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CO-OPERATION ON RISK ASSESSMENT: PRIORITISATION OF IMPORTANT ISSUES ON RISK ASSESSMENT OF MANUFACTURED NANOMATERIALS - FINAL REPORT

Series on the Safety of Manufactured Nanomaterials No. 38

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# **OECD Environment, Health and Safety Publications**

# Series on the Safety of Manufactured Nanomaterials

No. 38

Co-Operation on Risk Assessment: Prioritisation of Important Issues on Risk Assessment of Manufactured Nanomaterials - Final Report



Environment Directorate
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT
Paris, 2013

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#### **FOREWORD**

This document follows on from a report published by the Working Party on Manufactured Nanomaterials (WPMN), entitled *Important Issues on Risk Assessment of Manufactured Nanomaterials* (ENV/JM/MONO(2012)8).

The report on *Important Issues* identified a range of issues which the WPMN considered important in risk assessment and which should be addressed in the future. However, not all of these important issues could be considered by the WPMN at the same time. For this reason, a survey was subsequently circulated to delegations of the WPMN with the aim of identifying those issues described in the report for which further guidance should be developed by the WPMN as a priority. This document summarises the survey results, the methodologies used to analyse the survey, and the identified priorities. These priorities will be the primary focus of projects pertaining to approaches for risk assessments of manufactured nanomaterials. The remaining *Important Issues* will be considered as additional resources become available. The survey results indicate that the availability of experimental data on which guidance development is based differs greatly between the *Important Issues* - an observation that should be considered when designing research programmes.

The work to prepare this document was undertaken by steering group 6 (SG6) of the WPMN which addresses risk assessment methodologies and approaches. It is being published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology, which has agreed that it be declassified and made available to the public.

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#### **BACKGROUND**

- 1. Following finalisation of the report *Important Issues on Risk Assessment of Manufactured Nanomaterials* (ENV/JM/MONO(2012)8) a survey was initiated. The purpose of this survey was to identify those *Issues* described in the Report for which further guidance should be developed with priority. Further details and description of the *Issues* can be found in the report (ENV/JM/MONO(2012)8).
- 2. Steering Group 6 of the WPMN (SG6) plans to initiate projects to address specific *Important Issues* in order to produce scientific analyses that can form the basis for guidance and/or to more clearly specify knowledge gaps and respective data needs. As a first step SG6 prepared a *Call for Project Proposals* that SG6 intends to distribute to WPMN delegations following the 11<sup>th</sup> meeting of the OECD WPMN together with this final report of the prioritisation survey. Such projects may then be addressed by future work of WPMN. Under new direction from the Bureau, special consideration is given to priorities which directly feed into regulatory processes.
- 3. The present analysis of the survey is intended to guide the initiation of these SG6 projects. At the SG6 meeting in June 2012, a first preliminary analysis was presented. It was agreed, that a Task Force should develop a final, more detailed analysis, taking into account linkages between issues that were identified in the survey and proposing clusters of related issues that may be best addressed jointly.

#### FEED-BACK

- 4. A total of 12 delegations submitted responses to the survey (circulated March 23, 2012).
- 5. In section 1 of the survey, delegations characterised the issues in 4 categories: Importance, Expected availability of data, Inter-relationship of issues, Potential contribution to respective SG6 projects.
- 6. Importance was ranked very high high less with scoring as "very high" and "high" limited to a maximum of 6 and 12 issues, respectively. Rankings could be flagged with an "E" or "H" to allow for differentiation between environmental and human health & safety aspects.
- 7. In section 2 of the survey, delegations had the option to suggest further activities to support the development of specific guidance.

### **METHODOLOGY**

8. As the result of previous discussions during development of the SG6 *Important Issues* document, the SG expected significant overlap between priorities and linkages assigned to the individual *Issues* by the participants. However, while that was true in some instances, there were also many responses which were not common to the different participants. This lead to 348 identified linkages between the 64 identified *Issues*, thereby causing complexities in analysing and prioritizing for case studies. It is acknowledged that while some issues may not be linked with others, they still may be of particular importance and require further investigation. For the purposes of this exercise, it was determined that as a first step the SG should focus on identifying *Issues* which are the most inter-dependant and cross-cutting. By focusing on these issues first, the SG will be able to engage a broader audience to work on the activity and will allow for data generation for some of the other *Issues* based on the relationships. Three methodologies were employed to identify these inter-related and linked *Issues* and prioritise them. The respective methodologies are briefly described below:

## 1. Data Weighting

9. Importance. A score was calculated for the category Importance as follows by weighing "very high" scores with a factor of 10 and "high" scores with a factor of 5. Calculations were performed separately for the environmental and the human health & safety issues.

