg based on an average human weight of 70 kg.

9.2.19 As an internal dose is not suitable for setting and monitoring exposure limits, the external dose which generates the calculated retained dose needs to be derived. This is again based upon physiological, experimental and exposure parameters. Therefore the first step, is calculating the deposited dose which would result in a retained dose of the derived value based on the clearance rate of a typical human. This is then followed by calculating the inhaled dose that would result in the calculated deposited dose. To do this the deposition rate must again be calculated using the same aerodynamic diameter as the experimental system but instead for a human species. Once the inhaled dose rate is calculated, the human equivalent external exposure level which would result in the calculated inhaled dose rate is then derived. As with the initial calculations for the experimental animal, this calculation is based upon the RMV and the exposure duration over a period of a day. The RMV is calculated using the same equation as previously reported (Bide et al. 2000) but instead for a typical 70kg human which corresponds to a greater RMV. In addition the typical exposure period for a human worker (8hrs/day) is longer than that of an animal exposure period (6hr/per day) and as such the final calculation is based upon 480 minutes rather than 360 minutes. This results in a HED causing no observable adverse effects.

9.2.20 These calculations using the data presented within Pauluhn (2010) are summarised in the following:

9.2.21 Experimental/ Exposure information

- Rodent body weight – 0.35 kg
- Human Body weight – 70 kg
- Rodent exposure duration – 360 minutes (6hr/day)
- Worker exposure duration – 480 minutes (8hr/day)
- MMAD - ~3 µm
- Rat lung elimination halftime (*t* ½) – 60 days
- Human lung elimination halftime (*t* ½) – 365 days

9.2.22 Calculated information

9.2.23 *Respiratory Minute Volume*

9.2.24 The RMV is calculated based upon the generic rat weight of 0.35 kg and generic human weight of 70kg using the following equation of Bide et al. 2000. This results in the following species specific RMV's:

- $RMV_{rat} = 0.499 \times 0.35^{0.809} = 0.2$ l/min
- $RMV_{human} = 0.499 \times 70^{0.809} = 15.5$ l/min

9.2.25 As the unit of measurement for external exposure is m^3 rather than litres; the RMV is converted from l/min to m^3/min by the equation:

$$RMV_{m3/min} = RMV_{l/min} / 1000$$

9.2.26 This results in an RMV for a 0.35kg rat of 0.0002 m^3/min and a 70kg human as 0.0155 m^3/min.

9.2.27 Within the REACH guidance, the respiratory rate for a worker undertaking light activity is greater than that for a person at rest and the RMV calculate above corresponds to that of a person at rest. The REACH default respiratory volume of a worker over a period of an 8hr working day is 10 m^3 which

corresponds to an RMV of 0.0283 m^3/min. This daily respiratory rate is also used by Pauluhn and is used within the following example.

9.2.28 Lung Deposition

9.2.29 The rat and human alveolar lung deposition fractions shown were calculated by Pauluhn using MMPD software:

- Rat lung alveolar deposition fraction – 5.7 %
- Human lung alveolar deposition fraction – 11.8 %

