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**ENVIRONMENT DIRECTORATE  
JOINT MEETING OF THE CHEMICALS COMMITTEE AND  
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY**

**APPROACHES ON NANO GROUPING/ EQUIVALENCE/ READ-ACROSS CONCEPTS BASED ON  
PHYSICAL-CHEMICAL PROPERTIES (GERA-PC) FOR REGULATORY REGIMES**

**Results from the Survey  
Series on the Safety of Manufactured Nanomaterials  
No.64**

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ENV/JM/MONO(2016)3  
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**OECD Environment, Health and Safety Publications**

**Series on the Safety of Manufactured Nanomaterials**

**No. 64**

**APPROACHES TO DEVELOP OR USE CONCEPTS OF GROUPING, EQUIVALENCE  
AND READ-ACROSS BASED ON PHYSICAL-CHEMICAL PROPERTIES (GERA-PC)  
OF NANOMATERIALS FOR THEIR HUMAN HEALTH AND ECOSYSTEM HAZARD  
ASSESSMENT IN REGULATORY REGIMES: ANALYSIS OF A SURVEY**

**IOMC**

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

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- Nos. 44-54, These items are the dossiers derived from the Testing Programme on Manufactured Nanomaterials which are located at:  
<http://www.oecd.org/chemicalsafety/nanosafety/testing-programme-manufactured-nanomaterials.htm>
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The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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## FOREWORD

The OECD Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology (the Joint Meeting) held a Special Session on the Potential Implications of Manufactured Nanomaterials for Human Health and Environmental Safety (June 2005). This was the first opportunity for OECD member countries, together with observers and invited experts, to begin to identify human health and environmental safety related aspects of manufactured nanomaterials. The scope of this session was intended to address the chemicals sector.

As a follow-up, the Joint Meeting decided to hold a Workshop on the Safety of Manufactured Nanomaterials in December 2005, in Washington, D.C. The main objective was to determine the “state of the art” for the safety assessment of manufactured nanomaterials with a particular focus on identifying future needs for risk assessment within a regulatory context.

Based on the conclusions and recommendations of the Workshop [ENV/JM/MONO(2006)19] it was recognised as essential to ensure the efficient assessment of manufactured nanomaterials so as to avoid adverse effects from the use of these materials in the short, medium and longer term. With this in mind, the OECD Council established the OECD Working Party on Manufactured Nanomaterials (WPMN) as a subsidiary body of the OECD Chemicals Committee in September 2006. This programme concentrates on human health and environmental safety implications of manufactured nanomaterials (limited mainly to the chemicals sector), and aims to ensure that the approach to hazard, exposure and risk assessment is of a high, science-based, and internationally harmonised standard. This programme promotes international co-operation on the human health and environmental safety of manufactured nanomaterials, and involves the safety testing and risk assessment of manufactured nanomaterials.

This document presents responses to, and findings from, a questionnaire survey on approaches to develop or use concepts of grouping, equivalence and read-across based on physical-chemical properties (GERA-PC) of nanomaterials for their human health and ecosystem hazard assessment in regulatory regimes, conducted by the WPMN from October to December 2013.

The survey was proposed following the results of the WPMN work on risk assessment approaches to strengthen and enhance regulatory risk assessment capacity, which were made publicly available in the documents i) "*Important Issues on Risk Assessment of Manufactured Nanomaterials*" [ENV/JM/MONO(2012)8] and ii) "*Co-operation on Risk Assessment: Prioritisation of Important Issues on Risk Assessment of Manufactured Nanomaterials -- Final Report*" [ENV/JM/MONO(2013)18].

This document is being published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology.

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## EXECUTIVE SUMMARY

1. One of the objectives of the OECD WPMN project on Co-operation on Risk Assessment and Regulatory Programmes is to develop risk assessment approaches to strengthen and enhance regulatory risk assessment capacity.

2. The current document presents the information obtained from a questionnaire survey on approaches to develop or use concepts of grouping, equivalence and read-across based on physical-chemical properties (GERA-PC) of nanomaterials for their human health and ecosystem hazard assessment in regulatory regimes, conducted by the WPMN from October to December 2013. The findings are summarised in this document (see Annex for full responses).

3. The questionnaire contained three sections related to GERA-PC concepts of nanomaterials.

- **Section 1: Present use of GERA-PC concepts.** This section aimed to summarise information from respondents regarding which and how GERA-PC concepts of nanomaterials are employed for human and ecosystem health hazard assessment in regulatory regimes. The information includes the main issues that hampered the development of GERA-PC approaches in regulatory regimes. Respondents were also invited to indicate their general views on GERA-PC concepts of nanomaterials in relation to regulatory regimes.
- **Section 2: R&D activities on GERA-PC concepts.** This section aimed to summarise information from respondents regarding finished, on-going, or planned R&D activities on a concept of GERA-PC of nanomaterials for their human health and ecosystem hazard assessment. The information includes the main issues that hampered the development of GERA-PC approaches.
- **Section 3: Other information on GERA-PC concepts.** This section aimed to complement the above two sections by providing details, explanations or comments as well as information about cases where GERA-PC concepts of nanomaterials are effectively used for their human health and ecosystem hazard assessment in regulatory regimes other than respondents'.

4. By 3 December 2013, thirteen (13) responses were received from eight OECD member countries, one regional organisation, and one OECD partner, namely, Australia, Canada, Denmark, Germany, Japan, Switzerland, the United Kingdom (UK), the United States (US), the European Union (EU), and the Business and Industry Advisory Committee to the OECD (BIAC).

5. With regard to the present use of GERA-PC concepts, four member countries and a regional organisation responded that those were either in use or under preparation for use in hazard assessments in their regulatory regimes. Some member countries made reference to examples of the use of the GERA-PC concept by other organisations.

6. Six member countries and a regional organisation reported various R&D activities aimed to support the development of GERA-PC concepts for regulatory purposes. Some of those activities were reported by more than one respondent.

7. Additional responses to some open-ended questions were provided, addressing needs and challenges in the development and regulatory implementation of GERA-PC concepts as well as views on limitations and alternatives to those concepts. To identify common issues, these additional responses were "mapped" to a limited number of "issues" such as: (1) Scientific challenges; (1.1) Comprehensive and reliable data-sets with standardised testing methods; (1.2) Mechanistic understanding; (1.3) Dealing with surface modifications / properties; (2) Technical challenges, i.e., Sample preparation and material characterisation; (3) Regulatory implementation; and (4) Other suggestions.

8. Preliminary survey results including "issues" above were briefly presented at the OECD Expert Meeting on Categorisation of Manufactured Nanomaterials on 17 September 2014 in Washington D.C., US.

## I. INTRODUCTION AND BACKGROUND

9. There are plenty of potential nanomaterials of various chemicals and also of the same chemical, with distinctly or slightly different physical-chemical properties contributing to differences in their hazardous properties. This leads to increased testing efforts and thus animal use when traditional human health and ecosystem hazard assessments are performed for each of these different materials.

10. The OECD Working Party on Manufactured Nanomaterials (WPMN) includes the project "Risk Assessment and Regulatory Programmes" whose objectives include the evaluation of risk assessment approaches for manufactured nanomaterials through information exchange and the identification of opportunities to strengthen and enhance risk assessment capacity. In this area of work, the WPMN published the documents, "Important Issues on Risk Assessment of Manufactured Nanomaterials" released in March 2012 [ENV/JM/MONO(2012)8], and "Co-operation on Risk Assessment: Prioritisation of Important Issues on Risk Assessment of Manufactured Nanomaterials - Final Report" released in August 2013 [ENV/JM/MONO(2013)18].

11. The 2013 report analysed and concluded that "*Physico-chemical properties (and nanomaterial identity) was identified as a priority [...] Major gaps remain in understanding how traditional physico-chemical approaches can be used to assess the behaviour of nanomaterials, i.e., if and what physico-chemical properties are predictors of (eco)toxicity and environmental behaviour. [...] It is proposed that the [...] projects [...] address how to use physicochemical data for more efficient assessment of potential hazards [...] to support the regulatory/scientific risk assessment of nanomaterials. [...] [The] projects supporting physicochemical aspects will also promote WPMN work on grouping of nanomaterials.*"

12. Accordingly, at the 11th meeting of the WPMN in February 2013, it was agreed the WPMN that a survey would be initiated under the lead of Japan, as the third pilot project for the priority issues, addressing the issue of grouping based on physical-chemical properties. This resulted in the survey questionnaire, which was sent to all WPMN Delegations on 1 October 2013.

13. The objective of the survey was to develop a baseline for a common approach and guidance for grouping, equivalence and read-across based on physical-chemical properties (referred to as GERA-PC) of manufactured nanomaterials. In particular, the survey was intended:

- to compile member countries' approaches to develop or use concepts of GERA-PC of nanomaterials for their human health and ecosystem hazard assessment in regulatory regimes;
- to identify resources that may serve to develop or use these concepts (including research projects and data); and
- to form common understanding of this subject-matter including the terminology.

14. The scope of the survey covers member countries' approaches to develop or use GERA-PC concepts of nanomaterials for their human health and ecosystem hazard assessment in regulatory regimes, which can provide alternatives to testing individual nanomaterials and as a result should lead to a decrease in the use of animal testing. The questionnaire consists of three Sections:

- Section 1 Presents the use of GERA-PC concepts
- Section 2 R&D activities on GERA-PC concepts, and
- Section 3 Other information on GERA-PC concepts.

In these Sections, the following four categories of concepts of grouping, equivalence and read-across are used:

- **Concept of grouping:** This may be a category approach or an analogue approach, where nanomaterials are grouped based on their physical-chemical properties;
- **Concept of equivalence:** The equivalence of new and known nanomaterials is assessed on the basis of physical-chemical property criteria;
- **Concept of read-across:** This may be a technique of read-across, trend analysis or QSAR, e.g. data from a nanoform is read-across to another nanoform or data from a non-nanoform is read-across to a nanoform of the material; and
- Any other concept of similar nature.

15. In the survey questionnaire, there were explanations of terminology regarding concepts of grouping and read-across:

- **Analogue approach:** When the focus of the assessment is on filling data gaps for one specific chemical, empirical data from one or more similar chemical(s) ("the analogue(s)") or "source" chemical can be used to predict the same endpoint for the "target" chemical, which is considered to be "similar." This analogue approach is useful when the target and source chemicals share a known common mode (and/or mechanism) of action, and the adverse effect(s) driven by this mode (and/or mechanism) of action is evaluated. The analogue approach could also be used in the absence of effects or when no specific mode (and/or mechanism) of action is expected.
- **Category approach:** Chemicals whose physical-chemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or "category" of chemicals. The assessment of chemicals by using this category approach differs from the approach of assessing them on an individual basis, since the properties of the individual chemicals within a category are assessed on the basis of the evaluation of the category as a whole, rather than based on measured data for any one particular chemical alone.
- **Read-across** is a method of filling in data gaps for a chemical by using surrogate data from another substance. Read-across can be between two chemicals or through a group or category of chemicals. The groups are selected on the assumption that the properties of a series of chemicals with common structural features will show similar trends in their physical-chemical properties and in their toxicological effects or environmental fate properties.
- For a given category endpoint, the category members are related by a trend such that the properties of the category members change in a predictable manner and there is a pattern in the changing potency of the properties across the category. The trend could be related to molecular mass, carbon chain length, or to some other physical-chemical property. For example a category with increasing chain length, with a common functional group, will affect solubility / logKow, which in turn may

affect bioavailability and hence toxicity, both mammalian and aquatic. Analysis of these changes is referred to as **trend analysis**.

- A structure-activity relationship (SAR) is a qualitative relationship that relates a (sub)structure to the presence or absence of a property or activity of interest. SARs can be helpful in the qualitative evaluation of the analogues identified as belonging to a category. SARs have been encoded and implemented as "profilers" within expert systems including the OECD QSAR Toolbox. A quantitative structure-activity relationship (**QSAR**) is a quantitative (mathematical) relationship between a numerical measure of chemical structure, and/or a physicochemical property, and an effect/activity. QSARs often take the form of regression equations, and can make predictions of effects/activities that are either on a continuous scale or on a categorical scale.

16. Further details of concepts of grouping and read-across can be seen in an OECD document "Guidance on grouping of chemicals, Second edition" released in April 2014 [ENV/JM/MONO(2014)4], which also includes "Initial considerations applicable to manufactured nanomaterials".

## II. SUMMARY OF RESPONSES

17. By 3 December 2013, thirteen responses were received from eight OECD member countries, one regional organisation, and one OECD partner, namely, Australia, Canada, Denmark, Germany, Japan, Switzerland, the United Kingdom (UK), the United States (US), the European Union (EU), and the Business and Industry Advisory Committee to the OECD (BIAC). All the responses, with simplified text of the questionnaire, are compiled into Chapter VIII Annex.

18. With regard to the present use of concepts of grouping, equivalence and read-across based on physical-chemical properties (GERA-PC), five member countries or regional organisations responded that those were either in use or under preparation for use in hazard assessments in their regulatory regimes. Some member countries made reference to examples of the use of the GERA-PC concept by other organisations. A detailed description is provided in Chapter IV.

19. Various R&D activities aimed to support the development of GERA-PC concepts for regulatory purposes were reported. Some of those activities were reported by more than one respondent. Chapter V provides a consolidated list of reported research activities in the field.

20. Additional responses to some open-ended questions were provided, addressing needs and challenges in the development and regulatory implementation of GERA-PC concepts as well as views on limitations and alternatives to those concepts. To identify common issues, these additional responses were "mapped" to a limited number of "issues", which are described in Chapter VI.

### III. USE OF GERA-PC CONCEPTS

21. In section 1 of the survey questionnaire, respondents were asked to clarify whether they were either involved in or aware of any hazard assessment in which a concept of GERA-PC was used for a nanomaterials in a regulatory context. If this was the case, the respondent was asked to identify the particular regulatory regime, the governing organisation and the type of concept applied. Various legislations with relevant experience were identified (see Table 1). In addition, it was reported that a classification scheme for nanomaterials developed by the US-Canadian Regulatory Cooperation Council (RCC) Nanotechnology Initiative is considered for nanomaterials regulated under the New Substances Programs of US and the Canadian Environmental Protection Act, 1999. The Initiative concluded in February 2014 and its outcome including the classification scheme has been used to formulate, for example, Canada's proposed approach for existing substances.

**Table 1. Legislations for which GERA-PC concepts are used for nanomaterials**

<b>Regulatory regime and approach</b>	<b>Governing organisation</b>	<b>Type of approach</b>
REACH (1907/2006) <sup>1</sup> Article 13 and Annex XI	EC and ECHA	Grouping, read-across, QSAR and other alternative methods
CLP Regulation (1272/2008)	EC and ECHA	QSAR and other category approaches
Cosmetics Products Regulation (1223/2009)	EC	"a category approach to risk assessment is currently not feasible for nanomaterials, and risk assessment of each nanomaterial needs to be carried out on a case-by case basis."
Food Contact Materials Regulation (10/2011)	EC and EFSA	Read-across <sup>2</sup>
Biocidal Products Directive (98/8/EC) and Regulation (528/2012)	EC and ECHA, EU-Member States	Read-across (e.g. nanoscale silica / SAS)
Plant Protections	EC and EFSA	

<sup>1</sup> Also pointed out by UK and BIAC (CEFIC).

<sup>2</sup> Based on EFSA Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain.

Product Regulation (1107/2009)		
§ 31 German Plant Protection Law	Federal Office of Consumer Protection and Food Safety, Germany	Grouping and read-across
Toxic Substances Control Act (TSCA), Respirable Poorly Soluble Particulates Category	US EPA	Read-across or analogue
Industrial Chemicals (Notification and Assessment) (ICNA) Act, 1989 Human health hazard assessment and classification of carbon nanotubes (CNTs) <sup>3</sup>	National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Australia	Grouping (or categorisation) and read-across
Environmental assessments for NICNAS	Australian Government, Department of the Environment	Categorisation and grouping
<b><u>bilateral cooperation</u></b> Classification scheme for nanomaterials regulated under the New Substances Programs of US (TSCA) and the Canadian Environmental Protection Act, 1999	Regulatory Cooperation Council (RCC) Nanotechnology Initiative / US EPA, Environment Canada and Health Canada.	Grouping and read-across The Initiative's final report was published in March 2015, which can be found at <a href="http://nanoportals.gc.ca/default.asp?lang=En&amp;n=5A56CB00-1">http://nanoportals.gc.ca/default.asp?lang=En&amp;n=5A56CB00-1</a>
<b><u>pointed out by Germany</u></b> Decision	US EPA, Office of Pesticide Programs,	Grouping and read-across Published information on inhalation and oral toxicity of other nanosilver particles was used to characterise the risk from

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<sup>3</sup> Also pointed out by Germany.

Document: Conditional Registration of HeiQ AGS-20 as a Materials Preservative in Textiles, 1 December 2011 (Docket ID No. EPA-HQ-OPP- 2009-1012-0064) / Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)	Antimicrobials Division	exposures to nanosilver that may break away from the nanosilver composite AGS-20 or treated articles or arise during production. An additional (maximum) uncertainty factor of 10 was applied for quality of database.
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22. Respondents were also invited to point out specific examples or regulatory frameworks in which GERA-PC concepts were used effectively for nanomaterial assessment. Four responses mentioned:

- "Human Health Hazard Assessment and Classification of Carbon Nanotubes" prepared by Australia's NICNAS in October 2012  
[http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/725/Human\\_Health\\_Hazard\\_Assessment\\_and\\_Classification\\_of\\_Carbon\\_%20Nanotubes.pdf](http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/725/Human_Health_Hazard_Assessment_and_Classification_of_Carbon_%20Nanotubes.pdf)
- "Decision Document: Conditional Registration of HeiQ AGS-20 as a Materials Preservative in Textiles" published by US EPA on 1 December 2011 (EPA Docket ID No. EPA-HQ-OPP-2009-1012-0064) <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-1012-0064>
- Registration dossiers according to the EU REACH Regulation, for which guidance explicitly foresees the use of grouping and read-across for chemicals and should thus allow application of the concepts for nanomaterials (2 respondents).

23. Finally, a number of relevant guidance documents were identified. Seven of these are specifically aimed at nanomaterials while six others are more general for chemicals but do not exclude nanomaterials.

