Final minutes of the open session of the 12th meeting of ECHA–NanoMaterials Expert Group (ECHA-NMEG-12)

Time: 6-7 November 2018

Place: ECHA, Margot Wallström conference room

Participants: Representatives from the Member States Competent Authorities (MSCA), European Commission (COM: DG for Internal Market, Industry, Entrepreneurship and SMEs (DG GROW), DG for Environment (DG ENV), DG Joint Research Centre (DG JRC)), ECHA-NMEG Accredited Stakeholder Observers (ASO), EFSA and ECHA participated in the meeting.

The participant list is in Annex 1.

Meeting documents: The meeting agenda and presentations from the meeting are available on the dedicated CIRCABC site (https://webgate.ec.europa.eu/echa-scircabc)

I. Summary record of the proceedings

1. Introduction

The 12th meeting of the ECHA Nanomaterial Expert Group (NMEG) was held on 6-7 November 2018 (the previous meeting was held on 3-4 May 2018). This one and a half day event comprised a closed session (morning of day 1) and an open session (the rest of the time).

The purpose of the NMEG meeting is to discuss scientific and technical issues relating to the implementation of REACH, CLP and BPR for nanomaterials.

In the open session, this meeting addressed the Nordic Chemical Group (NGC) Project on the applicability of the GHS to manufactured nanomaterials, an overview of concepts and terms for the practical implementation of the nanomaterial definition, and the main guidance development needs to address the updated REACH Annexes for nanomaterials. Two topics in relation to read-across and grouping were presented: a grouping approach for uncoated cerium dioxide, and an overview of the ongoing GRACIOUS project. The activities of the NanoSafety Cluster were presented as well as some strategies to enable EU project outcomes to serve regulatory needs. Updates on the EU Observatory for Nanomaterials (EUON) and the outcome of substance evaluation on silver were described.

A closed session (restricted to MSCAs, COM DGs, and ECHA) was held in the morning of day 1, and discussed 1) the update on ongoing Substance Evaluation on TiO_2, 2) some considerations about the appropriate environmental risk assessment and classification for nanomaterials and 3) the CLH proposal on fibre-like multi-walled carbon (nano)tubes. A brief summary of the non-confidential discussion held during the closed session was presented to the Accredited Stakeholder Organizations (ASOs) in the open session on the afternoon of day 1 (AP 5).

A short overview of the presentations and discussion points in the open session of this meeting are given below.

2. The 12th ECHA Nanomaterials Expert Group meeting

AP 1. Welcome and introduction

The chair of the meeting, Frank Le Curieux (ECHA), welcomed the participants to the 12th NMEG meeting. New participants were introduced to the group. The draft agenda, shared with the group in advance of the meeting, was adopted.

The provisional dates for the next meetings were announced: **7-8 May 2019** (NMEG-13) and **5-6 November 2019** (NMEG-14).

AP 2. Adoption of minutes of NMEG-11

The chair outlined that the updated version (after commenting period) of the draft minutes from the last meeting were shared on the dedicated S-CIRCABC site. No additional comment was received from NMEG members. The minutes of NMEG-11 are thus considered as adopted and will be published on the NMEG page of the ECHA website.[1]

AP 3. Tour de table

The aim of the tour de table document is to share information on nanomaterials and to possibly propose topics for future discussion within the NMEG. No specific oral statement was made.

AP 4. Administrative issues on NMEG organisation

ECHA gave a presentation on the NMEG, reminding the main changes that occurred during the last years, and focusing on the update of the NMEG mandate and the renewal of expert nomination for the period 2019-2020. Regarding the mandate update, it was proposed to align with documentation used in the PBT and the ED expert groups and to prepare a 'NMEG manual' that contains the elements of the current NMEG mandate.

AP 5. Brief report for Accredited Stakeholder Organisations on the closed session

The representatives from FR-CA and DE-CA informed the ASO of the purpose and outcome of the closed session (items B, C and D, restricted to MSCAs, COM DGs, and ECHA).

5a. Update on ongoing Substance Evaluation on TiO_2 (item B)

The history of the case was briefly outlined: TiO_2 was listed in CoRAP list 2014 due to CMR concern and lack of information on TiO_2 as a nanomaterial. Before the SEv started, ECHA performed a compliance check requesting information on the substance name, composition and analytical methods. The decision was appealed by registrants contesting the legality of the requests; the Board of Apppeal (BoA) judged the appeal admissible and annulled the Contested Decision. In parallel FR-CA made a proposal for an EU harmonized classification as Carc 1B - H351 (inhalation) due to local tumours formation via inhalation and proposed to cover all forms of TiO_2. In September 2017, RAC concluded that TiO_2 should be classified as Carc. 2 – H351 (inhalation); at the moment there is discussion at the Commission on how to include this in the ATP.

[1] https://echa.europa.eu/regulations/nanomaterials/nanomaterials-expert-group

TiO_2 is now included in the CoRAP 2018 due to suspected CMR, worker exposure, general and sensitive population exposure, wide and dispersive use, high aggregated tonnage, suspected mutagenic, inconsistency in genotoxicity results, uncertainties regarding (eco)toxicological studies. The objective under SEv will be to investigate all forms of TiO_2 and focus particularly on nanoforms ($nTiO_2$).

The physico-chemical properties of the substance were summarised together with the boundary composition (BC). The plan is to include in the SEv draft decision a request to either modify the BC or modify the member's composition to stick to the BC or register apart from the JS (if the composition is not covered by the BC).

