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REPORT OF THE OECD EXPERT MEETING ON THE PHYSICAL CHEMICAL PROPERTIES OF MANUFACTURED NANOMATERIALS AND TEST GUIDELINES

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The Environment, Health and Safety Division publishes free-of-charge documents in eleven different series: **Testing and Assessment**; **Good Laboratory Practice and Compliance Monitoring; Pesticides; Biocides; Risk Management; Harmonisation of Regulatory Oversight in Biotechnology; Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents;** and **Safety of Manufactured Nanomaterials.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/chemicalsafety/).

This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organizations.

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

As part of its Programme on the Safety of Manufactured Nanomaterials, and in particular work on the testing and assessment of manufactured nanomaterials, OECD initiated a series of expert meetings to improve the applicability of the OECD Test Guidelines to nanomaterials. With this in mind, the Working Party on Manufactured Nanomaterials agreed to organise an expert meeting to address the Physico-chemical Properties of Manufactured Nanomaterials and Test Guidelines.

The meeting was organised in close collaboration with the International Organization for Standardization Technical Committee on Nanotechnologies (ISO/TC 229). ISO has vast experience in assessing the physico-chemical characteristics of nanomaterials. By working together, the workshop benefited from a broad range of experts on physico-chemical properties of manufactured nanomaterials in this field combining regulators and other governmental representatives, and well as industry and experts from academia.

The workshop on Physico-chemical Properties of Manufactured Nanomaterials and Test Guidelines took place on 28 February and 1 March 2013 in Queretaro, Mexico. It was hosted by the Mexican Ministry of Economy and the National Metrology Center (CENAM).

This document presents a report of the discussion and recommendations derived from the workshop.

The presentations given at the workshop are available in a separate document ENV/JM/MONO(2014)15/ADD, which is available from the secretariat on request.

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

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EXECUTIVE SUMMARY

The expert meeting on Physical-Chemical Properties of Manufactured Nanomaterials and Test Guidelines was held on 28 February and 1 March 2013 in Querétaro, Mexico. It was hosted by the Mexican Ministry of Economy and the National Metrology Center (CENAM).

This workshop was held in collaboration with the International Organization for Standardization Technical Committee on Nanotechnologies (ISO/TC 229) and in particular with experts from its Joint Working Group 2 (JWG2), Measurement and Characterisation and the Metrology Study Group. The co-operation between OECD and ISO/TC 229 provided an important dimension for the analysis of the physical-chemical properties of manufactured nanomaterials. The workshop addressed specific issues relevant to the physical-chemical properties of manufactured nanomaterials relevant from a regulatory perspective point of view. As anticipated, the workshop benefited from the expertise, as well as from the products developed by ISO/TC 229. Forty-four experts from the OECD and ISO participated in the workshop.

This document includes the summaries and recommendations derived from the discussion. The presentations made at the workshop are available in an accompanying document, ENV/JM/MONO(2014)15/ADD.

PHYSICAL-CHEMICAL PROPERTIES OF MANUFACTURED NANOMATERIALS AND TEST GUIDELINES

Background to the OECD series of workshops on manufactured nanomaterials and test guidelines

The OECD Working Party on Manufactured Nanomaterials (WPMN) initiated a series of expert meetings to assess the applicability of the OECD Test Guidelines (used for regulatory testing of chemicals) to nanomaterials. A preliminary report was published in 2009[1].

The current OECD Test Guidelines[2] series address agreed endpoints used for chemical safety assessment but were not specifically developed for addressing nanomaterials. It was expected that by reviewing the new findings from the OECD Sponsorship Programme for the Testing of Manufactured Nanomaterials (hereafter Testing Programme), experts will be in a better position for evaluating the applicability of current OECD Test Guidelines (TGs) to nanomaterials, or, if TGs were not applicable, to identify the need to update current or develop new test guidelines for those agreed endpoints that are relevant for safety and regulatory decision-making.

Physical-chemical Properties of Manufactured Nanomaterials

One of the starting points for risk assessments of chemicals are the physical-chemical properties and possible exposure pathways. With this in mind, OECD WPMN agreed a number of endpoints to investigate in its Testing Programme[3]. Likewise, the OECD publication *Important Issues on Risk Assessment of Manufactured Nanomaterials*[4] stressed that one of the general risk assessment research needs will be the "generation of high quality physico-chemical, fate and effects information". Based on this, the OECD decided to organise a workshop in order to address in detail the relevance of each physical endpoint for the regulation of nanomaterials.

This workshop was organised in close collaboration with the International Organization for Standardization Technical Committee on Nanotechnologies (ISO/TC 229) and in particular with experts from its Joint Working Group 2 (JWG2), Measurement and Characterisation and its Metrology Study Group. ISO/TC 229 has a network of experts with vast experience in assessing the physico-chemical characteristics of nanomaterials. By working together, the workshop benefited from a broad range of experts in this field combining regulators and other governmental representatives, and well as industry and experts from academia.

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[1] ENV/JM/MONO(2009)21. Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials.

[2] http://www.oecd.org/chemicalsafety/testing/

[3] See: i) List of Manufactured Nanomaterials and List of Endpoints for Phase One of the OECD Testing Programme [ENV/JM/MONO(2008)13/REV] and ii) Guidance Manual for the Testing of Manufactured Nanomaterials: OECD Sponsorship Programme: First Revision [ENV/JM/MONO(2009)20/REV].

[4] See publication Important Issues on Risk Assessment of Manufactured Nanomaterials [ENV/JM/MONO(2012)8].

The objective of the workshop was to: 1) assess the applicability of existing OECD Test Guidelines (TG) on Physical-chemical Properties of Manufactured Nanomaterials; and 2) identify the need to update current or develop new OECD Test Guidelines and/or OECD Guidance Documents (GD) which are relevant for safety and regulatory decision-making[5].

Structure of the Workshop

The workshop was structured by plenary sessions aiming at understanding the scope and objective of the meeting, highlighting the regulatory challenges, and identifying the issues and value of the different perspectives brought by the experts.

Based on the commonly applied risk assessment approaches and current knowledge about possible effects of nanomaterials, the discussion was focused on selected endpoints and those existing OECD Test Guidelines and other methods and protocols that are being used to address them.

The categories of endpoints selected were as follows:

1. *State of Dispersion, Aggregation and Agglomeration of Nanomaterials*
2. *Size (and Size Distribution) of Nanoparticles*
3. *Surface Area and Porosity*
4. *Surface Reactivity*

Consequently, four breakout groups were formed with the task to address the following questions:

- Identify the relevance of these endpoints as additions to conventional physical-chemical characterization; and if relevant, outline possible methods (i.e. new OECD test guidelines) based on the outcomes of the OECD Testing Programme and other sources of information;
- Identify whether there is a need for specific guidance documents for testing and assessment of the Physical-chemical properties of nanomaterials or adaptation of existing OECD Guidance Documents;
- Discuss whether specific sections should be developed for the "Guidance on Sample Preparation and Dosimetry" (GSPD) on the basis of the experiences obtained in the Testing Programme and other new developments in the area of testing and assessment of physical-chemical properties; and
- Identify whether specific endpoints and/or OECD test guidelines are relevant to different categories of nanomaterials.