**nanospecific:**

- "Guidance on information requirements and chemical safety assessment. Appendix R7-1 Recommendations for nanomaterials applicable to: Chapter R7a Endpoint specific guidance."  
[http://echa.europa.eu/documents/10162/13632/appendix\\_r7a\\_nanomaterials\\_en.pdf](http://echa.europa.eu/documents/10162/13632/appendix_r7a_nanomaterials_en.pdf)
- "Guidance on information requirements and chemical safety assessment. Appendix R7-1 Recommendations for nanomaterials applicable to: Chapter R7b Endpoint specific guidance."  
[http://echa.europa.eu/documents/10162/13632/appendix\\_r7b\\_nanomaterials\\_en.pdf](http://echa.europa.eu/documents/10162/13632/appendix_r7b_nanomaterials_en.pdf)
- "Guidance on information requirements and chemical safety assessment. Appendix R7-2 Recommendations for nanomaterials applicable to Chapter R7c Endpoint specific guidance"  
[http://echa.europa.eu/documents/10162/13632/appendix\\_r7c\\_nanomaterials\\_en.pdf](http://echa.europa.eu/documents/10162/13632/appendix_r7c_nanomaterials_en.pdf)

- "Guidance on information requirements and chemical safety assessment. Appendix R14-4 Recommendations for nanomaterials applicable to Chapter R.14 Occupational exposure estimation"  
[http://echa.europa.eu/documents/10162/13643/appendix\\_r14\\_05-2012\\_en.pdf](http://echa.europa.eu/documents/10162/13643/appendix_r14_05-2012_en.pdf)
- "Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain" <http://www.efsa.europa.eu/en/efsajournal/doc/2140.pdf>
- "Guidance on the safety assessment of nanomaterials in cosmetics" (SCCS/1484/12)  
[http://ec.europa.eu/health/scientific\\_committees/consumer\\_safety/docs/sccs\\_s\\_005.pdf](http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_005.pdf)
- "Human health hazard assessment and classification of carbon nanotubes (CNTs)"  
<http://www.safeworkaustralia.gov.au/sites/swa/about/publications/pages/human-health-hazard-assessment-and-classification-of-carbon-nanotubes>

**general:**

- "Guidance on information requirements and chemical safety assessment, chapter R.6"  
<http://echa.europa.eu/en/support/grouping-of-substances-and-read-across>
- "Practical Guidance 6. How to report read-across and categories"  
[http://echa.europa.eu/documents/10162/13655/pg\\_report\\_readacross\\_en.pdf](http://echa.europa.eu/documents/10162/13655/pg_report_readacross_en.pdf)
- "Practical guide 4: How to report data waiving"  
[http://echa.europa.eu/documents/10162/13655/pg\\_report\\_data\\_waiving\\_en.pdf](http://echa.europa.eu/documents/10162/13655/pg_report_data_waiving_en.pdf)
- "Practical Guide 5: How to report (Q)SARs"  
[http://echa.europa.eu/documents/10162/13655/pg\\_report\\_qsars\\_en.pdf](http://echa.europa.eu/documents/10162/13655/pg_report_qsars_en.pdf)
- How EPA uses chemical categories and the categories document  
<http://www.epa.gov/oppt/newchems/pubs/chemcat.htm>
- Some application of the concepts of categorisation and grouping of chemical substances developed by the OECD  
<http://www.oecd.org/env/ehs/risk-assessment/groupingofchemicalschemicalcategoriesandread-across.htm>

#### IV. R&D ACTIVITIES ON GERA-PC CONCEPTS

24. In section 2 of the survey questionnaire, respondents were asked to clarify whether they were aware of any finished, on-going, or planned R&D activities on a GERA-PC concept of nanomaterials for hazard assessment. A wide range of research activities were reported that are expected to contribute to the (further) development of GERA-PC concepts or alternative approaches in the mid-term (see Table 2). In many cases, these activities are representing collaborative efforts and were thus reported by more than one respondent.

25. A significant number of R&D projects with various scientific approaches are on-going in Europe under the co-ordination of the European Commission while Canada, US, Australia and Japan run their own focused R&D projects. Overall, most activities are aimed at concepts of grouping and read-across and some in Europe and Japan are aimed at a concept of equivalence.

Table 2. Summary of R&D activities on GERA-PC concepts for nanomaterials

Member country	R&D activity	Type of approach
EU	NanoSolutions <sup>4</sup> <a href="http://nanosolutionsfp7.com/">http://nanosolutionsfp7.com/</a>	To provide a means to develop a safety classification of engineered nanomaterials based on an understanding of their interactions with living organisms at the molecular, cellular, and organism levels based on their material characteristics. It takes a systems biology approach to the issue of grouping.
	NanoPuzzles <sup>5</sup> <a href="http://www.nanopuzzles.eu">www.nanopuzzles.eu</a>	Grouping and read-across To create new computational methods for comprehensive modelling the relationships between the structure, properties, molecular interactions and toxicity of engineered nanoparticles
	Mod-ENP-Tox <a href="https://fys.kuleuven.be/vsm/modenptox/index.php">https://fys.kuleuven.be/vsm/modenptox/index.php</a>	Grouping and equivalence
	PreNanoTox <a href="http://cordis.europa.eu/projects/rcn/106196_en.html">http://cordis.europa.eu/projects/rcn/106196_en.html</a>	Grouping

<sup>4</sup> Also listed by Germany.

<sup>5</sup> Also listed by Germany.

	ModNanoTox <sup>6 7</sup> <a href="http://www.birmingham.ac.uk/generic/modnanotox/index.aspx">www.birmingham.ac.uk/generic/modnanotox/index.aspx</a>	Grouping and read-across
	MembraneNanoPart <a href="http://www.membranenanopart.eu">www.membranenanopart.eu</a>	Grouping and equivalence
	ITS-Nano <a href="http://www.its-nano.eu">www.its-nano.eu</a> ENPRA <a href="http://www.enpra.eu">www.enpra.eu</a>	Grouping and read-across
	MODERN <a href="http://modern-fp7.biocent.cat/">http://modern-fp7.biocent.cat/</a>	Grouping and read-across
	NanoTransKinetics <a href="http://www.nanotranskinetics.eu">www.nanotranskinetics.eu</a>	Equivalence biomolecular corona
Germany	COST Modena <a href="http://www.modena-cost.eu/">www.modena-cost.eu/</a>	Definition of mechanistic categories
	EU NanoSafetyCluster <a href="http://www.nanosafetycluster.eu">www.nanosafetycluster.eu</a>	Correlation of physical-chemical properties and 'biomolecular corona'
	MODERN <a href="http://modern-fp7.biocent.cat/">http://modern-fp7.biocent.cat/</a>	
	NanoMILE <a href="http://www.nanomile.eu-vri.eu/">www.nanomile.eu-vri.eu/</a>	A framework for manufactured nanomaterials classification according to their biological or environmental impacts
	UDS: Uniform Description System for Materials on the Nanoscale - A Draft Framework	Uniqueness and Equivalency
	A national project dealing with grouping concerning human health and ecotoxicity is applied. Decision on sponsoring by the Federal Ministry on Education and Research is expected end of 2013.	Relative sensitivity / toxicity in biological systems
UK	The UK REACH Competent Authority is participating in a sub-group of ECHA's Nanomaterials Working Group (NMWG).	That is looking at how read-across could be used for nanomaterials within REACH.
	European FP7 project ITS-Nano <a href="http://www.its-nano.eu/">www.its-nano.eu/</a>	Considerations on grouping and ranking
	NanoReg <a href="http://www.nanoreg.eu/">http://www.nanoreg.eu/</a>	
	NanoFATE <a href="https://wiki.ceh.ac.uk/display/nanofate/Home;jsessionid=178C95CD7C72A0189CA3F6E91FE4BDC6">https://wiki.ceh.ac.uk/display/nanofate/Home;jsessionid=178C95CD7C72A0189CA3F6E91FE4BDC6</a> <a href="http://www.nanosafetycluster.eu/eu-nanosafety-cluster-projects/seventh-framework-programme-projects/nanofate.html">www.nanosafetycluster.eu/eu-nanosafety-cluster-projects/seventh-framework-programme-projects/nanofate.html</a>	Grouping, equivalence and read-across
	NanoTOES <a href="http://www.nanotoes.eu/">www.nanotoes.eu/</a>	

<sup>6</sup> Also listed by Germany

<sup>7</sup> Also listed by the UK.

	The UK-US funded TINE project <a href="http://www.ceh.ac.uk/news/news_archive/2011_news_item_03.html">www.ceh.ac.uk/news/news_archive/2011_news_item_03.html</a>	The assessment of hazard and ultimately by relating this information to usage and fate data to the determination of risk for ecological effects in soils and surface waters
	Natural Environment Research Council environmental nanotechnology initiative projects	
	NanoMile <a href="http://www.nanomile.eu-vri.eu/">www.nanomile.eu-vri.eu/</a>	Engineered nanomaterial mechanisms of interactions with living systems and the environment
US	Ongoing work being done by UCLA on predicting toxicology of carbon nanotubes and metals and metal oxides	Read-across and analogues
	Domestic and international projects such as ToxCast, Tox21, Comptox, and work being conducted by the National Institute of Environmental Health Sciences (NIEHS)	
Canada	The Government of Canada supports the need to further explore the effects of nano-properties on organisms which will inform on read-across.	Read-across Activities investigating the effect of size and surface functionality of nanomaterials on in vitro cytotoxicity / cell viability and environmental organisms
Australia	National Enabling Technologies Strategy: Laboratory research studies on the environmental fate and transformation of manufactured nanomaterials <a href="http://innovation.gov.au/Industry/Nanotechnology/NationalEnablingTechnologiesStrategy/Pages/default.aspx">http://innovation.gov.au/Industry/Nanotechnology/NationalEnablingTechnologiesStrategy/Pages/default.aspx</a>	Categorisation of manufactured nanomaterials based on environmental behaviour
Japan	Development of innovative methodology for safety assessment of industrial nanomaterials <a href="http://metinanoen.aist-riss.jp/">http://metinanoen.aist-riss.jp/</a>	Equivalence
The ILSI Research Foundation	<b><u>pointed out by BIAC (US)</u></b> NanoCharacter <a href="http://www.ilsil.org/NanoCharacter/Pages/NanoCharacter.aspx">http://www.ilsil.org/NanoCharacter/Pages/NanoCharacter.aspx</a>	To foster the development of practices leading to better use of grouping, equivalence and read-across based on physico-chemical properties

## V. ANALYSIS OF RESPONSES

26. Besides being covered by Chapters IV and V, additional responses were provided, particularly to the following open-ended questions:

- Q1.9: Views on using the GERA-PC concepts in regulatory regimes;
- Q1.8 & Q2.5: Main issue that may hamper the development of GERA-PC approaches; and
- Q4: Other details, explanations or comments.

27. These addressed needs and challenges in the development and regulatory implementation of GERA-PC concepts as well as views on limitations and alternatives to those concepts. To identify common issues, these additional responses were "mapped" to a limited number of "issues".

28. Firstly, forty-five comments were extracted from these responses. Secondly, the following issues were identified among the comments and then comments were distributed to the most relevant issue:

(1) Scientific challenges

(1.1) Comprehensive and reliable data-sets with standardised testing methods

(1.2) Mechanistic understanding

(1.3) Dealing with surface modifications / properties

(2) Technical challenges - Sample preparation and material characterisation

(3) Regulatory implementation

(4) Other suggestions

29. Table 3 shows all the comments extracted and then distributed to the most relevant issue.

30. The issue (1.1) Comprehensive and reliable data-sets with standardised testing methods is the single most important factor to developing and utilising GERA-PC. Addressing the issues (1.2) Mechanistic understanding and (1.3) Dealing with surface modifications/properties will need more data. Several respondents noted that the issue (3) Regulatory implementation was not possible until more reliable data was available. The first issue (1.1) can be illustrated by the following responses:

- The scarcity of reliable information obtained in a controlled and standardised way for a sufficient number of chemically different nanomaterials and a variety of nanoforms. [EU]
- Data availability. For most available assays only few physical-chemical properties are measured. The available data on specific species and endpoints are very sparse. [UK]

- Lack of scientific knowledge limits the confidence / applicability of this classification scheme for hazard classification. Improved correlations between properties and effects must still be established. [US & Canada]

31. The issue (1.2) Mechanistic understanding, or understanding complex/unique characteristics of nanomaterials, is important for ultimately understanding the reliability of data-sets and any corresponding approaches for GERA-PC. For example, respondents noted the following barriers:

- An understanding of the mechanisms and processes governing nanomaterial toxicity. [Germany]
- A potential barrier might be that each nanomaterial has own specificities and hence to extend those specificities to other similar classes of nanomaterials. [BIAC Europe]
- The complexity of the behaviour of nanomaterials in the environment and how this behaviour, particular transformation processes, can influence the effects that the nanomaterial (and its transformation products) can have on biota, especially in the aquatic compartment [Australia]

32. The issue (1.3) Dealing with surface modifications/properties is a complex issue that will require data sets that account for very different physico-chemical properties that are the result of only minor surface modifications. For example, respondents said that:

- Grouping should take into account, that some nanomaterials show very different physico-chemical properties, only depending on minor surface modifications. Therefore, grouping shall not be based on a chemical composition approach alone. [Switzerland]
- Selection of parameters for surface state or surface chemistry of nanomaterials that are important for toxicity and toxicokinetics. [Japan]

33. The issue (2) Sample preparation and material characterisation is a recognised technical challenge because of the variable nature of nanomaterials. There are numerous examples of technical challenges in trying to characterise nanomaterials that have been tested. These include a lack of standards, detection limits above relevant concentrations, and how to report results. Improper characterisation of tested nanomaterials makes available data difficult to compare and used for GERA-PC. For example, respondents noted on this issue that:

- A big hurdle is the lack of proper characterisation of nanomaterials. There is no standard set for characterisation and the available data is incomplete and difficult to compare. [EU]
- Methods of measurement and sample preparation for physical-chemical property characterisation are major issues. Especially it is very difficult to achieve any kind of in situ characterisation in the more complex media (e.g. soils and sediments or even natural waters). [UK]
- The research has identified a number of technical challenges associated with evaluating the properties of nanomaterials in realistic environmental matrices which require further investigation before useful predictive rules can be developed. [Australia]

34. The issue (3) Regulatory implementation of GERA-PC is already acknowledged as a valuable tool used for assessment of chemicals by regulatory entities. GERA-PC is also being used to a limited extent for certain nanomaterials. Several respondents to the survey expected that it will be used more in the future as better data becomes available. There are several reasons for this including the fact that it is not practical to test the large number of different forms of nanomaterials. Numerous commenters also noted that a scientific justification and more reliable data would be needed before adopting a regulatory implementation of this approach. For example, respondents noted that:

- No relevant legal data requirements. [Germany]

- More is needed, namely translation of research into guidance for assessment. [Germany]
- A pragmatic approach that is driven by the available evidence and applied on a case by case basis would be more desirable. [UK]

35. The issue (4) Other suggestions includes three ponderable comments:

- Further fundamental research, possibly focussed on the most commonly encountered / most hazardous nanomaterials will be needed to accompany the development of these approaches. [UK]
- Until nano-specific practices are developed, if needed, the OECD Guidance on Grouping of Substances provides a set of useful approaches that are generally applicable to nanomaterials. [BIAC Europe & US]
- A potential barrier is gaining wide-spread acceptance of the need to promote grouping, equivalence, read-across within the research community. [BIAC US]

**Table 3. Comments extracted from the responses and distributed to issues**

<b>(1) Scientific challenges</b>
<b>(1.1) Comprehensive and reliable data-sets with standardised testing methods (13 comments)</b>
use of such concepts --- will have an expansion in its use when an adequate body of scientific information is provided. This may include the development of an appropriate number of benchmarking experimental results and a transparent and conclusive assessment of the application of such models in comprehensive risk assessments. [EU Q1.9 4)]
the scarcity of reliable information obtained in a controlled and standardised way for a sufficient number of chemically different nanomaterials and a variety of nanoforms. [EU Q1.8]
The most significant risk for the development of grouping and read-across approaches is related to inappropriateness as well as insufficient number and quality of empirical data (on physico-chemical and toxicological endpoints) that are required for constructing models. More data are required to cover the nanomaterial space in a homogeneous and continuous way so that consistent nanoparticle categories can be properly identified and read-across performed within the homogeneous families of nanomaterials. [EU Q2.5]
The present lack of a, regularly updated, large data-base possessing data of high quality (possessing the ability to be replicated), having detailed information on the physico-chemical properties of the nanomaterials under the appropriate experimental environment, as well as the changes of these properties following penetration into cells. This database should also contain the protocols of all the experiments including physico-chemical characteristics measurement [EU Q2.5]
A machine-readable format for assays data and a standardized vocabulary would help to collect all given data for specific purposes. [EU Q2.5 & UK Q2.5]
Read-across needs a suitable dataset of endpoints for comparable substances. In many cases, such data do not exist or is not comparable due to differing testing protocols. In many such cases, testing of comparable substances cannot be requested because the substances may have been marketed for a long time, etc. [Switzerland Q2.5]
Of particular importance will be to ensure that testing methodologies are appropriate. [UK Q1.9 7)]
Data availability. For most available assays only few physical-chemical properties are measured. The available data on specific species and endpoints are very sparse. [UK Q2.5]

Another potential barrier is agreement on a single set of data elements. [BIAC US Q2.5]
Testing of environmental fate and transport end-points for nanoparticles is as important as purely ecotoxicological investigations. In some cases, adequate environmental fate testing may obviate the need for extensive ecotoxicological testing. [Australia Q1.9 4)]
The research has identified a number of technical challenges associated with evaluating the properties of nanomaterials in realistic environmental matrices which require further investigation before useful predictive rules can be developed. [Australia Q2.5]
Currently, environmental risk assessment of nanomaterials does not have a comparable body of knowledge to that which exists for conventional chemical substances and which allows the reliable application of expert judgement to fill data gaps using suitable analogues. [Australia Q1.9 2)]
Lack of scientific knowledge limits the confidence/applicability of this classification scheme for hazard classification. Improved correlations between properties and effects must still be established. [US Q1.8 & Canada Q1.8]
<b>(1.2) Mechanistic understanding (5 comments)</b>
The limited scientific understanding of the differences, if any, between chemicals and nanomaterials or between different forms of the same chemical (composition) has slowed down the development of methods for nanomaterials or impeded the application of available methods which are not validated for NM. [EU Q1.8]
An understanding of the mechanisms and processes governing nanomaterial toxicity. [Germany Q2.5]
For ecotox testing, exposure relevance and time scale may be more important than endpoint selection. The main novel issue for Nano in ecotox is getting the exposure to reflect and reproduce what is going to be relevant in the environment and also that the time scales of exposure development in terms of speciation to the most toxic form may exceed the standard tests by some margin. It is normally assumed that the standard protocols will lead to worst case (toxicity) exposures for “standard chemicals”, but for nanoparticles where processes such as dissolution may lead to increasing toxicity over time this must not be assumed per se and needs checking and controlling for. [UK Q2.5]
A potential barrier might be that each nanomaterial has own specificities and hence to extend those specificities to other similar classes of nanomaterials. [BIAC Europe Q2.5]
The complexity of the behaviour of nanomaterials in the environment and how this behaviour, particular transformation processes, can influence the effects that the nanomaterial (and its transformation products) can have on biota, especially in the aquatic compartment, and the consequences this has for the risk characterisation process. The current uncertainty in the environmental behaviour of manufactured nanomaterials on a category-by-category basis significantly limits the reliability of attempts to fill data gaps using techniques such as read-across. [Australia Q1.8]
<b>(1.3) Dealing with surface modifications / properties (6 comments)</b>
In the specific case, the approach could not be applied due to lack of information about the impact of different surface modification on toxicity following repeated inhalation exposure. [Germany Q1.8]
grouping will be necessary to consider all modifications of nanomaterials. By grouping, every nanomaterial has to be addressed and unpleasant surprises limited. [Germany Q1.9 7)]
Equivalence: The high diversity of surface-modified and coated nanomaterials makes it very