Concerning the environmental fate, the Registrants state there is no bioaccumulation or biomagnification of $nTiO_2$ (rutile/anatase). In bioaccumulation studies it is impossible to reach a steady state of equilibrium due to the formation of colloidal suspension and the only relevant route is the dietary route. Two studies with exposure through diet are available on fish and gastropods: in fish at low concentration the biomagnification factor (BMF) is below 1 thus showing lack of biomagnification, at higher concentration no steady state is reached; the same behaviour is observed in gastropods. A review of the scientific literature on bioaccumulation studies in fish and invertebrates show that there is no bioaccumulation of $nTiO_2$ in fish while in invertebrates high BCF values are observed due to adsorption of TiO_2 and uptake through the diet, which determines retention of $nTiO_2$ inside the gut of daphnia. The FR-CA concluded that invertebrates are the main target formulating the hypothesis that daphnia's specific pattern of adsorption favours the uptake of nanoscale particles and the formation of aggregates which makes it difficult for the organism to eliminate $nTiO_2$. On this basis, they are investigating the possibility that $nTiO_2$ is classified as B or vB.

Regarding human health, it was mentioned that the draft decision would contain a request on genotoxicity of $nTiO_2$ by inhalation, and that the SEv does not focus on E171 and the oral route, which is dealt by EFSA in another process. Some questions were raised in relation to oral repeated dose toxicity and reprotoxicity studies.

Concerning the ecotoxicology, available aquatic toxicity studies indicate that nano- and microsized TiO_2 are not toxic, neither acutely nor chronically to aquatic organisms. Based on the available data on fish, algae and invertebrates, a proposal for environmental classification for TiO_2 nano particles will be made.

5b. Some considerations about appropriate environmental risk assessment and classification for nanomaterials

The presentation from DE-CA (UBA) addressed the following question: considering the uncertainties regarding hazard and exposure information generation for nanomaterials (NM), how can these uncertainties be addressed for environmental risk assessment and classification?

5c: CLH proposal on fibre-like multi-walled carbon (nano)tubes.

DE-CA explained that the CLH proposal was for classification of the rigid forms of MWC(N)T as Carc. 1B (H350i) and STOT-RE 1 (H372). The proposed substance name is "Multi-Walled Carbon Tubes (synthetic graphite in tubular shape) with a diameter range ≥ 30 nm to < 3 µm and a length > 5 µm and aspect ratio ≥ 3:1, including Multi-Walled Carbon Nanotubes (MWCNT)". Sufficient evidence is available that MWCNT with fibre-like morphology are carcinogenic, similar to asbestos (mesothelioma, lung carcinoma). It is considered that the fibre pathogenicity paradigm is sufficient to explain the carcinogenic potential. Diameter is used as a surrogate parameter for fibre rigidity. Moreover, low-diameter MWCNT (< 15-30 nm in diameter) appear to lose fibre pathogenicity. Regarding exemption criteria, further discussion is required.

AP 6a. Information campaign on REACH relevant regulations for nanomaterials

Daniel Vest Christophersen from DHI presented information on the Nordic Chemical Group (NCG) project aimed at providing information on REACH relevant regulations relevant for nanomaterials. The general goal of the work is to set up an electronic tool that provides the user with a simple introduction to nanomaterials, and explains the information requirements of the regulation as they relate to nanomaterials. The main audience of the tool are small and medium enterprises lacking the necessary internal expertise. The new eREACH tool will be available only in English, and will be based on many (nearly 100) short videos, each not lasting more than 5 minutes.

A preliminary version of the tool is already available (http://ereachnano.com/), and the movies and necessary animations are expected to be finalised by the end of November 2018, with the tool itself published by the end of the year 2018. The DHI group has applied for additional funding/grants to further modify the tool before 2020 to include in the tool information the amendments of the REACH Annexes for nanomaterials.

AP 6b. Nordic Chemical Group Project - Applicability of GHS classification criteria to nanomaterials

Poul Bo Larsen (DHI, DK) presented preliminary results from the project "The applicability of the GHS classification criteria to NMs", which was initiated and sponsored by the Nordic Chemical Group and TUKES (Finnish Safety and Chemicals Agency).

Nanomaterials (NMs) with different physical properties were selected for assessment in the project. The focus of the presentation was the single walled carbon nanotubes (SWCNT), because they were fibre-like, were insoluble and had a high specific surface area (SSA), and zinc oxide (ZnO), because this represented metallic oxide particles which were described as semi-soluble and had a (relatively) lower SSA. Other NMs also included in the project were silicon dioxide, representing insoluble oxide particles with a high SSA and silver, comprising pure metallic, semi-soluble particles of high density.

An in-depth assessment of the available data using multiple data sources was conducted in relation to STOT RE (inhalation, lung) and acute toxicity for SWCNT and ZnO, and in addition eye damage/irritation for the SWCNT.

It was reported[2] (Lee et al., WHO, 2017) that due to high volume per mass of SWCNTs, it was impracticable to apply doses greater than 50 mg/kg BW (and even then the dose was divided), at which no deaths or clinical signs were observed in rats in an OECD technical guideline (TG) study. Similarly, in a dermal toxicity study, the maximum achievable dose of SWCNT applied to skin of rabbits in an OECD TG study was ca. 2.5 mg/kg bw, at which no clinical sign of toxicity occurred. Furthermore, although no acute toxicity study by inhalation of SWCNT has been conducted, the highest SWCNT dose tested (5 mg/m3, 4 days of exposure at 5 h/day in mice) was very much lower than the GHS numerical criteria for acute inhalation toxicity and resulted in an inflammatory response, collagen disposition and fibrosis. Moreover, in several studies using single exposure by lung aspiration or intratracheal instillation, similar effects were seen down to an exposure level of 10 µg SWCNT in mice. All this suggested that there were probably limitations in obtaining sufficient exposure doses or concentrations corresponding to any categories of Acute Toxicity with this material.

However, using the same 4-day inhalation study described above, criteria for classification of SWCNT as STOT RE 1 appear to be met.

