Draft minutes of the open session of the 10th meeting of ECHA–NanoMaterials Expert Group (ECHA-NMEG-10)

Time: 7-8 November 2017

Place: ECHA, Margot Wallström conference room

Participants: Representatives from the Member States Competent Authorities (MSCA), European Commission (DG Growth (DG Grow), DG 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: Presentations from the meeting are available on the dedicated S-CIRCABC site (https://webgate.ec.europa.eu/echa-scircabc)

I. Summary record of the proceedings

1. Introduction

The 10th meeting of the ECHA NanoMaterial Expert Group (NMEG) was held on 7-8th Nov 2017. The previous meeting was held on 16-17 May 2017. This one and a half day event was mostly an open-session, except for a 1-hour closed-session on the first day.
The purpose of the NMEG meeting is to discuss scientific and technical issues relating to the implementation of REACH, CLP and BPR for nanomaterials. This meeting was specifically focused on updates on the EU Observatory for Nanomaterials (EUON), on GHS and CLP work related to nanomaterials, on the development of OECD test guidelines (TGs) and guidance documents (GDs) for nanomaterials, as well as on results from European projects on nanomaterials such as NanoFASE (ongoing) and NanoDefine (completed). The meeting included half-day breakout group discussions focusing on possibilities for exposure asessment of nanomaterials, on the need to adapt the TGs currently used under REACH for to test NMs for human health hazard, and on nanomaterial´s physico-chemical characterization. A closed session (restricted to MSCAs, COM DGs, EFSA and ECHA) was held to discuss the implications of the Board of Appeal decisions and evaluation of nanomaterials under REACH.

A short overview of the presentations and discussion points in the group per agenda item are given below.

2. The 10th ECHA Nanomaterials Expert Group meeting

AP1. Welcome by ECHA executive director

ECHA executive director (ED) Geert Dancet welcomed the participants to the 10th Nanomaterials Expert Group meeting. In a brief speech to the audience, he first highlighted the reasons why nanomaterials remain a strategically important issue for the successful implementation of the REACH Regulation. Nanomaterials shall not be seen solely as a topic isolated from other substances, as, in many cases, the decisions taken on nanomaterials have an impact on decision taken on other substances such as UVCBs.

He gave the background on nanomaterials in the context of the REACH, CLP and Biocides regulations. Nanotechnology has been identified as a Key Emerging Technology (so called KET) in the EU as part of the Horizon 2020 Framework program[1] and can improve quality of life and contribute to industrial competitiveness in Europe. However, Mr Dancet outlined that uncertainties about potential hazard of nanomaterials, as well as lack of information about the current uses of nanomaterials and exposures through lifecycle may hamper the realization of the great opportunities that nanotechnology may offer.

The ED pointed out how ECHA has always been of the view that REACH and CLP regulations, even if not specifically addressing nanomaterials, deal with substances in whatever size, shape or physical state. The absence of specific provisions in the REACH regulation has however given room to legal uncertainties that led to numerous Appeals of both compliance check and substance evaluation decisions. The amendment of the REACH Annexes to ensure appropriate implementation for nanomaterials as well as the review of the EU recommendation for a definition of nanomaterials would clarify the perceived legal uncertainty relating to the registration obligations for nanomaterials under REACH. In the meantime, ECHA has drafted guidance updates and new guidance, available for 2018 registration, addressing specifically nanoforms.

Geert Dancet then referred to the Malta Project, an initiative from Germany to speed up the revision of the OECD test guidelines and guidance documents for nanomaterials by actively engaging EU-MSs and ensuring financial support from the Commission. He outlined that the NMEG has played an important role to pave the way for the Malta Project and shared his hope that the 10th NMEG can result in an agreement on this future essential work and on the steps to ensure smooth implementation. He noted that the work of OECD has already improved our understanding of NM and the adaptations to address the specifities of NMs form a crucial building block to make EU legislation fit for NMs.

He outlined that the EU observatory on nanomaterials (EUON) was launched in June 2017 and ECHA will ensure, in close collaboration with stakeholders, further improvements in each of the years to come. A next update of the content of the EUON is scheduled for June 2018.

His final point was on the importance of the NMEG and of the 5 years of discussions held on nanomaterials at ECHA. He noted that the NMEG, created in October 2012, is acting independently and, by hosting the NMEG, ECHA relies on experts and their efforts. As a final note, Geert Dancet highlighted that REACH can only stimulate innovation if REACH processes can address all forms of substances. He shared his view that this will determine the overall success of the REACH regulation.

AP 2. Welcome and introduction

The chair of the meeting, Frank Le Curieux (ECHA), welcomed the participants to the 10th Nanomaterials Expert Group meeting. New participants were introduced to the group. The draft agenda shared with the group in advance of the meeting was agreed. The provisional dates for the next meetings were announced: the next meetings will be held on **3-4 May 2018** (NMEG-11, the original dates of 15-16 May had to be modified because of conflict with SETAC conference) and **6-7 Nov 2018** (NMEG-12).

AP 3. Adoption of minutes of NMEG-9

The chair outlined that the revision 2 version of the draft minutes from the last meeting were shared on the dedicated S-CIRCABC site. Some additional comments were received from the Netherlands. The chair went through those comments and, in absence of further remarks, it

[1] https://ec.europa.eu/programmes/horizon2020/en/area/key-enabling-technologies

was stated that the minutes will be considered as final and they will be published on the NMEG page of the ECHA website.[2]

AP 4. Tour de table:

The aim of the tour de table document is to share information on nanomaterials and to agree on topics for future discussion within the NMEG. Some colleagues made oral statements:

1. The representative from Spain reported on the work ongoing at OECD level on the applicability for nanomaterials of OECD Test Guideline 305 (Bioaccumulation in Fish: Aqueous and Dietary Exposure). Some experiments were performed and the general thinking at the moment is that the OECD TG 305 is applicable to nanomaterials, although an additional Guidance Document is needed. Some papers are published on this topic and the work on the nanospecific guidance document will continue next year

2. COM gave a brief overview on the roadmaps for review of the nanomaterial definition and the revision of the REACH Annexes.