[5] For example, the Guidance manual for the testing of manufactured nanomaterials: OECD's Sponsorship programme; Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials, Guidance on sample preparation and dosimetry for the safety testing for manufactured nanomaterials.

Characterizing Nanomaterials for Regulatory Safety Assessment

Hubert Rauscher (Joint Research Centre - JRC - European Commission)

Dr. Rauscher provided a keynote lecture[6] on the importance of characterization of manufactured nanomaterials for the regulatory safety assessment and highlighted the areas that need to be addressed. For instance, he underlined that physico-chemical properties can have nano-specific aspects (for example size, settling) and that suitable reference or at least benchmark materials must be used in developing the methods needed to assessing them. Dr Rauscher also stressed the importance for establishing nanomaterial-specific sample preparation protocols and for developing Test Guidelines and guidance documents that are applicable to nanomaterials.

Testing for Physical-Chemical Properties

This session aimed at providing an overview of available information on physical-chemical properties of nanomaterials following the Testing Programme). This included a summary of existing Test Guidelines developed by OECD and ISO. It was also an opportunity to introduce the audience to the work ISO is doing in the area of metrology, traceability and validation.

[6] Dr. Rauscher's presentation can be found in Annex IV.

ASSESSMENT OF THE STATE OF DISPERSION, AGGREGATION AND AGGLOMERATION OF NANOMATERIALS

This Break out Session was chaired by Hubert Rauscher with the support from Gert Roebben (both from the Joint Research Centre - JRC - European Commission).

a. "Dispersion/agglomeration/aggregation"

The focus of the discussion was on how to assess the state of dispersion. Also, it was agreed not to discuss the measurement of the strength of agglomerates and aggregates. With respect to the latter, it was recognised that the term *agglomerate* is used for weakly bonded particles, and *aggregate* for strongly bonded particles, with the understanding that the boundary between them depends on the circumstances.

General discussion and remarks

i. Regulatory relevance

Different regulatory needs were identified that make the discussion on dispersion/agglomeration/aggregation relevant for OECD WPMN. The issue is relevant for:

- Categorisation: is the material aggregated/agglomerated or not?

- Fate and exposure assessment (mobility is affected by the dynamic state of agglomeration and by dispersion stability). It was noted there is an important need for methods that can be used for in situ measurements of the dispersion/agglomeration/aggregation state in actual test media

- Hazard assessment (based sometimes on the (size of) primary particles, but more often on the size of aggregates at 'maximum dispersed state')

ii. Available OECD test guidelines

None

iii. Relevant measurands

As there is no OECD test guideline available, relevant measurands were identified in the discussion[7]:

- Number of primary particles per aggregate or agglomerate;

- agglomerate or aggregate size distribution;

- The average primary particle size;

[7] It was noted that for agglomerated or aggregated systems, there might not be an 'ultimate dispersion' since both of these types are sensitive to shear and protocol changes.

- The effective particle size distribution (either at ultimate dispersion or after an agreed dispersion protocol)

- *In situ* measurement of the agglomerate and aggregate size distribution

- Surface area distribution (surface-area based particle size distribution)

iv. Available methods

With the above measurands in mind, a number of available ISO documents were identified as useful:

- ISO TR 13097[8] on dispersion stability This report lists methods that can be used to monitor the rate of change of several possible suspension properties; including also methods other than morphology (particle size) based methods, and including in-situ methods.

- There are a number of ISO standards available describing methods to assess the size distribution in a (nano-)particle population. Centrifugal liquid sedimentation, dynamic light scattering, small-angle x-ray scattering are commonly used in the analysis of nanoparticle suspensions. Several methods are under development, and have yet to be standardised, such as single-particle ICPMS, particle tracking analysis and field flow fractionation.

- It was noted that some more additional indirect methods are being used for the assessment of agglomeration or aggregation. These methods are based on a combination of measurements (such as measurements of refractive index, mass concentration and primary particle size).

- ISO has also produced a number of documents about the use of transmission electron microscopy and x-ray diffraction that can be used to make a (rough) determination of average or nominal primary particle sizes and size distributions.

v. Conclusions

The dispersion/agglomeration/aggregation state is relevant for the purposes of the OECD. The group concluded there is a need for a new Test Guideline (TG), which can refer to existing ISO standards. The TG would have to specify the exact intended use of the measurements, and define the relevant dispersion protocols for the different end-points for which dispersion/aggregation/agglomeration need to be assessed.

b. "Water solubility"

i. Background

An important point is the distinction between solubility and dispersability[9]. Further, it was also noted there is a fundamental difference between (water) solubility and degradation (in water) e.g. as the consequence of chemical reaction between (nano-)material and water.

ii. Regulatory relevance

[8] ISO/TR 13097 2013-06 Guidelines for the characterization of dispersion stability

[9] See OECD Guidance on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials ENV/JM/MONO(2012)40

The regulatory needs identified are similar as the ones identified for the dispersion/aggregation/agglomeration discussion:

- Categorisation (is the material soluble or not?); *e.g.,* EC Regulation on Cosmetic Products limits its current definition of nanomaterial to insoluble materials. For the purposes of such a categorisation it may be necessary to define a threshold below which a material is regarded as insoluble.

- hazard assessment (after dissolution, the nano-specific effects of nanomaterials are no longer present, and the material should further be assessed as any other soluble chemical).

iii. Available OECD test guidelines

OECD TG 105 (Water Solubility) exists and is already used for aggregated and agglomerated nanomaterials. There is a need to adapt it to make it more useful, especially for nanomaterials that disperse into small primary nanoparticles. For these materials, the elution method needs to be adapted with appropriate particle detection methods, and the flask method needs to be adapted to have more relevant cut-off values when removing undissolved particles.

In the discussion after the break-out session it was noted that the current TG does not allow to differentiate between solubility and degradation (as by chemical reaction) for normal chemicals. The results of the method therefore always need to be interpreted with other basic properties of the test material in mind.

iv. Other relevant measurands

The discussion also identified a few alternative measurands:

- There are chemistry-based methods that allow distinguishing between particles and dissolved elements/ions/molecules;

- One can use particle size analysis methods to measure the change (decrease) of particle size over time.

v. Conclusions

Water solubility is a relevant property. The existing OECD TG 105 needs to be revised and refined. Alternative approaches exist and can be considered in this revision process.

c. "Zeta potential"

i. Regulatory relevance

Different regulatory needs were identified that make the measurement of zeta potential relevant for OECD WPMN. The issue is relevant for:

- Fate and exposure. Zeta potential is one of the factors determining whether particles agglomerate, aggregate (this implies chemical reactions or physical fusing), settle, flocculate, or whether they stay in suspension as nanoparticles. In this respect, the measurement of the Zeta potential over a pH range, a to determine the material's iso-electric point, is especially useful.

- Accident remediation (the Zeta potential is a factor to be taken into account when choosing remediating action in case of accidents, such as spills);

ii. Available OECD test guidelines

None

iii. Relevant measurands

As there is no OECD test guideline available, the discussion had first to identify relevant measurands:

- Zeta potential as such;

- The iso-electric point (pH at which the zeta potential = 0 mV);

- Electrophoretic mobility (a parameter from which the Zeta potential can be calculated).

iv. Available methods

- The ISO 13099-X[10] documents describe several methods to determine the Zeta potential, and are also applicable to nanomaterials. The documents distinguish between electrophoretic and electro-acoustic methods.