[2] Lee et al., WHO, 2017 Which hazard category should specific nanomaterials or groups of nanomaterials be assigned to and how? WHO 2017. http://apps.who.int/iris/bitstream/handle/10665/259682/WHO-FWC-IHE-17.4-eng.pdf;jsessionid=9EAFDA0D6F9874B8DC72BE9053F9BE2C?sequence=1

In studies addressing eye damage or eye irritation the maximum achievable dose of SWCNT in an OECD TG *in vivo* study was 0.1 mg (and no eye irritation was seen), while the TG recommends that up to 100 mg should be used. In an OECD TG *in vitro* Reconstructed Human Cornea-like Epithelium study conducted using 50 mg SWCNT, a positive response was observed, but it is not possible to discriminate between classification for Eye Irrit. 2 and Eye Dam. 1 in this assay; only discrimination between non-classification and classification is possible.

The GHS criteria for acute oral and dermal toxicity were found to be applicable to both NM and micro-sized particles of ZnO, which has a lower SSA, and no classification was found to apply for either acute toxicity category. On the other hand, the LD50 was in the range of 25-50 µg ZnO NM (12 nm) after a single dose by intratracheal instillation in mice, indicating severe pulmonary toxicity. Although currently no inhalation studies were available for acute toxicity by inhalation, these findings suggested that the GHS criteria were presumably applicable for classification of NM ZnO, albeit guidance may be needed for the use of intratracheal studies for assessing acute inhalation toxicity.

The highest dose levels used in repeated dose toxicity studies (4.5 mg/m^3 (90 days) and 8 mg/m^3 (28 days)) are very low compared to the guidance values in the GHS classification criteria. It was concluded that the GHS STOT RE criteria were presumably adequate for classification of nano-ZnO, but further guidance/criteria may be needed on how to use subtle pulmonary toxicity effects observed at very low exposure levels for STOT RE classification.

A number of learnings were obtained concerning the applicability of GHS criteria for the hazard classes investigated. For acute toxicity, the criteria appeared to be only partly relevant for voluminous NMs (such as SWCNT) because only low, non-lethal doses could be achieved in oral and dermal acute toxicity studies, and this was also likely to be the case for acute inhalation toxicity (but there were no data to confirm this). For less voluminous substances (such as ZnO), classification via the oral and dermal routes appeared to be possible, and probably via the inhalation route as well (but again this could not be confirmed due to lack of data).

The *in vivo* model for eye damage/irritation was also found to not be applicable for voluminous NMs due to exposure limitations, and while effects can be detected in the available *in vitro* study design, it cannot distinguish between eye damage and eye irritation.

Development of guidance (criteria) was needed on classification via the inhalation route for acute toxicity and STOT RE based on data from instillation/aspiration studies. Classification for STOT RE may be possible for both voluminous and less voluminous substances but where more subtle effects were observed at very low dose levels (few mg/m^3 or less), data may need to be accompanied by mode of action (MoA) and adverse outcome pathway (AOP) analyses to establish whether the findings are sufficiently severe for classification.

The presenter emphasised that the conclusions presented were those of DHI, and not of the CAs that commissioned the project.

In the discussion, it was noted that how these findings will be provided to the GHS for them to consider as part of their ongoing project on applicability of GHS to NMs is up to the Nordic Group of Member States who have commissioned the project, but eventually the final report would be published and shared.

Since the focus of the project was on NM, the data on non-nano forms was not examined in detail.

AP 7. Update on the nanomaterial definition: an overview of concepts and terms for its practical implementation

The EC recommended definition of nanomaterial (2011/696/EU) (EC NM definition[3]) has been reviewed and next step would have been public consultation. However, the public consultation is currently on hold for an undetermined amount of time and the definition cannot be revised before the public consultation is finished.

JRC has been tasked to prepare two reports concerning the EC NM definition: one on concepts and terms and another one on practical recommendations on how to assess a material against criteria in the definition mainly through measurements. As the NM definition (20117696/EU) is adopted in several regulations, it is appropriate to support its implementation. It was therefore decided that the JRC provides scientific advice on its implementation now. . Should the definition be revised, a relevant guidance will be developed later based on the revised definition.

The JRC Report 1 concerning concepts and terms used in the EC NM definition is in a final draft stage. The JRC Report 2 concerning advice on assessment of a material against the criteria in the definition is under preparation and will be published in 2019.

The JRC Report 1 clarifies issues such as:

- Definition is based on the range of a material's (minimum) external dimension (particle size).
- Material is a generic term and it can be replaced by a more specific term for sector specific legislations.
- Internal structures and surface structures do not have relevance for the EC NM definition.
- Terms 'constituent particle', 'aggregate' and 'agglomerate'.

Until the JRC Report 2 has been published the Methods Manual and the Decision flow scheme with supporting E-tool developed in the context of the NanoDefine project[4] are recommended to be used to implement the EC NM definition.

The nanomaterial definition for cosmetics and food legislation are different from the EC NM definition but there is intention to harmonise as far as possible all the definitions on the EU level.

The JRC scientific advice will take into account the development of technical guidelines for nanomaterials at OECD level. JRC is part of the project group to develop the test guideline for the size distribution measurements and is leading the project for the development of the guideline for the specific surface area.

AP 8. Update on Guidance to implement revised REACH annexes for nanomaterials

ECHA made some reminders on the ECHA guidance process, and gave an update on the main guidance development needs triggered by the positive vote on the revised REACH Annexes for NMs at the REACH Committee (26 April 2018), and its future entry into application (1 January 2020).

Guidance documents are planned to be prepared or updated on 4 topics: nanoforms (including registration and Substance Identity (SID) issues); grouping and read-across; information requirements for environmental and physico-chemical endpoints; and information requirements for human health endpoints.