3. Germany gave an overview of a stakeholder meeting held at UBA on 10-11 October 2017[3]. A report will be prepared and can be shared with the NMEG.

4. ECHA advertised that at the SETAC Europe 28th Annual Meeting in Rome[4] a session will be held on recent developments in risk assessment of NMs and that anyone who would like to discuss on the topic would be welcome. ECHA also highlighted that a webinar on the nano-specific guidance updates will be held at ECHA on 30th November 2017.[5]

AP 5. Update on EUON

ECHA gave an update on the **EU Observatory for Nanomaterials** (EUON)[6]. A background for the EUON was first provided, together with an explanation of 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 in a friendly way.

It was outlined that the ECHA plan was to build up the observatory in three different phases. For the first phase, the use of already available information on nanomaterials was foreseen. Currently ECHA is at phase 1 of implementation: a microsite is available as of June 2017 with general information on nanomaterials. The content differs depending on the different audience and ECHA is working on further developing it. Following the launch, a stakeholder dialogue was held on 30 June 2017: the aim was to receive feedbacks from 1st launch as well as discuss the content for 2nd and 3rd phases of the EUON, the connection to other platforms and the identification of success factors in three years of EUON development. All invitees for the stakeholder dialogues were asked to answer a survey and generally positive feedbacks were provided with useful suggestions for improvement and ideas for future developments. The

[2] https://echa.europa.eu/regulations/nanomaterials/nanomaterials-expert-group
[3] https://www.umweltbundesamt.de/en/scientific-stakeholder-meeting-on-nanomaterials-in
[4] https://rome.setac.org/
[5] https://echa.europa.eu/-/updated-reach-guidance-for-nanomaterials-what-you-need-to-know
[6] https://euon.echa.europa.eu/

workshop outcome was summarised and used for planning of next phases.[7] ECHA outlined how the input from stakeholders is extremely important: the ideas provided by stakeholders will shape the future content development and everyone's active contribution (e.g. making information on nanomaterials available to EUON) will make a difference for the development of the observatory.

It was outlined that the work for the launch of the 2nd phase has already started internally at ECHA. The current plan is to expand the observatory content, to have a stakeholder discussion in Q1 2018 in preparation for the 2nd phase and by June 2018, a new launch is foreseen with additional information on substances/products containing nanomaterials, regulation of NMs, research output and positive aspects of nanomaterials. New data sources such as NanoData[8], information from EU funded research projects (eNanoMapper[9]) and national registries will also be included. ECHA is also harvesting new information on nanomaterials from other EU sources (EFSA, EMA, EU-OSHA, EEA), Commission services, and other legislations. The EUON will also conduct two external studies on NM: one literature study on the risks of the use of well-known pigments in consumer products and for workers; and a second study on parameters and data sources used to produce market studies on nanomaterials and their relevance and reliability.

In the concluding remarks, ECHA outlined how the three ongoing policy discussions on REACH Annexes, the review of the definition and the EUON are linked, and pointed out that ECHA's aspiration is that the EUON will be a trustworthy source of information which will contribute to the public debate by raising awareness on these materials. The audience was invited to provide, when available, additional suggestions for improvement, e.g. on possible new content and features, on any new data sources and planned activities on NM.

In the discussion, the following points were raised:

- the big challenge of communicating to consumers (e.g. contentwise how consumers will be addressed, e.g. use of social media)
- how/if standardization activities (CEN[10], ISO[11] websites) will be included
- timeframe for the two external studies
- eventual inclusion of Woodrow Wilson[12], Danish databases on consumer products[13] and possible criteriafor inclusion/exclusion of such databases
- if market vigilance activities for adverse reaction of e.g. nanomedicine is among activities of the EUON
- advice was given to contact national agencies and institutions that have consumer safety on their focus to learn/share with them.

ECHA replied with the following:

- ECHA's communication team is taking into account various different possible strategies to communicate with consumers (including use of social media)
- Concerning CEN/ISO activities, all work that aims at standardization is important for the observatory and content is already included under international activities

[7] The report and presentations from the EUON Stakeholder dialogue Meeting held on June 30th 2017 are available on the EUON webpage https://euon.echa.europa.eu/
[8] http://www.jiip.eu/dweb/projects/nanodata-providing-services-support-research-and-policy-field-nanosciences-and-nanotechnologies
[9] https://enanomapper.net/
[10] https://www.cen.eu/work/areas/nanotech/Pages/default.aspx
[11] https://www.iso.org/committee/381983.html
[12] Consumer Products Inventory; An inventory of nanotechnology-based consumer products introduced on the market at http://www.nanotechproject.org/cpi/
[13] https://www.nanopartikel.info/en/denmark/1026-nano-database-en

- Time frame for external studies: the procurements were already launched internally. The work will start this year and continues until early next year. The time frame for the two studies will be different as the content will be different.
- All possible sources are considered, the aim is however to maximise what can be provided with the resources available. At the moment, the website contains links to some sources but not integrated websites. For now, ECHA focused on NanoData and eNanoMapper, and other sources of information will be included in the future.
- Post market vigilance of nanomedicines is an activity under the responsibility of EMA and it would be out of the scope of the EUON.
- ECHA appreciated the suggestions to contact other institutions and made a request to the NMEG to communicate about any activity on nanomaterials.

AP 6. GHS & CLP work related to nanomaterial

The presentation gave an overview of the scope and purpose of the work of the informal correspondence group (ICG) on nanomaterials of the UN SubCommittee of Experts on the GHS (UNSCEGHS) and suggested the involvement of the NMEG in this work. The ICG on nanomaterials of the UNSCEGHS was set up in 2013 and its mandate is to review the applicability of the GHS to manufactured nanomaterials taking into account the progress in international scientific work. The UNSCEGHS ICG on nanomaterials decided in 2014 to perform a classification exercise on selected NMs: carbon nanotubes (CNTs) and titanium dioxide (TiO_2). Finland volunteered for the ENV hazard part (TiO_2, CNTs) while France volunteered for HH hazards (TiO_2, carcinogenicity). A presentation on this topic was given at NMEG-9. The progress on these activities have so far been slow.