- There are a number of simpler methods to assess the iso-electric point.

v. Conclusions

The group concluded that the Zeta potential is a relevant property, and there is a need for a new TG, which can refer to existing ISO standards. The TG would have to specify the exact intended use of the measurements, and define the relevant dispersion protocols for the different end-points for which zeta potential need to be assessed.

d. "Octanol-water partition coefficient"

i. Regulatory relevance

The fate of nanomaterials and their preference for distribution to fatty or aqueous media is relevant. However, a large consensus was reached about the irrelevance of the octanol-water partition coefficient for the assessment of nanomaterials. The distribution of nanomaterials is not governed by the fundamental mechanisms for which the octanol-water partition coefficient test was developed.

ii. Available OECD test guidelines

OECD TG 107 (Partition Coefficient (n-octanol/water): Shake Flask Method), 117 (Partition Coefficient (n-octanol/water), HPLC Method) and 123 (Partition Coefficient (1-Octanol/Water): Slow-Stirring Method).

[10] ISO 13099-1:2012 Colloidal systems -- Methods for zeta-potential determination -- Part 1: Electroacoustic and electrokinetic phenomena; ISO 13099-2:2012 Colloidal systems -- Methods for zeta-potential determination -- Part 2: Optical methods; and ISO/DIS 13099-3 Methods for zeta potential determination -- Part 3: Acoustic methods.

These TGs should not be applied to nanomaterials. An exception may be the fullerenes. (It was noted that fullerenes can be considered as any other chemical molecule anyway.)

iii. Conclusions

The group concluded that the octanol-water partition coefficient should not be assessed for nanomaterials. The new test methods that need to be designed instead, considering other kinetic and surface chemical effects, are not yet sufficiently developed for standardisation or for becoming OECD TGs.

DETERMINATION OF THE SIZE (AND SIZE DISTRIBUTION) OF NANOPARTICLES

This breakout session was chaired by Eric Grulke (University of Kentucky, USA) with the support from Norma González Rojano (CENAM, Mex)

Background

NMIs, industry, academic and regulatory representatives participated in this break out session. A review of particle size distribution methods was carried out. There are a number of different lists for these methods.

Particle size measurements have a direct impact on the reliability of nanoparticle-based products and provide essential underpinning metrology for toxicological studies of nanoparticles. However, particle sizing methods are based on different physical principles, such as light diffraction, particle transport properties in various media, or electron microscopy of dry samples. These different techniques often have different bases for the particle size and particle size distribution (for example number, size, surface area, volume, or intensity-based). Validated methods and traceable measurement results can be obtained when certified reference materials are available for the method. The participants discuss the importance of the availability of reference materials as well as the use of harmonised vocabulary.

Regulatory perspective

Key regulatory needs include:

- Methods that are relevant, sensitive, and accurate for specific measurands,
- Reference materials that are available for specific methods,
- Metrology that underpins toxicological studies of nanoparticles,
- Statistics that are appropriate for measurand and their measurement uncertainty,
- Well-understood and harmonized vocabulary.

- Regulators need to have a set of methods for measuring size and size distributions, with quantifiable measurement uncertainty. Accuracy issues can be answered when validated methods

and reference materials are used. Statistical analyses used to evaluate the results might depend on the method, the type of nanoparticles, sample preparation, and other factors.

Industry perspective

Key industry needs include:

- Measurements and regulations that are appropriate for trade
- Measurement methods that directly impact nanoparticle-based products
- Well-understood and harmonized vocabulary

When there is no information about some type of nanomaterial or no methods available to measure regulatory required information, industry often work with to be able to fill the information gap.

OECD perspective

Current OECD Test Guidelines are, by nature general, as they are developed to be applied to all chemicals (as far as possible), thus not necessarily specifying the method to use, but focusing on scope and acceptability criteria. ISO standards are often referred to within these guidelines. Existing OECD Test Guidelines[11] have substantial information, which was reviewed by the team. Table D lists specific entries relevant to particle size and particle size distributions in each of these references.

Metrology perspective

The metrology perspective asks questions about how to make the measurements, including:

- Whether the particle shape can affect the measurement results (spheroidal vs. non-spheroidal)
- Whether the method can discriminate between discrete particles and those that are agglomerated or aggregated,
- Whether aerosol particle size methods should be included,
- How the methods might be affected by biological, environmental, and toxicological studies,
- Whether concentration measurements should be considered,
- What effects sample preparation might have, particularly for size distribution methods (particle size can be altered in test media, for example),
- What complementary methods might be used (the team believed that most of the size measurement methods should be confirmed using another method),
- Can the method be applied to single particles or collections of different particles, and
- Is the measurement made on single particles or on the ensemble.

General discussion and remarks

[11] OECD, 2009. Guidance Manual for the Testing of Manufactured Nanomaterials: OECD Sponsorship Programme: First Revision [ENV/JM/MONO(2009)20/REV]; OECD, 2009. Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials [ENV/JM/MONO(2009)21]; OECD, 2012; Guidance on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials [ENV/JM/MONO(2012)40]; and OECD, 2012 Important Issues on Risk Assessment of Manufactured Nanomaterials [ENV/JM/MONO(2012)8].

A recent report by the Joint Research Centre of the European Commission (Linsinger, 2012) provided a careful review of size measurement methods for nanoparticles. The authors selected a reduced set of methods: these are relevant from regulatory and industry standpoints as they are well known and generally available. ***Table C*** provides brief summaries of the measurement principles for these methods. More detailed descriptions and additional references are provided in the report itself (Linsinger, 2012). ***Table D*** is a replica of the specific table used as the discussion framework. Single particle ICPMS was added to this list by the team; it is a relatively new technique with much promise, but it requires further development and validation.

The breakout group accomplished the following:

- Reviewed particle size distribution methods and indicated which are relevant from regulatory and industry standpoints – ISO NWIP and JRC report.
- Evaluated whether the technique can differentiate between single particles and collections.
- Evaluated whether the technique can distinguish between aggregates and agglomerates.
- Evaluated media effects.
- Considered spheroidal, non-spheroidal and EHS needs.
- Identified complementary techniques to improve information.
- Reviewed test protocols for particle size distributions[12] and identified gaps.

Three different screening criteria were applied to the technique matrix (***Table D***): size measurements for spheroidal particles, size measurements for non-spheroidal, agglomerate, and aggregate particles, and size measurements for environmental, health, and safety evaluations. Each technique was classified as preferred (green), use with caution (yellow), and not recommended (red) (see ***Table 1*** and ***Table 2***).

Spheroidal nanoparticles

Two methods were preferred: SEM and TEM. CLS, SAXS, FFF, PTA, AFM and single particle ICPMS should be used with caution. DLS, x-ray diffraction and BET are generally not recommended. Liquid-based measurement systems, DLS, CLS, FFF, and PTA, all depend on hydrodynamic diameters as estimated by the Stokes-Einstein or the Stokes sedimentation equations. Therefore, they do not distinguish between discrete, agglomerated, or aggregated nanoparticles. AFM, SEM, and TEM can be used with mixtures of sizes of nanoparticles. Therefore, they are listed as complementary to other methods; the team felt strongly that results from even preferred methods should be compared to results from complementary methods. TEM, SEM, PTA, AFM, and single particle ICPMS all make measurements on individual nanoparticles.