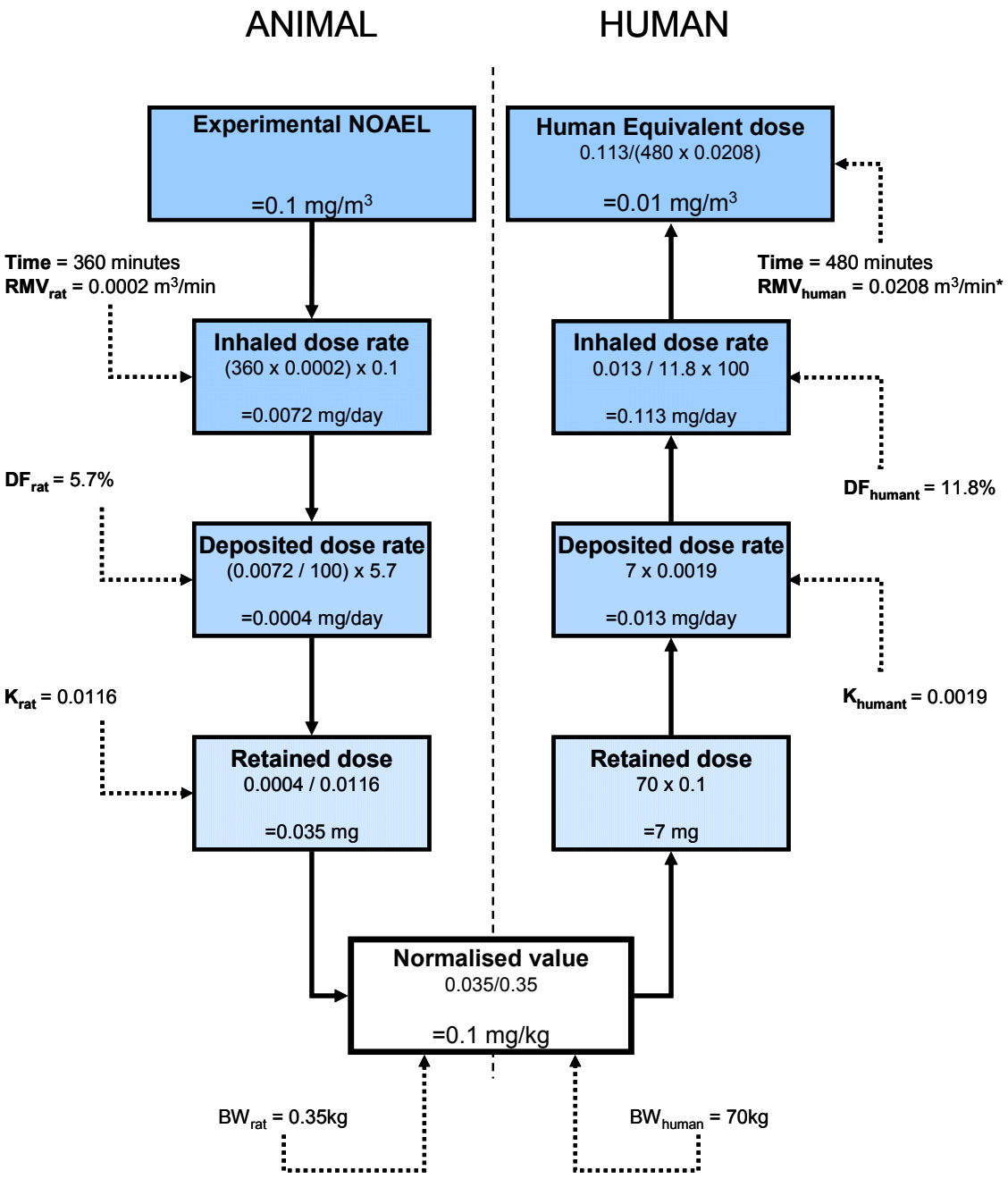
9.2.30 *Clearance rate (k)*

9.2.31 The elimination halftime reported in Pauluhn 2010a for a rat was 60 days and the elimination half time of a human was reported as ~ 365 days based on the data of Snipes et al. (1989) which is in agreement with the literature and is subsequently used here. Based on the above equation the clearance rates for rats and humans are:

$$K_{rat} = \ln(2)/60 = 0.0116$$

$$K_{human} = \ln(2)/365 = 0.0019$$

9.2.32 Based on the above experimental and calculated parameters, the HED based on rat NOAEL of 0.1 mg/m^3 is summarised in figure 3.



9.2.33 **Figure 3: Diagram of the computational process for deriving a human equivalent exposure based on an experimentally derived rat NOAEL from Pauluhn 2010. *human RMV based upon a higher ventilation rate than a standard 70kg human resting.**

9.2.34 As a process, this would result in a more accurate calculation of the interspecies difference when extrapolating from a test animal to a human taking into account corrections for time and ventilation rates. However, other differences may also need to be addressed between species such as

toxicokinetic and toxicodynamic differences. The approach of both Pauluhn and NEDO was that the effects seen were localised and as a result of the deposited dose within the lung. As such no additional correction for differences in toxicokinetics would be required and this is a perfectly valid conclusion based on the evidence shown within the Pauluhn study 2009 which detected no systemic effects. However such a conclusion would need to be based upon valid scientific justification, as presented with the Pauluhn study, and in situations where systemic effects are noted or translocation of particles is thought to be a driving force behind an adverse effect, an additional correction for toxicokinetics may be required. In relation to nanomaterials, it is hypothesised that increased translocation and systemic availability may occur due to their small size. However there is considerable uncertainty if this is truly the case and to what extent differences occurs based on particle size, shape, surface properties and material type.