The GHS work programme on nanomaterials for the biennium 2017-2018[14] foresees the following activities:

(a) monitoring of the work concerning classification-related issues of nanoforms made by other bodies, including the OECD Working party on Manufactured Nanomaterials and other relevant research projects on nanomaterials (worldwide);
(b) discuss which findings are relevant from the viewpoint of classification;
(c) develop a plan on how to continue this work after the coming biennium.

Two topics for work were proposed to the NMEG:

1. The creation of case studies on classification of NMs. The work would include selection of appropriate data, assessment of data and evaluating whether the current classification criteria are applicable. The results and conclusions would be reported in a discussion paper.
2. A literature review on the applicability of GHS criteria to NMs. Issues to be considered could include if the classification criteria can be used for NMs and to which extent, if the current toxicity ranges defined for each hazard class and category (and the metrics used) are relevant and if NMs have hazardous properties that are not covered by the current classification system.

A series of 8 questions were administered to the NMEG members before the 10th NMEG meeting and very useful comments were received from six members during the commenting period 12-20 October 2017. A summary of the responses to each question was given during the presentation at NMEG-10 as well as some final conclusions on the comments received. The work related to NM classification was considered important and some support was received on the possible contribution of the NMEG to such activities. However, some doubts have also been raised. Topic 1 (the case studies on classification NMs) was considered as a good starting point while regarding topic 2, an approach was suggested by one expert. It was highlighted that some questions were not answered by most experts, in particular those

[14] https://www.unece.org/fileadmin/DAM/trans/doc/2016/dgac10c4/UN-SCEGHS-32-INF27.pdf

relating to responsibilities, participating volunteers, interest in providing comments, and that generally the number of participants who provided comments was low. The commenting period will therefore be extended until the end of January 2018.

Finally, it was highlighted that it is important that the CLP regulation is up to date for NMs, as it is not possible to carry out REACH tasks without CLP, therefore REACH and CLP regulations should be updated together.

In the discussion the following was noted:

- The Commission follows this work and, in relation to REACH/CLP, has assumed that this GHS project would provide input and thefore did not want to duplicate their work.
- Applicability, for NMs, of thresholds and dose metrics used in classification shall be looked at, as well as severity of effects (relevant for classification).
- It was highlighted that the correct forum to discuss GHS would be the RAC or that an expert from RAC shall be included in this work.
- It would be useful to look at ENV endpoints, e.g. aquatic toxicity, in parallel with OECD work.
- A good connection shall be maintained between people involved in REACH, CLP and OECD work for nanomaterials.

AP 7. BoA decisions & evaluation of nanomaterials under REACH

[AP 7 was a closed session – see separate minutes]
A summary of the main discussion points was presented as AP 14.

AP 8. EU priorities on OECD TGs/GDs: comments received (follow up of NMEG-9)

ECHA gave an overview of the past discussion at NMEG on the OECD work on test guidelines (TGs) and guidance documents (GDs). The importance of test methods/standards for the successful implementation of legal frameworks, as well as the timelines for the development of an OECD TG were highlighted. An overview of the OECD Working Party on Manufactured Nanomaterials (WPMN) priorities presented at NMEG-8 meeting was given. The follow up was outlined and the NMEG-9 addressed ENV related TGs (bioaccumulation potential GD, transformation TGs, Adsorption/desorption TGs) and HH related TGs/GDs (toxicokinetic TG 417, Genotoxicity). The relevance of physicochemical properties was also highlighted, in particular with respect to the EU definition of nanomaterial and the decision tree for physicochemical parameters developed by the WPMN. The need for TGs for particle size distribution, water solubility, volume-specific surface area, surface chemistry was also described.

The follow-up from the 9th NMEG was outlined together with the questions posed at that time to the group: i.e. whether the NMEG agrees with the formulated priorities and if the problem description for environment is in line with NMEG's views.

An overview of the current state of play was finally given. What now needs to be achieved is the agreement on problem descriptions for HH and ENV and to see what is needed, with concrete proposals, to ensure the applicability of existing TGs/GDs. As no comments were received on the already set priorities, there seems to be already a consensus on this point.

It was reminded that the discussion on the technical content of the TGs would continue on the second day of the NMEG-10.

General comments and summary of following discussions:

- It was noted that the new acute inhalation test guideline (TG 433: Acute Inhalation Toxicity: Fixed Concentration Procedure) has just been adopted but does not have specific provisions for NMs. However, as the commission proposals for amending the REACH Annexes has not yet been finalised, it remains uncertain what will be required in the end. Therefore, the excel sheet distributed to the NMEG in advance of the meeting, and which is also used for the Malta project, will remain a living document.
- It appears that some of the concerns are relating to the choice of the most appropriate route of exposure. If this is the case, such aspects are better addressed in the legal text rather than through the amendments of the OECD test guidelines.
- The current Commission proposal is indicating that the inhalation route may be more appropriate for nanomaterials.
- One stakeholder also highlighted that in their view, it would be better to perform short inhalation studies (5 days) rather than acute studies for nanomaterials. It was mentioned that there is no OECD test guideline for the 5-day study.
- The importance of toxicokinetic studies for NMs was highlighted, as well as the need to better define the difference in terminology between kinetics and toxicokinetics.

AP 9. Considerations on nanomaterials toxicokinetics

In this presentation RIVM gave an overview on nanomaterials toxicokinetics. The kinetic behaviour of nanomaterials and the differences with non-particulate chemical substances were highlighted, as well as the need for toxicokinetic studies for nanomaterials. Practical examples were given on kinetics of Ag and TiO_2 nanoparticles and CNTs. The prolonged blood circulation after polyethylene glycol (PEG) coating of gold nanorods was shown as an example of the effect of surface coating on toxicokinetics. Considerations for risk assessment approaches were outlined with specific considerations for nanomaterials (dissolution, timing, measurement in tissues, route of administration, dose dependency, tissue distribution). The considerations for discussion were that the kinetics of particles differs from comparable dissolved compound kinetics and that kinetic studies are essential in identifying target organs and hazard of nanoparticles. It was finally pointed out that the revision of the REACH annexes may imply that toxicokinetic studies may be needed after 2020. The activities related to toxicokinetics in the context of OECD WPMN and of ISO TC 229 were also presented to the audience.