The distribution basis for these methods differs (***Table D***). If the distribution has been modelled, then the conversion from intensity-based to volume-based to number-based size distributions or average sizes can be made. Regulators need to select the basis for their metrics.

Tables 1-3 provide guidance for preferred nanoparticle size and nanoparticle size distribution measurements of spheroidal, non-spheroidal, as well as EHS sample.

[12] OECD, 2009. Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials [ENV/JM/MONO(2009)21].

Table 1. *Particle size and particle size distributions methods for spheroidal particles*

Spheroidal	Comments	Mixtures of particles	Discrete (D), ensemble (E) technique	Complementary
TEM	Instrument is expensive	yes	D	SEM, AFM, ensemble techniques
SEM	Small particles may have high measurement uncertainty	yes	D	TEM, AFM, ensemble techniques
DLS	May not link to actual PSD	No	E	
Centrifugal liquid sedimentation	Can separate size fractions of polydisperse samples; validated for spheroidal particles	no	E	EM
Small angle X-ray scattering	Bimodal distributions? resource intensive	no	E	EM
Field flow Fractionation	Resource intensive	no	E	EM
particle tracking analysis	Relatively low cost	no	D	EM
Atomic force microscopy	Resource intensive; statistics	yes	D	EM
X-ray diffraction	Not suitable for size distributions	no	E	
BET	Average size	no	E	
Single particle ICPMS	Standardization just starting	no	D	EM, AFM

***Abbreviations**: TEM = transmission electron microscopy; SEM = scanning electron microscopy; EM = electron microscopy; DLS = dynamic light scattering; CLS = centrifugal liquid sedimentation; SAXS = small angle x-ray scattering; FFF = field flow fractionation; PTA = particle tracking analysis; AFM = atomic force microscopy; XRD = x-ray diffraction; BET = Brunauer, Emmett, Teller (surface area analysis); D = discrete particle measurement; E = ensemble particle measurement.

Non-spheroidal, agglomerates, and aggregate nanoparticles

The application of these methods to non-spheroidal, agglomerated, or aggregated samples adds to the list of concerns regarding the quality of the measurements. The fluid-based methods usually use spherical models for the hydrodynamic diameter. Other models (cylinders, disks) might be used, but shapes would have to be assumed. Particle mixtures with different shapes would be difficult to deconvolute. Agglomerates and aggregates have unknown packing densities, so the apparent density with the hydrodynamic volume around these structures are usually not known either; this affects the use of the Stokes-Einstein equation or other equations providing apparent particle diameters.

***Table 2**. Particle size and particle size distributions techniques for non-spheroidal particles, agglomerates, and aggregates.*

Non-spheroidal + aggregates	**Additional comments**
TEM	Not for > 1 micrometre
SEM	Measurement uncertainty for small nanoparticles may be high
DLS	Hydrodynamic diameter assumes a spherical model; may show stability and relative changes
CLS	Stokes' diameter assumes a spherical model
SAXS	Can be used with aggregates; scattering models available for spheres, cylinders, and disks; resource intensive
FFF	Hydrodynamic diameter assumes a spherical model; resource intensive
PTA	Hydrodynamic diameter assumes a spherical model; semi-quantitative
AFM	Resource intensive; statistics
XRD	Size information for primary particles in aggregates
BET	Average size
Single particle ICPMS	Standardization just starting, effect of shape not known

EHS evaluations of nanoparticles

EHS evaluations of nanoparticles often are affected by dosing conditions, coatings on the nanoparticles, and other factors. In this case, cryostage TEM measurements may be useful. However, this is an exotic technique with few current practitioners. DLS is a useful complementary technique, as it can show changes in apparent particle size with temperature, salt concentration, types of ions, and surface-active agents.

Table 3. *Particle size and particle size distributions methods for environmental, health, and safety evaluations.*

EHS samples	Comments
TEM -CryoTEM ?	May not indicate agglomeration
SEM	Small?
DLS	Relative stability
CLS	Cell growth media
SAXS	Bimodal? Resource intensive
FFF	Resource intensive
PTA	Semi-quantitative
AFM	Resource intensive; statistics
XRD	Only small size
BET	Average size
Single particle ICPMS	Sample preparation

Conclusions

Tables 1-3 provide guidance for preferred nanoparticle size and nanoparticle size distribution measurements of spheroidal, non-spheroidal, and EHS samples.

There are gaps in methods listed in preliminary review of OECD Test Guidelines[13], particularly with respect to aerosol systems. Aerosol systems were not discussed extensively by the team. However, ***Table E*** (see annex I) provides a list of methods appropriate for aerosols.

The guidance information for particle size/size distributions[14] might be updated using the information provided in Tables 1-3, as well as the JRC report[15].

[13] OECD, 2009 (3). Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials [ENV/JM/MONO(2009)21]

Physical chemical properties and identified standards (OECD, 2009 (3); pp .22-23) has a section on hydrodynamic size/particle size measurement/distribution that might be updated using the information of Tables 1-3 plus the JRC report (Linsinger, 2012).

[14] Pages pp. 56-57 of the OECD, 2009 (2). Guidance Manual for the Testing of Manufactured Nanomaterials: OECD Sponsorship Programme: First Revision [ENV/JM/MONO(2009)20/REV].

[15] Linsinger, 2012, Requirements on measurements for the implementation of the European Commission definition of the term "nanomaterial", JRC Reference Report, EUR 25404, ISBN 978-92-79-25603-5.

DETERMINATION OF THE SURFACE AREA AND POROSITY

This breakout session was chaired by Yasir Sultan (Environment Canada), with the support from Brian Lee (US EPA)

Surface Area

1. Further clarification is needed on the regulatory relevance of surface area.

   - Surface area may be an appropriate predictor of toxicity when extrapolating within the same[16] type of material, however, it is likely not appropriate for extrapolating between different nanomaterials.

   - Surface area is an important parameter for predicting exposure (vs. toxicity above).

   - Surface area is likely useful for identification (when used with other techniques) as it can give good information on size.

     - However, it is unclear if this size to surface area correlation is appropriate in complex environments and/or for polydisperse samples and shapes.

2. For dry, powdered forms of nanomaterials, the Brunauer Emmett Teller (BET) method works well to determine surface area.

   - It can also provide information on the internal surface or porosity; however, it is important to differentiate between internal surface area (caused by porosity) and the external surface area of primary particles (which is generally linked to an average primary particle size).

   - Caveat: may not be useful for very small particles.

   - BET method was utilized in the Nanogenotox Project (EU) together with small-angle X-ray scattering (SAXS) and transmission electron microscopy (TEM) and good correlations were found between techniques.

   - Caveat: need standardization on parameters (e.g., type of gas, sample preparation, apparatus, external reference, etc).

   - Caveat: May only be appropriate for certain classes of nanomaterials (such as metal oxides).

   - Caveat: BET likely good for as-synthesized nanomaterials, but may not be appropriate for subsequently modified nanomaterials. It is not generally useful for polymeric materials.

[16] Same type refers to sameness in chemical composition

- Additional information is needed from the OECD Sponsorship program on user experience and lessons learned using the BET method.

- Different countries have used BET for CeO_2, ZnO, and TiO_2 nanoparticles and found consistency in measurements.