difficult to define the identity of a nanomaterial based on its core constituent alone. This restriction also applies to the concept of equivalence to corresponding macroscopic forms of a nanomaterial. Furthermore, this question is of high relevance for regulatory purposes. [Switzerland Q2.5]
Grouping should take into account, that some nanomaterials show very different physico-chemical properties, only depending on minor surface modifications. Therefore, grouping shall not be based on a chemical composition approach alone. A specific set of physico-chemical endpoints reflecting the multitude of “tuning” possibilities of nanomaterials must be considered. A different and furthergoing grouping approach may (additionally) take into account basic toxicological, ecotoxicological and environmental fate endpoints. [Switzerland Q2.5]
Dealing with a variety of surface modifications, is a problem of logistics that ideally should be solved by industry being open about what design options are irrelevant for operational production so these can be excluded from testing efforts. [UK Q2.5]
Selection of parameters for surface state or surface chemistry of nanomaterials that are important for toxicity and toxicokinetics. [Japan Q2.5]
<b>(2) Technical challenges - Sample preparation and material characterisation (5 comments)</b>
A big hurdle is the lack of proper characterisation of nanomaterials. There is no standard set for characterisation and the available data is incomplete and difficult to compare. [EU Q1.8]
Methods of measurement and sample preparation for physical-chemical property characterisation are major issues. Especially it is very difficult to achieve any kind of in situ characterisation in the more complex media (e.g. soils and sediments or even natural waters). For aquatic media most characterisation equipment has detection limits well above the relevant concentrations for even acute aquatic effects in short term tests. Hence the characterisation chemistry undertaken is often at extremely high concentrations meaning it is questionable to what extent data obtained for e.g. aggregation rates and forms are relevant to the true chemistry at realistic doses (e.g. one may consider if homoaggregation would ever occur at realistic ratios of dissolved organic carbon in natural waters). The situation in soil is even more challenging. Here methods for the direct measurement of the concentration and state of nanomaterials in this medium are still only in the early stages of development and it will be sometime before these can be rolled out as robust and fully validated approaches. [UK Q2.5]
Measurement issues associated with data reliability associated with nanomaterial dispersion characterisation e.g. lack of fit for purpose tools, lack of standard protocols, lack of reference materials, how to report findings. [UK Q2.5]
Preparation of series of nanomaterials with different physical-chemical properties, i.e. commercial availability and sample preparation. [Japan Q2.5]
Quantitative analytical methods of nanomaterials in tissues for toxicokinetic studies. The detection limit is higher than actual expected concentration of nanomaterials in tissues, or there is no appropriate measurement method. [Japan Q2.5]
<b>(3) Regulatory implementation (13 comments)</b>
Agree. As outlined above these concepts are already applied in practise in certain pieces of EU legislation. The use and reliability will strongly benefit from further work and consolidation. [EU Q1.9 1]
It is in general important to also consider grouping as an issue in relation to defining nanomaterials in regulatory context. Issues such as sameness should be considered. [Denmark Q1.9 7)]
it is important that grouping, sameness etc. are considered as a part of the definition of

nanomaterials. [Denmark Q4]
No relevant legal data requirements. [Germany Q1.8]
more is needed, namely translation of research into guidance for assessment. [Germany Q1.9 5)]
Such concepts are necessary in regulatory regime. [Germany GFEA Q1.9 1]
Yes. It will not be practical to test all nanoforms therefore, in order to fulfil the information requirements under REACH (the EU chemicals legislation) and to establish hazard profiles for risk assessment it will likely be necessary to use these non-testing approaches where based on scientific evidence. Concepts of grouping, equivalence or read-across for nanomaterials could be very useful in the future in the development of approaches for their risk assessment. However, further fundamental research, possibly focussed on the most commonly encountered/most hazardous NMs will be needed to accompany the development of these approaches [UK Q1.9 1]
A pragmatic approach that is driven by the available evidence and applied on a case by case basis would be more desirable. [UK Q1.9 4)]
grouping or read-across will need to be applied using scientific evidence on a case by case basis. [UK Q1.9 7)]
In the case of nanomaterials, the read-across has to apply within the same substance and therefore, there is a need for a better understanding how to use this approach for nanomaterials. [BIAC Europe Q1.8]
read-across approach should be scientifically justified and currently there is no proper explanation on how this justification should be provided. [BIAC Europe Q4]
Because EPA employs concepts of grouping, equivalence and read-across for chemical substances, it is expected that these concepts will also apply to certain nanomaterials. EPA has identified groups of nanomaterials submitted as new chemical substances under TSCA based on their chemical composition. EPA is compiling physical-chemical properties of each of these groups to determine if read-across or equivalence concepts apply based on those properties. [US Q1.9 1]
This approach may be required for nanomaterials, considering the potential variability of the same substance e.g. particle size, surface coatings etc. The concept of grouping is useful to fill data gaps where significant variation in health hazards within a family of substances is not anticipated. In particular grouping will be useful in assessing nanoforms of existing chemicals where it can be scientifically justified. [Australia Q1.9 1)]
<b>(4) Other suggestions (3 comments)</b>
further fundamental research, possibly focussed on the most commonly encountered/most hazardous NMs will be needed to accompany the development of these approaches. [UK Q1.9 1)]
Until nano-specific practices are developed, if needed, the OECD Guidance on Grouping of Substances provides a set of useful approaches that are generally applicable to nanomaterials. [BIAC Europe & US Q1.9 7)]
A potential barrier is gaining wide-spread acceptance of the need to promote grouping, equivalence, read-across within the research community. [BIAC US Q2.5]

## VI. CONCLUSIONS

36. This survey provides the readers with a snapshot, at the time of December 2013, of OECD member countries' approaches to develop or use concepts of grouping, equivalence and read-across based on physical-chemical properties (GERA-PC) of nanomaterials for their human health and ecosystem hazard assessment in regulatory regimes. All the respondents believed that future regulatory regimes need to employ GERA-PC concepts for hazard assessment of nanomaterials but many of them pointed out that they were facing scientific, technical and implementation challenges for realising their positive prospects.

37. The preliminary survey results including mapped issues described in Chapter VI were briefly introduced at the OECD Expert Meeting on Categorisation of Manufactured Nanomaterials on 17 September 2014 in Washington D.C., US. The Expert Meeting did not conclude any specific ways of categorisation for nanomaterials but the following final recommendation [extracted from ENV/CHEM/NANO(2015)24]:

*Discussion and conclusions from the meeting can be used to develop fit-for-purpose decision frameworks that can be utilized under different regulatory systems for manufactured nanomaterials. To support this, the expert meeting **recommends**:*

1. *Identifying and developing, where needed, methods for characterization of relevant physical-chemical characterization of properties for toxicokinetics, fate, hazard assessment, and exposure assessment*
  - *Use of methods that enable comparability, are reliable, and use the OECD Guidance on Sample Preparation and Dosimetry [ENV/JM/MONO(2012)40].*
2. *Agreeing on or developing experimental models (e.g., in-vitro and in-vivo assays) that are predictive of human health and environment effects and that support categorization.*

***Acknowledge** that tools and methodologies for categorization might be different for the different parts needed for the assessment of nanomaterials.*

***Acknowledge** that definitions and terminologies need to be clarified and consistently applied.*

***Support** adapting existing approaches for conventional substances to fit specificities of categorization frameworks for manufactured nanomaterials.*

***Support** case studies that inform categorization schemes as they are developed and refined.*

38. Following the Expert Meeting on Categorisation, a two-day EU-sponsored OECD workshop on grouping and read-across specific issues regarding nanomaterials was proposed, with the objective of identifying criteria that need to be considered when applying alternative approaches for nanomaterials for the purpose of hazard assessment of nanomaterials in a regulatory context, in addition to those applicable in general to other types of chemicals.

39. It is well expected that through the discussion at the Expert Meeting and Workshop mentioned above and through stakeholders' day-to-day practices on hazard assessment of nanomaterials and their R&D activities regarding GERA-PC, common approaches to challenging issues identified by this survey can be developed. For this prospect, some good progress has already been made:

- Researchers of the University of California Los Angeles, US EPA and others published on 20 March 2015 "Nanomaterial Categorization for Assessing Risk Potential To Facilitate Regulatory Decision-Making", the main part of which is based on the results of R&D project listed in Table 2 in Chapter V.  
<http://pubs.acs.org/doi/ipdf/10.1021/acsnano.5b00941>
- The ECETOC Nano Task Force published on 26 March 2015 "A decision-making framework for the grouping and testing of nanomaterials (DF4nanoGrouping)", which was funded by the EU FP7 project MARINA that is not listed in Table 2 in Chapter V.  
[www.ecetoc.org/index.php?mact=Newsroom,cntnt01,details,0&cntnt01documentid=279](http://www.ecetoc.org/index.php?mact=Newsroom,cntnt01,details,0&cntnt01documentid=279)  
[www.sciencedirect.com/science/article/pii/S0273230015000549](http://www.sciencedirect.com/science/article/pii/S0273230015000549)
- US EPA proposed on 6 April 2015 (EPA's news release on 25 March 2015) "Chemical Substances When Manufactured or Processed as Nanoscale Materials; TSCA Reporting and Recordkeeping Requirements", where the concept of equivalence is employed in the definition of "discrete form of a reportable chemical substance".  
[www.gpo.gov/fdsys/pkg/FR-2015-04-06/pdf/2015-07497.pdf](http://www.gpo.gov/fdsys/pkg/FR-2015-04-06/pdf/2015-07497.pdf)
- Researchers of the Federal Office of Public Health of Switzerland published on 3 June "Sameness: The regulatory crux with nanomaterial identity and grouping", whose core concept "sameness" might be similar to the concept of equivalence, and is also mentioned in Denmark's response (see the second and third entries under (3) Regulatory implementation in Table 3).  
[www.sciencedirect.com/science/article/pii/S0273230015001476](http://www.sciencedirect.com/science/article/pii/S0273230015001476)
- The National Institute for Public Health and the Environment (RIVM) of The Netherlands published on 4 June 2015 "Grouping nanomaterials: A strategy towards grouping and read-across", which concluded that "improvement is needed for the documentation of the information from the laboratory testing of nanomaterials to support read-across. Particularly relevant physico-chemical properties of the nanomaterials and test conditions need more detailed descriptions. Furthermore, the scientific community needs to continue developing test methods that can characterize certain behaviours of nanomaterials to support read-across."  
[www.rivm.nl/bibliotheek/rapporten/2015-0061.html](http://www.rivm.nl/bibliotheek/rapporten/2015-0061.html)
- The Government of Canada published on 25 July 2015 a mandatory information gathering survey to determine the commercial status of certain nanomaterials in Canada. The survey targets 206 substances considered to be potentially in commerce at the nanoscale. The list of 206 substances was developed using outcomes from the Canada-United States Regulatory Cooperation Council (RCC) Nanotechnology Initiative, which is described in paragraph 21 and listed in Table 1 in Chapter IV. The information gathered by the survey will feed into the Government's proposed approach to address nanomaterials on the Domestic Substances List.  
<http://gazette.gc.ca/rp-pr/p1/2015/2015-07-25/html/notice-avis-eng.php>

40. The OECD Working Party on Manufactured Nanomaterials could consider conducting a follow-up survey on GERA-PC concepts within a few years.

## ANNEX. COMPILATION OF RESPONSES

41. This Annex compiles the responses in the order of EU, Denmark, Germany, Switzerland, UK, BIAC, US, Canada, Australia, and Japan.

42. Attention should be given to the followings:

- The responses are as they were in October - December 2013 and may contain outdated descriptions, to which relevant descriptions in Chapters IV and V are updated to the extent it was possible;
- Questions are italicised with the answers beneath them while some answers include italicised texts;
- To minimise the volume of the compilation, most of question texts are, to the possible extent, shortened from the originals in the questionnaire;
- Within each response, unanswered questions are not indicated; and
- To questions Q.1.2 and Q1.9, some respondents answered by selecting some parts and deleting other parts of the question texts.

## EUROPEAN UNION

This has been prepared by the following services of the European Commission: DGs Environment, Enterprise and Industry, the Joint Research Centre, Research and Innovation and Health and Consumers. Input has also been received from the European Chemicals Agency (ECHA).

### Section 1: Present use of concepts of grouping, equivalence and read-across based on physical-chemical properties

**Q1.** *Are you involved in, or aware of, any human and ecosystem health hazard assessment in a regulatory regime governed by your organisation, or of your country, for which a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials is or has been employed?*

Yes. In the EU there are several pieces of legislation that allow or encourage the use of grouping, equivalence and read-across, details are provided below.

#### **Q1.1** *Name of the regulatory regime and its governing organisation:*

- REACH (1907/2006): EC and ECHA
- Biocidal Products Directive (528/2012): EC and ECHA
- Plant Protections Product Regulation (1107/2009): EC and EFSA
- Cosmetics Products Regulation (1223/2009): EC. As far as cosmetics' ingredients are under REACH, then the same approaches may apply, however, for nanomaterials in cosmetic products there is currently no such approach. See Guidance on the Safety Assessment of Nanomaterials in Cosmetics (SCCS/1484/12). "The SCCS considers that a category approach to risk assessment is currently not feasible for nanomaterials, and risk assessment of each nanomaterial needs to be carried out on a case-by case basis."
- CLP Regulation (1272/2008): EC and ECHA
- Food Contact Materials Regulation (10/2011): EC and EFSA

#### **Q1.2** *Which type of approach is employed?*

- 1) *Concept of grouping*
- 2) *Concept of equivalence*
- 3) *Concept of read-across*
- 4) *Any other concept of similar nature (Please give a short description):*

1), 2) and 3) may be employed in REACH as well as QSARs

3) is suggested in the guidance of EFSA on nanomaterials applied in food and feed.

For Cosmetics there is currently no such approach. The SCCS "Guidance on the Safety Assessment of Nanomaterials in Cosmetics" says: "In the absence of a sufficient knowledgebase on nanomaterial properties, behaviour, and effects that can allow a read-across, the SCCS considers that a category approach to risk assessment is currently not feasible for nanomaterials, and risk assessment of each nanomaterial needs to be carried out on a case-by-case basis. It is, however, inevitable that the on-going research and development in this area will increase understanding of the key parameters that drive the properties, biological interactions and toxicological effects of nanomaterials. With the availability of the new knowledge, it will be possible to derive the underlying rules that allow a read-across, and mathematical models that enable a category approach to risk assessment of nanomaterials in the future."

***Q1.3 The proper name of the approach and URLs for websites or documents that explain or concern the approach:***

REACH supports the Union's strategy to promote alternative test methods as a priority. Article 13 of REACH states that information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI (general rules for adaptation of the standard testing regime) are met. In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, in vitro methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across). Testing of repeated dose and reproductive toxicity may be omitted where justified by information on exposure and implemented risk management measures as specified in Annex XI, section 3. Article 25 of REACH also states that in order to avoid animal testing, testing on vertebrate animals for the purposes of REACH shall be undertaken only as a last resort and it is necessary to take measures limiting duplication of other tests.

The web page of the European Chemicals Agency (ECHA) publishes the guidance documents developed for the implementation of REACH, and the guidance was updated in April 2012 regarding nanomaterials.

The general web page is <http://echa.europa.eu>.

The specific guidance relevant for this questionnaire is:

"Guidance on information requirements and chemical safety assessment. Appendix R7-1

Recommendations for nanomaterials applicable to: Chapter R7a Endpoint specific guidance."

[http://echa.europa.eu/documents/10162/13564/appendix\\_r7a\\_clean\\_draft\\_caracal\\_en.pdf](http://echa.europa.eu/documents/10162/13564/appendix_r7a_clean_draft_caracal_en.pdf)

[http://echa.europa.eu/documents/10162/13632/appendix\\_r7a\\_nanomaterials\\_en.pdf](http://echa.europa.eu/documents/10162/13632/appendix_r7a_nanomaterials_en.pdf)

"Guidance on information requirements and chemical safety assessment. Appendix R7-1

Recommendations for nanomaterials applicable to: Chapter R7b Endpoint specific guidance."

[http://echa.europa.eu/documents/10162/13632/appendix\\_r7b\\_nanomaterials\\_en.pdf](http://echa.europa.eu/documents/10162/13632/appendix_r7b_nanomaterials_en.pdf)

"Guidance on information requirements and chemical safety assessment. Appendix R7-2

Recommendations for nanomaterials applicable to Chapter R7c Endpoint specific guidance"

[http://echa.europa.eu/documents/10162/13632/appendix\\_r7c\\_nanomaterials\\_en.pdf](http://echa.europa.eu/documents/10162/13632/appendix_r7c_nanomaterials_en.pdf)

"Guidance on information requirements and chemical safety assessment. Appendix R14-4

Recommendations for nanomaterials applicable to Chapter R.14 Occupational exposure estimation"

[http://echa.europa.eu/documents/10162/13643/appendix\\_r14\\_05-2012\\_en.pdf](http://echa.europa.eu/documents/10162/13643/appendix_r14_05-2012_en.pdf)

For CHEMICALS:

ECHA has developed an approach to grouping of substances and read-across to support companies to comply with their obligations under REACH:

<http://echa.europa.eu/en/support/grouping-of-substances-and-read-across>

"Guidance on information requirements and chemical safety assessment, chapter R.6"

"Practical Guidance 6. How to report read-across and categories"

[http://echa.europa.eu/documents/10162/13655/pg\\_report\\_readacross\\_en.pdf](http://echa.europa.eu/documents/10162/13655/pg_report_readacross_en.pdf)

"Practical guide 4: How to report data waiving"

[http://echa.europa.eu/documents/10162/13655/pg\\_report\\_data\\_waiving\\_en.pdf](http://echa.europa.eu/documents/10162/13655/pg_report_data_waiving_en.pdf)

"Practical Guide 5: How to report (Q)SARs."

[http://echa.europa.eu/documents/10162/13655/pg\\_report\\_qsars\\_en.pdf](http://echa.europa.eu/documents/10162/13655/pg_report_qsars_en.pdf)

The web page of the European Food Safety Authority (EFSA) publishes the guidance documents developed for the risk assessment methodologies applied to food and feed. The guidance on the risk

assessment of nanomaterials was published in 2011. The general web page is <http://efsa.europa.eu>. The specific guidance relevant for this questionnaire is:

"Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain"

<http://www.efsa.europa.eu/en/efsajournal/doc/2140.pdf>

"Guidance on the safety assessment of nanomaterials in cosmetics" (SCCS/1484/12):

[http://ec.europa.eu/health/scientific\\_committees/consumer\\_safety/docs/sccs\\_s\\_005.pdf](http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_005.pdf)

**Q1.4** *How is the approach implemented within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

In REACH, the guidance documents listed above explain in detail the information requirements. Further guidance is available regarding the use of this data in the chemical safety report.

The Guidance of EFSA on the risk assessment of nanomaterials in food and feed, (including food additives, enzymes, flavourings, food contact materials, novel foods, feed additives and pesticides) has developed a practical approach for assessing potential risks arising from applications of nanoscience and nanotechnologies in the food and feed chain.

**Q1.5** *Is the approach (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

In REACH the approach is always substance by substance and endpoint by endpoint. A nanomaterial may be considered as nanoform of a substance or as distinct substance where the case-by-case approach applies\*.

\* Second Regulatory Review on Nanomaterials (COM(2012) 572 final, page 7)

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2012:0572:FIN:EN:PDF>

Currently, for the safety assessment of nanomaterials used as cosmetic ingredients "the SCCS considers that a category approach to risk assessment is currently not feasible for nanomaterials, and risk assessment of each nanomaterial needs to be carried out on a case-by-case basis":

[http://ec.europa.eu/health/scientific\\_committees/consumer\\_safety/docs/sccs\\_s\\_005.pdf](http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_005.pdf)

For food and feed, the approach is also on a case by case basis. Prior to commencing a detailed risk assessment of the nanomaterial, an appropriate physico-chemical characterisation, first and an anticipated exposure scenario should be outlined. Further guidance can be found in "Guidance on information requirements and chemical safety assessment", Chapter R6; QSARs and grouping of chemicals: [http://echa.europa.eu/documents/10162/13632/information\\_requirements\\_r6\\_en.pdf](http://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf)

Furthermore, additional guidance on how to document and report read across and categories can be found in the Practical guide 6:

[http://echa.europa.eu/documents/10162/13655/pg\\_report\\_readacross\\_en.pdf](http://echa.europa.eu/documents/10162/13655/pg_report_readacross_en.pdf)

**Q1.6** *How does the approach contribute to limiting the testing costs or numbers of animals used?*

Please see the general conditions set by REACH under Q1.3. Whenever the approach is successfully employed, either already available information is accepted thereby avoiding additional testing, or in vitro or in-silico testing is accepted, or the testing performed may be applied for more than one chemical. All these, of course, reduce the need of testing, thus saving time and costs, and reducing the number of animals to be used.