The following discussion points were noted:

- Toxicokinetics studies are considered fundamental for NMs. These and other important parameters can be addressed in additional satellite groups which may be added to a 28-day or 90-day study.
- After inhalation, there is a low translocation of NPs mainly to spleen and liver, but accumulation and persistence in lung, reproductive system and brain also need to be taken into consideration for nanoparticles.
- The toxicity of metal particles may be different from the toxicity of metal salts up to the point that the particle dissolves/degrades to ions/molecules. Undissolved particles may end up in phagocytic system and therefore influence the immune system. This is one of the reasons why toxicokinetic studies are extremely useful for NMs.
- The toxicokinetics of NMs is not driven by concentration gradients as particles are actively removed from the blood circulation.

AP 10. NanoFASE project and preliminary learnings

A partner from the EU funded NANOFASE project[15] gave an overview on the project and on the key results to date. He outlined that different models are available as output of the project

[15] http://nanofase.eu/

and they will hopefully be standardized in the near future.

AP 11. The NanoFASE model

The NanoFASE model framework was presented: this is a complex research model that will have a number of features allowing for flexibility. The potentially infinite physicochemical variety of nanomaterials and their transformation products can be incorporated into the modelling framework. The model will predict environmental concentrations of NMs as mass and number of particles. A number of modules representing environmental compartments will be linked by a submodel for transport between compartments and grid cells. This submodel will simulate processes such as water flow and sediment deposition in rivers, and soil erosion and runoff. A key emphasis of the NanoFASE experimental work is on deriving parameters as functions of the environmental compartment chemistry (e.g. pH) rather than as single values. In a risk assessment context, the model framework is most likely to be suitable for higher tier investigations. There are a number of more advanced possibilities; for example predicting how variations in the design of manufactured products may influence environmental exposure; for example changes in the degradability rate of a manufactured particle coating. Finally, the model could be used to predict the consequences of accidents; a single, high concentration input of 'as manufactured' particles into the environment at a single location.

AP 12. SimpleBox4nano (part of NANOFASE)

The tool meant for environmental exposure modelling of nanomaterials was presented to the audience. SimpleBox4nano is a variant of the SimpleBox model[16]. SimpleBox has served as 'regional distribution module'' in the European Union System for the Evaluation of Substances (EUSES). SimpleBox4nano is designed to simulate the specific environmental behaviour of nanomaterials. The main adaptation consists of adding three particulate chemical species to the dissolved species already included in SimpleBox. SimpleBox4.0-nano calculates mass flows of nanomaterials by simultaneously solving mass balance equations for 4 different chemical species for each environmental compartment in the model. A beta version is available for download from http://www.rivm.nl/en/Topics/S/Soil_and_water/SimpleBox4nano.

After the two presentations on the NanoFASE models the following was noted:

- The attachment efficiency and hetero-aggregation rate constant can both be used for describing a binary particle system. But the hetero-aggregation rate constant is more system specific, e.g. for a specific particle size and shear rate.
- The mobility of particulate and the effect of coating's stability are considered in the model.
- There may be no need to calculate PNEC for each form – tiered approach to be used and case by case evaluation (e.g. if mass of silver ions is considered and there is a large margin of exposure there is no need to calculate PNEC of other forms).
- Protocols are available for the attachment efficiency parameter: environmental compartments considered are soil and water. Protocols used for the two compartments have a different level of complexity, however the aim is to converge them to one protocol.
- Dissolution and degradation due to the presence of aquatic organisms are not considered yet. If found to be relevant in experimental studies they will be included.
- Models have been developed by using metal/metal oxides examples. Chemical diversity of NMs will have to be considered next.
- Update of ECHA guidance for what concerns environmental exposure assessment can only be considered after a stable revised text of the REACH Annexes will be available

from the Commission. More confidence on the software is also needed before drafting guidance.

AP 13. Nanodefine tools to support implementation of EC definition

In this presentation by JRC, an overview of the outcomes of the EU funded NanoDefine project[17] was provided to the audience. NanoDefine has been a four years FP7 project aimed at the development of an integrated approach to support the implementation of the EC recommendation for a definition of nanomaterial. The mission of the project was to provide enterprises and regulators with the tools to implement the EC definition of nanomaterial. The different pillars of the decision process were presented:

- Knowledge Base (evaluated sizing techniques, techniques performance database, material characteristics and templates),
- Material classification system (a method-driven system that uses properties which determine the suitability of a sizing technique, to match materials with appropriate size measurement techniques)
- Data input (measurements, nanosizer, sp ICP-MS)
- Decision flow scheme (logical flow scheme that leads to 'nano' or 'non-nano' classification)

The decision flow scheme developed within the project first considers screening methods to decide if a material is a nanomaterial or not, while, in borderline situations, more demanding and expensive tier 2 confirmatory methods need to be considered to make the final decision on nanomaterial/not nanomaterial. Examples of application of the tool with two real cases were provided: the material used were $CaCO_3$ IRMM-384 (fine grade) and kaolin IRMM-385.

A summary on how the e-tool can help to determine the nanomaterial status was provided: the Decision Flow Scheme, NanoDefiner e-tool and Manual are comprehensive tools to facilitate the regulatory confirmation of nanomaterial status (e.g. for registration purposes) and the tools can be adapted to changes in the regulatory requirements. It is however outside of the scope of the e-tool to provide details on preparation, give detailed instructions on methods, consider methods in development, give legally valid advice and substitute expert assessment.

It was finally outlined that the NanoDefine methods manual will become publicly available as JRC Technical Report. The NanoDefiner e-tool is already available now and can be tested (via website and as a standalone version, https://labs.inf.fh-dortmund.de/NanoDefiner). The NanoDefiner methods manual will be made available in Q1/2018. It is a task of JRC to provide training on the tool: a school for interested people who need to classify NM is planned. JRC is also preparing guidance on the implementation of the EC definition of nanomaterials which will benefit from NanoDefine results. The work at OECD level on TGs for size measurement of nanomaterials lead by Germany shall also benefit from the Nanodefine project outcomes.