Regarding the guidance on nanoforms, it will be based on the existing practical guide (PG) on registration of nanoforms, considering that some recommendations contained in the PG are now legal requirements in the revised REACH annexes. The guidance is proposed to be an

[3] https://ec.europa.eu/research/industrial_technologies/pdf/policy/commission-recommendation-on-the-definition-of-nanomater-18102011_en.pdf
[4] http://www.nanodefine.eu/index.php/nanodefiner-e-tool

Appendix to the Guidance documents on registration and SID. It will contain explanations on the nanoform concept, how to build sets and justify them, on Annex III and general issues on information requirements, and on the requirements for characterisation in Annex VI (size, shape, surface chemistry, specific surface area).

For the guidance on grouping and read-across, it is planned to have a minor update (fast track) to align it with the definition of nanoforms (and the inclusion of sets) in the revised REACH Annexes.

Concerning the guidance on environmental endpoints, the proposed update includes the revision of the section on water solubility (including the limitation of the waiving possibilities for nanomaterials), the development of a new section on dissolution rate (relevant for human health and the environment), the limitation of the partition coefficient octanol /water (need to use dispersion stability when not applicable), adsorption/desorption (need to use dispersion stability and other methods), and the development of a new section for dustiness. Other updates also foreseen are in relation to:

- Aquatic pelagic toxicity: recommendations already available that now are requirements (e.g. limitations of waivers, considerations on chronic testing)
- Revision of the section on degradation/biodegradation and transformation (e.g. make clear that testing for transformation, and coating degradation is mandatory - now only recommended in guidance)
- Revision of the section on bioaccumulation to strengthen the message on waiving limitations, and when possible provide advice on testing for bioaccumulation
  Revision of the section on soil toxicity: limitations of use of the Equilibrium Partitioning Method.

In relation to human health, most changes are already included as recommendations in the current guidance. Some minor alignments are proposed regarding the advice on testing strategy, repeated dose toxicity, acute toxicity, mutagenicity and carcinogenicity. The section on toxicokinetics should be revised and advice should be provided on indirect genotoxicity.

In terms of timeline, the formal PEG consultation is planned to be launched in December 2018/January 2019.

It should be noted that a specific workshop is organised on 8-9 November 2018 (back-to-back with this NMEG-12) in order to support the implementation of the REACH information requirements for nanomaterials. Breakout group discussions are planned to address four topics: implementation of nanoforms and sets of nanoforms; physico-chemical characterisation; environmental endpoints; and human health endpoints.

AP 9. Case study presenting a grouping approach for CeO_2 (45 min)

Representatives from industry presented a case study describing a grouping approach for cerium dioxide (CeO_2) using the framework described in ECHA guidance for grouping and read-across (Appendix R.6-1 for nanomaterials applicable to the guidance on QSARs and Grouping of chemicals (Version 1,0, May 2017)). The main aim of the case study was to assess how to use a read-across approach for nanomaterials using data from the scientific literature.

The endpoints covered in the case study were physico-chemical, toxicological (toxicokinetics, repeated dose toxicity and in vivo genotoxicity) and ecotoxicological (algae, earthworm and acute invertebrates) properties. It was further explained that the forms used in the case study were from the OECD test program and were all uncoated nanometric CeO_2 (NM-211, NM-212

and other CeO_2) and uncoated micrometric (NM-213) CeO_2. All the forms were reported to be insoluble, to be non-coated spheroidal-like, and to have variable sizes and surface.

Based on the assessment of the data from scientific literature for the physico-chemical endpoints, some variation was detected for the purity, primary particle size, surface area, particle size distribution for the same form. It was explained that the variations may be due to the (uncertainty of the) measurements methods. It was also noted that for several forms the data on characteristics were lacking.

For the toxicological endpoints it was noted that the toxicokinetic data from the literature with the different forms of CeO_2 showed a similar rate of elimination for the oral route. For the inhalation route small differences in pulmonary deposition were observed although the differences were not consistent. Finally, when intratracheal instillation was employed qualitative similarities were observed in retention rate in the lungs, elimination half-life, distribution and elimination. The repeated dose toxicity data via inhalation route showed similar toxicity profiles however, NM-211 seemed to be the most potent form. For *in vivo* genotoxicity the non-guideline data provided was mainly performed with NM-212. Therefore no conclusions can be drawn for the read-across approach.

Based on the data, the representatives of industry concluded that *"whatever the size, the surface area (or the shape), the non-surface treated, virtually insoluble cerium oxide, will form aggregates/agglomerates, and then, will have the same behaviour and distribution, and thus, will cause similar (eco)-toxicological effects"*.

For the ecotoxicological endpoints, toxicity to aquatic plants and earthworms with data derived from assessment of two literature studies and similar results were obtained with NM-212, NM-211 and NM-213 for earthworm survival and reproduction and algae growth.

The main conclusions for nanomaterials were: the particle size distribution needs to be reported and discriminated from (primary) particle size, the aggregation/agglomeration state needs to be considered, references to measurement methods in the guidance documents could be helpful and that measurement methods need to be specified in the technical dossier.

In the discussion after the presentation a key question was raised on whether the forms described in the presentation were representative of the CeO_2 registered under REACH. It was responded that the presentation did not cover the situation in the technical dossier. The main aim of the case study was to assess the read-across approach according to the nano-guidance document for certain endpoints. DE-CA pointed out that the results of this case study will be recognized within the planned SEv, but will not prevent the DE-CA from evaluating the substance in the way DE-CA considers to be the most appropriate one.

AP 10. The GRACIOUS project – Grouping and Read-Across of Nanomaterials

Eric Bleeker (NL-CA) gave a presentation on the GRACIOUS project, a European project started in January 2018. The main aim of the project is to generate a framework to enable practical application of grouping, leading to read-across and classification of nanomaterials (NMs) and nanoforms (NFs). ECHA guidance on grouping, together with the CEFIC proposal (DF4Nano) on grouping, were considered as starting points for this project.