**Q1.7** *Is the approach specific to nanomaterials or expanded from chemicals in general?*

The approach is expanded from chemicals in general.

**Q1.8** *What was the main issue OTHER THAN BUDGET that hampered the development of the approach and how was the issue resolved?*

All the examples mentioned in the question are known and relevant factors that may hamper the development of the approach. The limited scientific understanding of the differences, if any, between chemicals and nanomaterials or between different forms of the same chemical (composition) has, of course, slowed down the development of methods for nanomaterials or impeded the application of available methods which are not validated for NM. This hints as well to the scarcity of reliable information obtained in a controlled and standardised way for a sufficient number of chemically different nanomaterials and a variety of nanoforms.

For cosmetics, from the SCCS guidance: "In the absence of a sufficient knowledgebase on nanomaterial properties, behaviour, and effects that can allow a read-across, the SCCS considers that a category approach to risk assessment is currently not feasible for nanomaterials, and risk assessment of each nanomaterial needs to be carried out on a case-by case basis. It is, however, inevitable that the ongoing research and development in this area will increase understanding of the key parameters that drive the properties, biological interactions and toxicological effects of nanomaterials. With the availability of the new knowledge, it will be possible to derive the underlying rules that allow a read-across, and mathematical models that enable a category approach to risk assessment of nanomaterials in the future."

A big hurdle is the lack of proper characterisation of nanomaterials. There is no standard set for characterisation and the available data is incomplete and difficult to compare.

**Q1.9** *Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:*

1) *In the future, concepts of grouping, equivalence or read-across for nanomaterials may be necessary in the regulatory regime.*

Agree. As outlined above these concepts are already applied in practise in certain pieces of EU legislation. The use and reliability will strongly benefit from further work and consolidation.

2) *In the future, concepts of grouping, equivalence or read-across for nanomaterials may not be necessary in the regulatory regime.*

Disagree

3) *Currently, the regulatory regime does not specifically deal with nanomaterials.*

In general, nanomaterials are considered to be chemicals/substances hence regulatory frameworks governing chemicals/substances also address nanomaterials. Some regimes are already addressing NM explicitly (cosmetic products, biocides, food contact materials) and several regimes (in particular REACH Annexes) are currently under revision.

4) *Each individual nanomaterial should be tested for all toxicological endpoints foreseen by the regulatory regime.*

The overall aim of regulating chemicals is to ensure safety and minimise negative impacts on human health and the environment. In doing so, a proper hazard characterisation is a corner stone but should be seen in conjunction with the potential for exposure and applying proper risk management measures. We have already indicated that the concepts that are subject of this survey in principle are applicable also to nanomaterials (save when used in cosmetics), provided that appropriate information is available. In our opinion an increased use of such concepts will be appropriate and necessary and will have an expansion in its use when an adequate body of scientific information is provided. This may include the development of an appropriate number of benchmarking experimental results and a transparent and conclusive assessment of the application of such models in comprehensive risk assessments.

5) *Necessary R&D activities are on-going to develop and employ such concepts of grouping, equivalence or read-across for nanomaterials in the regulatory regime.*

Yes, see next section on Research

6) *An internationally harmonised guidance (e.g. OECD guidance) on grouping, equivalence or read-across for nanomaterials for regulatory regimes is awaited.*

Could be useful on scientific and technical aspects.

## **Section 2: R&D activities on concepts of grouping, equivalence and read-across based on physical-chemical properties**

**Q2.** *Are you aware of any finished, on-going, or planned R&D activities on a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials for their human health and ecosystem hazard assessment?*

**Q2.1** *Which type of approach is employed?*

- 1) *Concept of grouping*
- 2) *Concept of equivalence*
- 3) *Concept of read-across*
- 4) *Any other concept of similar nature*

	Gr	Eq	R-A	Other similar concept and/or comments
NanoSolutions				NanoSolutions aims to develop understanding the fundamental characteristics of ENM underpinning their biological effects will provide a sound foundation with which to classify ENM according to their safety. Therefore, the overarching objective of this research is to provide a means to develop a safety classification of ENM based on an understanding of their interactions with living organisms at the molecular, cellular, and organism levels based on their material characteristics. It takes a systems biology approach to the issue of grouping.
NanoPuzzles	X		X	
Mod-ENP-Tox	X	X		The MOD-ENP-TOX project tries to link physico-chemical characteristics of materials (metal based NPs MeNPs and their oxides) to their biological effects. In the development of an in silico model the project concentrates mainly on the basis of equivalence and where possible it will try to group toxicological patterns (the basis of our model is therefore

				orientated on mode of action rather than anything else). The primary objectives are: - Identify structural and physico-chemical characteristics that drive the toxicity of metal based NPs. - Identify the relation of MeNPs descriptors to toxicological endpoints and classify a training set of MeNPs into groups of regular toxicity patterns. - Development of a Computational Mechanistic Package (CMP) to predict MeNP toxicity. - Develop a kinetic and dynamic model based on PBPK to predict MeNPs toxicity in human health.
PreNanoTox	X			
ModNanoTox	X		X	
MembraneNanoPart	X	X		The project is developing the concepts of Grouping and Equivalence of nanomaterials. At this point a Read-across approach is trying to be avoided as there is no solid information of what properties are relevant and whether the existing characterisation is sufficient for making a predictive model. Additional information such as the uptake pathway or size distribution might be required in the future
ITS-Nano, ENPRA	X		X	
MODERN	X		X	The approach that will be implemented in MODERN includes both, category identification and development and assessment of read-across model
NanoTransKinetics		X		While admittedly in a very early stage of development, the project believes a strategy that is based upon the concept of a 'biomolecular corona' would be beneficial. The basis of this strategy is expounded upon in the following document: <a href="http://dx.doi.org/10.1038/nnano.2012.207">http://dx.doi.org/10.1038/nnano.2012.207</a> Additionally, the EU FP7 project FutureNanoNeeds (currently under negotiation), where more complex shapes and curvature effects of the next-generation of nanomaterials (nanocubes, nanostars, nanoflowers etc.) will be investigated, will base its classification activities on the same concept.

**Q2.2 The proper name of the R&D activity and URLs for websites or documents that explain or concern the activity:**

NANOSOLUTIONS—"Biological Foundation for the Safety Classification of Engineered Nanomaterials (ENM): Systems Biology Approaches to Understand Interactions of ENM with Living Organisms and the Environment" - <http://nanosolutionsfp7.com/> Contacts Kai Savolainen (Kai.Savolainen@ttl.fi), Rob Aitken (rob.aitken@iom-world.sg)

NanoPUZZLES (and NanoBridges): "Modelling properties, interactions, toxicity and environmental behaviour of engineered nanoparticles". The project has started in January this year. Results of the research task - Development of the conceptual framework for further grouping of NPs - are not available yet. In the near future, the results will be placed on the project website. [www.nanopuzzles.eu](http://www.nanopuzzles.eu). & [www.nanobridges.eu](http://www.nanobridges.eu)  
Contact: Tomasz Puzyn (puzi@qsar.eu.org)

MOD-ENP-TOX: "A Generic Modelling Platform to Predict the Toxicity of Metal-based Nanoparticles".  
<https://fys.kuleuven.be/vsm/modenptox/index.php> - Contact: Jean-Pierre Locquet  
 (JeanPierre.Locquet@fys.kuleuven.be)

PreNanoTox: "Predictive toxicology of engineered nanoparticles". Project factsheet:  
[http://cordis.europa.eu/projects/rcn/106196\\_en.html](http://cordis.europa.eu/projects/rcn/106196_en.html) Contact: Rafi Korenstein (korens@tau.ac.il)

ModNanoTox: "Modelling nanoparticle toxicity: principles, methods, novel approaches".  
<http://www.birmingham.ac.uk/generic/modnanotox/index.aspx> Contact: Éva Valsami-Jones  
 (e.valsamijones@bham.ac.uk)

MembraneNanoPart: "Modelling the mechanisms of nanoparticle-lipid interactions and nanoparticle effects on cell membrane structure and function". [www.membranenanopart.eu](http://www.membranenanopart.eu) Contact: Vladimir Lobaskin  
 (Vladimir.lobaskin@ucd.ie)

ITS-Nano ([www.its-nano.eu](http://www.its-nano.eu)) , ENPRA ([www.enpra.eu](http://www.enpra.eu)), and Marina ([www.marina-fp7.eu](http://www.marina-fp7.eu)). Contact: Lang Tran  
 (lang.tran@iom-world.org)

MODERN: "Modelling the Environmental and Human Health Effects of Nanomaterials" - <http://modern-fp7.biocent.cat/> - Contact: FrancescGiralt (fgiralt@urv.cat)

NanoTransKinetics: "Modelling basis and kinetics of nanoparticle interaction with membranes, uptake into cells, and sub-cellular and inter-compartmental transport" - [www.nanotranskinetics.eu](http://www.nanotranskinetics.eu) - Contact: Kenneth Dawson  
 (kenneth.a.dawson@cbni.ucd.ie)

Other relevant projects:

Project	Webpage	Duration
NanoTEST	<a href="http://cordis.europa.eu/projects/rcn/86691_en.html">http://cordis.europa.eu/projects/rcn/86691_en.html</a> <a href="http://www.nanotest-fp7.eu/">http://www.nanotest-fp7.eu/</a>	2008-04-01 2012-03-31
NANOMILE	<a href="http://cordis.europa.eu/projects/rcn/106943_en.html">http://cordis.europa.eu/projects/rcn/106943_en.html</a> <a href="http://www.nanomile.eu/">http://www.nanomile.eu/</a>	2013-03-01 2017-02-28
NANOREG	<a href="http://cordis.europa.eu/projects/rcn/107159_en.html">http://cordis.europa.eu/projects/rcn/107159_en.html</a> <a href="http://www.nanoreg.eu/">http://www.nanoreg.eu/</a>	2013-03-01 2016-08-31
NANORETOX	<a href="http://www.nanorettox.eu/">http://www.nanorettox.eu/</a>	2008-12-01 2012-11-30

### ***Q2.3 How was/is the approach being developed?***

NanoSolutions: The project, which has only just started takes a systems biology approach to the question of nanotechnology risk. Within this concept, multiple end points will be considered simultaneously. Key envisaged steps are as follows;

The corona of biomolecules on the surface of ENM is influenced by the nature, size, shape, and surface modification of ENM; these interactions determine their biological interactions, behaviour and fate within cells/organisms/animals.

It will be possible to identify commonalities between ENM classes/categories and their hazard potential and these can be modelled once the associations between the relevant physico-chemical properties and biological end-points have been clarified.

The interaction of ENM with cells/organisms will induce a set of common gene/protein "fingerprints" closely associated (but not necessarily identical) and shared across species; these can be identified using proteomics, transcriptomics and epigenetic approaches, coupled with advanced bioinformatics and systems biology.

Refined in vitro assays, compared with outcomes from a range of different model organisms, will be used to a large extent to replace conventional animal testing of ENM i.e. we will be able to create predictive in vitro models.

All these data, when collected across species, from different cell and animal models with biokinetic modelling of ENM, over the life-cycle of ENM, will provide a comprehensive understanding of the specific features of ENM that contribute to their safety and risks, i.e. we will have created a science-based classification of their safety.

**NanoPuzzles:** The approaches for grouping and read-across of NPs will be developed within next two years. The preliminary purpose will be to develop categories or groupings of nanoparticles on a rationale structural basis. Initial groupings will be made primarily of structural similarity (e.g. analogues or a functional group) but also taking account, or including, where possible, similar mechanisms of toxic action where possible. Later approaches will implement pattern recognition techniques to identify classes of nanoparticles with similar properties on the basis of the calculated descriptors. NanoPuzzles project will focus on the endpoints describing the peculiar characteristics of engineered nanoparticles and their resulting possible capacity to reach and react directly at the cellular level. For consistency of the experimental measurement protocols all endpoints and test methods used in this study will be based on existing OECD (Organization for Economic Co-operation and Development) Test Guidelines - (No. 25 ENV/JM/MONO (2009)20/Rev).

**Mod-ENP-Tox:**

physical-chemical properties: we will focus initially on 9 characteristics: particle size/size distribution; agglomeration and/or aggregation; chemical composition (including degree of oxidation); crystal structure/crystallinity; purity; shape; surface area; surface charge; surface chemistry  
in vivo / in vitro endpoints: general toxicity (cytotoxicity (in vitro) and LD50 (in vitro)); Inflammation; Genotoxicity; Tissue accumulation

**PreNanoTox:** addresses three currently missing critical elements needed to develop a platform for predictive nanotoxicology and our suggested approach of providing them: (1) There is a current lack of unified large database – We suggest to form this database by applying cutting edge information extraction tools on large repository of scientific articles; (2) There is a need for better understanding the underlying mechanisms of the primary interaction of NP with the cell membrane – We suggest to apply appropriate theory and simulation assuming that the surface chemistry of a NP (affecting NP's surface reactivity, hydrophobicity, or surface electrostatics) as well as its other physical properties (e.g. size and shape) determine the interaction with a cell's surface, leading beyond a certain adhesion-strength threshold, to efficient uptake of the NPs; (3) There is a need to extend the traditional QSAR paradigm to the field of nanotoxicology – This will be carried out by linking appropriate NP descriptors, with emphasis on those which determine the strength of adsorption of NPs to cells, with biological responses. The PreNanoTox consortium is made up of four research groups (from three scientific organizations), which lead in information technology, soft matter modeling, computational chemistry and in-vitro toxicology, yielding a synergetic output. This project is expected to assist in safe designing of new engineered NPs as well as reducing the extent needed for empirical testing of toxicity.

ModNanoTox: Molecular simulations, QSAR models and biodynamic models. The grouping approach is used by the Lazar algorithm for local QSAR modelling therefore we selected mortality endpoints and physical-chemical properties (Particle size distribution, Specific surface area and Zeta potential). But due to the limited data input no local model building was possible.

MembraneNanoPart: We are developing theoretical, molecular based models for studying interaction of nanoparticles with cell membranes. We include the following physical-chemical properties: particle size, chemical composition and crystalline state, shape, solubility, surface potential. We study the cytotoxicity effects: membrane disruption, triggering apoptosis, genotoxicity, and oxidative stress after nanoparticle uptake from blood. The endpoints are: bloodstream (liver, kidney), cell membrane, endosome, cell membrane, cytosol.

ITS-Nano, ENPRA & MARINA: The approach linking the nanoparticle physico-chemical properties with the in vitro endpoints currently is via QSAR Approach as in FP7 ENPRA project ([www.enpra.eu](http://www.enpra.eu)). The model developed in ENPRA used the dose-response data generated from in vitro experiments covering different body systems (e.g. pulmonary, cardiovascular, etc...) and different adverse endpoints (per system), such as oxidative stress, inflammation, genotoxicity, etc... The doses of nanoparticles (initially expressed as mass) were re-quantified in terms of other characteristics such as surface area, charge, etc...and the combination of the nanoparticle characteristics which best describe the dose-response relationship, for a given response, for the range of nanoparticles used in the project (TiO<sub>2</sub>, ZnO, Silver, MWCNT, etc...) was identified as the best descriptors for this set of chosen nanoparticles. For example, characteristics such as surface area (size), surface charge and solubility (and the release of ions) were identified as key factors driving oxidative stress and inflammation (for metal oxides). In FP7 MARINA, the QSAR approach is currently being extended further to cover other particles such as silica and combined with the method of control banding to create a useful tool for risk management of engineered nanomaterials ([www.marina-fp7.eu](http://www.marina-fp7.eu)). The type of models developed in ENPRA and MARINA can be used for read across.

MODERN: The information that will be used for category identification will include several physicochemical properties (e.g. surface area, surface charge, primary size, and aggregate size), quantum-chemical nanodescriptors and biological activity profiles.

NanoTransKinetics: The approach is based upon consideration not of the physico-chemical properties of the nanomaterials themselves, but on what adsorbs to the nanomaterials in a biological milieu. Thus, nanomaterials in a biological milieu will rapidly adsorb a cohort of biomolecules, termed a 'biomolecular corona'. The working hypothesis is that most interactions between nanomaterials and living systems are mediated by this corona, rather than by the bare nanomaterial. It is envisaged that grouping of nanomaterials based upon their corona will enable more rapid progress (though, ultimately, the physico-chemical properties of the nanomaterial determines the corona). End-points would mainly include nanoparticle biodistribution in organisms, while the situation with toxicity end-points is more complex.

#### ***Q2.4 Was/Is the approach specific to nanomaterials or expanded from chemicals in general?***

specific	expanded
NanoSolutions	ModNanoTox (the QSAR modelling partner extended their prediction framework to the nanomaterials requirements).
NanoPuzzles	
Mod-ENP-Tox	ENPRA, MARINA (the approach is expanded from the QSAR approach used in chemical toxicology)
PreNanoTox	
ModNanoTox	Modern (The approach is based on techniques used for chemicals but will be implemented with specific information about properties and behaviour of nanomaterials)
MembraneNanoPart (the approach is specific to nanomaterials as we are studying only particles/aggregates of certain minimum size, 2 to 100 nanometres)	
NanoTransKinetics (the approach is specific to	

nanomaterials, as the concept of a biomolecular corona is not (commonly) relevant to chemicals and has been explicitly developed for nanomaterials)	
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**Q2.5 What was/is the main issue OTHER THAN BUDGET that may hamper the development of the approach?**

All projects: The most significant risk for the development of grouping and read-across approaches is related to inappropriateness as well as insufficient number and quality of empirical data (on physico-chemical and toxicological endpoints) that are required for constructing models. More data are required to cover the nanomaterial space in a homogeneous and continuous way so that consistent nanoparticle categories can be properly identified and read-across performed within the homogeneous families of nanomaterials. The present lack of a, regularly updated, large data-base possessing data of high quality (possessing the ability to be replicated), having detailed information on the physico-chemical properties of the nanomaterials under the appropriate experimental environment, as well as the changes of these properties following penetration into cells. This database should also contain the protocols of all the experiments including physico-chemical characteristics measurement A machine-readable format for assays data and a standardized vocabulary would help to collect all given data for specific purposes

The yet non-sufficient validation of the in-vivo/in-vitro relationship in terms of biological end-point (PreNanoTox)

Unavailability of clear, quantitative criteria of toxicity (MembraneNanoPart)

At present there are not sufficient precise theoretical methods to calculate the physico-chemical properties of nanoparticles (PreNanoTox)

Current measurement techniques for characterising the biomolecular corona are still insufficiently developed to assess eventual subpopulations (nanomaterials with different coronae) and the full functionality (whether a biomolecule in the corona is actually functional).(NanoTransKinetics)

Examples of visible (or even invisible) problems: (Mod-ENP-Tox):

Product "characterisation" quality: it has been experienced that producers claim a certain quality of their product (which may have been determined at a certain stage of the production), which is often not in line with what they deliver. This makes it often impossible to compare experiments with the same material (but from another batch). In fact the research should do a complete characterisation (and not rely on earlier ones) due to poor quality control of producers. In addition to this, impurities can play a large role.