In the discussion the following was addressed:

- Time and effort needed to get to the decision "nanomaterial/ non-nanomaterial": when size measurements are already available, it takes around 30 minutes to reach a decision, while in other situations the time needed depends on the size measurements to be performed. It was noted that extraction of nanomaterials from matrices can be a difficult and time expensive step to be performed before measurements.
- Industry opinions (either taking part or not to the project) on the tool were quite positive, as well as opinions of regulators
- Use of dispersion route to measure particle size distribution : if a material is in powder form, the user can decide whether to bring it to dispersion. If the material is supplied

[17] http://www.nanodefine.eu/

in dispersion, there is of course no other method that can be used. JRC indicated that using the dispersion route or not will not lead to different conclusions on the material being a nanomaterial or not: the user would eventually fall in the borderline region and would need to go to tier 2 measurements (e.g. electronic microscopy), but the final conclusion reached will be the same.

- Results of the analysis are influenced by persons that perform the measurement; some methods give more reliable results, while others are more sensitive; the latter, even if included in the project, are not recommended by the project.

AP 14. Brief report for ASOs on 'BoA decisions & evaluation of nanomaterials under REACH'

A brief report on the closed session for the Board of Appeal (BoA) decisions for nanomaterials was provided by the Chair of the meeting. ECHA's view on REACH implementation for nanomaterials was first provided. Scientific and legal challenges faced in the evaluation of NMs were also pointed out. A summary of the BoA decisions on the evaluation cases relating to nanomaterials was then given: substances involved are silicic acid aluminium sodium salt (NAS), titanium dioxide (TiO_2) and synthetic amorphous silica (SAS). ECHA concluded that, although the BoA decisions do not directly challenge the fundamental assumption that 'REACH implicitly covers nanomaterials', these decisions make it more challenging to verify the safe use of nanomaterials on the EU market. ECHA nanomaterials activities will be discussed during an open session with institutional partners at ECHA 48th meeting of the Management Board in December 2017 in Brussels[18].

During the discussion that followed the presentation, it was mentioned that ECHA will work on updating guidance documents only after stable updated REACH Annexes are available.

AP 15. Wrap up of 1st day plenary session and introduction to the breakout groups

A wrap up of the 1st day plenary session was provided by the chair of the meeting:

- It was reminded, as a practical outcome of the meeting, that colleagues involved on CLP and GHS work shall also be involved in the development of OECD guidelines for nanomaterials.
- The NMEG will focus on discussing the technicalities for the development of OECD guidance for nanomaterials.
- There were interesting discussions on toxicokinetics, and on the 3 presentations on the NanoFASE models. JRC provided very useful and practical advices on the NanoDefine project.
- A short introduction of the break out groups of Day 2 (on PC, HH, ENV) was given.

Day 2

AP 17a. Feedback from breakout group ENV and discussion

At the breakout group on ENV, the discussion was built around four questions:

Q1: What aspects need to be covered with the modelling tools in exposure assessment of NMs?

18 https://echa.europa.eu/documents/10162/23601668/mb_04_2017_agenda_mb48_en.pdf/fa4b22cb-2a41-cb2b-5d48-0cea4bc9f605

- It was seen beneficial to have flexibility in selecting different "processes" within the model as that would allow tiered environmental exposure modelling approach;
- How much refined algorithms or parameters would help to increase the reliability of the model and decrease uncertainty? The level of uncertainty depends on the parameters used and/or how detailed is the model used.

Q2: What are the model input parameters?

- The main input parameters were considered to be dissolution rate, attachment efficiency, transformation and characterisation of the nanoform and related coating;
- Information on how and how well those parameters can be measured is important; the need for standard methods and/or protocols was considered crucial to derive the input parameters;
- Attachment efficiency: is a TG needed? Would it be possible to derive attachment efficiency based on measurement of dispersion stability under TG 318?
- What is the worst case for exposure e.g. free particles, attached?
- Many environmental and nanomaterial conditions may influence parameter values (e.g. pH, organic matter) – how representative are measured parameter values? And how can relevant ranges of environmental variables be defined?
- What chemical transformations should be considered for Tier I modelling and read-across?
- Sulphidation was seen as a leading example of an important transformation;
- Degradation (chemical/biological) likely to be important for some nanomaterials and their coatings;
- Could overarching Guidance on transformation be developed e.g. in context of OECD TG 303 for transformations in waste water treatment plants?
- Simple testing could be employed to establish whether processes such as coating degradation need to be considered in the model in the context of modelling the behaviour in the environment, or whether such processes might generally be complete before entry to the environment, e.g. during sewage treatment;
- Degradation of the coating and acquisition of natural corona is missing from SimpleBox 4nano;
- Should NM shape be explicitly accounted for in exposure modelling? Neither of the models discussed explicitly account for the shape of the particle. Currently models assume that the particle is spherical. It may be possible to represent "unusual" shapes e.g. rods, fibres, using current model algorithms;
- Possible to use WoE approach based on scientific data other than GD/TG;
- All the above discussion on the parameters needed for the modelling may be considered in discussing the priorities for OECD TG and GD development.

Q3: Output of the models

- Applicability domain of the model should be clearly defined;
- What level of detail is needed for the regulatory decision making depends on the use of the information and the legislative framework;
- NanoFASE model: the 5 x 5 km scale and vertical distributions is adequate for local scale considerations. EUSES uses 200 x 200 km scale in regional exposure assessment predictions and for local scale a standard town of 10,000 inhabitants.
- For substances which dissolve to non-nanoforms, combining nano-specific and conventional modelling approaches may be needed (analogy to parent compound/metabolites relationship);
- There is a need for the ability to model transformations and coating effects;
- Having Tier 1 predictions of exposure and the behaviour of the different nanoforms in the environment was seen as a potential way of refining the grouping of nanoforms and developing a defined testing strategy and related exposure and risk assessments;
- Priorities for NanoFASE delivery: dissolution, transformation and coatings for particles

(stability, how much goes in environment), behaviour during the whole lifecycle.