Within the project, a draft framework for Grouping and Read-Across of Nanomaterials was created, including a document on terminology and legislation that addresses NMs and NFs. A first version of the framework was discussed in Paris in September 2018 and a scheme of the draft framework was presented to the NMEG audience.

The framework is hypothesis driven: a hypothesis is used as a rationale that can underpin the grouping. The user needs to test if the hypothesis applies and justify the use of the grouping. Testing will be guided via IATAs (Integrated Approach to Testing and Assessment) tailored to the hypothesis. The final goal is to have a grouping decision with a justification. The starting

point of the framework is either a single nanoform or a provisional group of nanoforms that have similar phys-chem properties (composition, particle size distribution, particle shape, chemical nature of the surface, specific surface area, water solubility/dissolution) and intended uses. The purpose for grouping must also be clearly known at this stage. A list of predefined groups that can be quickly substantiated and have clear implications are provided (e.g. quickly dissolving nanoforms, respirable High Aspect Ratio Nanomaterial, nanoforms larger than 5 nm, nanoforms incorporated in solid matrix) as part of the framework. This list includes groups that can relatively quickly be substantiated to meet the needs of the user. The list can be expanded in time. If it is not possible to insert materials in those pre-defined groups, then a new/expanded hypothesis will need to be created through refinement steps.

It was explained that the next steps of the project will include further collection of inputs from stakeholders on the framework, assessment of scientific validity of hypotheses, development of IATAs for justification of grouping, and simplification of the framework itself. Case studies on certain selected nanomaterials will also be performed. The final version of the GRACIOUS framework will be delivered in 2021.

In the discussion after the presentation the following points were raised:

- How would the grouping concepts presented in the framework align with the terminology "sets of similar nanoforms" that is now included in the REACH Annexes? It was highlighted that how to define set/nanoform is a regulatory discussion, however outcomes of research projects will also help in refining regulatory concepts. It was highlighted that for nanomaterials the "devil" is in the details, therefore it will be important to substantiate (also with case studies) how to deal in practice with nanomaterials with different sizes and with the different available size measurement methods.
- Data quality will be assessed within the project mainly by using expert judgment. Klimisch score may also be considered as a method to assess data quality/reliability.
- How IATA will include considerations for distinguishing if the nanoparticles have reached or not the target organs. It was explained that these considerations are already included in IATAs, which are based on "what they are", "where they go", "what they do". However, how to actually measure the particles inside organs is a major challenge and development in methods is needed. Developments of new methods (e.g. within OECD activities) will be looked at within the project, to the extent possible.
- The IATA will aim to gather data for each endpoint, therefore one IATA for each specific endpoint will be created.
- Inflammation shall be looked at in more details: it is a common aspect for nanoparticles but can have different features for different nanomaterials. There is therefore a lot of substrate for new grouping that can be done based on this.
- The framework presented is complex and one important goal should be to simplify it so that it can be easily used in a regulatory context.
- It was suggest that the predefined groups in the concept might be rather important endpoint related parameters that need to be considered to establish/justify a group than a group itself.

AP 11. NanoSafety Cluster activities and strategies to enable EU projects' outcomes to serve regulatory needs

Éva Valsami-Jones from the University of Birmingham gave a presentation highlighting current activities of the EU NanoSafety Cluster (NSC) and their relevance for regulatory activities.

An overview of all NSC projects is available in the NSC compendium, which can be downloaded from the NSC website https://www.nanosafetycluster.eu. An updated version of the compendium is expected by the end of the year.

The presentation focused on presenting selected ongoing/ended NSC projects, particularly such ones that are related to regulatory needs or activities. Five large projects (NANOSOLUTIONS, NanoMILE, eNanoMapper, GUIDEnano and SUN), all finished in 2017, arranged a joint final conference in February 2017, and also published a paper in Nature Nanotechnology[5]. The paper presents some of the key advances in the hazard and risk assessment of engineered NMs, particularly emphasizing systems biology and high throughput screening approaches.

The NanoMILE project produced large data libraries on characterization (with an emphasis on aged NMs and aging protocols), NM-biomolecule interactions, and development of models (ecotoxicology and human toxicology). The main aim of the project was to develop a better understanding of the mechanisms of nanomaterial interactions with living systems and the environment.

In an ongoing project called ACEnano, the focus is on the development of a widely implementable and robust tiered approach for the physico-chemical characterisation of nanomaterials. This includes toolbox building, creation of a training cascade concept, and building a data warehouse. The outcome of several other NSC projects forms an important ground for the ACEnano project.

Data management and data sharing are important topics of basically all ongoing NSC projects. The NanoCommons project focuses on implementing data management in everyday scientific research and a common aim is to achieve interoperability and reusability of data. An important element is the use of ontological data annotation to combine datasets from different sources. E-notebooks were mentioned as useful tools in data management.

NanoSolveIT (Innovative **Nano**informatics models and tools: towards a **Sol**id, **ve**rified and **I**ntegrated Approach to Predictive (eco)**T**oxicology) is a new project, starting in February 2019.

In relation to the "Malta Initiative", activities are currently ongoing to identify which NSC projects can provide input to which of the Malta TG projects.

After the presentation it was discussed how the outcome of the research projects and regulatory projects best could be linked to each other. Éva Valsami-Jones explained how the different NSC working groups have been re-organized. Currently there is one working group (WG G) named Regulations & Risk Governance. It is chaired by the NANoREG coordinator Tom van Teunenbroek. The aim of this WG is to serve as an interface between science and regulations. In addition it can be noted that one of the four members of the NSC coordination team is Flemming Cassee (RIVM), who is coordinating the regulatory activities of the NSC.

Within the NSC it is possible to launch a specific task force, having a deadline of 6 months for moving the task force forward. Current task forces include for example a task force on nano TiO_2 safety communication and one on safer-by-design definition.