Endpoints used: similar endpoints can be measured in biological assays using different techniques, sometimes it is difficult to combine this type of data

Metrics used: how is dose reported? Mass/ml, particles n°/ml, mass/m<sup>3</sup>, particle/m<sup>3</sup>, mass/cm<sup>2</sup>, particle/cm<sup>2</sup>, surface area/ ml or per cm<sup>2</sup>, OR in molar conc (this molar can reflect a molar conc on basis of moles present or it can be moles of particles (in fact number conc). It is often impossible to recalculate/convert if the researcher does not explain well!

The approach is novel and is therefore at this point is unproven (NanoSolutions)

**Q2.6 If the developed approach is supposed to be employed in a regulatory regime, the name of regulatory regime and the governing organisation:**

The projects are not designed to target a specific regulatory regime. In the EU all the regulations mentioned in answer to Q1.1 are important regulatory regimes where it would be relevant to consider the scientific recommendations and results.

***Q2.7 If the developed approach is supposed to be employed in a regulatory regime, may it be (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in a regulatory regime?***

Like in the case of other substances, the assessment of applicability will always be a case-by-case assessment. As knowledge and robustness improve the number of cases where concepts of grouping, equivalence and read-across can be used successfully will grow in parallel. This will continue to be the case for as long as demonstration of safe use is the driver for testing.

The following EU projects have been launched to contribute to this development:

NanoSolutions (it is the objective of the project)

NanoPuzzles (Employment of developed read-across approach for nanomaterials in a regulatory regime should always be considered individually).

PreNanoTox (employed regularly)

MembraneNanoPart

ENPRA (the developed approach can be used in a regulatory regime once validated)

MODERN (The proposed read-across can be applied to homogeneous categories that include enough nanoparticles with complete characterization data. Proper thresholds to define the reliability of a given category must be identified and validated before the application of read-across estimates for regulatory purposes / REACH).

***Q2.8 If the developed approach is supposed to be employed in a regulatory regime, how may it be used within the human health and ecosystem hazard assessment of nanomaterials?***

NanoPuzzles: the developed read-across approach will allow treating a closely related (or similar) group of nanomaterials as a category. Within the category toxicological data will exist for some, but not all of the NPs for the endpoints of interest. Thus data gaps are likely to exist for some of the properties or endpoints for each nanomaterial, with it being likely that differing data gaps will exist for different NPs within the category. It is for these data gaps that structure-activity relationship methods (such as read across) will have to be utilised to make predictions for the missing toxicological data. On a practical level only when a battery of read-across/grouping/QSAR models for predicting various toxicological endpoints and/or physicochemical properties for NPs will be developed, it would be possible to comprehensively evaluate the health and environmental impact of engineered NPs without an extensive use of animal testing and high costs of the analysis. In a longer perspective, this strategy will lead to designing safe nanomaterials with assistance of the in silico techniques.

Mod-ENP-Tox: the primary objectives include (i) the development of a Computational Mechanistic Package (CMP) to predict MeNP toxicity and (ii) the development of a kinetic and dynamic model based on PBPK to predict MeNPs toxicity in human health. To reach these goals finally, probably more is needed than a small project as ours, notwithstanding this the ambition is to set out the lines needed to come to a predictive model for human toxicity.

PreNanoTox: be instrumental for hazard assessment in these two fields

MembraneNanoPart: The approach assumes computer modelling and would allow a pre-fabrication screening of the nanomaterials for possible cytotoxicity effects.

ENPRA: It will be used to predict/derive the NO Effect Level (DNEL) as a function of the particle physico-chemical characteristics then back calculated into an exposure level as a derived control limit (e.g. for inhalation exposure).

MODERN: Read across will facilitate hazard assessment by providing hazard estimates for new nanomaterials based on similarity principles (i.e., grouping). Well-characterized nanomaterials will be used

to provide property and activity estimates for new “similar” nanomaterials. The approach should facilitate the implementation of safe-by-design strategies.

***Q2.9 If the developed approach is supposed to be employed in a regulatory regime, how may it contribute to limiting the testing costs or numbers of animals used?***

It is not possible to quantify this at this stage but successful implementation of the projects will reduce the need for animal testing by contributing towards a predictive framework for nanotoxicity (all projects) The validated approach can predict and derive DNEL without the need for experimentation. So, it can contribute considerably to reducing testing costs and (possibly) animal experimentation. Remember that the approach uses in vitro data generally. The issue of extrapolation from in vitro to in vivo is not considered here. So, even if the approach works for in vitro tests, there is still the issue of extrapolation to in vivo and ultimately the extrapolation from in vivo animals to in vivo humans (ENPRA).

## **DENMARK**

### ***THE DANISH ENVIRONMENTAL PROTECTION AGENCY***

*Section 1: Present use of concepts of grouping, equivalence and read-across based on physical-chemical properties*

*Q1. Are you involved in, or aware of, any human and ecosystem health hazard assessment in a regulatory regime governed by your organisation, or of your country, for which a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials is or has been employed?*

No

***Q1.9 Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:***

- 1) In the future, concepts of grouping, equivalence or read-across for nanomaterials may be necessary in the regulatory regime.*

Yes, since the concepts already are part of the existing regulation for chemicals (REACH)

- 2) In the future, concepts of grouping, equivalence or read-across for nanomaterials may not be necessary in the regulatory regime.*

This could also be the case, but given the early stage in developing the regulation it is still difficult to answer this question.

- 3) Currently, the regulatory regime does not specifically deal with nanomaterials.*

In the EU, several regulations for chemicals (e.g. cosmetics, biocides) are already dealing with nanomaterials by asking for declaration of nano-content in the products and that the authorities should be informed about this. The overarching regulation for chemicals, REACH, does however, at present not deal specifically with nanomaterials.

- 4) *Each individual nanomaterial should be tested for all toxicological endpoints foreseen by the regulatory regime.*

Under REACH, this is only the case when a nanomaterial is identified individually as a separate chemical substance and therefore is falling under the normal rules for chemicals.

- 5) *Necessary R&D activities are on-going to develop and employ such concepts of grouping, equivalence or read-across for nanomaterials in the regulatory regime.*

Several R&D activities are ongoing, but it is not possible to assess whether these activities are suitable.

- 6) *An internationally harmonised guidance (e.g. OECD guidance) on grouping, equivalence or read-across for nanomaterials for regulatory regimes is awaited.*

Discussions have started on EU-level so an OECD guidance in this area would be most helpful.

- 7) *Other (Please describe your views):*

It is in general important to also consider grouping as an issue in relation to defining nanomaterials in regulatory context. Issues such as sameness should be considered.

## **Section 2: R&D activities on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q2. Are you aware of any finished, on-going, or planned R&D activities on a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials for their human health and ecosystem hazard assessment?*

No

## **Section 3: Other information on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q3. Are you aware of a case where concepts of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials are used, or supposed to be used, much effectively for their human health and ecosystem hazard assessment in a regulatory regime governed by another country or organisation?*

Since the concepts are intended to be used under REACH for chemicals, they could also be used for nanomaterials.

*Q4. Other details, explanations or comments:*

As stated under Q1.9.7, it is important that grouping, sameness etc. are considered as a part of the definition of nanomaterials.

**GERMANY**

**BFR**

**Section 1: Present use of concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q1. Are you involved in, or aware of, any human and ecosystem health hazard assessment in a regulatory regime governed by your organisation, or of your country, for which a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials is or has been employed?*

<< Assessment of 2 plant strengthening products (reported in subsection 1A) and 2 biocidal active substances (reported in subsection 1B). >>

*Subsection 1A*

*Q1.1 Name of the regulatory regime and its governing organisation:*

German Plant Protection Law / Federal Office of Consumer Protection and Food Safety

*Q1.2 Which type of approach is employed?*

Concept of grouping

*Q1.3 The proper name of the approach and URLs for websites or documents that explain or concern the approach:*

The hazard assessment did not discriminate between different nanoforms of silver. All information available for nanoscaled silver forms was considered and an assumption was made, that the particular nanoscaled silver under assessment would behave similar. An additional uncertainty factor to account for this assumption was discussed. Refer to Workshop Report ENV/JM/MONO(2010)10 Annex III.

*Q1.4 How is the approach implemented within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

Not implemented.

*Q1.5 Is the approach (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

Case-by-case.

*Q1.6 How does the approach contribute to limiting the testing costs or numbers of animals used?*

Reducing testing and costs, details not known.

*Q1.7 Is the approach specific to nanomaterials or expanded from chemicals in general?*

Not nanospecific.

*Q1.8 What was the main issue OTHER THAN BUDGET that hampered the development of the approach and how was the issue resolved?*

No relevant legal data requirements.

*Subsection 1B*

*Q1.1 Name of the regulatory regime and its governing organisation:*

Biocidal Product Directive 98/8/EC / European Commission (Rapporteur: Member State: France)

*Q1.2 Which type of approach is employed?*

Concept of read-across

*Q1.3 The proper name of the approach and URLs for websites or documents that explain or concern the approach:*

Not publicly available. Read-across of data on repeated dose inhalation toxicity between nanoscale silica with different surface modifications was discussed but dismissed.

*Q1.4 How is the approach implemented within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

A guidance document in support of the regulation allows use of the approach (read-across) in general in order to waive (replace) an animal study and fulfil the legal data requirement.

*Q1.5 Is the approach (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

Case-by-case decision (expert judgement).

*Q1.6 How does the approach contribute to limiting the testing costs or numbers of animals used?*

Reducing testing and costs, details not known.

*Q1.7 Is the approach specific to nanomaterials or expanded from chemicals in general?*

Not nanospecific.

*Q1.8 What was the main issue OTHER THAN BUDGET that hampered the development of the approach and how was the issue resolved?*

In the specific case, the approach could not be applied due to lack of information about the impact of different surface modification on toxicity following repeated inhalation exposure.

*Q1.9 Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:*

- 1) *In the future, concepts of grouping, equivalence or read-across for nanomaterials may be necessary in the regulatory regime.*

YES

- 2) *In the future, concepts of grouping, equivalence or read-across for nanomaterials may not be necessary in the regulatory regime.*

NO

- 3) *Currently, the regulatory regime does not specifically deal with nanomaterials.*

YES

- 4) *Each individual nanomaterial should be tested for all toxicological endpoints foreseen by the regulatory regime.*

NO, individual decision required for each endpoint

- 5) *Necessary R&D activities are on-going to develop and employ such concepts of grouping, equivalence or read-across for nanomaterials in the regulatory regime.*

YES, but more is needed, namely translation of research into guidance for assessment.

- 6) *An internationally harmonised guidance (e.g. OECD guidance) on grouping, equivalence or read-across for nanomaterials for regulatory regimes is awaited.*

YES

## **Section 2: R&D activities on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q2. Are you aware of any finished, on-going, or planned R&D activities on a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials for their human health and ecosystem hazard assessment?*

*Q2.1 Which type of approach is employed?*

- 1) *Concept of grouping*
- 2) *Concept of equivalence*
- 3) *Concept of read-across*
- 4) *Any other concept of similar nature*

Not clear or as indicated below for the specific project.

*Q2.2 The proper name of the R&D activity and URLs for websites or documents that explain or concern the activity:*

COST Modena (<http://www.modena-cost.eu/>): Definition of mechanistic categories

EU NanoSafetyCluster ([www.nanosafetycluster.eu](http://www.nanosafetycluster.eu)): Correlation of physchem and biological properties, esp. in Working Groups 1, 2 and 6

NanoPuzzles (EU FP7 project): The main objective of the NanoPuzzles project is to create new computational methods for comprehensive modelling the relationships between the structure, properties, molecular interactions and toxicity of engineered nanoparticles. The methods will be based on the Quantitative Structure - Activity Relationship approach, chemical category formation and read-across techniques. These methods have been widely used in risk assessment of other groups of priority chemicals but for specific reasons, they cannot be applied directly to nanoparticles. The project partners will be developing novel methods within four complimentary areas ("puzzles"), namely: (i) evaluation of physico-chemical and toxicological data available for nanoparticles (NanoDATA), (ii) developing novel descriptors of nanoparticles' structure (NanoDESC), (iii) investigating interactions of nanoparticles with biological systems (NanoINTER), and (iv) quantitative structure - activity relationships modelling (NanoQSAR).

ModNanoTox (<http://www.birmingham.ac.uk/generic/modnanotox/index.aspx>)

MODern (<http://modern-fp7.biocenit.cat/>)

NanoMILE (<http://www.nanomile.eu-vri.eu/>): expected outcome includes “a framework for MNMs classification according to their biological or environmental impacts;”

NanoSOLUTIONS([www.nanosolutionsfp7.com](http://www.nanosolutionsfp7.com)): The overarching aim of the NANOSOLUTIONS consortium is to provide a means to develop a safety classification for engineered nanomaterials (ENM) based on an understanding of their interactions with living organisms at molecular, cellular and organism levels.

UDS: Uniform Description System for Materials on the Nanoscale - A Draft Framework (developed by the CODATA/VAMAS Working Group, [udsnano@udsnano.org](mailto:udsnano@udsnano.org)): “The purpose of the UDS for materials on the nanoscale is twofold: Uniqueness and Equivalency. By Uniqueness, we mean the system has the ability within the broad range of disciplines and user communities to differentiate one nanomaterial from every other nanomaterial and to establish which particular nanomaterial or instance of a nanomaterial is being described. By Equivalency, we mean that the system can establish that two nanomaterials or nanomaterial instances are the same, as judged by different disciplines or user communities, in the sense that the set of descriptors adopted by the two or more communities are the same.”

*Q2.3 How was/is the approach being developed?*

Ongoing activities.

*Q2.4 Was/Is the approach specific to nanomaterials or expanded from chemicals in general?*

nanospecific

*Q2.5 What was/is the main issue OTHER THAN BUDGET that may hamper the development of the approach?*

An understanding of the mechanisms and processes governing nanomaterial toxicity.

*Q2.6 If the developed approach is supposed to be employed in a regulatory regime, the name of regulatory regime and the governing organisation:*

Not applicable (general R&D activities).

*Q2.7 If the developed approach is supposed to be employed in a regulatory regime, may it be (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in a regulatory regime?*

Currently not applicable.

*Q2.8 If the developed approach is supposed to be employed in a regulatory regime, how may it be used within the human health and ecosystem hazard assessment of nanomaterials?*

Currently not applicable.

*Q2.9 If the developed approach is supposed to be employed in a regulatory regime, how may it contribute to limiting the testing costs or numbers of animals used?*

Currently not applicable.

***Section 3: Other information on concepts of grouping, equivalence and read-across based on physical-chemical properties***

*Q3. Are you aware of a case where concepts of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials are used, or supposed to be used, much effectively for their human health and ecosystem hazard assessment in a regulatory regime governed by another country or organisation?*

*Q3.1 Name of the (potential) regulatory regime(s) and its governing organisation:*

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) in support of Safe Work Australia's Nanotechnology Work Health and Safety Program

/ Australian Government Department of Health and Ageing

Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) / U.S. Environmental Protection Agency, Office of Pesticide Programs, Antimicrobials Division

*Q3.2 Which type of approach are you aware of?*

Concept of grouping

Concept of read-across

*Q3.3 The proper name of the approach/R&D activity and URLs for websites or documents that explain the approach/activity or are otherwise relevant:*

Human Health Hazard Assessment and Classification of Carbon Nanotubes, October 2012 ([http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/725/Human\\_Health\\_Hazard\\_Assessment\\_and\\_Classification\\_of\\_Carbon\\_%20Nanotubes.pdf](http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/725/Human_Health_Hazard_Assessment_and_Classification_of_Carbon_%20Nanotubes.pdf))

Decision Document: Conditional Registration of HeiQ AGS-20 as a Materials Preservative in Textiles, December 1, 2011 (EPA Docket ID No. EPA-HQ-OPP-2009-1012-0064)

*Q3.4 How does/will the approach work within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

In the absence of information proving non-relevance of data or material specific data, relevant data on hazard potential (carcinogenic potential) is extrapolated to all members of a category (here CNT)

Published information on inhalation and oral toxicity of other nanosilver particles was used to characterise the risk from exposures to nanosilver that may break away from the nanosilver composite AGS-20 or treated articles or arise during production. An additional (maximum) uncertainty factor of 10 was applied for quality of database.

*Q4. Other details, explanations or comments:*

None.

### **GERMAN FEDERAL ENVIRONMENT AGENCY**

#### **Section 1: Present use of concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q1. Are you involved in, or aware of, any human and ecosystem health hazard assessment in a regulatory regime governed by your organisation, or of your country, for which a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials is or has been employed?*

NO

*Q1.9 Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:*

- 1) In the future, concepts of grouping, equivalence or read-across for nanomaterials may be necessary in the regulatory regime.*

Such concepts are necessary in regulatory regime.

- 2) In the future, concepts of grouping, equivalence or read-across for nanomaterials may not be necessary in the regulatory regime.*

Not true

- 3) Currently, the regulatory regime does not specifically deal with nanomaterials.*

In the new European regulation on biocidal products provisions dealing with nanomaterials were inserted. Also the cosmetics regulation and the regulations on food information and on plastic materials and articles intended to come into contact with food contain nanomaterialspecific provisions. For the basic European chemicals regulation REACH nanospecific adaptations are still necessary.

- 4) Each individual nanomaterial should be tested for all toxicological endpoints foreseen by the regulatory regime.*

That is true only for nanomaterials which are or will be placed on the market and as long as concepts on grouping/read-across are not available or test waiving cannot be scientifically justified.

- 5) *Necessary R&D activities are on-going to develop and employ such concepts of grouping, equivalence or read-across for nanomaterials in the regulatory regime.*

Ongoing and planned

- 6) *An internationally harmonised guidance (e.g. OECD guidance) on grouping, equivalence or read-across for nanomaterials for regulatory regimes is awaited.*

An internationally harmonised guidance should be aspired.

## **Section 2: R&D activities on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q2. Are you aware of any finished, on-going, or planned R&D activities on a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials for their human health and ecosystem hazard assessment?*

Yes

*Q2.1 Which type of approach is employed?*

- 1) Concept of grouping*
- 2) Concept of equivalence*
- 3) Concept of read-across*
- 4) Any other concept of similar nature (Please give a short description):*

A national project dealing with grouping concerning human health and ecotoxicity is applied. The concept is based on the relative sensitivity / toxicity in biological systems. A similar toxicity pattern shall be used to identify comparable bioavailability of nanomaterials. Based on this grouping the PC-properties which may be responsible for the outcome shall be identified. This will be done for human toxicity and ecotoxicity in a separate approach. It is expected by such an experimental approach that relevant PC-properties which are not yet considered can be identified. The first step will be a literature review. In a second step assumed relevant PC-properties will be verified by experiments.

Decision on sponsoring by the Federal Ministry on Education and Research is expected end of 2013. Moreover, the German Federal Environment Agency plans to launch a project in 2014

*Q2.6 If the developed approach is supposed to be employed in a regulatory regime, the name of regulatory regime and the governing organisation:*

It is supposed to use for REACH but also other regulation are thinkable (e.g. biocides, pesticides, pharmaceuticals) by German Federal Environmental Agency

*Q2.7 If the developed approach is supposed to be employed in a regulatory regime, may it be (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in a regulatory regime?*

Not clear yet

*Q2.8 If the developed approach is supposed to be employed in a regulatory regime, how may it be used within the human health and ecosystem hazard assessment of nanomaterials?*

Endpoint specific grouping/read-across between nanoform and bulkform of the same substance as well as between different nanoforms of the same substance.