9.2.35 Toxicodynamics relates to differences in species sensitivities to an agent. In the case of rats an increased sensitivity has been well documented in relation to lung overload. The phenomenon of rat lung overload is discussed more fully in the RNC/RIP-oN2/FPR/1/FINAL report (section 4.1.211, page 229) and is a situation which can occur during repeated exposure to high concentrations of poorly soluble low toxicity particles. At the point of overload, the steady state of particle deposition and particle clearance shifts in favour of particle deposition as clearance slows and then fails leading to a rapid increase in retained dose, driving an adverse effect such as inflammation. Humans and indeed other rodent species are more resistant to this effect and as such a rat is indentified as a more sensitive species. The approach of NEDO was to assign a toxicodynamic value of 1 to their calculation which due to the increased sensitivity of rats to lung overload they suggested erred on the side of caution.

9.2.36 Within the Pauluhn study the difference in sensitivity to lung overload were accounted for using a direct extrapolative calculation based on differences in alveolar macrophage volume and number. This approach was taken as within the alveolar region of the lung it is the alveolar macrophage which is tasked with clearing deposited particles and it is this clearance mechanism which becomes overloaded. Of the various driving mechanism of lung overload, as

discussed in RNC/RIP-oN2/FPR/1/FINAL (section 4.1.211), volumetric overload of the macrophage is considered to be a potential driver and is the driver attributed within the Pauluhn study. Volumetric overload is considered to begin once roughly 6% of the macrophage volume has been filled with particles resulting in a reduction of macrophage mobility. Once 60% of the macrophage is filled, macrophage clearance ceases (Morrow 1988). As pointed out in the Pauluhn study, there are differences within the macrophage populations in humans and rats which generate an interspecies difference. In humans macrophages are larger and more numerous than in rats and as such, due to the volumetric hypothesis used by Pauluhn, these differences were accounted for a greater resistance to overload in humans. By calculating the total macrophage volume (total macrophage number x average macrophage volume) Pauluhn noted that humans had a ~6-fold higher total macrophage volume than rats. This is an interesting approach and of debatable merit as this correction is applied within the Pauluhn study at a concentration that does not result in overload (the NOAEL) but rather at a normal steady state. It could be argued that such a difference is already accounted for because within this region of the lung, clearance is via macrophages and within Pauluhn's calculations the difference in clearance rate is already accounted for. Indeed when looking at the difference in macrophage capacity (as a figure of macrophage number and volume) as outlined by Pauluhn, this actually corresponds very well to the difference in clearance kinetics. Specifically the difference between macrophage capacity and clearance rate is 5.75 and 5.27 respectively.

9.2.37 Depending on the driving factor behind the observed affect, other toxicodynamic differences may need to be accounted for. In the case of a soluble component driving an adverse effect, a species difference in the ability or rate of metabolism of the soluble component would be an example of a toxicodynamics difference which would need to be accounted for.

9.2.38 The final human equivalent aerosol concentration would also be subject to assessment factors accounting for further uncertainties which cannot be addressed by extrapolation. These would include intraspecies differences, differences in duration of exposure, issues relating to dose response and quality of the whole database; all of which would still be equally valid and

require careful consideration. In relation to these further uncertainties the REACH approach could be followed either through the use of substance specific information to deviate from the default factors or the use of default factors in the absence of such information. In the example outlined above, a HED was calculated experimental animal data using information presented in Pauluhn (2010). This derived value is now subject to the following REACH assessment factors based on the reasoning outlined in RNC/RIP-oN3/C1/2/FINAL report to derive a hypothetical derived no effect level (DNEL):

- Intraspecies differences -5
- Differences in duration of exposure -2
- Issues related to dose-response -1
- Quality of whole database -1

9.2.39 These additional assessment factors are calculated to generate an overall assessment factor using the following equation:

- Overall assessment factor = $AF_{\text{intraspecies (worker)}} \times AF_{\text{duration (sub-chronic to chronic)}} \times AF_{\text{dose-response}} \times AF_{\text{database quality}}$) = 5*2*1*1 =10

9.2.40 This overall assessment factor is then applied to the calculated HED as follows:

- 0.01/ 10 = 0.001 mg/m^3

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