Q4: Selection criteria for NanoFASE (and other) models for transfer into SimpleBox4Nano to best serve a regulatory context

How can the NMEG support the implementation of the outcome?

(a) How such a relatively complex expert tool could be of use for risk assessment?;
(b) If there are any features that could potentially be included that would increase the usefulness of the model for such a purpose?;
(c) Are the models presented useful for a screening level exposure modelling (simplebox4nano)?
(d) Would you prefer conservative approach or defined assessment with exclusion of the influence of bigger particles?

Q5. Discussion

- NMEG may offer support by providing opinion and guidance on the applicability of the developed model(s) for the regulatory use. NMEG was encouraging the NanoFASE colleagues to shape the models/approaches to eventually be included in the ECHA Guidance as potential or recommended tools to be used in regulatory exposure assessment;
- For instance, registrants/users could continue using EUSES if a few parameters are changed to reflect the nanospecific input;
- If product/NM can be proven not to be released at specific points in its lifecycle, this is useful information for regulators and industry;
- For a screening level model, it is preferred to take a conservative approach (not exclude a fraction based on bioavailability) and refine prediction/modelling approaches if required (take into account the bioavailability);
- Take home messages: a GD on how to use the model in the next 2 years including regulators to look at this and potential applicability would be useful;
- Need for a OECD GD or TG on attachment efficiency. For this activity support from NanoFASE colleagues was seen very beneficial.

After the presentation the following issues were introduced:

- Distinction between dissolution and degradation was discussed;
- For coatings, there is a need to look for rate of degradation.
- For metals, you may consider oxidation or dissolution as transformation, or abiotic degradation parameters.
- Would it be possible to extend better the models to air compartment?
  - ✓ Both models have capacity to model atmospheric concentration of NPs as well as deposition in land. Atmosphere is included and it is possible to simulate emission in atmosphere.
  - ✓ Looking at ENV risk assessment the atmosphere is a route of exposure to water and soil. It is a useful compartment but is less important for direct environmental risk assessment.

AP 17b. Feedback from breakout group HH and discussion

The breakout group on HH discussed which of the current TGs used under REACH need to be adapted for NM testing, what are the priorities and what is the current understanding on what may be needed to be done for this adaptation. The conclusions reached per toxicological endpoint are summarized below:

GENOTOXICITY:

- Ames test (OECD TG 471): the test is informative if results are positive; if negative gene mutation in mammalian cells should be considered. There is a general view that a test on mammalian cells should always be used instead of the bacterial Ames test.
- Proof of uptake is not sufficient, adsorption may be also an issue.
- A battery of tests should be considered for genotoxicity testing.
- There is already a project at OECD level to develop guidance regarding genotoxicity testing of nanomaterials (Project 4.95: Guidance Document on the Adaptation of In Vitro Mammalian Cell Based Genotoxicity TGs for Testing of Manufactured Nanomaterials). This project has been initiated with experimental work to see characterization of material, uptake, and other aspect (lead by JRC). JRC will not have capacity to continue leading this OECD project. BIAC volunteered to take lead for in vitro mammalian genotoxicity tests. (OECD 476/490 and OECD 487)
- An important issue for in vivo genotoxicity testing is the exposure of the target organs. Whenever the bioavailability of the substance/nanomaterial is questioned, site of contact genotoxicity should be considered.

TOXICOKINETICS:

A new document (TG/GD) on toxicokinetics for NM or revision of existing TG 417?

- Route to route extrapolation is difficult for NMs because different distribution may occur in the body via different routes (the existing TG uses oral).
- Extension of the 14-d exposure period should be considered for NM to detect accumulation and persistence in distant tissues especially for the non degrading/dissolving solid NM (e.g nanoTiO_2).
- Toxicokinetics informs on internal dose, important for extrapolation to human equivalent concentrations.
- Review of the available information (toxicity as well as human exposure data) to draw some preliminary conclusion on the target organs.
- Take into account the possible different behaviour of new materials.
- There are analytical challenges but they should not hamper the development of a new TG (e.g. the recent spICP-MS).
- At OECD, a new SPSF for Toxicokinetics is lead by NL.
- ISO plans to release by the end of 2018 a technical report on the current knowledge of NM toxicokinetics.
- What toxicokinetic information may be currently derived from the OECD TG 412/413 studies and how could it be used in regulatory context?
  - ✓ Organ burden measurements should be possible.
  - ✓ Particles may be seen in histopathology investigations.

SENSITIZATION:

Applicability of current TGs for nanomaterials was discussed.

In vitro:

- Stability of the dispersion is a critical factor.
- Direct Peptide Reactivity Assay is not suitable for metals.
- Not validated for NMs.

In vivo:

- Useful to perform guinea pig maximisation test first? This test is very sensitive and covers the whole range of sensitization key events.
- Need for reference materials (positive control).
- Applicability of LLNA is not an issue specific to nanomaterials, but for insoluble substances (related to dissolution rate).

ACUTE TOXICITY:

- Oral route can be relevant for some applications of NM.
- Inhalation route relevance was debated with regard to overload.
- A case-by–case approach should be considered.
- An extended exposure time may compensate perhaps for using a lower dose to avoid mechanical effects.

REPRODUCTIVE TOXICITY:

- Placental barrier penetration: some studies showed placental transfer
- Preferred exposure route (oral vs. inhalation).
- Toxicokinetic information is important in deciding the exposure route

AP 17c. Feedback from breakout group PC and discussion

The main points discussed during the breakout group on PC were presented in plenary. A short explanation of the different stages that brings to registration[19] (using the simplified 7 stages developed to help potential registrants prepare for the 2018 registration deadline) was first provided. It was reminded where and by whom the determination of nanomaterial status is needed:

- Potential registrants: nanomaterial status to be considered in stages 1-4 for preparing Annex VII-XI information.
- Reporting in IUCLID: ECHA how to guide.
- Existing registrants (stage 7): update of dossier including nanoform information.
- ECHA, MSCA (after stage7): assessment of reported information in registration dossiers.