- There are existing ISO standards on the BET method; however these are not specifically for nanoparticles. These and other methods may already be applicable for nanomaterials or may need minor modifications.

  - ISO standard "Determination of specific surface area of ceramic powders by gas adsorption using the BET method" (ISO 18757:2003).

  - ISO standard "Determination of the specific surface area of solids by gas adsorption BET method" (BS ISO 9277:2010)

  - ASTM standard "Standard Test Method for Metal Powder Specific Surface Area by Physical Adsorption" (ASTM B922 - 10).

- OECD round robin test underway currently on BET.

  - Need to conduct testing in complex media

- Other possible methods for measuring surface area include

  - SAXS (works both for liquids and powders)

    - However, not widely available and methods not available

  - TEM

3. For surface area in liquids, SAXS was identified as a possible technique which has been studied within the Nanogenotox project

   - However, there are no standard methods and the technique is not widely available

   - Other techniques include Cryo-TEM

4. Theoretical calculations can be performed to calculate theoretical surface area in liquids.

5. This end-point is important for regulatory bodies because (1) most industrial nanomaterials are synthesized and used from liquid phases; and (2) fate and toxicity testing is conducted in liquid media.

6. There are currently no methods which can be adapted as technical standards for liquids. Surface area in liquids remains a priority and should be developed through scientific research and once ready will become a technical standard.

   - Further discussion is needed within OECD if this is a relevant predictor in regulatory processes

7. Considerations for primary particles, agglomerates and aggregates need to be taken into account in method development for surface area.

Porosity

8. The BET method is not developed sufficiently for porosity

   - ISO would be interested in the experiences from the OECD Sponsorship Program on measuring porosity

9. Porosity may be important for nanostructured materials

10. Applicability of test methods for porosity to certain classes of nanomaterials

11. Current methods to measure porosity are not nanospecific but may be applicable or adaptable

    - "Pore size distribution and porosity of solid materials by mercury porosimetry and gas adsorption – Part 1: Mercury porosimetry" (ISO 15901-1:2005)

    - "Pore size distribution and porosity of solid materials by mercury porosimetry and gas adsorption – Part 2: Analysis of mesopores and macropores by gas adsorption" (ISO 15901-2:2006)

    - "Pore size distribution and porosity of solid materials by mercury porosimetry and gas adsorption – Part 3: analysis of micropores by gas adsorption" (ISO 15901-3:2007)

Aerosols

General discussion and remarks

1. Linkages important with ISO/TC 24/SC4[17]

2. Possible method: Laser induced incandescence

3. Air is an important compartment for method development

   - Need to look at outputs from OECD Expert Meeting on inhalation

Conclusions of the Session

- Further clarification needed on relevance of surface area in the regulatory analysis.

- BET is a useful technique for correlating surface area to exposure and toxicity and for identification of nanomaterials (vs. non-nano) with appropriate caveats – e.g., surface area can be used to predict toxicity for the same types of nanomaterials but not across nanomaterials

- Questions remain regarding the usefulness of BET in complex environments and realistic industrial samples (e.g., heterogeneous polydisperse).

[17] ISO Technical Committee on Particle characterization.

- It was agreed that there is sufficient information to move forward with a technical standard for a BET method for metal oxide nanomaterials. In addition, a guidance document will need to accompany the method which highlights relevant caveats.
  - BET method for other classes of nanomaterials still requires scientific research and may be conducted in parallel to the technical standard on metal oxides or can follow it.
- ISO needs collaboration from experts within the OECD Sponsorship program on their experiences and lessons learned on using BET. This exercise should be a joint effort
- Volunteers are needed to lead the development of this BET technical standard
- OECD needs to develop a mechanism to be able to share information from the Sponsorship Program
- Outputs from this workshop should be available for the OECD workshop on categories/classes[18]

[18] Planned for 2014

SURFACE REACTIVITY

This breakout session was chaired by Yasir Sultan (Environment Canada),with the support from Brian Lee (US EPA)

Surface chemistry

12. There are a variety of different methods to characterize surface chemistry, which include qualitative and quantitative methods

    - Regulators at this stage need to know what is on the surface, however this does not need to be quantitative at this stage

13. Methods include:

    - Fourier-transform infrared spectroscopy, time-of-flight secondary-ion mass spectrometry, matrix-assisted laser desorption time-of-flight mass spectrometry, auger electron spectroscopy, XPS, electron energy loss spectroscopy, UV-vis, molecular spectroscopy (including Raman, x-ray), ICP-MS, ICP-AAS, LC-MS, GC-MS, TGA

14. The information sought is the composition so that predictive toxicity and extrapolations can be performed

15. While regulators need methods for semi-quantitative information at the moment (such as what chemical groups are on the surface), methods may also need to be developed to take into account:

    - Arrangement of functional groups
    - Orientation on the surface
    - Level of coverage on the surface
    - Information on the core, covalent vs. non-covalent interactions
    - Location and packing density

16. Surface charge is very important in predicting qualitatively potential toxicity

    - Round-robin tests recently performed by JRC-IRMM and currently being prepared between JRC and NIST looking at monodisperse silicas

- Two round-robin tests currently underway for zeta potential[19]
- If important to OECD, ISO can prioritize to move towards a technical standard faster[20]

17. Media has an effect for determining surface chemistry since this can affect cytotoxicity, and other fate and effect endpoints. Media can be looked at under the different round robin tests currently underway

18. Chemisorption techniques can also play a role in determining surface chemistry but these are still largely in the research arena

19. It was acknowledged that multiple techniques are needed to adequately characterize nanomaterials

    - Need to ensure instrumentation/techniques are widely available and not an excessive burden

20. Sample preparation affects surface chemistry. Sample preparation is an evolving science (such as sonication and stirring)

    - There is an ongoing project under WG3 of ISO/TC 229 addressing sample preparation. This project should also have linkages with JWG2 and OECD WPMN experts to ensure that there is cross-fertilization and alignment between different methods being developed and approaches being considered
    - It is very important that there is alignment between how the samples are being prepared for physico-chemical endpoints and fate and toxicity endpoints

Photocatalytic Activity

- DCFH – fluorescence based analysis for reactive oxygen species (possible nanoparticle interference with the assay)
- Colorimetric methods (possible nanoparticle interference with the assay)
- Electron spin resonance
- Quartz crystal microbalance
- Gas-phase techniques such as gas-chromatography

Reactive Oxygen Species (ROS) generation

General discussion and remarks

1. Method development needed to measure ROS generation from photo-active nanomaterials
2. Uncertainty regarding the relevance in regulatory risk assessments of in-vitro methods

[19] These test are performed by Dr. Iseult Lynch

[20] ISO has published 2 zeta-potential standards in 2012 (ISO 13099-1 and -2) and is preparing a third one (13099-3).

3. Since this is a new endpoint from the original OECD List of endpoints for Sponsors

   - Does this provide value for regulators?
   - Is it a good screening level endpoint?

Conclusions of the Session

1. ISO together with OECD WPMN to prepare a table or document on what techniques/methods are available for measuring surface chemistry along with appropriate caveats, e.g., which classes of nanomaterials are appropriate for the methods.

2. Move forward with a technical standard for zeta potential.

- This will need further input from the experts utilizing zeta potential in the OECD Testing programme.