There was also discussion on how to obtain information on NMs not included in the registration dossier of a substance, but studied in research projects. The advice was to check the NSC compendium to get information on which NMs are investigated in different projects, and to contact the relevant project coordinators or the NSC coordination team. More common questions could be addressed in a public way on the EUON website.

AP 12. Update on the development of the EUON

ECHA gave an update on the developments since the EU Observatory for Nanomaterials

[5] Fadeel et al., 2018 Advanced tools for the safety assessment of nanomaterials, https://doi.org/10.1038/s41565-018-0185-0

(EUON)[6] was presented to the NMEG in their previous meeting.

ECHA reminded participants about the main aims of the observatory:

- to provide objective and reliable information on the market and safety of nanomaterials in the EU,
- to collect and analyse information from a variety of existing sources,
- to supplement existing information with external studies,
- to present the information on uses and safety of nanomaterials for laypersons.

Since the NMEG-11 meeting, the EUON has been updated with the incorporation of new databases, NanoData[7] and the eNanoMapper[8]. The website has a new, more dynamic look focused on new content and there are more regular news updates. The EUON was also updated with new web pages in 23 EU languages in June 2018.

In addition, the EUON has concluded two studies, one on the key parameters to be used for market studies on nanomaterials and the other on nanopigments. Both study reports are available on the EUON website[9]. As an outcome of the pigments study, the EUON published an inventory of 81 nano-pigments[10] found on the EU market and linked the information to ECHA's search for chemicals where visitors can find more information on the different substances.

ECHA explained that NanoData was fully taken over and incorporated into the Observatory. NanoData presents market information on different nanomaterials by products and sectors including patent information and helps users to visualise statistics through charts.

The EUON also carried out a light integration of the eNanoMapper database which allows the searching and filtering of data from different EU-funded research projects on the health and safety of nanomaterials.

ECHA's consumer microsite[11] was launched in March 2018 and also includes content on nanomaterials intended for the general public. ECHA highlighted the interactive 360 degree apartment[12] where users can navigate a flat and click on different products to find out how nanomaterials are used. The apartment was among the most popular EUON content and has brought a lot of traffic to the website.

ECHA presented the future data integration plans for the EUON. Currently, EUON allows users to search for REACH registrations with substances in nanoforms, and to find information on the nanomaterials used in cosmetics, EU-funded research projects through the eNanoMapper as well as the NanoData knowledgebase. Over the coming months, ECHA will explore the creation of a search tool allowing users to have a single search for REACH registrations, cosmetics notifications and data from national inventories. The search results are to be integrated with ECHA's search for chemicals.

The EUON is planning to conduct additional studies in 2019. A study on the state of play of "next generation" nanomaterials and relevant terminology as well as a study on the public perception of nanomaterials started. The results of the studies are expected in Q3 2019. A mid-term review will also be carried out among EUON visitors and stakeholders and published in June 2019 assessing the impact and usefulness of the EUON.

The EUON will continue to add new content to the observatory to give users regular updates and a dynamic website. The plans for new content in 2019 includes opinion pieces on current

[6] https://euon.echa.europa.eu/
[7] NanoData: nano technology knowledge base
[8] eNanoMapper: data and tools for nanomaterials risk assessment
[9] EUON: published reports
[10] EUON: nano-pigments inventory
[11] ECHA's consumer microsite: "Chemicals In Our Life"
[12] ECHA nanomaterials in our life: interactive apartment

topics and trends relating to nanomaterials, more visual and dynamic content such as audio-visual and infographics to engage audiences as well as information on tools and ongoing research topics related to the safe use of nanomaterials.

In conclusion, ECHA reminded that the EUON is a European-wide initiative and called for feedback and contribution from participants to ensure its success.

AP 13. Substance Evaluation Conclusion on Silver

Eric Bleeker from RIVM/NLCA gave an update on the silver substance evaluation decision and follow up process.

The silver dossier includes both, nanoforms and non-nanoforms of silver. Difficulties were encountered to identify the different forms and their uses. It was also unclear how the different nanoforms were included in the registration.

After publishing the decision in July 2016, the MSCA and registrant(s) met (November 2016 and May 2017), and the initial range finding results, test set-up for definitive tests and draft results of definitive tests were discussed. The registrant(s) updated the dossier in 2017, and the final conclusion document[13] was issued in November 2018.

The information requested in the decision included physico-chemical characterisation of two nanosilver test materials (incl. particle size, agglomerate size, zeta potential, isoelectric point and pour density). The characterisation of the 2 forms was used to choose the "worst case" nanomaterial for testing. The choice was driven by their ability to agglomerate and to dissolve, and the main parameters to decide upon further testing between the forms was determined to be the size and surface area.

Based on the characterization data or physico-chemical results, dissolution/transformation tests on *Daphnia*, algal medium and soil pore waters, and ecotoxicity tests on algae (OECD TG-201), *Daphnia magna* (OECD TG-211) and soil microorganisms (OECD TG 216), were requested on the smallest nanosilver form with highest surface area, and on the silver ion ($AgNO_3$). The silver nitrate salt was tested in parallel, to distinguish between the toxicity of the nanoparticles and that of free ionic silver.

In the aquatic ecotoxicity studies, test media were adapted to minimise complexation of silver ions: EDTA was minimised and chloride salts were replaced by nitrate salts. Three silver size fractions were distinguished for measurements (< 3 kDa; < 450 nm; total silver).

In the dissolution/transformation test, it was observed that nanoparticles in the modified algal medium tended to remain in suspension, while in modified *Daphnia* medium they tended to settle out of the medium. A release of ionic silver (< 3 kDa) was observed with time in this case.

Silver salt showed to be more toxic than the silver nanoform on both organisms, and algae more sensitive than Daphnia. The highest toxicity found was observed in the 3 kDa centrifuge filtered (ionic silver) fraction, when testing either silver salt or nanosilver on both, algae and *Daphnia*. Overall, the $AgNO_3$ resulted to be the most toxic (0.005 mg/L) on algae. In this case, the silver salt resulted to be 34 times more toxic to algae than nanosilver when comparing EC_{10} results. Thus, it was concluded that silver nitrate can be considered as the "worst case".