Score = 
$$\frac{10 \text{ x "very high" scores} + 5 \text{ x "high" scores}}{\text{total number of scores}}$$

10. Data availability. A score was calculated for expected data availability by addition of responses for availability "expected" from Sponsorship Programme and "expected" from other sources minus responses for "not expected", divided by the number of overall responses.

## 2. Clustering

- 11. With the survey, responses were collected with regard to pairwise linkages between identified Issues. A preliminary analysis suggested that when considering these linkages and grouping *Issues* into clusters in which they should be followed up collectively, this may have a significant impact on the ranking outcome.
- 12. Therefore, an analysis of linkages between issues was performed to propose groups (clusters) of *Issues* to be addressed preferentially within one project.
- 13. For the analysis, duplications of linkages identified by the same respondent were eliminated. For each pair, the number of responses was determined. In order to achieve some level of selectivity, only pairs that were identified by at least 3 respondents were included in building a cluster core. Issues that were linked to a member of the cluster core by at least two respondents were included as core cluster satellites. Linkages (pairs) to the cluster core identified by one respondent only were considered incidental and not included in the analysis.

#### 3. Mind-mapping

14. Mind-mapping is an exercise in using expert judgement to link (through arrows) connected issues together. This technique, developed by Tony Buzan is meant to identify relationships quickly. Brinkmann¹ provides a complete review on using mind mapping as an efficient tool. Here, only the environment group was analysed using mind-mapping. It was expected that the outcomes between the environment and human health theme will not vary in terms of identifying underlying linked issues. It is also acknowledged that the mind map is not comprehensive, but for the purposes of this document it appears sufficient.

<sup>&</sup>lt;sup>1</sup> A. Brinkmann, 2003. Graphical Knowledge Display – Mind Mapping and Concept Mapping as Efficient Tools in Mathematics Education, Mathematics Education Review, 16: 35-48.

#### **OUTCOMES**

# 1. Weighted Analysis of Importance

- 15. The full results of this exercise are summarised in Annex I. Please note that only issues that were ranked "very high" or "high" are listed in this Annex.
- 16. The following *Issues* received the highest (top 10) scores.

#### **Environment:**

- Transformation, degradation and persistence
- Nanomaterial identification
- Bioaccumulation
- Use of data on close analogues
- Applicability of tools for exposure modelling
- · Hazard assessment for classification and labelling
- Non-nanomaterial to nanomaterial extrapolation
- Applicability of testing methods
- Quantifying risk
- Physico-chemical properties / Selection of assessment endpoints / Adaptation of tools for exposure modelling <sup>2</sup>

#### Human Health:

- Hazard assessment for classification and labelling
- Dose metrics
- Nanomaterial identification
- Selection of assessment endpoint
- Non-nanomaterial to nanomaterial extrapolation
- Linking material properties to ADME<sup>3</sup> and toxic effects

<sup>&</sup>lt;sup>2</sup> An identical score was obtained for these issues.

<sup>&</sup>lt;sup>3</sup> Absorption, Distribution, Metabolism and Excretion.

- Use of data on close analogues
- Physico-chemical properties
- Effective dose
- Applicability of testing methods, Nanomaterial to nanomaterial extrapolation, and Quantifying Risk <sup>4</sup>
- 17. It should be noted that 6 of these *Issues* are present in both the top scores for environment as well as those for human health.

14

<sup>&</sup>lt;sup>4</sup> An identical score was obtained for these issues.