*Q2.9 If the developed approach is supposed to be employed in a regulatory regime, how may it contribute to limiting the testing costs or numbers of animals used?*

Not clear yet

## **FRAUNHOFER INSTITUTE FOR MOLECULAR BIOLOGY AND APPLIED ECOLOGY**

### **Section 1: Present use of concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q1. Are you involved in, or aware of, any human and ecosystem health hazard assessment in a regulatory regime governed by your organisation, or of your country, for which a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials is or has been employed?*

NO

*Q1.9 Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:*

I expect that grouping will be necessary to consider all modifications of nanomaterials. According to my point of view testing them all will not be possible. By grouping, every nanomaterial has to be addressed and unpleasant surprises limited. I expect that grouping will be considered in every regulatory regime. In Germany R&D activities on grouping are planned – sponsored by national regulatory bodies. But national activities are not sufficient. A harmonized approach is necessary and I expect that it will be achieved.

### **Section 2: R&D activities on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q2. Are you aware of any finished, on-going, or planned R&D activities on a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials for their human health and ecosystem hazard assessment?*

*Q2.1 Which type of approach is employed?*

- 1) Concept of grouping
- 2) Concept of equivalence
- 3) Concept of read-across

*4) Any other concept of similar nature (Please give a short description):*

A national project dealing with grouping concerning human health and ecotoxicity is applied. The concept is based on the relative sensitivity / toxicity in biological systems. A similar toxicity pattern (e.g. comparable high toxicity in test with algae, no/low toxicity in test with fish and daphnids) shall be used to identify comparable bioavailability of nanomaterials. Based on this grouping the PC-properties which may be responsible for the outcome shall be identified. This will be done for human toxicity and ecotoxicity in a separate approach. It is expected by such an experimental approach that relevant PC-properties which are not yet considered can be identified.

The first step will be a literature review. In a second step assumed relevant PC-properties will be verified by experiments.

*Q2.2 The proper name of the R&D activity and URLs for websites or documents that explain or concern the activity:*

There is no decision on sponsoring yet due to the elections in Germany in September. A decision is expected by December 2013.

*Q2.3 How was/is the approach being developed (for example, which physical-chemical properties and in vivo / in vitro endpoints are addressed)?*

At least in a first step, the approach will be based – but not limited - on standard tests required for the assessment of conventional chemicals within regulatory purposes. It is expected that most data will be available for such tests.

*Q2.5 What was/is the main issue OTHER THAN BUDGET that may hamper the development of the approach?*

Until now it is the budget. We have not started yet. Therefore, we don't know where there may be further difficulties.

*Q2.6 If the developed approach is supposed to be employed in a regulatory regime, the name of regulatory regime and the governing organisation:*

*Q2.7 If the developed approach is supposed to be employed in a regulatory regime, may it be (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in a regulatory regime?*

*Q2.8 If the developed approach is supposed to be employed in a regulatory regime, how may it be used within the human health and ecosystem hazard assessment of nanomaterials?*

*Q2.9 If the developed approach is supposed to be employed in a regulatory regime, how may it contribute to limiting the testing costs or numbers of animals used?*

2.6 – 2.9: not yet relevant; the approach does not yet exist physically (just in mind)

**SWITZERLAND****FEDERAL OFFICE FOR THE ENVIRONMENT (FOEN)****Section 1: Present use of concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q1.9 Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:*

- 1) *In the future, concepts of grouping, equivalence or read-across for nanomaterials may be necessary in the regulatory regime.*
- 6) *An internationally harmonised guidance (e.g. OECD guidance) on grouping, equivalence or read-across for nanomaterials for regulatory regimes is awaited.*

**Section 2: R&D activities on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q2.5 What was/is the main issue OTHER THAN BUDGET that may hamper the development of the approach?*

- Equivalence: The high diversity of surface-modified and coated nanomaterials makes it very difficult to define the identity of a nanomaterial based on its core constituent alone. This restriction also applies to the concept of equivalence to corresponding macroscopic forms of a nanomaterial. Furthermore, this question is of high relevance for regulatory purposes.

- Grouping should take into account, that some nanomaterials show very different physico-chemical properties, only depending on minor surface modifications. Therefore, grouping shall not be based on a chemical composition approach alone. A specific set of physico-chemical endpoints reflecting the multitude of “tuning” possibilities of nanomaterials must be considered. A different and furthergoing grouping approach may (additionally) take into account basic toxicological, ecotoxicological and environmental fate endpoints.

- Read-across needs a suitable dataset of endpoints for comparable substances. In many cases, such data do not exist or is not comparable due to differing testing protocols. In many such cases, testing of comparable substances cannot be requested because the substances may have been marketed for a long time, etc.

**UNITED KINGDOM****Section 1: Present use of concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q1. Are you involved in, or aware of, any human and ecosystem health hazard assessment in a regulatory regime governed by your organisation, or of your country, for which a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials is or has been employed?*

No.

*Q1.9 Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:*

- 1) In the future, concepts of grouping, equivalence or read-across for nanomaterials may be necessary in the regulatory regime.*

Yes. It will not be practical to test all nanoforms therefore, in order to fulfil the information requirements under REACH (the EU chemicals legislation) and to establish hazard profiles for risk assessment it will likely be necessary to use these non-testing approaches where based on scientific evidence. Concepts of grouping, equivalence or read-across for nanomaterials could be very useful in the future in the development of approaches for their risk assessment. However, further fundamental research, possibly focussed on the most commonly encountered/most hazardous NMs will be needed to accompany the development of these approaches.

- 2) In the future, concepts of grouping, equivalence or read-across for nanomaterials may not be necessary in the regulatory regime.*
- 3) Currently, the regulatory regime does not specifically deal with nanomaterials.*

Whilst overarching EU legislation for the regulation of chemicals does not currently specifically refer to nanomaterials, they are implicitly covered by a number of other pieces of legislation, including REACH and COSHH. They are also explicitly addressed in sectoral EU legislation on cosmetics, novel food and biocides. The main European regulatory framework for chemicals (REACH) only captures chemicals produced in quantities over one tonne, or chemicals that are very hazardous (carcinogenic, mutagenic, affecting reproductivity, or persistent and bioaccumulative in the environment). Since the production of most nanomaterials is often below one tonne, specific nanomaterials are often not captured by this legislation, just as other chemicals produced in small amounts are not captured.

- 4) Each individual nanomaterial should be tested for all toxicological endpoints foreseen by the regulatory regime.*

This would appear to be disproportionate given that many NM's are likely to be of similar or less hazard than their bulk counterparts. A pragmatic approach that is driven by the available evidence and applied on a case by case basis would be more desirable (and in line with UK policies governing the balance between safety, innovation and economic growth).

- 5) Necessary R&D activities are on-going to develop and employ such concepts of grouping, equivalence or read-across for nanomaterials in the regulatory regime.*

Yes, significant R&D activities being undertaken by ECHA and under EU Framework Programme funded research as well as UK research council funded research. Please see Question 2 for more information.

- 6) An internationally harmonised guidance (e.g. OECD guidance) on grouping, equivalence or read-across for nanomaterials for regulatory regimes is awaited.*

Yes.

- 7) Other (Please describe your views):*

Work is ongoing in the EU to identify how best nanomaterials can be captured in EU legislation, in particular improving clarity of the application of REACH to nanomaterials. Of particular importance will

be to ensure that testing methodologies are appropriate. In order to prevent an overly burdensome approach, it is likely that some grouping or read-across will be needed for nanomaterials but that will need to be applied using scientific evidence on a case by case basis.

Grouping, equivalence and read across are not strictly speaking applicable to the food/feed sector in the EU. Engineered nanomaterials (ENM) for food or food contact materials are assessed and therefore regulated on a case by case basis as separate substances and the pathway for a risk assessment of any given ENM for food/food contact material application varies depending on the ENM being assessed. That said, there is some degree of relaxation of data requirements depending on the behaviour of the ENM. For the food/feed sector, guidance produced by the European Food Safety Authority (EFSA) in 2011 <http://www.efsa.europa.eu/en/efsajournal/pub/2140.htm>, serves as guidance for risk assessors across the EU. This advice is consistent with the advice from COT/COC/COM<sup>1</sup> that has been used since 2005.

## **Section 2: R&D activities on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q2. Are you aware of any finished, on-going, or planned R&D activities on a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials for their human health and ecosystem hazard assessment?*

The UK REACH Competent Authority is participating in a sub-group of ECHA's Nanomaterials Working Group (NMWG) that is looking at how read-across could be used for nanomaterials within REACH. The European Commission is developing a grouping approach to help companies meet their registration obligations under REACH. We expect that ECHA and the European Commission will also be responding to this questionnaire and will provide more information about these activities in their responses.

The UK has research groups working on the following EU funded projects (as well as non-EU funded projects) which all include research on aspects of characterisation: ITS-Nano, ModNanoTox, NanoReg, NanoFATE, NanoTOES, UK-US TINE, Natural Environment Research Council environmental nanotechnology initiative projects, NanoMile.

*Q2.1 Which type of approach is employed?*

- 1) Concept of grouping*
- 2) Concept of equivalence*
- 3) Concept of read-across*
- 4) Any other concept of similar nature (Please give a short description):*

NanoFATE, for example, is focused on testing the applicability of all approaches 1-3 above. Researchers at the Centre for Ecology and Hydrology are doing so in depth, using pairs of commercial Ag and ZnO NPs, testing and comparing their environmental behaviour in natural media and the resulting effects seen on a range of exposed species. For specific studies these key commercial particles have been augmented with a range of specifically designed particles with ranging sizes and coatings.

In the UK-US funded TINE project a set of ZnO, Ag and TiO<sub>2</sub> NPs are being dosed into the inlet of a pilot scale waste water treatment plant (WWTP) and their fate followed. There are 3 lines in the pilot plant control, NP dosed and a concentration matched line dosed with ionic metal forms (Zn and Ag). The resulting WWTP sludge is tested for toxicity to a range of terrestrial species (microbe, plants and invertebrates). There is an additional laboratory based arm to this project looking to understand the transformation mechanisms and incorporate these into models for transformation and soil type effects on NP bioavailability and hazard potential.

The focus of both these project is on the assessment of hazard and ultimately by relating this information to usage and fate data to the determination of risk for ecological effects in soils and surface waters.

Considerations on grouping and ranking form part of the European FP7 project: “ITS-Nano – Research prioritisation to deliver an intelligent testing strategy for the human and environmental safety of nanomaterials”.

*Q2.2 The proper name of the R&D activity and URLs for websites or documents that explain or concern the activity:*

<http://www.birmingham.ac.uk/generic/modnanotox/index.aspx>

<https://wiki.ceh.ac.uk/display/nanofate/Home;jsessionid=178C95CD7C72A0189CA3F6E91FE4BDC6>

<http://www.nanosafetycluster.eu/eu-nanosafety-cluster-projects/seventh-framework-programme-projects/nanofate.html>

<http://www.nanoreg.eu/>

<http://www.nanotoes.eu/>

[http://www.ceh.ac.uk/news/news\\_archive/2011\\_news\\_item\\_03.html](http://www.ceh.ac.uk/news/news_archive/2011_news_item_03.html)

<http://www.its-nano.eu/> Specifically, see chapter 4 in the final project report downloadable from <http://www.its-nano.eu/wp-content/uploads/2013/08/ITS-Nano-2.pdf>

*Q2.3 How was/is the approach being developed?*

The grouping/ranking of NMs for risk assessment purposes is a multi-factorial process and ideally should encompass critical components such as hazard and exposure of humans and the environment as well as key physicochemical properties of the NMs themselves. The future research emphasis for grouping/ranking is inherently reliant on and interlinked to those advances already stated for Physicochemical ID, Hazard-ID, and Exposure-ID in the other chapters of the ITS-Nano report. The grouping/ranking chapter highlights the specific needs pertinent to grouping/ranking that have arisen from consideration of Physicochemical ID, Hazard-ID, and Exposure-ID in the context of the parameters required to group/rank nanomaterials and the standards or data comparison protocols required. For ITS-NANO, these needs are arranged in a diagram which identifies the components required for the development of a grouping/ranking approach for NMs. Hexagon colours relate to PC ID (blue), Exposure (brown), Hazard (green), Cross-cutting issues (purple), implementation into a RA framework (grey) and the final goal of the ITS (white). The diagram is intended to start on the left (NM) and finish on the right, but there is no strict order of passage between the hexagons to achieve the final goal. The order of priority is graded across the diagram, with hexagons to the left being of short term-priority (<5 years) stretching to longer term and distant priorities on the right (>15 years). It is important to note that contrary to similar representations in preceding chapters of the report, the hexagons for grouping/ranking are not necessarily intrinsically linked, but overall contribute to progress towards grouping and/or ranking of NMs as well as modelling.

In terms of Phys-Chem properties for the particles the variations have mainly been of size and surface coating (and as a result surface charge) for the Ag and ZnO NPs in NanoFATE. For example aquatic algae were tested with a range of 8 different Ag NPs forming a matrix of coatings and sizes. Additionally the effects of media properties on particle properties, behaviour (e.g. aggregation/sedimentation rates) are included in the assessment. In TINE we have looked at the behaviour, uptake and toxicity of variously aged forms of Ag and ZnO (i.e. mainly phosphorised vs. mainly Sulphurised forms).

In terms of Phys-Chem properties of the exposure media NanoFATE has covered a range of standard ecotox test media as well as the widest possible ranges of natural variation that the organisms would allow

or was realistic in media chemistry (e.g. pH and Organic matter content). For example the same particles have been tested in up to seven different soils media that range in pH, organic matter content, as well as related properties.

In terms of endpoints NanoFATE covers a range of endpoints within several species from marine, freshwater and terrestrial systems. This ranges from targeted mechanistic biomarkers of physiological effect to changes in community structure (for algal and bacterial communities). The analysis of comparability and spread in the observed results and sensitivities is being undertaken following the principle of Species Sensitivity Distributions. It is clear that the ranking of species sensitivities to the ionic form of a metal does not infer the ranking of the same species sensitivity to the nano forms, nor do sensitivities to one nano particle read-across very well to another NP of the same core metal. A data-base of toxicity data generated from studies conducted within and outside the project is being used to investigate these relationships in greater depth.

As well as the empirical investigations described above, modelling approaches such as QSAR have been used for the grouping of nanomaterials based on existing data. These approaches are at a preliminary stage.

#### *Q2.4 Was/Is the approach specific to nanomaterials or expanded from chemicals in general?*

In both NanoFATE and TINE, researchers are aiming to modify approaches from “standard chemicals” as little as necessary to make them workable for use with nano. This goes both for exposure (predicting environmental concentrations), toxicity testing, bioavailability and analytical protocols. On the toxicity testing side, protocols have mainly needed modification either in the methodology for dosing or mixing the “chemical” into the media. In aquatic media, modifications had to be made to the frequency at which the dosed media is renewed (balancing handling stress, the temporal stability of the nano form in suspension and waste production). The main theoretical approaches we are trying to make work for NPs are those covering bioavailability, where the current methods rely on chemical equilibrium, which will not work for nanoparticles where the speciation between states is dynamic and models will have to be based on the rates of transfer between “states”. This consideration will require a substantial revision of current concepts which rely on equilibrium relationships.

In ITS-Nano, the approach is applicable to both, but was developed for the purposes of nanomaterials.

Modelling approaches such as QSAR are generally specific to nanomaterials only.

#### *Q2.5 What was/is the main issue OTHER THAN BUDGET that may hamper the development of the approach?*

Methods of measurement and sample preparation for physical-chemical property characterisation are major issues. Especially it is very difficult to achieve any kind of in situ characterisation in the more complex media (e.g. soils and sediments or even natural waters). For aquatic media most characterisation equipment has detection limits well above the relevant concentrations for even acute aquatic effects in short term tests. Hence the characterisation chemistry undertaken is often at extremely high concentrations meaning it is questionable to what extent data obtained for e.g. aggregation rates and forms are relevant to the true chemistry at realistic doses (e.g. one may consider if homoaggregation would ever occur at realistic ratios of dissolved organic carbon in natural waters). The situation in soil is even more challenging. Here methods for the direct measurement of the concentration and state of nanomaterials in this medium are still only in the early stages of development and it will be sometime before these can be rolled out as robust and fully validated approaches.

Dealing with a variety of surface modifications, is a problem of logistics (which could be solved with BUDGET) that ideally should be solved by industry being open about what design options are irrelevant for operational production so these can be excluded from testing efforts.

For ecotox testing, exposure relevance and time scale may be more important than endpoint selection. The selection of relevant in vivo / in vitro endpoints seems more an issue for human than ecosystem health due to the protection goal being the individual's health, the protection of which may require novel endpoint testing where new route of uptake and internal trafficking or Modes of Action may be suspected. In ecotox where the protection goal is the population the standard endpoints will in principle still guard this goal irrespective of how the effect is caused or occurs. The main novel issue for Nano in ecotox is getting the exposure to reflect and reproduce what is going to be relevant in the environment and also that the time scales of exposure development in terms of speciation to the most toxic form may exceed the standard tests by some margin. It is normally assumed that the standard protocols will lead to worst case (toxicity) exposures for "standard chemicals", but for nanoparticles where processes such as dissolution may lead to increasing toxicity over time this must not be assumed per se and needs checking and controlling for.

Measurement issues associated with data reliability associated with nanomaterial dispersion characterisation e.g. lack of fit for purpose tools, lack of standard protocols, lack of reference materials, how to report findings.

Data availability.

For most available assays only few physical-chemical properties are measured. The available data on specific species and endpoints are very sparse. A machine-readable format for assays data and a standardized vocabulary would help to collect all given data for specific purposes.

*Q2.6 If the developed approach is supposed to be employed in a regulatory regime, the name of regulatory regime and the governing organisation:*

The EU-funded work is all geared to provide answers to how existing EU regulation (REACH, TSCA, EU Biocides Regulation No 528/2012 and Water Framework Directive 2000/60/EC) can be made "fit for nano" with minimum changes. ECHA oversees chemicals legislation in the EU. In the UK, the regulatory authority for the main chemicals legislation, REACH, is Defra, but the enforcement agencies are the Health and Safety Executive and the Environment Agency. Sectoral or media-specific legislation lies either with Defra or another central government department.

*Q2.7 If the developed approach is supposed to be employed in a regulatory regime, may it be (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in a regulatory regime?*

The answer to this question is dependent on a number of outcomes. A case by case basis is likely to be useful because, like their bulk counterparts, NM's vary/are likely to vary widely in the degree of hazard associated with them. However, it may be possible to develop protocols that enable risk assessment based on (comparison by) grouping, equivalence and read across within one or more regulatory regimes. For example, risk assessment of medicines with a nano component might be effectively undertaken using pharmaceutical legislation and authorisation frameworks but by employing recognised standards of G, E & R. However, these standards have yet to be fully developed, perhaps first using the most commonly encountered/most hazardous NMs and then using a wider range of NMs. The anticipated degree of exposure / nature of use will be an important consideration. For example the risks posed by therapeutic 'nano-medicines' are likely to have completely differently environmental profile compared with those posed by nano-bioremediation.

*Q2.8 If the developed approach is supposed to be employed in a regulatory regime, how may it be used within the human health and ecosystem hazard assessment of nanomaterials?*

Risk assessment. See answer to Q2.7.