When testing soil microorganisms (i.e., potential nitrification rate and substrate induced nitrification) 3 soil types were used (Rots, Lufa 2.2 and Poelkapelle), representing a range of different soils. Results differed between them. The highest toxic effects were observed on Poelkapelle in both tests, where ionic silver resulted to be about 3 times more toxic than nanosilver in all cases (i.e., EC_{10}, EC_{50} and both tests). Based on these results it was concluded

[13] https://echa.europa.eu/documents/10162/3f2ad1e1-0fe2-4802-b

that silver nitrate can be considered as "worst case" even though the difference in toxicity was not as large as for aquatic toxicity tests results.

Based on these results and the dissolution/transformation test, NLCA agreed with the Registrant on their hypothesis: data on silver nitrate can be used as a worst case scenario for the toxicity of nanosilver in the environment. PNEC values for $AgNO_3$ can serve also for nanosilver.

Regarding exposure assessment, specific exposure scenarios were provided. These exposure scenarios, although not detailed, seemed relevant. PECs for the nanosilver were estimated using EUSES, and the derived RCRs did not show risk for any environmental compartment. Moreover, RCRs for nanosilver were considered negligible compared to the updated RCRs for the ionic form.

As a follow up action, NLCA considered that a stricter self-classification of nanosilver is not needed, and that the same classification as for $AgNO_3$, i.e. Aquatic Acute 1, Aquatic Chronic 1, applied M factors 1000 and 100 respectively, can be applied for the nanosilver form. Although, they also mentioned that a more stringent classification or proposal for CLH on $AgNO_3$ based on the latest results could be considered.

Currently, the biocidal use of the nanoforms of silver is assessed by Sweden, and it was suggested that they could use the data generated in this process for the assessment of the different active silver nanoforms.

During the discussion, a question was raised on the existence of new registration of nanosilver. Apparently none was performed between July and October 2018.

The possibility to distinguish between attached nanoparticles and dissolved ions was also questioned, in particular for the Daphnia test. In the data reported, such distinction was not made nor was it requested by NLCA. It was concluded that it is not known if increased effects would be visible once the particles attach or adsorb on the organisms. In soil the dissolution test was performed for 3 months and both the bigger fractions (total and > 450 nm) decreased over time in the pore water. For the smallest fraction (< 1 kDa) clear differences in behaviour were observed between $AgNO_3$ and nanosilver. When testing nanosilver an increase in silver (< 1 kDa) was observed in the pore water in the first few weeks, followed by a steady decrease for the remaining weeks, while for silver nitrate a steady decrease in silver concentrations (< 1 kDa) was observed directly from the onset of the study. Nevertheless, both $AgNO_3$ and nanosilver showed similar silver concentrations in the pore water after 3 months.

The adaptations used to derive nanosilver PECs with EUSES was also questioned, since EUSES is not yet adapted to estimate PECs for particles. It was acknowledged that this is the case and that NL-CA were not aware of any used adaptation. However, since the nanosilver tonnage is very low and the PNEC was derived based on silver ion results, while nanosilver is less hazardous than silver ion, the risk was considered low for nanoforms, even with the uncertainties in the PEC estimation from EUSES.

The chairman thanked the presenter for the presentations and the members for the discussion.

AP 14. Update on NMEG rolling plan – Wrap-up and conclusions

The chair provided an update on the rolling action plan and reminded the topics that are currently on the rolling plan for 2019:

- EC nanomaterial definition: JRC is in the lead for the development of two reports related to the EC definition of the term nanomaterial. Depending on the progress, this topic may be presented at a future NMEG meeting.

- Revision of OECD TGs/GDs (Malta Initiative): the NMEG will provide scientific and technical input on common generic issues to ensure regulatory relevance and applicability of OECD TGs/GDs.
- Discussion on specific nano cases:
    - Examples on approaches for hazard assessment (including grouping and read-across) for nanomaterials may be presented at NMEG-13.
    - Upcoming CLH proposals and Biocides dossiers involving nanomaterials are monitored.
- Learning from research projects may be presented at future meeting.
- Several administrative issues have to be handled by the end of 2018: the review of NMEG mandate, the renewal of nomination for NMEG experts for 2019-2020.

ECHA will distribute a draft rolling plan on 5 December 2018, at the same time as the draft minutes of NMEG-12, and the NMEG members will be invited to provide comments by 16 January 2019.

END OF ECHA-NMEG-12 MEETING

II. List of participants of open session of NMEG-12

Surname	First Name	Country/Organization
Aitasalo	Tuomas	ECHA
Alessandrelli	Maria	Italy
Amenta	Valeria	ECHA
Andersen	Sjur	Norway
Aruoja	Villem	Estonia
Ball	Elanor	United Kingdom
Bleeker	Eric A.J.	Netherlands
Boisen	Anne	Denmark
Bonev	Chavdar	Bulgaria
Caley	Jane	ECHA
Carlander	David	NiA
Carvalho	Félix	EUROTOX
Constantin	Camelia	ECHA
Cudicini	Corinne	Solvay
De Saint Jores	Jérémy	France
Deydier	Laurence	ECHA
Elwan	Adam	ECHA
Falck	Ghita	ECHA
Fernandez-Cruz	Maria-Luisa	Spain
Gadermann	Angelina	Germany
Gaidukovs	Sergejs	Latvia
Gottardo	Stefania	Joint Research Centre
Helminen	Ulla	ECHA
Herzberg	Frank	Germany
Holmqvist	Jenny	ECHA
Hyytinen	Eija-Riitta	Finland
Jacquet	Cyril	ECHA
Jomini	Stéphane	France
Jurgelėnė	Živilė	Lithuania
Kapanen	Anu	ECHA
Karjalainen	Ari	ECHA
Kinzl	Maximilian	Austria
Kobe	Andrej	European Commission DG ENV
Korjus	Pia	ECHA
Kos Durjava	Mojca	Slovenia
Krop	Hildo	ETUI
Larsen	Poul Bo	DHI