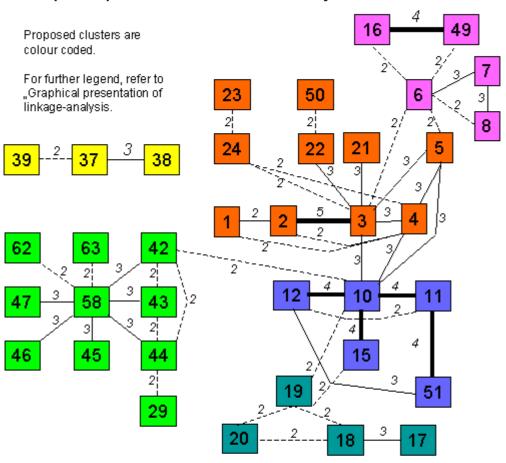
### 2. Weighted Analysis of Data Availability

- 18. Results of the weighted analysis for data availability are summarised in Annex IIa and IIb. Those risk assessment issues for which data to support guidance development was expected to be available (i.e. expressed as score > 0.00) are listed in Annex IIa.
- 19. Issues for which data was expected to be rather not available (score  $\leq 0$ ) are found in Annex IIb. Substantial experimental work will likely be required to generate a suitable database for development of guidance on those risk assessment issues.
- 20. A score of 0.50 or higher was calculated for the following *Issues*, implying that according to the feedback a majority expects suitable data to be available for development of initial guidance from either the WPMN Sponsorship Programme or other sources:
  - Nanomaterial identification
  - Physico-chemical properties
  - Nanomaterial to nanomaterial extrapolation
  - Effective dose
  - Dose metrics
  - Non-nanomaterial to nano material extrapolation
  - Selection of assessment endpoint
  - Endpoints assessed
  - Target organs
  - Internal exposure following inhalation
  - Internal exposure following ingestion
  - Interspecies extrapolation
  - Testing plan
  - Applicability of testing methods
  - Internal exposure following dermal exposure
  - Internal exposure through distribution
  - Definition of biologically relevant properties
  - Conceptual exposure models

## 3. A - Linkages between Issues and Clustering

- 21. A total of 397 responses were received regarding potential links between *Issues*. When duplications of linkages identified by the same respondent were removed, this number was reduced to 348.
- 22. Based on these responses, a total of 251 different links (pairs) were identified between the 64 *Issues* (theoretical maximum = 2016 pairs).
- 23. Of these, 1 pair was identified simultaneously by 5 respondents, 5 pairs by 4 respondents, 19 pairs by 3 respondents, 40 pairs by 2 respondents and the remaining 186 pairs were identified by 1 respondent only.
- 24. Annex III lists all links between *Issues* that were identified by at least 3 respondents.
- 25. A cluster analysis was performed based on the feedback received. *Issues* that were considered to be linked to other *Issues* by at least three respondents were considered as cluster core. All other *Issues* that were linked to core issues by at least two respondents were included in the analysis. All other issues were excluded from the cluster analysis to retain a sufficient degree of selectivity.
- 26. A graphical representation of the outcome of this cluster analysis is shown below. Suggested subclusters were colour-coded.
- 27. Notably, a number of issues that did receive one of the ten highest individual priority scores, were not identified as clustered *Issue* with this analysis. This encompasses *Issues* 14 (Env+Health: Hazard assessment for classification and labelling), 52 (Env+Health: Nanomaterial identification), 53 (Env+Health: Physico-chemical properties), as well as 35 (Env: Applicability of tools for exposure modelling), 55 (Env: Transformation, degradation and persistence), 57 (Env: Bioaccumulation), and 16 (Health: Dose metrics), 19 (Health: Linking material properties to ADME and toxic effects).