*Q2.9 If the developed approach is supposed to be employed in a regulatory regime, how may it contribute to limiting the testing costs or numbers of animals used?*

It is hoped that these approaches will contribute towards a predictive framework for nanotoxicity thereby reducing the need for animal testing. The work has given consideration to the issues such as better use of historical data, more informed decision making around testing, weight of evidence approaches and using grouping/ranking, all of which are intended to contribute to the development of an intelligent testing strategy and thereby limit testing costs and the number of animals used. However, in some cases empirical data from animal research may need to be generated to answer specific questions on ecotoxicity/human health risks.

### **Section 3: Other information on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q3. Are you aware of a case where concepts of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials are used, or supposed to be used, much effectively for their human health and ecosystem hazard assessment in a regulatory regime governed by another country or organisation?*

Read across has been used to fill data gaps in some REACH registration dossiers. We expect ECHA will be responding to this questionnaire and will be able to provide more information in their response.

*Q3.1 Name of the (potential) regulatory regime(s) and its governing organisation:*

REACH, ECHA.

*Q3.2 Which type of approach are you aware of?*

- 1) Concept of grouping*
- 2) Concept of equivalence*
- 3) Concept of read-across*
- 4) Any other concept of similar nature (Please give a short description):*

All of these.

## THE BUSINESS AND INDUSTRY ADVISORY COMMITTEE TO THE OECD

### CEFIC

#### **Section 1: Present use of concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q1. Are you involved in, or aware of, any human and ecosystem health hazard assessment in a regulatory regime governed by your organisation, or of your country, for which a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials is or has been employed?*

Within the EC/1907/2006 REACH Regulation under the Annex XI, it states that when “*substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar may be considered as a group or category and data on phys-chem., human health and environmental effects may be predicted from data for reference substance within the group by interpolation to other substances in the group (read-across).*”

*Q1.6 How does the approach contribute to limiting the testing costs or numbers of animals used?*

This approach avoids the need to test every substance for every endpoint, and definitely to reduce the animal testing and costs especially for SMEs.

*Q1.7 Is the approach specific to nanomaterials or expanded from chemicals in general?*

Under REACH framework, the read-across approach applies for all chemicals.

*Q1.8 What was the main issue OTHER THAN BUDGET that hampered the development of the approach and how was the issue resolved?*

Basically, as it is defined under the REACH Regulation, read-across approach applies from a substance to another one with similar properties. In the case of nanomaterials, the read-across has to apply within the same substance and therefore, there is a need for a better understanding how to use this approach for nanomaterials. However, at European level, ECHA, the Competent Authorities, the Commission and industry are working together for developing of this approach for nanomaterials.

*Q1.9 Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:*

Although the concept of equivalence is not de facto applicable, application of grouping and read-across within regulatory regimes can provide benefits when well defined for nanomaterials and used appropriately. For the time being, there are running or almost to be launched FP7 research projects that are generating information and approaches to grouping, modelling and read-across that will ultimately be useful. Until nano-specific practices are developed, if needed, the OECD Guidance on Grouping of Substances provides a set of useful approaches that are generally applicable to nanomaterials.

## **Section 2: R&D activities on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q2. Are you aware of any finished, on-going, or planned R&D activities on a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials for their human health and ecosystem hazard assessment?*

*Q2.1 Which type of approach is employed?*

Under the FP7 umbrella there are some relevant projects covering read-across, grouping approaches such as: NanoREG (grouping of nanomaterials based on their behaviour and mode of toxicological action and to develop state of the art modelling of both nanoparticles and *in-silico* behaviour as a tool supporting grouping strategies which will be launched soon).

*Q2.4 Was/Is the approach specific to nanomaterials or expanded from chemicals in general?*

Specific to nanomaterials.

*Q2.5 What was/is the main issue OTHER THAN BUDGET that may hamper the development of the approach?*

A potential barrier might be that each nanomaterial has own specificities and hence to extend those specificities to other similar classes of nanomaterials.

*Q2.6 If the developed approach is supposed to be employed in a regulatory regime, the name of regulatory regime and the governing organisation:*

The results of the FP7 projects should be taken into account when apply read-across approach for nanomaterials in order to create a good explanatory basis of it under the existing regulatory framework.

*Q2.9 If the developed approach is supposed to be employed in a regulatory regime, how may it contribute to limiting the testing costs or numbers of animals used?*

In principle, if nanomaterials can be grouped based on different properties/uses, than certainly it will be a huge benefit for not to repeat testing and so reducing the costs.

## **Section 3: Other information on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q4. Other details, explanations or comments:*

However, read-across approach should be scientifically justified and currently there is no proper explanation on how this justification should be provided.

**BIAC US**

**Section 1: Present use of concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q1. Are you involved in, or aware of, any human and ecosystem health hazard assessment in a regulatory regime governed by your organisation, or of your country, for which a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials is or has been employed?*

We are not aware of any regulatory regimes where the concepts of grouping, equivalence or read-across based on physical or biological properties of nanomaterials have been employed as part of regulatory decision making.

*Q1.9 Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:*

The application of grouping, equivalence and read-across within regulatory regimes can provide benefits when used appropriately. It should not be assumed that these concepts can always be used so there will continue to be a need for case-by-case assessments for some nanomaterials. Presently, there are many research projects that are generating information and approaches to grouping, equivalence and read-across that will ultimately be useful. Until nano-specific practices are developed, if needed, the OECD Guidance on Grouping of Substances provides a set of useful approaches that are generally applicable to nanomaterials.

**Section 2: R&D activities on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q2. Are you aware of any finished, on-going, or planned R&D activities on a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials for their human health and ecosystem hazard assessment?*

*Q2.1 Which type of approach is employed?*

The NanoCharacter project coordinated by the ILSI Research Foundation intends to foster the development of practices leading to better use of grouping, equivalence and read-across based on physico-chemical properties.

*Q2.2 The proper name of the R&D activity and URLs for websites or documents that explain or concern the activity:*

<http://www.ilsi.org/NanoCharacter/Pages/NanoCharacter.aspx>

*Q2.3 How was/is the approach being developed?*

NanoCharacter has not settled on a single set of P-Chem properties and this may evolve during the project. The project is informed by previous work such as the MINChar Initiative and others:

<http://characterizationmatters.org/>

*Q2.4 Was/Is the approach specific to nanomaterials or expanded from chemicals in general?*

Specific to nanomaterials.

*Q2.5 What was/is the main issue OTHER THAN BUDGET that may hamper the development of the approach?*

A potential barrier is gaining wide-spread acceptance of the need to promote grouping, equivalence, read-across within the research community. Another potential barrier is agreement on a single set of data elements.

*Q2.6 If the developed approach is supposed to be employed in a regulatory regime, the name of regulatory regime and the governing organisation:*

Not initially intended for regulatory purposes. This may happen later. Representatives of US EPA and Environment Canada participated in the initiative.

*Q2.7 If the developed approach is supposed to be employed in a regulatory regime, may it be (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in a regulatory regime?*

Not initially intended for regulatory purposes. This may happen later. The approach should regularly facilitate comparisons of test results used in regulatory EHS assessments.

*Q2.8 If the developed approach is supposed to be employed in a regulatory regime, how may it be used within the human health and ecosystem hazard assessment of nanomaterials?*

Not initially intended for regulatory purposes. This may happen later. By having a more standard set of parameters available for materials similarities and differences will be more readily noted both in the materials themselves and their biological effects.

*Q2.9 If the developed approach is supposed to be employed in a regulatory regime, how may it contribute to limiting the testing costs or numbers of animals used?*

In theory, if it can reasonable concluded that materials are substantially equivalent or can be used to predict the properties of other materials repeated testing will not be needed.

**UNITED STATES**

***ENVIRONMENTAL PROTECTION AGENCY***

**Section 1: Present use of concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q1. Are you involved in, or aware of, any human and ecosystem health hazard assessment in a regulatory regime governed by your organisation, or of your country, for which a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials is or has been employed?*

Respirable Poorly Soluble Particulates Category

*Q1.1 Name of the regulatory regime and its governing organisation:*

Toxic Substances Control Act (TSCA) administered by the US EPA.

*Q1.2 Which type of approach is employed?*

Concept of read-across/or analogue

*Q1.3 The proper name of the approach and URLs for websites or documents that explain or concern the approach:*

EPA uses the chemical category of respirable poorly soluble particulates to evaluate the potential hazard and risks of nanomaterials submitted as new chemical substances under TSCA.

The URL that explains how EPA uses chemical categories and the categories document: <http://www.epa.gov/oppt/newchemicals/pubs/chemcat.htm>

Below is the summary of the category:

**Category: Respirable, Poorly Soluble Particulates Health Only**

**Definition.** This category includes a variety of inorganic, poorly soluble (as designated in ILSI 2000) particulates. Typically, they are oxides of various metals or nonmetals (i.e., silicon)

**Boundaries.** There is a potential for respirability if there are any particles  $\leq 10 \mu$  in diameter in the material being handled by workers. Summarized below are currently available test data on five different poorly soluble particulates: silica, talc, titanium dioxide, PMN 9see-175 (lithium manganese oxide), and carbon black. The suitability of one or more of these analogues for a particular PMN particulate must be determined on a case-by-case basis. Risk is to be assessed by the margin of exposure method for the reason stated in the next paragraph.

**Hazard Concerns.** The category concerns discussed here are limited to effects on the lung as a result of inhaling the particles. Broadly, as shown in rat inhalation studies, these effects range from inflammation to fibrosis to, potentially, cancer. Because it is still not known with certainty whether high lung burdens of poorly soluble particulates can lead to lung cancer in humans via mechanisms similar to those of the rat, in the absence of mechanistic data to the contrary, it must be assumed that the rat model can identify potential carcinogenic hazards to humans. Since the apparent responsiveness of the rat model at overload is dependent on coexistent chronic active inflammation and cell proliferation, at lower lung doses in which chronic active inflammation and cell proliferation are not present, no lung cancer hazard is anticipated (ILSI 2000).

Some of the particulates may contain metals, for example, chromium, that may present other and more imminent toxicities, depending on the bioavailability of the metal ions. Thus, the toxicities of the metal components of the particulates must also be assessed, and on a case-by-case basis.

*Q1.4 How is the approach implemented within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

EPA uses the hazard information in the category to evaluate the potential hazard and risk of certain nanomaterials, when the physical-chemical properties of the nanomaterial fit those in the category.

*Q1.5 Is the approach (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

It is employed on a case-by-case basis based on the properties stated in the category, however, EPA finds that it applies to many nanomaterials.

*Q1.6 How does the approach contribute to limiting the testing costs or numbers of animals used?*

TSCA does not have prescribed testing for new chemical submissions. This approach does not limit testing costs or number of animals used for testing. This approach is one factor used in assessing potential human health hazard and determining which testing would address that hazard. Other factors including overall risk and available data are also considered when determining

*Q1.7 Is the approach specific to nanomaterials or expanded from chemicals in general?*

This approach applies to all chemical substances including nanomaterials that fit the parameters of the category.

*Q1.8 What was the main issue OTHER THAN BUDGET that hampered the development of the approach and how was the issue resolved?*

This approach was developed based on experience with new chemical submissions and their physical-chemical properties under TSCA. The examples given above are issues that must also be assessed when developing the risk assessment for a new chemical nanomaterial.

*Q1.9 Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:*

- 1) *In the future, concepts of grouping, equivalence or read-across for nanomaterials may be necessary in the regulatory regime.*
- 6) *An internationally harmonised guidance (e.g. OECD guidance) on grouping, equivalence or read-across for nanomaterials for regulatory regimes is awaited.*

Because EPA employs concepts of grouping, equivalence and read-across for chemical substances, it is expected that these concepts will also apply to certain nanomaterials. EPA has identified groups of nanomaterials submitted as new chemical substances under TSCA based on their chemical composition. EPA is compiling physical-chemical properties of each of these groups to determine if read-across or equivalence concepts apply based on those properties.

**Section 1: Present use of concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q1. Are you involved in, or aware of, any human and ecosystem health hazard assessment in a regulatory regime governed by your organisation, or of your country, for which a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials is or has been employed?*

Under the Regulatory Cooperation Council Nanotechnology Initiative, the United States and Canada is considering a proposed classification scheme for nanomaterials to help guide the selection of analogue/read-across information.

After discussions with stakeholders and experts, it was thought that this classification scheme, based on chemical composition could be applied to physical-chemical, fate, and release endpoints and could potentially be used to increase the weight-of-evidence, where appropriate.

It is recognized that it is premature to apply this classification approach for toxicological assessment. Once additional science on nano-properties and their mode-of-actions on organisms have been discovered, further relationships may be drawn.

The US and Canada will bring forward this classification scheme for discussion at the OECD WPMN meeting on categories in April, 2014.

*Q1.1 Name of the regulatory regime and its governing organisation:*

TSCA which is administered by the US EPA.

*Q1.2 Which type of approach is employed?*

Concept of grouping

Concept of read-across

*Q1.3 The proper name of the approach and URLs for websites or documents that explain or concern the approach:*

Development of a classification scheme for nanomaterials regulated under the New Substances Programs of the United States and Canada.

The final report is anticipated to be published following the final Regulatory Cooperation Council Nanotechnology Initiative stakeholder meeting planned for January, 2014.

*Q1.4 How is the approach implemented within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

The classification scheme developed is not being used as it is currently being considered and discussed by both countries.

*Q1.5 Is the approach (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

Since this approach is still under development, we are still considering the application/applicability of this approach on a case-by-case basis.

*Q1.6 How does the approach contribute to limiting the testing costs or numbers of animals used?*

Since this approach is still under development, the implications to testing costs/# of animals cannot be predicted.

*Q1.7 Is the approach specific to nanomaterials or expanded from chemicals in general?*

Specific to nanomaterials

*Q1.8 What was the main issue OTHER THAN BUDGET that hampered the development of the approach and how was the issue resolved?*

Lack of scientific knowledge limits the confidence/applicability of this classification scheme for hazard classification. Improved correlations between properties and effects must still be established.

*Q1.9 Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:*

- 1) *In the future, concepts of grouping, equivalence or read-across for nanomaterials may be necessary in the regulatory regime.*
- 6) *An internationally harmonised guidance (e.g. OECD guidance) on grouping, equivalence or read-across for nanomaterials for regulatory regimes is awaited.*

## **Section 2: R&D activities on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q2. Are you aware of any finished, on-going, or planned R&D activities on a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials for their human health and ecosystem hazard assessment?*

There is ongoing work being done by UCLA on predicting toxicology of carbon nanotubes and metals and metal oxides. There are also domestic and international projects such as ToxCast, Tox21, Comptox, and work being conducted by the National Institute of Environmental Health Sciences (NIEHS). The critical issue is the validation of these screening tests and models before their utilization especially in regulatory risk assessment.

*Q2.1 Which type of approach is employed?*

Concept of read-across and analogues

## CANADA

### **Section 1: Present use of concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q1. Are you involved in, or aware of, any human and ecosystem health hazard assessment in a regulatory regime governed by your organisation, or of your country, for which a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials is or has been employed?*

Canada, together with the United States under the Regulatory Cooperation Council Nanotechnology Initiative is considering a proposed classification scheme for nanomaterials to help guide the selection of analogue/read-across information.

After discussions with stakeholders and experts, it was thought that this classification scheme, based on similarities in chemical composition could be applied to physical-chemical, fate, and release endpoints and could potentially be used to increase the weight-of-evidence, where appropriate.

It is recognized that it is premature to apply this classification approach for toxicological assessment. Once additional science on nano-properties and their mode-of-actions on organisms have been discovered, further relationships may be drawn.

Canada along with the US will bring forward this classification scheme for discussion at the OECD WPMN meeting on categories in April, 2014.

*Q1.1 Name of the regulatory regime and its governing organisation:*

Canadian Environmental Protection Act, 1999 - administered jointly by Environment Canada and Health Canada.

*Q1.2 Which type of approach is employed?*

Concept of grouping

Concept of read-across

*Q1.3 The proper name of the approach and URLs for websites or documents that explain or concern the approach:*

Development of a classification scheme for nanomaterials regulated under the New Substances Programs of Canada and the United States

The final report is anticipated to be published following the final Regulatory Cooperation Council Nanotechnology Initiative stakeholder meeting planned for January, 2014.

*Q1.4 How is the approach implemented within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

The classification scheme developed is not being used as it is currently being considered and discussed by the two countries.

*Q1.5 Is the approach (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

Since this approach is still under development, we are still considering the application/applicability of this approach on a case-by-case basis.

*Q1.6 How does the approach contribute to limiting the testing costs or numbers of animals used?*

Since this approach is still under development, the implications to testing costs/# of animals cannot be predicted.

*Q1.7 Is the approach specific to nanomaterials or expanded from chemicals in general?*

Specific to nanomaterials

*Q1.8 What was the main issue OTHER THAN BUDGET that hampered the development of the approach and how was the issue resolved?*

Lack of scientific knowledge limits the confidence/applicability of this classification scheme for hazard classification. Improved correlations between properties and effects must still be established.

*Q1.9 Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:*

- 1) *In the future, concepts of grouping, equivalence or read-across for nanomaterials may be necessary in the regulatory regime.*
- 3) *Currently, the regulatory regime does not specifically deal with nanomaterials.*

Nanomaterials are assessed under the same regime as bulk chemicals. There is no specific regulatory regime for nanomaterials.

- 5) *Necessary R&D activities are on-going to develop and employ such concepts of grouping, equivalence or read-across for nanomaterials in the regulatory regime.*
- 6) *An internationally harmonised guidance (e.g. OECD guidance) on grouping, equivalence or read-across for nanomaterials for regulatory regimes is awaited.*

## **Section 2: R&D activities on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q2. Are you aware of any finished, on-going, or planned R&D activities on a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials for their human health and ecosystem hazard assessment?*

Canada is fostering research capacity to look at classes of nanomaterials

*Q2.1 Which type of approach is employed?*

Concept of read-across

*Q2.2 The proper name of the R&D activity and URLs for websites or documents that explain or concern the activity:*

The Government of Canada supports the need to further explore the effects of nano-properties on organisms which will inform on read-across. It has initiated some work in this area including activities investigating the effect of size and surface functionality of nanomaterials on *in vitro* cytotoxicity/cell viability and environmental organisms.

*Q2.3 How was/is the approach being developed?*

For environmental *in vitro/in vivo* endpoints, cell lines of organisms including fish along with whole organism studies on fish, daphnia, algae have been studied on modified metal oxides (titanium dioxide, silicon nanoparticles, zinc oxide, copper oxide), modified metal nanoparticles (silver) and carbon nanotubes.

*Q2.4 Was/Is the approach specific to nanomaterials or expanded from chemicals in general?*

The approach being considered is taken from traditional chemicals.

*Q2.6 If the developed approach is supposed to be employed in a regulatory regime, the name of regulatory regime and the governing organisation:*

The regulatory regime is the New Substances Notification Regulations developed under the mandate of the Canadian Environmental Protection Act (CEPA, 1999) and jointly administered by Health Canada and Environment Canada.

*Q2.7 If the developed approach is supposed to be employed in a regulatory regime, may it be (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in a regulatory regime?*

Eventually we hope it could be used regularly but currently it is on a case by case basis.