3. OECD WPMN to provide ISO experts currently involved in round robin testing OECD media which should be tested to ensure validity and applicability of the methods being developed.

ANNEX I. REFERENCE MATERIALS USED FOR THE DISCUSSION ON THE DETERMINATION OF THE SIZE (AND SIZE DISTRIBUTION) OF NANOPARTICLES

Table A. List of Nanomaterials and Physical-Chemical Endpoints Addressed by the OECD Testing Programme[21]

Nanomaterials	Physical-Chemical Endpoints[22]
Fullerenes (C_{60}) Single-wall carbon nanotubes (SWCNTs) Multiwall carbon nanotubes (MWCNTs) Silver nanoparticles Iron nanoparticles Titanium dioxide Aluminium oxide Cerium oxide Zinc oxide Silicon dioxide Dendrimers Nanoclays Gold nanoparticles	Agglomeration/ aggregation Water solubility/ Dispersability Crystalline phase Dustiness Crystallite size Representative Electron Microscopy (TEM) picture(s) Particle size distribution – dry and in relevant media Specific surface area Zeta potential (surface charge) Surface chemistry (where appropriate) Photocatalytic activity Pour density Porosity Octanol-water partition coefficient, where relevant Redox potential Radical formation potential Other relevant Physical-Chemical Properties and Material Characterization information (where available)

Table B. Particle size and particle size distribution content in OECD guidance documents

Document	Title or topic	Page
Risk assessment [OECD, 2012 #1]	25. Occupational exposure limits	20
	53. Dose metrics	28
	74. Parameterisation of conceptual exposure models	33

[21] Extracted from OECD publication ENV/JM/MONO(2010)46.

[22] Detailed information regarding these endpoints is provided in the document Guidance Manual for the Testing of manufactured Nanomaterials: OECD's Sponsorship Programme; First Revision [OECD, 2009 #2]

	86. Dose metrics	35
	105, 106. Model predictions	38, 39
	109. SG3 Sponsorship Programme	40
	128. Minimum characterization initiative	43
OECD Guidance Manual for the Testing of Manufactured Nanomaterials: OECD Sponsorship Programme: First [ENV/JM/MONO(2009)20/REV]	Effective mean particle size. Methods = TEM, PCS/DLS, BET, SAXS, SMPS	31
	Electron microscopy measurement, particle size distribution	33
	In vitro genotoxicity; did the particle size change in the culture?	45
	Particle size distribution as a characterization requirement (see reference 29)	51
	In the case of agglomeration or aggregation, the effective cross-section should be the measurand.	54
	Relevance to toxicology/ecotoxicology	55
	Box 2. Guidance Information for particle size/size distribution	56
	Box 2. Recommended test methods: SMPS, DLS, SEM/TEM, DMA, AFM, size exclusion chromatography	57
Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials [OECD, 2009]	pre-requisites for toxicological assessment	17
	ANNEX I-1 TABLE OF RESULTS FROM THE REVIEW OF OECD TEST GUIDELINES FOR PHYSICAL CHEMICAL PROPERTIES FOR THEIR APPLICABILITY TO MANUFACTURED NANOMATERIALS	19
	ANNEX I-2 PHYSICAL CHEMICAL PROPERTIES	20

	AND IDENTIFIED STANDARDS (DRAFT)	
	Grain size, differential mobility analysis	22
	1.2.3 Concentration	31
	1.4.4 metrics and measurement	33
Guidance on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials [OECD, 2012]	A.1.1 Particle size, shape, and size distribution	24
	A1.2 Particle Size Distribution	26
	A.1.3 Aggregation and Agglomeration	26

Table C. Measurement principles of common particle size measurements

Method	**Measurement principles**
Electron microscopy	a two-dimensional image of the particle is the basis for a variety of measurands
Dynamic light scattering	The method measures the hydrodynamic diameter of the particle in Brownian motion, detected by light scattered from the particles. An autocorrelation function of the scattered light intensity is used to compute an average diffusion coefficient for the particles, which can be transformed to an average diameter using the Stokes-Einstein relationship. The intensity of the scattered light is inversely proportional to the sixth power of the nanoparticle diameter.
Centrifugal liquid sedimentation	Sedimentation rate at high centrifugal forces measures the equivalent hydrodynamic diameter; nonspheroidal shapes can preferentially align in the flow field, leading to both under- and over-predictions of the average size; particle density needs to be well-known
Small angle x-ray scattering	SAXS measures particle size based on x-rays scattered at the particle surfaces. The scattering angle depends on the wavelength (0.1 nm to 1 nm) and the particle size (1 nm and 100 nm). Scattering intensity varies with both size and shape, which can be estimated for spheres, disks, or cylinders.
Field flow fractionation	Particles are separated by hydrodynamic size in two fields: a laminar flow induced by a pump, and a perpendicular flow induced by another pump, electric, magnetic, or other forces. Retention times can be linked to hydrodynamic diameter either by particle size

	standards or by theoretical calculations.
Atomic force microscopy	A sharp tip mounted on a cantilever is moved over a surface; forces between the tip and the sample lead to a deflection of the cantilever. The cantilever is kept, e.g., at constant distance to the surface or at constant resonance oscillation frequency: adjustment is done by a feedback loop. Height changes due to this adjustment are recorded. The tip shape can affect the results, so the height measurement is the most accurate. Particles should be well-separated on the mounting surface and fixed in place.
Particle tracking analysis	Particle tracking analysis is a method for visualizing and analyzing particles in liquids that relates the rate of Brownian motion to particle size. Otherwise, the rate of movement is related only to the viscosity and temperature of the liquid.
X-ray diffraction	If X rays impinge on a sample that contains a crystalline phase, then they are diffracted by the periodic lattice of the crystalline material according to Bragg's law, which captures how the electrons surrounding the atoms interact with the incoming X ray photons. The diffraction pattern is generated by constructive interference.

Table D. Summary table Linsinger, 2012

Method	**Limiting factors**	**Type of particle size distribution**	**Polydispersity**	**Non-spherical particles**	**Low density materials**	**Aggregates**	**Standards**
EM	D > 1 nm; dry (dynamic range)	Number-based	+	Long: + Flat: -	--	--	Yes
DLS	5 nm < D < 500 nm; suspension (sedimentation, scattering intensity	Scattering-intensity-based (no distribution?)	--	--	+	--	Yes
CLS	D > 20 nm; suspension (particle density)	Extinction-intensity-based	+	--	--	--	Yes
SAXS	D > 5 nm; suspension (dynamic range)	Scattering-intensity-based	0	--	0	--	Yes
FFF	1 nm < D < 200 nm; suspension (scattering intensity)	Depends on detector	+	--	+	--	No
PTA	D > 25 nm; suspension (scattering intensity)	Number-based	+	--	0	--	No
AFM	D > 1 nm; dry (usually) (dynamic range)	Number-based	+	Long: + Flat: +	0	--	Yes
XRD	D > 1 nm; dry (crystalline materials)	No distribution	--	--	--	+	Yes

Abbreviations: D = particle diameter (dimension); EM = electron microscopy; DLS = dynamic light scattering; CLS = centrifugal liquid sedimentation; SAXS = small angle x-ray scattering; FFF = field flow fractionation; PTA = particle tracking analysis; AFM = atomic force microscopy; XRD = x-ray diffraction:

Symbols: ++ = very well; + = well; 0 = moderately; - = not well; -- = not at all

Table E. Relevant particle size/particle size distribution methods for aerosols. Courtesy of G. Smallwood, NRC

Method	Mean size	Size distribution	Aggregates, agglomerates	Other
Differential mobility analyzer (DMA) + condensation particle counter (CPC)	Yes	Yes	Yes	
Real-time mobility sizer (DMS; EEPS)	Yes	Yes	Yes	
Electrical low-pressure impactor (ELPI)	Yes	Yes	Yes	
Elastic light scattering	Yes	Yes	Yes	
Particle mass analyzer (APM; CPMA)	Yes	Yes	Yes	Measures mass; needs density to determine size
Optical particle counter	Yes	Yes	Yes	
Diffusion battery + CPC	Yes	Yes	Yes	
Laser-induced incandescence (LII)	Yes	Yes	No	Also measures surface area and mass concentration
Aerosol time of flight mass spectroscopy	Yes	Yes	Yes	Also measures composition

ANNEX II. REFERENCES

Boyd, R.D., et al., 2011 Good practice guide for the determination of the size distribution of spherical nanoparticle samples, in Measurement Good Practice Guide No. 119. 2011, National Physical Laboratory.

Linsinger, 2012, Requirements on measurements for the implementation of the European Commission definition of the term "nanomaterial", JRC Reference Report, EUR 25404, ISBN 978-92-79-25603-5.

OECD, 2012 (1). Important Issues on Risk Assessment of Manufactured Nanomaterials [ENV/JM/MONO(2012)8].

OECD, 2009 (2). Guidance Manual for the Testing of Manufactured Nanomaterials: OECD Sponsorship Programme: First Revision [ENV/JM/MONO(2009)20/REV].

OECD, 2009 (3). Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials [ENV/JM/MONO(2009)21]

OECD 2009 (4) List of Manufactured Nanomaterials and List of Endpoints for Phase One of the OECD Testing Programme [ENV/JM/MONO(2008)13/REV]

OECD, 2012. Guidance on sample preparation and dosimetry for the safety testing of manufactured nanomaterials [ENV/JM/MONO(2012)40]

ISO 13099-1:2012 Colloidal systems -- Methods for zeta-potential determination -- Part 1: Electroacoustic and electrokinetic phenomena;

ISO 13099-2:2012 Colloidal systems -- Methods for zeta-potential determination -- Part 2: Optical methods;

ISO/DIS 13099-3 Methods for zeta potential determination -- Part 3: Acoustic methods.

ISO, Nanotechnologies - Measurement method matrix for manufactured nano-objects, JWG2, Editor 2013, ISO.

ISO, 2013 ISO/TR 13097 2013-06 Guidelines for the characterization of dispersion stability

ANNEX III. AGENDA FOR THE WORKSHOP

OECD Expert Meeting on Physical-chemical Properties of Manufactured Nanomaterials and Test Guidelines in collaboration with ISO/TC 229: Nanotechnologies

28 February - 1 March 2013
Querétaro, Mexico
Draft Agenda

BACKGROUND TO THE OECD SERIES OF WORKSHOPS ON MANUFACTURED NANOMATERIALS AND TEST GUIDELINES

The OECD Working Party on Manufactured Nanomaterials (WPMN) has initiated a series of expert meetings to improve the applicability of the OECD Test Guidelines (used for regulatory testing of chemicals) to nanomaterials. A preliminary report was published in 2009[23]. The methodology will be reviewed based on the experience gained from the OECD Sponsorship Programme on the Testing of Manufactured Nanomaterials (hereafter OECD Testing Programme) and inspired by new findings and insights obtained in the relevant research communities.

The current OECD Test Guidelines series addresses already agreed endpoints used for chemical safety assessment but which are not specifically designed for nanomaterials. The Testing Programme and the review of its results will provide an empirical evaluation of the applicability of current OECD Test Guidelines to nanomaterials and on the need to update current or develop new test guidelines for those agreed endpoints that are relevant for safety

[23] ENV/JM/MONO(2009)21. Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials.

and regulatory decision-making. In addition, the OECD Testing Programme suggested assessing a number of additional (new) endpoints for nanomaterials and the need to develop new OECD Test Guidelines for these endpoints.

Overall focus and scope of the OECD series of workshops

1. **For the endpoints already agreed for chemicals safety assessment under the OECD chemical's programme:**

- Consider and confirm the relevance of these endpoints;
- To discuss whether there is a need to update the currently existing Test Guidelines and for developing new ones adapted to nanomaterials characteristics, or whether specific guidance documents are needed; and
- If updates are considered necessary, discuss what kind of changes or developments would be needed and which further steps need to be taken (if new Test Guidelines are deemed necessary a similar approach should be followed);

2. **For the nanospecific endpoints addressed in the OECD Testing Programme:**

- Identify the relevance of these endpoints as additions to conventional Physical-chemical characterization[24]; and if relevant, outline possible methods (i.e. new OECD test guidelines) based on the outcomes of the OECD Testing Programme and other sources of information;
- Identify whether there is a need for specific guidance documents for testing and assessment of the Physical-chemical properties of nanomaterials or adaptation of existing OECD Guidance Documents;
- Discuss whether specific sections should be developed for the "Guidance on Sample Preparation and Dosimetry" (GSPD) on the basis of the experiences obtained in the Testing Programme and other new developments in the area of testing and assessment of physical-chemical properties; and
- Identify whether specific endpoints and/or OECD test guidelines are relevant to different categories of nanomaterials.

3. **For the identified needs (if any):**

- Find volunteers for preparing and submitting proposals with the Standard Project Submission Form (SPSF) to the OECD Test Guidelines Programme and lead the subsequent work.

Collaboration with ISO/TC 229

This workshop is organised in collaboration with ISO/TC 229 (Nanotechnologies) and especially its experts within Joint Working Group 2 (JWG2), Measurement and Characterisation and the Metrology Study Group. The co-operation between the OECD WPMN and ISO/TC 229 provides an important dimension for the analysis and use of data derived from the OECD Testing Programme and is consistent with the formal liaison relationships each organisation has with the other. It is anticipated that the WPMN and ISO/TC229 will mutually benefit from this meeting. OECD will benefit by taking advantage of ISO/TC229 expertise and work products and possibly accelerating the development of modified or new test guidelines needed for safety and regulatory decision-making; and ISO/TC 229 by learning of the needs of governments and incorporating them into the planning for its activities roadmaps.

[24] For example, selecting information from the Annex.

OBJECTIVES OF THE MEETING

The purpose of the workshop is to assess the applicability of existing OECD Test Guidelines (TG) on Physical-chemical Properties of Manufactured Nanomaterials and to identify the need to update current or develop new OECD Test Guidelines and/or Guidance Documents (GD), in particular those that are relevant for safety and regulatory decision-making. Given the commonly applied risk assessment approaches and current knowledge about possible effects of nanomaterials, it is anticipated that the discussions may focus on the selected endpoints and currently existing Test Guidelines / methods[25] and on other methods and protocols that could potentially better address these endpoints for nanomaterials. This could be obtained in several ways, for example by integrating them in current OECD TGs or GD, or by developing new Test Guidelines or Guidance Documents. In assessing the applicability of existing OECD Test Guidelines on Physical-chemical Properties and in the determination to update current or develop new guidelines, it would be helpful to consider the applicability to different categories of nanomaterials, such as fullerenes, metals, metal oxides. Test Guidelines might be to be updated differently for some categories of nanomaterials.