# Graphical presentation of cluster-analysis



Conceptual exposure model, parametrisation and validation

Factors for uncertainty, extrapolation for description of risk

Relevant material properties - material heterogeneity

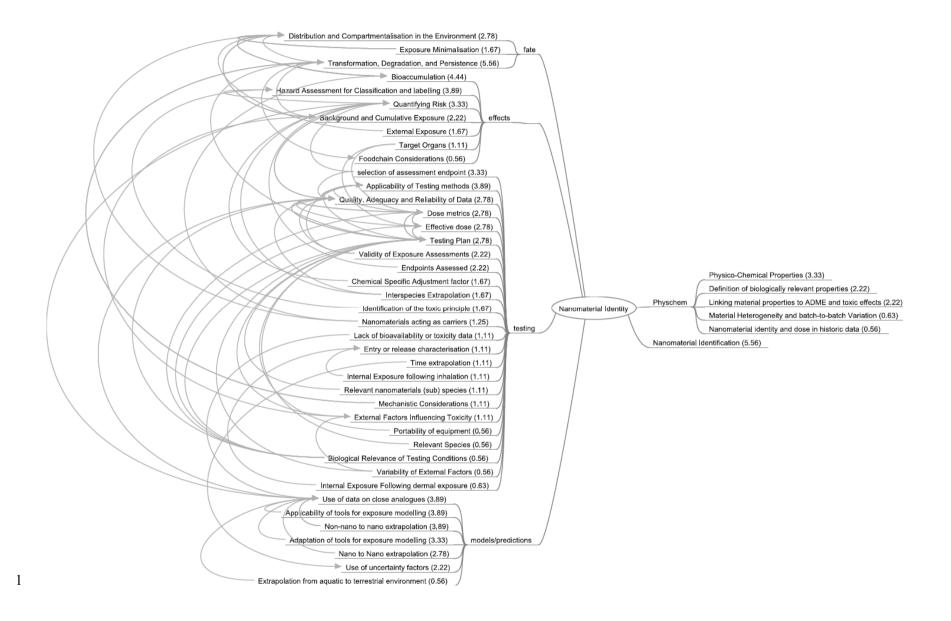
Mechanistic issues and read-across / bridging

Effective Dose – Dose metrics

Testing Plan – Targets - Endpoints – Applicability / Relevance of Testing Methods

# 3. B. - Mind-mapping

28. To complement the cluster analysis, linkages between issues were sought through a mind-mapping exercise, first focussing at the environment theme. An example of the mind-map is shown below. Although not comprehensive, the example does illustrate that there are many linkages across the various issues as discussed in 3A. In addition, it has been identified that the issue that relates the most is "nanomaterial identification", which includes physico-chemical properties. This is also consistent with the average score from Annex I (i.e., nanomaterial identity > models/prediction > effects > fate > testing). For example, under the category of environment, physico-chemical characteristics, such as dissolution rate, are needed to understand transformation, degradation, and persistence from a regulatory standpoint. The preliminary outcomes of this exercise have resulted in a new project lead by Canada to address how to utilize dissolution as a function of surface modification in regulatory risk assessments. Outcomes from this Canadian project will also feed into other issues that link to physico-chemical identification, such as distribution and compartmentalization in the environment, bioaccumulation, quantifying risk, target organs, etc.



#### **CONCLUSIONS**

- 29. All issues identified by in the report (ENV/JM/MONO(2012)8) are important and ultimately need to be addressed.
- 30. The combination of mind-mapping and cluster analysis enabled the movement towards a prioritization process which identified linkages between issues. The issues most cross-cutting were identified as priorities.
- 31. This does not mean that only cross-cutting issues should be considered as projects and more "isolated" issues for which data weighting identified a high scoring for importance should be excluded.
- 32. However, SG6 members have limited resources thus an essential part of the prioritization process is to reduce the list of issues to a manageable size.
- 33. It is also recognized that many of the individual issues identified in the survey may be included in other subjects so there may be ways to combine efforts. Therefore, it is proposed to prioritise groups of strongly interlinked issues as these may present a gap to many of the downstream issues and allow the involvement of different members, across different steering groups and perhaps Working Parties.
- 34. Based on the prioritising exercises described in this document, the following high level categories are identified:
  - Physical chemistry use of information about physico-chemical properties in risk assessment (cf. paragraphs 108-110 of ENV/JM/MONO(2012)8)
  - Nanomaterial identification properties relevant to identification of a material rather than characterisation (cf. paragraphs 35, 47, 52, 54-57, 107 of ENV/JM/MONO(2012)8)
  - Environmental fate and effects how to use physico-chemical properties to conduct and inform on environmental fate and effects endpoints (cf. Sections 4.b.iii-vii of ENV/JM/MONO(2012)8)
  - Exposure models Concepts should be evaluated, potentially adapted, as well as further parameterized (cf. paragraphs 21-22, 71-78, 8585 of ENV/JM/MONO(2012)8)
  - Adverse effects Description of effective dose and dose metrics (cf. paragraphs 43-46, 53, 86, 105-106, 134 of ENV/JM/MONO(2012)8)
  - Testing Testing plan, targets and endpoints assessed, relevance/reliability/reproducibility of methods/results (cf. paragraphs 38-42, 58-61, 100-101 of ENV/JM/MONO(2012)8)
  - Extrapolation Extrapolation of data between/within materials, species and exposure situations (cf. paragraph 48-49, 79-84, 102-103, 130-133 and 142-145 of ENV/JM/MONO(2012)8)