The discussion was then based on a series of questions for both industries and regulators:

1. Is there a need to facilitate the identification of nanomaterials for regulatory purposes (REACH)?

   Consensus was reached that:

- Guidelines, decision tree etc. enable comparison of data generated.
- Being able demonstrate non-nanoform status is important.
- Knowing the nanoform status already at stage 1 in the registration process is crucial.
- It is also needed for stages 2 and 3.

Pros/cons of having defined tools such as the decision flow scheme and the e-tool from NanoDefine for identification were discussed:

- For registrants:

  ✓ Useful for SMEs to check nanoform status of their powders.
  ✓ Facilitate SIEF discussions and joint submission.
  ✓ All SIEF members use the same decision tree.
  ✓ Decision trees always desirable.
  ✓ Can take confidential business information into account (standalone installation).
  ✓ Harmonise nanoform-status across a joint submission.

[19] https://echa.europa.eu/reach-2018/know-your-portfolio

However,

- ✓ May not yet cover all possible nanomaterials.
- ✓ Validity of tool not yet fully understood (would be useful to test the methodology on more materials).
- ✓ If a party uses/develops its own methodology, this tool would put them at a disadvantage if they need to use this one.
- ✓ Co-registrants may already have agreed on a tool.

- For ECHA/MSCA:

  - ✓ Evaluation: who are the nanomaterial registrants in a joint submission if e.g. requests are made under substance evaluation.
  - ✓ Registrants can demonstrate non-nanoform status using an accepted methodology (brings certainty).
  - ✓ Can facilitate cost-sharing disputes on relevance of test data / who needs to contribute to costs for generating data on nanomaterials (or non-nanomaterials).
  - ✓ Arbitration possible if the same methodology (and protocol) used.

  As only drawback, system maintenance needs to be ensured.

2. How to integrate NanoDefine tools in REACH regulatory framework?

- Do not wait for test guideline development and rather work with what we have (consider protocols used).

- Integrate tool into Guidance - easier and more flexible/adaptable than including in legal text.

The final part considered the need for a guidance document on how to use the flow scheme and the e-tool from NanoDefine. The following was concluded:

- Reference to flow scheme could be included in the horizontal Guidance
- REACH Guidance can refer to horizontal guidance.

The guidance needs for industry preparing registration files are as described below:

- Documentation that outlines range of methods and field of applicability.
- Guidance on how to assess the data that comes from using the range of methods
- Hands-on guidance.
- After determining nanoform-status, documentation that outlines the next steps.
- An outline of how to go from stages 1 to 7 in the registration process (complexity of joint submission).
- Data quality considerations (NB: Annex VI quality considerations are different from Annex VII-XI data).

ECHA/MSCA do not need specific guidance for assessment of data reported using the tools and generally rely on the same Guidance provided for industries.

Finally, use of alterative tools was discussed: transparency is key in the decision making process. It is important to have clear documentation of how a decision was reached: e.g. protocols used, sample preparation, processing of data obtained. Alternative tools should follow logical methodology and be documented (may need to be made available on request). Other tools are available: industry have decision trees that they use to determine nanomaterial/non-nanomaterial status, US EPA has guidance for the one-off nanomaterial reporting scheme (but a different nanomaterial definition is used).

The following was discussed after the presentation in plenary:

- ✓ When conflicting results are reached: conflicting approaches should be reported as transparently as possible, so an assessor can decide which approach would be preferable.
- ✓ 1-100 nm as size range to define a nanomaterial: not linked to adverse effect – most relevant parameters change at sizes below 30 nm for certain type of nanomaterials. The threshold of 50% used in the EC nanomaterial definition takes into account the fact that the material has some part that is not a nanomaterial.
- ✓ Second generation nanomaterials that are different from metal and metal oxide particles are being developed. The importance of considering particulate toxicity and not standard chemistry was discussed.

AP 18. Update on NMEG rolling plan – Wrap-up and conclusions

The chair gave an update on the rolling action plan. He outlined that the desired outcome of each NMEG is:

- Agree on a rolling agenda.
- Allocate tasks among NMEG members.
- Agree and set timelines on deliverables.

The topics in the 2018-2020 rolling plan were given:

- Guidance development (EU recommendation and revised REACH annexes)
- Revision of TGs/GDs (Malta project)
- Discussion on specific nanomaterial cases
- Read-across case study example
- SEv for the nanomaterial cases
- Upcoming CLH proposals
- Learning from research project
- Review of applicability of GHS/CLP criteria for nanomaterials
- Different activities at ISO.

ECHA will distribute a proposal for the rolling plan following the NMEG-10. The NMEG participants are invited to provide comments by the end of January 2018.
It was finally pointed out that the NanoSafety Cluster coordinates all the EU projects, therefore it could be a useful entry point to find useful information on all EU projects.

END OF ECHA-NMEG-10 MEETING

II. List of participants of open session of NMEG-10

Surname	First Name	Country / Organization
Aitasalo	Tuomas	ECHA
Alessandrelli	Maria	Italy
Amenta	Valeria	ECHA
Andersen	Sjur	Norway
Ball	Elanor	United Kingdom
Bleeker	Eric A.J.	Netherlands
Bonev	Chavdar	Bulgaria
Carlander	David	NiA
Carvalho	Félix	EUROTOX
Constantin	Camelia	ECHA
De Jong	Wilhelmus	RIVM
Deydier	Laurence	ECHA
Einola	Juha	Finland
Ekokoski	Elina	Finland
Esposito	Dania	Italy
Falck	Ghita	ECHA
Gaidukovs	Sergejs	Latvia
Groenewold	Monique	Netherlands
Gryspeirt	Celia	IMA Europe
Hansen	Steffen Foss	EEB
Helminen	Ulla	ECHA
Herzberg	Frank	Germany
Holmqvist	Jenny	ECHA
Ivask	Angela	Estonia
Jacquet	Cyril	ECHA
Jomini	Stéphane	France
Jurgelėnė	Živilė	Lithuania
Kapanen	Anu	ECHA
Karjalainen	Ari	ECHA
Kinzl	Maximilian	Austria
Kobe	Andrej	DG Environment
Kos Durjava	Mojca	Slovenia
Krop	Hildo	ETUI
Le Curieux	Frank	ECHA
Lofts	Stephen	NERC-CEH
Melbourne	Jodie	PISC