Le Curieux	Frank	ECHA
Leinonen	Riitta	Finland
Mazzega Sbovata	Silvia	ECHA
Melbourne	Jodie	PISC
Mendonça	Elsa	Portugal
Moore	Gregory	Sweden
Quinn	Bernadette	ECHA
Rauscher	Hubert	Joint Research Centre
Rodriguez Ruiz	Amaia	ECHA
Rodriguez Unamuno	Virginia	ECHA
Roebben	Gert	European Commission DG GROW
Schoonjans	Reinhilde	EFSA
Schwirn	Kathrin	Germany
Sergent	Jacques-Aurélien	Solvay
Serrano Ramon	Blanca	Cefic
Spirlet	Christine	Eurometaux
Stockmann-Juvala	Helene	ECHA
Sumrein	Abdelqader	ECHA
Tanarro	Celia	ECHA
Valsami-Jones	Eva	NanoSafety Cluster
Vest Christophersen	Daniel	DHI
Vomastkova	Milada	Czech Republic
Walkowiak	Bogdan	Poland
Wiench	Karin	ECETOC

Apologies:

Agnieszka Dobrak-Van Berlo (BE), Claudia Sorina Dumitru (RO)

III. Final Agenda

12th meeting of the ECHA Nanomaterials Expert Group (ECHA-NMEG-12)
6-7 November 2018, Helsinki, Finland

MARGOT WALLSTRÖM CONFERENCE ROOM

Final agenda

Chair: Frank Le Curieux, Evaluation 3, ECHA

DAY 1 – Tuesday 6 November 2018		
MORNING - CLOSED SESSION		
09.30	Registration for closed session & coffee (30 min)	
10.00	**A. Welcome and introduction** (5 min)	Chair
10.05	**B. Update on ongoing SEv on TiO2** (1 h)	Stéphane JOMINI, FR-CA
11.05	**C. Considerations about appropriate environmental risk assessment and classification for nanomaterials** (45 min)	Kathrin Schwirn, DE-CA
11.50	**D. CLH Proposal on Fibre-Like Multi-Walled Carbon (Nano)Tubes** (45 min)	Frank Herzberg, DE-CA
12.35	*Lunch (1 h 25 min)*	
AFTERNOON - OPEN SESSION		
13.30	Registration for Open session (30 min)	
14.00	**1. Welcome and introduction** (10 min)	Chair
14.10	**2. Adoption of minutes of NMEG-11** (10 min)	Chair, all
14.20	**3. Tour de table** (10 min)	All
14.30	**4. Administrative issues on NMEG organisation** (20 min) **4a. Update of NMEG mandate** **4b. Renewal of nomination for 2019-2020**	Chair, all
14.50	Coffee Break (30 min)	
15.20	**5. Brief report for Accredited Stakeholder Organisations on the closed session** (30 min)	FR-CA & DE-CA
15.50	**6. Update on 2 projects by DHI group, Denmark** **6a. Information campaign on REACH relevant regulations for nano-materials** (10 min) **6b. Nordic Chemical Group Project - Applicability of GHS classification criteria to nanomaterials'** (30 min)	Daniel Vest Christophersen, DHI Poul Bo Larsen, DHI
16.30	**7. Update on the nanomaterial definition: an overview of concepts and terms for its practical implementation** (30 min)	Hubert Rauscher, JRC
17.00	**8. Update on Guidance to implement revised REACH**	Celia Tanarro, ECHA

	annexes for nanomaterials (30 min)	
17.30	**End of day 1 of NMEG-12 meeting**	
19.00	*Dinner outside ECHA (for colleagues who expressed interest)*	

DAY 2 – Wednesday 7 November 2018		
09.30	**9. Case study presenting a grouping approach for CeO2** (45 min)	Corinne Cudicini & Jacques-Aurélien Sergent, Solvay
10.15	**10. The GRACIOUS project – Grouping and Read-Across of Nanomaterials** (60 min)	Eric Bleeker, NL-CA
11.15	Coffee Break (30 min)	
11.45	**11. NanoSafety Cluster activities and Strategies to enable EU project outcome to serve regulatory needs** (45 min)	Éva Valsami-Jones, University of Birmingham, UK
12.30	**12. Update on the development of the EUON** (30 min)	Abdelqader Sumrein, ECHA
13.00	*Lunch (1h)*	
14.00	**13. Substance Evaluation Conclusion on Silver** (30 min)	Eric Bleeker, NL-CA
14.30	**14. Update on NMEG rolling plan – Wrap-up and conclusions** *(30 min)*	Chair, all
15.00	**End of ECHA-NMEG-12 meeting**	

IV. Main Action Points from NMEG-12 (6-7 November 2018)

CONCLUSIONS / DISCUSSIONS	ACTIONS REQUESTED
AP 2 – Minutes of NMEG-11	
NMEG adopted the draft minutes as provided for the meeting.	**ECHA** to upload final version of the minutes on NMEG- S-CIRCABC and on ECHA NMEG website without undue delay.
AP 12 – NMEG Rolling Plan update for 2019	
NMEG took note of the main elements of updated NMEG Rolling Plan for 2019 by ECHA.	**ECHA** to upload on NMEG S-CIRCABC, for comments, the updated NMEG rolling plan following the NMEG-12 meeting.
AP 12 – Wrap-up and conclusion	
NMEG chair wrapped up the main action points of NMEG-12 at the meeting.	**ECHA** to include the main action points from NMEG-12 meeting in the draft minutes.