#### MOVING FORWARD

- 35. Physico-chemical properties (and nanomaterial identity) was identified as a priority and may be considered the most fundamental category of those identified above. Current regulatory regimes for nanomaterials rely on existing legislative authorities and to a large extent follow chemical risk assessment paradigms. Traditionally, the starting point for risk assessments of chemicals is an assessment of the physico-chemical properties and possible exposure pathways. Major gaps remain, however, 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.
- 36. In addition, nanomaterial identification is integrally linked to physical chemistry and is accordingly grouped for the purposes of this exercise. SG6 will not be discussing nanomaterial identification but will inform physical chemical approaches that will feed into the chemical and biological identification discussions and categorisation of nanomaterials. It is proposed that SG6 commit to projects that address how to use physicochemical data for more efficient assessment of potential hazards and exposure as well as environmental fate and behaviour to support the regulatory/scientific risk assessment of nanomaterials. Reasons that support this proposal include:
  - Survey respondents expected data for development of guidance on this area to be available (highest weighted data availability score for physico-chemical properties and nanomaterial identification, rf. to Annex IIa).
  - Physicochemical information includes characterization elements (e.g. size, size distribution, solubility, etc. as described in the WPMN Guidance Manual for Sponsors, ISO TR 13014 and www.characterizationmatters.org) that are an integral part of the other four categories.
  - There is still little clarity in using physico-chemical data in a meaningful way in the regulatory process i.e., using physico-chemical endpoints to inform on environmental fate and effects in a predictable and nano-relevant manner.
  - SG6 projects on physicochemical aspects will benefit from cooperative work being initiated between SG3/4/7 and ISO TC 229. Collaboration between SG6 and these cooperative projects will allow all to advance quicker.
  - SG6 projects supporting physicochemical aspects will also promote WPMN work on grouping of nanomaterials. Presently it is difficult to group nanomaterials based on physical-chemical or (eco)toxicological properties and it is even more difficult in doing this in a manner useful from a regulatory perspective, i.e., when can read-across and analogue information be used within groups/classes of nanomaterials for assessing potential adverse effects. It is expected that this SG6 exercise will lead to better informed discussions within the OECD on this subject-matter.
  - The focus of SG6 is Risk Assessment which requires good quality data
- 37. SG6 members are invited to propose specific projects that will inform regulatory processes and/or regulatory decision-making. Members are encouraged to be aware of the work between the WPMN and ISO TC229 and projects underway or proposed by ISO TC229, CEN TC352, ASTM E56, the Nanomaterial Registry, the NanoCharacter project and others.
- 38. SG6 invites members to begin projects which feed into their expertise. It is suggested using cross-cutting issues identified herein as priorities as starting points to engage as many experts as possible.

Finding ways to address these issues (including but not limited to those involving physico-chemical aspects) will be of most benefit in the short to medium term. In addition, issues that were regarded to be of higher regulatory importance should be pursued first.

39. Finally, SG6 intends on working closely with other Steering Groups of OECD WPMN and to involve relevant experts along with engaging outside entities such as scientific organisations to leverage expertise and to take on relevant projects.

## **ANNEX I:**

# Issues scored "high" or "very high" importance (without clustering)

No.	ISSUE TITLE (ENVIRONMENT)	SCORE
55	Transformation. degradation and persistence	5.56
52	Nanomaterial identification	5.56
57	Bioaccumulation	4.44
51	Use of data on close analogues	3.89
35	Applicability of tools for exposure modelling	3.89
14	Hazard assessment for classification and labelling	3.89
11	Non-nano material to nanomaterial extrapolation	3.89
3	Applicability of testing methods	3.89
63	Quantifying risk	3.33
53	Physico-chemical properties	3.33
36	Adaptation of tools for exposure modelling	3.33
1	Selection of assessment endpoint	3.33
56	Distribution and compartmentalisation in the environment	2.78
50	Quality. adequacy and reliability of data	2.78
16	Dose metrics <sup>5</sup>	2.78
12	Nanomaterial to nanomaterial extrapolation	2.78
6	Effective dose	2.78
2	Testing plan	2.78
58	Use of uncertainty factors	2.22
48	Validity of exposure assessments	2.22
29	Background and cumulative exposure	2.22
20	Definition of biologically relevant properties	2.22
19	Linking material properties to ADME and toxic effects	2.22
4	Endpoints assessed	2.22
61	Exposure minimisation	1.67
45	Chemical-specific adjustment factors	1.67
42	Interspecies extrapolation	1.67
28	External exposure	1.67
15	Identification of the toxic principle	1.67
13	Nanomaterials acting as carriers	1.25
62	Lack of bioavailability or toxicity data	1.11
54	Entry or release characterisation	1.11
44	Time extrapolation	1.11
30	Internal exposure following inhalation	1.11
18	Relevant nanomaterials (sub) species	1.11