Moore	Gregory	Sweden
Nahmias	Marco	ETRMA
Navas	José M	Spain
Quik	Joris	RIVM
Quinn	Bernadette	ECHA
Rauscher	Hubert	DG Joint Research Centre
Riego Sintes	Juan	DG Joint Research Centre
Rodriguez Unamuno	Virginia	ECHA
Schoonjans	Reinhilde	EFSA
Schwirn	Kathrin	Germany
Serrano Ramon	Blanca	Cefic
Spirlet	Christine	Eurometaux
Sumrein	Abdelqader	ECHA
Svendsen	Claus	NERC-CEH
Vomastkova	Milada	Czech Republic
Walkowiak	Bogdan	Poland
Weiss	Angelina	Germany
Wiench	Karin	ECETOC

By WEBEX / phone connection:

During the Agenda points in plenary of Day 1 and 2:

Agnieszka Dobrak-Van Berlo (BE), Anne Boisen (DK).

Apologies:

Agnieszka Dobrak-Van Berlo (BE), Anne Boisen (DK).

III. Final Agenda

10th meeting of the ECHA Nanomaterials Expert Group (ECHA-NMEG-10)
7-8 November 2017, Helsinki, Finland

MARGOT WALLSTRÖM CONFERENCE ROOM

Agenda

Chair: Frank Le Curieux, Evaluation 3, ECHA

DAY 1 – Tuesday 7 November 2017		
MORNING - OPEN SESSION		
8:30	Registration (30 min)	
9:00	**1. Welcome by ECHA executive Director** (10 min)	Geert Dancet, ECHA ED
9:10	**2. Welcome and introduction** (10 min)	Chair, all
9:20	**3. Adoption of minutes of NMEG-9** (15 min)	Chair, all
9:35	**4. Tour de table** (15 min)	All
9:50	Coffee Break (30 min)	
10:20	**5. Update on EUON** (30 min)	Abdel Sumrein, ECHA E2
10:50	**6. GHS & CLP work related to nanomaterial** (30 min)	Elina Ekokoski, Tukes, FI
MORNING - CLOSED SESSION		
11:20	**7. BoA decisions & evaluation of nanomaterials under REACH**	Cyril Jacquet, ECHA B2
12:30	*Lunch*	
AFTERNOON – OPEN SESSION		
14.00	**8. EU priorities on OECD TGs/GDs: comments received (follow up of NWMG-9)** (25 min)	Jenny Holmqvist, ECHA B0
14.25	**9. Considerations on nanomaterials Toxicokinetics** (30 min)	Wim De Jong, RIVM, NL
15.00	Coffee Break (30 min)	
15.30	**10. NanoFASE project and preliminary learnings** (20 min)	Claus Svendsen, CEH, UK
15.50	**11. The NanoFASE model** (20 min)	Stephen Lofts, CEH, UK
16.10	**12. SimpleBox4nano (part of NANOFASE)** (20 min)	Joris Quik, RIVM, NL
16.30	**13. Nano or not – the NanoDefine project** (30 min)	Hubert Rauscher, JRC
17.00	**14. Brief report for ASOs on `BoA decisions & evaluation**	Chair

	of nanomaterials under REACH' (20 min)	
17.20	**15. Wrap up of 1st day plenary session and introduction to the breakout groups** (15 min)	Chair
18.00	*Reception*	
19.00	**End of day 1 of NMEG-10 meeting**	

DAY 2 – Wednesday 8 November 2017		
MORNING - OPEN SESSION		
8:45	**16a. Breakout group discussions** **- BoG ENV: Regulatory relevance of the new tools in the environmental exposure and risk assessment** **- BoG HH: OECD TGs/GDs for HH** **- BoG PC: Nano or not nano**	All All All
10:15	Coffee Break (20 min)	
10:35	**16b. Breakout groups: finalise discussions and prepare presentation for feedback to plenary**	All
11:45	Lunch	
AFTERNOON – OPEN SESSION		
12:45	**17a. Feedback from breakout group ENV and discussion**	Stephen Lofts
13:15	**17b. Feedback from breakout group HH and discussion**	Camelia Constantin
13:45	**17c. Feedback from breakout group PC and discussion**	Bernadette Quinn
14:15	*Coffee Break (20 min)*	
14:35	**18. Update on NMEG rolling plan – Wrap-up and conclusions**	Chair, All
15:00	**End of ECHA-NMEG-10 meeting**	

IV. Main Action Points from NMEG-10 (7-8 November 2017)

CONCLUSIONS / DISCUSSIONS	ACTIONS REQUESTED
AP 3 – Minutes of NMEG-9	
NMEG adopted the draft minutes as provided for the meeting.	**ECHA** to upload final version of the minutes (in pdf format) on NMEG- S-CIRCABC and on ECHA NMEG website without undue delay.
AP 5 – Update on EUON	
NMEG members agreed that it would be useful to have a specific section for feedback/ideas on EUON in the Tour de Table document.	**ECHA** to add, from now on, in the Tour de Table document a specific section for feedback/ideas on EUON.
AP 6 – GHS & CLP work related to nanomaterial	
NMEG members from Finland requested that the commenting period would be extended until the end of January 2018.	**Finland** to transmit to ECHA any additional information/document. **ECHA** to remind NMEG members of the extension of the commenting period and to upload on S-CIRCABC any additional relevant information.
AP 18 – NMEG Rolling Plan update for 2018	
NMEG members took note of the main elements of the updated NMEG Rolling Plan for 2018 presented by ECHA.	**ECHA** to upload on NMEG S-CIRCABC, for comments, the updated NMEG rolling plan following the NMEG-10 meeting.
AP 18 – Wrap-up and conclusion	
NMEG chair wrapped up the main action points of NMEG-10 at the meeting.	**ECHA** to include the main action points from NMEG-10 meeting in the draft minutes.
AOB – Presentation of ISO activities at future NMEG	
UK member suggested an item for a future meeting to enable the NMEG to hear about the work of ISO TC 229 and possibly other relevant standards setting bodies.	**ECHA** to discuss further with UK member and possible contacts at ISO.