*Q2.8 If the developed approach is supposed to be employed in a regulatory regime, how may it be used within the human health and ecosystem hazard assessment of nanomaterials?*

The approach is still under development, but once implemented, it is expected to allow risk assessors to draw on data sets from similar substances that have been deemed suitable (by the approach) as read across (e.g., for fate and exposure predictions); specifically for hazard determination the concept of read-across would only be used currently to increase weigh-of-evidence until more rigorous scientific information is available.

*Q2.9 If the developed approach is supposed to be employed in a regulatory regime, how may it contribute to limiting the testing costs or numbers of animals used?*

Unknown at this time as it is still in development.

### **Section 3: Other information on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q3. Are you aware of a case where concepts of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials are used, or supposed to be used, much effectively for their human health and ecosystem hazard assessment in a regulatory regime governed by another country or organisation?*

Yes

*Q3.1 Name of the (potential) regulatory regime(s) and its governing organisation:*

As the classification scheme being considered is being developed jointly with the US EPA, all of the previous responses may apply here.

*Q3.2 Which type of approach are you aware of?*

1) *Concept of grouping*

3) *Concept of read-across*

*Q3.3 The proper name of the approach/R&D activity and URLs for websites or documents that explain the approach/activity or are otherwise relevant:*

See Section 2

*Q3.4 How does/will the approach work within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

See Section 2

## **AUSTRALIA**

### **NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)**

#### **Section 1: Present use of concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q1. Are you involved in, or aware of, any human and ecosystem health hazard assessment in a regulatory regime governed by your organisation, or of your country, for which a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials is or has been employed?*

Yes

The Australian Government industrial chemicals regulator, NICNAS, conducted the ‘Human health hazard assessment and classification of carbon nanotubes (CNTs)’ in 2012. This report is available at:

<http://www.safeworkaustralia.gov.au/sites/swa/about/publications/pages/human-health-hazard-assessment-and-classification-of-carbon-nanotubes>

In addition, the Australian Government Department of the Environment has been in the problem formulation stage of risk analysis, with a focus on how existing frameworks for environmental risk assessment would cope with nanomaterials.

<< NICNAS Note: Section 1 has been duplicated for these parallel activities. They are identified as Section 1A and Section 1B, respectively. >>

*Section 1A: Information provided by NICNAS*

*Q1.1 Name of the regulatory regime and its governing organisation:*

Industrial Chemicals (Notification and Assessment) (ICNA) Act, 1989/National Industrial Chemicals Notification and Assessment Scheme (NICNAS).

*Q1.2 Which type of approach is employed?*

- 1) *Concept of grouping*
- 2) *Concept of equivalence*
- 3) *Concept of read-across*
- 4) *Any other concept of similar nature (Please give a short description):*

Concept of grouping (or categorisation)

The assessment included both single-walled (SW-) CNTs and multi-walled (MW-) carbon nanotubes (CNTs). The assessment noted that MWCNTs have been shown to induce mesothelioma in rodents after single intraperitoneal or intrascrotal dosing. The carcinogenic potential of carbon nanotubes is not determined solely by the length of the individual carbon nanotubes, but by their ability to present as a fibre with pathogenic dimensions, either as the individual fibre or through aggregation. Based on the limited data available on mesothelioma formation in animal studies and difficulty in conclusively determining whether a specific MWCNT can present as a fibre of pathogenic dimensions, the report recommended that all MWCNTs should be considered carcinogenic.

Concept of read-across

Due to the limited data available on SWCNTs, studies investigating health effects of single-walled carbon nanohorns (SWCNHs) were utilised to fill data gaps where relevant, e.g. acute toxicity.

No studies were available to demonstrate that SWCNTs cause mesothelioma. Neither was there evidence to suggest SWCNTs behave any differently to MWCNTs with respect to the potential to form granulomas or mesotheliomas given they have been shown to be durable and have shown to elicit a fibre pathogenic response through the ability to form rigid fibre-like structures through aggregation inside the body. Hence a precautionary approach was utilised and SWCNTs were considered to be carcinogenic based on read across data from MWCNTs.

*Q1.3 The proper name of the approach and URLs for websites or documents that explain or concern the approach:*

The report does not include references for the approaches used for grouping or read-across. However, the approaches used in the report comply with the explanations provided in this document (extracted from the OECD [ENV/JM/HA(2013)5/PROV]).

*Q1.4 How is the approach implemented within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

NICNAS uses the approaches listed under Q1.2 to assess conventional chemicals. NICNAS is yet to assess nano-forms of new chemicals for regulatory purposes.

*Q1.5 Is the approach (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

Not applicable (see response to Q1.4).

*Q1.6 How does the approach contribute to limiting the testing costs or numbers of animals used?*

This CNT report only used the data from published journal articles and reviews. Therefore, this question is not applicable.

However, broad grouping of SWCNTs and MWCNTs is considered a pragmatic approach to limit the cost of testing costs and reduce numbers of animals used. If significant variations can be anticipated in the toxicity profile, for example due to high impurity levels, such substances may be considered separately. In general, NICNAS encourages analogue and read across approaches to minimise the use of animal testing.

*Q1.7 Is the approach specific to nanomaterials or expanded from chemicals in general?*

The grouping/read-across approaches are used in the assessment of conventional chemicals.

*Q1.8 What was the main issue OTHER THAN BUDGET that hampered the development of the approach and how was the issue resolved?*

Not applicable.

*Q1.9 Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:*

- 1) *In the future, concepts of grouping, equivalence or read-across for nanomaterials may be necessary in the regulatory regime.*

Yes. This approach may be required for nanomaterials, considering the potential variability of the same substance e.g. particle size, surface coatings etc. The concept of grouping is useful to fill data gaps where significant variation in health hazards within a family of substances is not anticipated. In particular grouping will be useful in assessing nanoforms of existing chemicals where it can be scientifically justified.

- 2) *In the future, concepts of grouping, equivalence or read-across for nanomaterials may not be necessary in the regulatory regime.*

There will be limited use of these concepts for assessing new nanomaterials as these are specific/unique and well characterised.

- 3) *Currently, the regulatory regime does not specifically deal with nanomaterials.*

Although the regulatory regime specifically introduced measures for the regulation of nanoforms of new chemicals (since 2011), the number of these substances notified for assessment has been very small. A process for regulating nanoforms of existing chemicals is under development.

- 4) *Each individual nanomaterial should be tested for all toxicological endpoints foreseen by the regulatory regime.*

Nanomaterials are regulated within the framework applicable to conventional industrial chemicals. In the case of new chemicals, data required for nanomaterials are the same as data required for conventional chemicals within a particular notification category. The regulatory regime has the power to request additional data for the purposes of the assessment where this is warranted.

- 5) *Necessary R&D activities are on-going to develop and employ such concepts of grouping, equivalence or read-across for nanomaterials in the regulatory regime.*

Not known.

- 6) *An internationally harmonised guidance (e.g. OECD guidance) on grouping, equivalence or read-across for nanomaterials for regulatory regimes is awaited.*

Harmonised guidance would assist in applying these concepts.

*Section 1B: Information provided by the Australian Government Department of the Environment*

*Q1.1 Name of the regulatory regime and its governing organisation:*

Australia / Australian Government Department of the Environment – provides environmental assessments for NICNAS

*Q1.2 Which type of approach is employed?*

- 1) *Concept of grouping*
- 2) *Concept of equivalence*
- 3) *Concept of read-across*
- 4) *Any other concept of similar nature (Please give a short description):*

Concepts of categorisation and grouping

*Q1.3 The proper name of the approach and URLs for websites or documents that explain or concern the approach:*

Some application of the concepts of categorisation and grouping of chemical substances developed by the OECD are useful for qualitative purposes in the preliminary problem formulations stage of assessing the environmental risks of manufactured nanomaterials:

<http://www.oecd.org/env/ehs/risk-assessment/groupingofchemicalschemicalcategoriesandread-across.htm>

*Q1.4 How is the approach implemented within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

Manufactured nanomaterials can be usefully grouped into broad categories such as carbonaceous molecular nanomaterials (e.g., C60), carbonaceous fibrous nanomaterials (e.g., carbon nanotubes), metallic nanoparticles, and metal oxide as a first step in the problem formulation stage of risk assessment. These broad groups can be used to identify the combination of key physico-chemical properties, environmental fate properties, and environmental effects which might be common to each of these major categories of manufactured nanomaterial.

For example, dissolution behaviour of metal oxide nanomaterials and aquatic effects of released metal ions for metal oxide nanoparticles as a likely common feature of risk assessment of uses of metal oxide nanoparticles resulting in aquatic exposure.

*Q1.5 Is the approach (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in the regulatory regime?*

Environmental risk assessment of manufactured nanoparticles for regulatory purposes has not occurred very often in the last 5 years.

*Q1.6 How does the approach contribute to limiting the testing costs or numbers of animals used?*

*No information available.*

*Q1.7 Is the approach specific to nanomaterials or expanded from chemicals in general?*

Extensive experience in categorisation and grouping of conventional chemical substances using sophisticated tools such as the OECD QSAR Toolbox has not proved to be readily transferrable to nanomaterials due to the absence of well-developed rules and guidance on how categorisation could be usefully carried out for the environment related aspects of nanomaterials.

*Q1.8 What was the main issue OTHER THAN BUDGET that hampered the development of the approach and how was the issue resolved?*

A key challenge in using data from broad categories of manufactured nanomaterials to fill data gaps using techniques such as read-across is the complexity of the behaviour of nanomaterials in the environment and how this behaviour, particular transformation processes, can influence the effects that the nanomaterial (and its transformation products) can have on biota, especially in the aquatic compartment, and the consequences this has for the risk characterisation process. The current uncertainty in the environmental behaviour of manufactured nanomaterials on a category-by-category basis significantly limits the reliability of attempts to fill data gaps using techniques such as read-across. The application of QSA(P)Rs to nanomaterials is not currently used for regulatory purposes.

*Q1.9 Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:*

- 1) In the future, concepts of grouping, equivalence or read-across for nanomaterials may be necessary in the regulatory regime.*

Concepts of categorisation and grouping are useful for preliminary stages of problem formulation. Read-across methods for filling data gaps have limited current applicability for environmental risk assessment.

- 2) *In the future, concepts of grouping, equivalence or read-across for nanomaterials may not be necessary in the regulatory regime.*

These concepts will become more important in the future as more data is collected on the behaviour of nanomaterials in the environment. Currently, environmental risk assessment of nanomaterials does not have a comparable body of knowledge to that which exists for conventional chemical substances and which allows the reliable application of expert judgement to fill data gaps using suitable analogues.

- 3) *Currently, the regulatory regime does not specifically deal with nanomaterials.*

Risk assessment of nanomaterials is currently infrequent in this jurisdiction.

- 4) *Each individual nanomaterial should be tested for all toxicological endpoints foreseen by the regulatory regime.*

Testing of environmental fate and transport end-points for nanoparticles is as important as purely ecotoxicological investigations. In some cases, adequate environmental fate testing may obviate the need for extensive ecotoxicological testing.

- 5) *Necessary R&D activities are on-going to develop and employ such concepts of grouping, equivalence or read-across for nanomaterials in the regulatory regime.*

A series of laboratory research projects have been conducted in Australia to characterise the environmental fate properties of manufactured nanomaterials that are important for risk characterisation. These projects have been published in the scientific literature and these have already been useful in categorisation of nanomaterials by environmental fate characteristics.

- 6) *An internationally harmonised guidance (e.g. OECD guidance) on grouping, equivalence or read-across for nanomaterials for regulatory regimes is awaited.*

This could be useful, especially if it includes categorisation approaches based on environmental fate characteristics.

*Section 2: R&D activities on concepts of grouping, equivalence and read-across based on physical-chemical properties*

*Q2. Are you aware of any finished, on-going, or planned R&D activities on a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials for their human health and ecosystem hazard assessment?*

Yes

The Australian Government Department of the Environment has collaborated with Australian researchers in such activities.

## Section 2: Information provided by the Australian Government Department of the Environment

*Q2.1 Which type of approach is employed?*

- 1) *Concept of grouping*
- 2) *Concept of equivalence*
- 3) *Concept of read-across*
- 4) *Any other concept of similar nature (Please give a short description):*

Categorisation of manufactured nanomaterials based on environmental behaviour.

An extensive set of laboratory research studies on the environmental fate and transformation of manufactured nanomaterials have been commissioned by the Australian Government and published in the open scientific literature. Additional research on the environmental transformation of carbonaceous molecular nanomaterials is currently underway.

*Q2.2 The proper name of the R&D activity and URLs for websites or documents that explain or concern the activity:*

This research was carried out as part of the National Enabling Technologies Strategy.

<http://innovation.gov.au/Industry/Nanotechnology/NationalEnablingTechnologiesStrategy/Pages/default.aspx>

*Q2.3 How was/is the approach being developed?*

The research studies are directed at identify the combination of key characteristics of both nanomaterials and the environmental compartment in which they occur which can be used to understand the fate of the nanomaterials upon release to the environment. The data obtained will allow some level of categorisation based on environmental fate properties of nanomaterials which would also inform the need for, and conduct of, relevant additional testing, including ecotoxicological testing.

*Q2.4 Was/Is the approach specific to nanomaterials or expanded from chemicals in general?*

No. The laboratory research was conducted based on an understanding of the unique properties of nanomaterials, especially their colloidal properties, and the way this influences the reliability of data derived for risk assessment purposes.

*Q2.5 What was/is the main issue OTHER THAN BUDGET that may hamper the development of the approach?*

The research has identified a number of technical challenges associated with evaluating the properties of nanomaterials in realistic environmental matrices which require further investigation before useful predictive rules can be developed.

*Q2.6 If the developed approach is supposed to be employed in a regulatory regime, the name of regulatory regime and the governing organisation:*

These approaches may be used in the environmental hazard assessment of nanomaterials that are used as industrial chemicals or pesticides in Australia.

*Q2.7 If the developed approach is supposed to be employed in a regulatory regime, may it be (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in a regulatory regime?*

The categorisation rules based on environmental fate properties of nanomaterials determined under Australia conditions would be used if the properties of the nanomaterial were sufficiently similar to the materials that have been studied.

*Q2.8 If the developed approach is supposed to be employed in a regulatory regime, how may it be used within the human health and ecosystem hazard assessment of nanomaterials?*

The research results obtained to date allow better use of evidenced-based categorisation to be undertaken for manufactured nanomaterials, which will facilitate more reliable problem formulation for risk assessment activities.

*Q2.9 If the developed approach is supposed to be employed in a regulatory regime, how may it contribute to limiting the testing costs or numbers of animals used?*

The more reliable grouping of manufactured nanomaterials for problem formulation that is now possible will allow better targeting of any additional testing that is required to support environmental risk assessment of nanomaterials.

## **JAPAN**

### **MINISTRY OF ECONOMY, TRADE AND INDUSTRY**

#### **Section 1: Present use of concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q1. Are you involved in, or aware of, any human and ecosystem health hazard assessment in a regulatory regime governed by your organisation, or of your country, for which a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials is or has been employed?*

NO

*Q1.9 Regarding your regulatory regime, please indicate your views on such concepts of grouping, equivalence or read-across for nanomaterials:*

- 1) In the future, concepts of grouping, equivalence or read-across for nanomaterials may be necessary in the regulatory regime.*

Maybe YES

- 3) *Currently, the regulatory regime does not specifically deal with nanomaterials.*

No

- 4) *Each individual nanomaterial should be tested for all toxicological endpoints foreseen by the regulatory regime.*

Not yet decided

- 5) *Necessary R&D activities are on-going to develop and employ such concepts of grouping, equivalence or read-across for nanomaterials in the regulatory regime.*

Not decided for regulatory regime or non-regulatory purpose

- 6) *An internationally harmonised guidance (e.g. OECD guidance) on grouping, equivalence or read-across for nanomaterials for regulatory regimes is awaited.*

Yes

## **Section 2: R&D activities on concepts of grouping, equivalence and read-across based on physical-chemical properties**

*Q2. Are you aware of any finished, on-going, or planned R&D activities on a concept of grouping, equivalence or read-across based on physical-chemical properties of nanomaterials for their human health and ecosystem hazard assessment?*

*Q2.1 Which type of approach is employed?*

Concept of equivalence

*Q2.2 The proper name of the R&D activity and URLs for websites or documents that explain or concern the activity:*

"Development of innovative methodology for safety assessment of industrial nanomaterials"

<http://www.aist-riss.jp/projects/reti-nano/en/>

*Q2.3 How was/is the approach being developed?*

In this R&D programme, equivalence criteria has been developed by carrying out rat intratracheal administration studies of nanomaterials with the same chemical composition and different size, shape and surface treatment for assessment of adverse human health effects associated with inhalation exposure to nanomaterials. At present, several metal oxides are under examination. The programme investigates a contribution of nanomaterial's physical-chemical properties to toxicity. Based on the contribution, equivalence criteria, a range that toxicity is regarded as substantially equivalent, is to be established. For example, if particle size is within some definite range, it is considered as equivalent in terms of toxicity.

The programme examines effects in the lung -- mainly inflammation and fibrosis by histology and BALF analysis --, clearance from the lung and translocation to other organs.

Based on ISO/TR 13014:2012 and OECD ENV/JM/MONO(2012)40, the programme selected or may select the following physical-chemical properties for characterising nanomaterials: size, size distribution, agglomeration, aggregation state as administered, shape, surface area, chemical composition, surface chemistry, surface charge i.e. zeta potential and isoelectric point, solubility or dispersibility, and density.

*Q2.4 Was/Is the approach specific to nanomaterials or expanded from chemicals in general?*

Our approach is specific to nanomaterials and not expanded from chemicals in general.

*Q2.5 What was/is the main issue OTHER THAN BUDGET that may hamper the development of the approach?*

- 1) Preparation of series of nanomaterials with different physical-chemical properties, i.e. commercial availability and sample preparation.
- 2) Quantitative analytical methods of nanomaterials in tissues for toxicokinetic studies. The detection limit is higher than actual concentration of nanomaterials in tissues, or there is no appropriate measurement method.
- 3) Selection of parameters for surface state or surface chemistry of nanomaterials that are important for toxicity and toxicokinetics.

*Q2.6 If the developed approach is supposed to be employed in a regulatory regime, the name of regulatory regime and the governing organisation:*

Once a result of the programme comes, relevant Ministries will examine if the developed approach can be employed in a regulatory regime.

*Q2.7 If the developed approach is supposed to be employed in a regulatory regime, may it be (from the technical perspective) employed regularly or on a case-by-case basis, within the human health and ecosystem hazard assessment of nanomaterials in a regulatory regime?*

Once a result of the programme comes, relevant Ministries will examine if the developed approach can be employed in a regulatory regime.

*Q2.8 If the developed approach is supposed to be employed in a regulatory regime, how may it be used within the human health and ecosystem hazard assessment of nanomaterials?*

The developed approach may be used for hazard assessment of new nanomaterials, as necessary. Here, "new nanomaterials" are not limited to completely new nanomaterials, but can include variations that size, shape or surface treatment are slightly modified from existing nanomaterials. First, based on physical-chemical properties of a new nanomaterial, it is determined if the new nanomaterial is equivalent to known nanomaterials whose hazard data has been already obtained. When the new nanomaterial is regarded as substantially equivalent, toxicity testing is not required for it. Otherwise, toxicity testing is required for it.

*Q2.9 If the developed approach is supposed to be employed in a regulatory regime, how may it contribute to limiting the testing costs or numbers of animals used?*

When a new nanomaterial is regarded as substantially equivalent to known nanomaterials whose hazard data has been already obtained, it is possible to utilize the existing hazard data, and thus, to reduce costs and animal use.