-

<sup>&</sup>lt;sup>5</sup> Different aspects of the *Issue* "Dose metrics" were discussed: Issue No. 16 relates to the choice of metrics for biologically appropriate hazard characterisation (cf. paragraph 53 of <a href="ENV/JM/MONO(2012)8">ENV/JM/MONO(2012)8</a>) while Issue No. 49 relates to the choice of metrics for limit values in the context of comparison to exposure data and risk characterisation (cf. paragraph 86 of <a href="ENV/JM/MONO(2012)8">ENV/JM/MONO(2012)8</a>).

10	Mechanistic considerations	1.11
7	External factors influencing toxicity	1.11
5	Target organs	1.11
32	Internal exposure following dermal exposure	0.63
17	Material heterogeneity and batch-to-batch variation	0.63
59	Food chain considerations	0.56
41	Portability of equipment	0.56
25	Nanomaterial identity and dose in historic data	0.56
24	Relevant species	0.56
23	Extrapolation from aquatic to terrestrial environment	0.56
21	Biological relevance of testing conditions	0.56
8	Variability of external factors	0.56

No.	ISSUE TITLE (HUMAN HEALTH)	SCORE
14	Hazard assessment for classification and labelling	4.58
16	Dose metrics <sup>5</sup>	4.58
52	Nanomaterial identification	4.58
1	Selection of assessment endpoint	4.17
11	Non-nano to nano extrapolation	4.17
19	Linking material properties to ADME and toxic effects	4.17
51	Use of data on close analogues	4.17
53	Physico-chemical properties	4.17
6	Effective dose	3.75
3	Applicability of testing methods	3.33
12	Nano to nano extrapolation	3.33
63	Quantifying risk	3.33
30	Internal exposure following inhalation	2.92
58	Use of uncertainty factors	2.92
2	Testing plan	2.50
15	Identification of the toxic principle	2.50
20	Definition of biologically relevant properties	2.50
35	Applicability of tools for exposure modelling	2.50
44	Time extrapolation	2.50
50	Quality. adequacy and reliability of data	2.50
55	Transformation, degradation and persistence	2.50
61	Exposure minimalisation	2.50
28	External exposure	2.08
29	Background and cumulative exposure	2.08
48	Validity of exposure assessments	1.82
4	Endpoints assessed	1.67
10	Mechanisticconsiderations	1.67
36	Adaptation of tools for exposure modelling	1.67
57	Bioaccumulation	1.67
13	Nanomaterials acting as carriers	1.36
5	Target organs	1.25
9	Definition of adversity	1.25
18	Relevant nanomaterials (sub) species	1.25
42	Interspecies extrapolation	1.25
45	Chemical-specific adjustment factors	1.25
27	Epidemiological and medical data	1.15
21	Biological relevance of testing conditions	0.83
54	Entry or release characterisation	0.83
62	Lack of bioavailability or toxicity data	0.83
17	Material heterogeneity and batch-to-batch variation	0.77
31	Internal exposure following ingestion	0.77
32	Internal exposure following dermal exposure	0.77
33	Internal exposure through distribution	0.77
22	Assessment of the quantitative relevance of testing conditions	0.42
25	Nanomaterial identity and dose in historic data	0.42
38	Parameterisation of conceptual exposure models	0.42
43	Intraspecies extrapolation	0.42
47	Consequences of large assessment factors	0.42
49	Dose metrics <sup>5</sup>	0.42
56	Distribution and compartmentalisation in the environment	0.42
59	Food chain considerations	0.42

# ANNEX II - ISSUES SCORED FOR DATA AVAILABILITY

Annex IIa: Issues with weighted scores > 0.00 (data expected)