Thursday 28 February 2013 9h00 - 18h00		
Registration 8h30 - 9h00		
SESSION I. WELCOMING REMARKS 9h00 - 10h00 Chaired by Peter Kearns, OECD		
9h00	**Welcoming Remarks**	**Mexico**
9h30	**Objectives and Expected Outcomes from the Expert Meeting** This presentation will provide the background to this meeting; explain the objectives and expected outcomes, as well as highlighting the advantage for this synergistic collaboration between ISO/TC229 and OECD/WPMN to achieve these goals.	**Mar Gonzalez** OECD Secretariat
9h50	**Keynote Lecture: Characterizing Nanomaterials for Regulatory Safety Assessment** This presentation will set the scene on the current State of the Art regarding the characterisation of nanomaterials.	**Hubert Rauscher** Joint Research Centre-European Commission
SESSION II. TEST GUIDELINES ON PHYSICAL-CHEMICAL PROPERTIES 10h30-13h30 Chaired by Simon Holland/ Rapporteur Mar Gonzalez		

[25] These test methods were selected from those used in the OECD Testing Programme.

10h30	**Overview of available information on Physical-chemical properties of nanomaterials[26] following the OECD WPMN testing.** This presentation will outline outcomes of the application of existing methods for nanomaterials testing, needs for updating existing guidelines, needs for new test guidelines and needs for additional test guidelines to address (new) endpoints.	**Maria Doa** US Environmental Protection Agency
11h00	**Targeted physical-chemical needs for risk assessment – An OECD WPMN perspective** This presentation will: (1) provide an overview of OECD's activities on harmonizing risk assessment approaches for nanomaterials; (2) describe current physical-chemical challenges associated with nanomaterial risk assessments; and (3) what is required from new/modified test guidelines on physical-chemical properties from a risk assessment point of view.	**Yasir Sultan** Environment Canada
Coffee 11h30 – 12h00		
12h00	**ISO Guidelines** This presentation will outline existing and planned ISO documents for nanomaterials relevant for Physical-chemical characterisation.	**Angela Hight Walker** National Institute of Standards and Technology (NIST) – USA
12h30	**Metrology, traceability and validation** This presentation will outline relevant metrological considerations in the measurement and characterization of nanomaterials and the highly desired traceability to the International System of Units (SI). Furthermore, a description of the international round robins completed, underway and planned, as well as the critical information and insight gained will be presented.	**Alan Steele** National Research Council of Canada
13h00	**Dispersion Protocols: Outcomes from previous OECD Experts Meetings** Reproducible, representative and reliable preparation of dispersions has been identified as one of the stumbling blocks for developing harmonised Test Guidelines for Regulatory Hazard Assessment. A summary of discussions in previous OECD workshops and other initiatives will be presented as this issue will influence as well how the physico-chemical characterisation of nanomaterials as received is performed and the needs of dispersions' and "in situ" characterisation.	**Klaus Steinhaeuser** German Federal Environment Agency
Lunch 13:30 – 15:00		
SESSION III. PHYSICAL-CHEMICAL CHARACTERISATION OF MANUFACTURED NANOMATERIALS Chaired by Juan Riego Sintes/ Rapporteur Shaun Clancy		
15h00	**Need for developing additional Test Guidelines and/or Guidance Documents** Based on the presentations made during Session II, it is expected that a number of questions be raised regarding further needs for developing new Test Guidelines or Guidance Documents. This will be the background for the discussions during the Breakout Sessions.	**Juan Riego Sintes** JRC - EC **Shaun Clancy** Evonik

[26] C60, CNTs, TiO_2, Silver, SiO_2, CeO_2, ZnO, Dendrimers, Nanoclays and Gold.

15h30	**Introduction to the Break Out session/ expected outcomes** These sessions are regrouping the physical-chemical endpoints that were considered of regulatory relevance by the OECD's WPMN. They are organised in the areas in which they will be generally approached by regulators. A number of guiding questions/ Background documents will be introduced in order to guide the discussion of each breakout session.	**Juan Riego Sintes** JRC - EC **Shaun Clancy** Evonik
END OF THE FIRST DAY 16h30		

Friday 1st March 2013 9h00 - 18h00			
SESSION IV. BREAK OUT GROUPS PHYSICAL-CHEMICAL CHARACTERISATION OF MANUFACTURED NANOMATERIALS 9h00-13h00 Co-chaired by Juan Riego Sintes and Shaun Clancy			
Break Out Session A: Dispersion, Aggregation and Agglomeration of Nanomaterials **Chair:** Hubert Rauscher JRC-EC **Rapporteur:** Gert Roebben JRC-EC	**Break Out Session B: Determination of the Size (and Size Distribution) of Nanoparticles** **Chair:** Eric Grulke University of Kentucky **Rapporteur:** Norma Gonzalez CENAM	**Break Out Session C: Determination of the Surface Area and Porosity** **Chair:** TBC **Rapporteur:** TBC	**Break Out Session D: Surface Reactivity** **Chair:** Yasir Sultan (Environment Canada) **Rapporteur:** TBC
Needs, available techniques, suitable candidates. Water solubility, Zeta potential (surface charge), octanol-water partition coefficient, where relevant	Needs, available techniques, suitable candidates: microscopy-based and not microscopy-based techniques	BET methods for powders, alternative methods for other cases	Redox potential, Radical formation, Photo-catalytic activity, Surface chemical composition
10:45 - 11:15 Coffee Break			
Lunch 13:00 – 14:30			
SESSION IV (Cont). REPORTS FROM BREAKOUT-GROUPS 14h30-16h30			
14h30	**Assessment of the State of Dispersion, Aggregation and Agglomeration of Nanomaterials**		**Gert Roebben** Joint Research Centre - European Commission
15h00	**Determination of the Size (and Size Distribution) of Nanoparticles**		**Norma Gonzalez** Centro Nacional de Metrología (CENAM-Mexico)
15h30	**Determination of the Surface Area and Porosity**		Rapporteur Session C
16h00	**Surface Reactivity**		Rapporteur Session D

Coffee Break 16h30-17h00		
SESSION V. CONCLUSIONS AND RECOMMENDATIONS **17h30-18h00** Chaired by Peter Kearns, OECD		
17h30	**Recommendations on Test Guidelines / Guidance Documents needed for assessing Physical-chemical Properties of Manufactured Nanomaterials**	**Juan Riego Sintes** JRC - EC **Shaun Clancy** Evonik
18h00	**Concluding Remarks** Concluding Remarks from the Chair of ISO/TC229 and from the OECD Head of the Programme on Manufactured Nanomaterials.	**Simon Holland** Chair of ISO TC229 **Peter Kearns** Head of the OECD Programme on the Safety of Manufactured Nanomaterials
END OF THE MEETING		

ANNEX III. PARTICIPANTS LIST

Participants list for OECD Expert Meeting on Physical-Chemical Properties of Manufactured Nanomaterials and Test Guidelines in collaboration with ISO TC 229: Nanotechnologies/Liste des participants pour Groupe de travail sur les nanomatériaux manufacturés

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