No.	ISSUE TITLE	SCORE
52	Nanomaterial identification	0.73
53	Physico-chemical properties	0.73
12	Nano to nano extrapolation	0.71
6	Effective dose	0.69
16	Dose metrics <sup>5</sup>	0.69
11	Non-nano to nano extrapolation	0.67
49	Dose metrics <sup>5</sup>	0.67
1	Selection of assessment endpoint	0.64
4	Endpoints assessed	0.64
5	Target organs	0.64
30	Internal exposure following inhalation	0.64
31	Internal exposure following ingestion	0.64
42	Interspecies extrapolation	0.64
2	Testing plan	0.60
3	Applicability of testing methods	0.60
32	Internal exposure following dermal exposure	0.60
33	Internal exposure through distribution	0.60
20	Definition of biologically relevant properties	0.50
37	Conceptual exposure models	0.50
40	Detection limits	0.45
51	Use of data on close analogues	0.45
58	Use of uncertainty factors	0.43
24	Relevant species	0.40
28	External exposure	0.40
43	Intraspecies extrapolation	0.40
50	Quality, adequacy and reliability of data	0.40
55	Transformation. degradation and persistence	0.40
19	Linking material properties to ADME and toxic effects	0.38
10	Mechanistic considerations	0.33
17	Material heterogeneity and batch-to-batch variation	0.33
56	Distribution and compartmentalisation in the environment	0.33
57	Bioaccumulation	0.33
60	Abiotic effects	0.33
61	Exposure minimalisation	0.33
36	Adaptation of tools for exposure modelling	0.25
62	Lack of bioavailability or toxicity data	0.25
21	Biological relevance of testing conditions	0.20
44	Time extrapolation	0.20
41	Portability of equipment	0.14
63	Quantifying risk	0.14
14	Hazard assessment for classification and labelling	0.11

# ANNEX IIB: ISSUES WITH WEIGHTED SCORES ≤ 0 (SUITABLE DATA UNLIKELY)

No.	ISSUE TITLE	SCORE
7	External factors influencing toxicity	0,00
18	Relevant nanomaterials (sub) species	0,00
26	Toxicological endpoints in historic data	0,00
34	Other routes of exposure	0,00
38	Parameterisation of conceptual exposure models	0,00
54	Entry or release characterisation	0,00
25	Nanomaterial identity and dose in historic data	-0,11
13	Nanomaterials acting as carriers	-0,14
29	Background and cumulative exposure	-0,14
59	Foodchain considerations	-0,14
64	Iterative risk assessments	-0,20
35	Applicability of tools for exposure modelling	-0,25
39	Validation of conceptual exposure models	-0,25
47	Consequences of large assessment factors	-0,33
8	Variability of external factors	-0,43
9	Definition of adversity	-0,43
15	Identification of the toxic principle	-0,43
22	Assessment of the quantitative relevance of testing conditions	-0,43
45	Chemical-specific adjustment factors	-0,43
48	Validity of exposure assessments	-0,43
23	Extrapolation from aquatic to terrestrial environment	-0,50
46	Additional uncertainties	-0,50
27	Epidemiological and medical data	-0,75

#### ANNEX III

# LINKAGES IDENTIFIED BETWEEN ISSUES AND ISSUE CLUSTERING

A- Links between Issues identified by at least 3 respondents

frequency	lower issue no.	higher issue no.	identi	fied by			
5	2	3	che	deu	esp	jpn	usa
4	10	11	biac	che	esp	usa	
4	10	12	biac	che	esp	usa	
4	10	15	biac	deu	esp	jpn	
4	11	51	biac	can	deu	nld	
4	16	49	biac	deu	nld	usa	
3	3	4	che	deu	nld		
3	3	5	esp	jpn	nld		
3	3	10	deu	esp	nld		
3	3	21	che	deu	esp		
3	3	22	che	deu	esp		
3	4	5	che	deu	esp		
3	4	10	che	deu	esp		
3	5	10	che	deu	esp		
3	6	7	che	deu	nld		
3	7	8	biac	che	deu		
3	12	51	biac	deu	nld		
3	17	18	che	deu	nld		
3	37	38	che	esp	jpn		
3	42	58	deu	jpn	swe		
3	43	58	deu	jpn	swe		
3	44	58	deu	jpn	swe		
3	45	58	deu	jpn	swe		
3	46	58	deu	jpn	swe		
3	47	58	deu	jpn	swe		