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ENVIRONMENT DIRECTORATE
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Working Party on Manufactured Nanomaterials

GROUPING AND READ-ACROSS IN HAZARD ASSESSMENT REGARDING SPECIFIC ISSUES FOR NANOMATERIALS

REVISED DRAFT FOR THE WORKSHOP PROPOSAL

15th Meeting of the Working Party on Manufactured Nanomaterials
4-6 November 2015
OECD Conference Centre, Paris, France

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English - Or. English

At its 14th Meeting, the EU proposed to host a workshop on *grouping and read-across in hazard assessment regarding specific issues for nanomaterials*. The proposal was welcomed at WPMN14, however, it was not possible to hold the workshop in 2015.

This revised proposal will be presented at SGTA for agreement. Document will be first discussed at the meeting of SGTA that will be held on the 3rd November. Amendments to this document, if any, will be presented at WPMN15. The revised document will then be posted on the password restricted site.

SGTA will be invited to discuss this proposal and agree on the next steps.

ACTION REQUIRED: ***The Working Party is invited to take note of this document and to agree on the recommendations and next steps, as suggested by SGTA.***

CONCEPT NOTE FOR AN OECD EXPERT MEETING ON GROUPING AND READ-ACROSS IN HAZARD ASSESSMENT REGARDING SPECIFIC ISSUES FOR NANOMATERIALS

1. Draft revised following the comments received after WPMN-14.

1. BACKGROUND

2. Manufactured Nanomaterials (MN) are being developed in many different variations, including different sizes and shapes. While this is a positive driver for economic development and innovation, it does give rise to the need for both public regulatory authorities and Industry to assess the environmental, health and/or safety concerns for MNs. Some regulatory regimes require availability of specific information on the inherent properties of chemicals, including MNs (nanoforms), as the condition to access the market or to trigger/guide specific regulatory actions. The concerns associated with a MN may be different to the one(s) for a corresponding bulk material, if existing. Concerns are usually associated with uncertainty and lack of information on hazard and other properties. Conversely, for MNs, for which robust hazard data is already available and the hazard profile can be drawn, the level of concern may be less than for MNs without such a data. For those MNs there is a need to generate the missing data. Whenever possible, such information should be generated by means other than vertebrate animal testing.

3. The use of non-testing approaches for regulatory assessment of safety is not new in context of chemicals legislation. Recently the OECD updated its '*Guidance on grouping*[1] *of chemicals, second edition'*, ENV/JM/MONO(2014). For MNs, in addition to structural similarity a set of additional physicochemical properties need to be considered for grouping. That is already identified in the OECD guidance's Section 6.9 *Initial considerations applicable to manufactured nanomaterials*, of which the full text can be found in the Annex. This Section was on purpose not further developed based on the recognition that a better understanding of the relationships between NMs' physicochemical properties, their (eco)toxicological behaviour and environmental fate is necessary before establishing accepted principles for grouping of MNs and provide more explicit guidance on e.g. how to use existing data from bulk materials or other MNs (nanoforms), as far as this is possible.

4. To generate information, it is important to identify the relevant MNs (nanoforms) and understand how they evolve through the lifecycle as well as what the appropriate route(s) of

[1] The term 'grouping' or 'chemical grouping' describes the general approach for considering more than one chemical at the same time. It can include formation of a chemical category or identification of (a) chemical analogue(s) with the aim of filling data gaps as appropriate. (ENV/JM/MONO(2014)4)

exposure are. Concepts of Grouping and Read Across[2] aim to identify a specific set of properties and associated conditions (i.e. applicability domain) that enable reasonable prediction of a hazard property for a specific material without additional testing. This can be done either by concluding that the material is 'similar' to the already tested material(s) and then creating a group on the basis of the information from an analogue chemical or from the information on a set of chemicals within the applicability domain; subsequently the read across technique can be applied. Though knowledge and experience regarding the application of grouping and read across are increasing, it may still be insufficient to reach meaningful conclusions for many MNs as they are currently marketed. However, starting from a premise of different yet well characterised MNs (nanoforms), experience from different regulatory regimes together with results from the associated research activities worldwide can already inform more targeted justification criteria for grouping and read-across of MNs. This development could lead to a more effective and consistent application with comparable and robust documentation.

5. In addition, the analysis of other important contributions such as the data from the OECD WPMN Testing Programme and the outcomes from the OECD WPMN Expert meeting on Categorization should be considered. Industry has started to develop approaches for grouping and read-across (ECETOC 2015) while several research activities and projects plan deliverables related to the topic later in 2015 and 2016. EU is also progressing the discussions on read-across of MNs under REACH by the development of a stock taking paper illustrating how read across between MNs (nanoforms) could be done and properly justified, which is scheduled to be finished by end of 2015.

6. Further presentation of approaches and case-studies related to the hazard assessment of MNs by applying grouping and read across in different regulatory regimes would aid a more in-depth discussion and provide complementary information to be considered for the future possible update of the OECD Guidance Section 6.9. Parties are invited to identify such activities so they can be included in the workshop planning.

2. THE EXPERT MEETING OBJECTIVE AND TASKS

7. The Workshop will build on information from the OECD WPMN Programme on Safety Testing of Manufactured Nanomaterials, outcomes from scientific programmes and projects at Member Country level, and outcomes from OECD WPMN Expert Meetings, including the discussions and recommendations from the WPMN Expert Meeting on 'Categorization'. Practical experiences from day to day regulatory work on MN and best practices/case studies on applying grouping and read-across to MNs from OECD Member Countries' experts on physicochemical characterisation and hazard assessment (both for HH and ENV) directly involved in regulatory work will as well provide a firm basis for the discussions. Accordingly the objectives of the two-day EU sponsored OECD WPMN expert meeting are to:

1. **Identify, in a regulatory context, specific aspects to be considered when applying grouping and read-across for hazard assessment of Manufactured Nanomaterials**

[2] The principle of the read-across technique is that endpoint or test information for one chemical is used to predict the same endpoint or test for another chemical, which is considered to be similar by scientific justification. (ENV/JM/MONO(2014)4)

2. Provide initial input for the possible updating process of the OECD Guidance' Section 6.9

8. The objectives will be achieved by addressing the following tasks:

a) Critically discuss a review on a start of the art document that will be e used as a thought-starter and will be prepared prior to the expert meeting

b) Based on a top-down[3] approach identify criteria or uses where MN differ from other chemicals to an extent where the OECD '*Guidance on grouping of chemicals, second edition*' is not applicable or needs to be supplemented.

c) Share experience(s) on application of grouping/read across to MN hazard assessment from selected projects from different regulatory regimes, aiming to inform tasks below.

d) Focus explicitly on criteria for applying read-across/grouping for MN hazard assessment to generate an adequate scientific justification in a regulatory context for the applied approach. The elements would include characterisation of the MN, definition of the applicability domain, description of the hypothesis underlying the approach together with the identification of proxies and ways to generate supporting evidence.

e) In addition, it is expected that the criteria would help in the preparation of 'plausible grouping' that should, in absence of adequate information, guide a testing strategy. If test results eventually support the initial hypothesis or enable derivation of an improved one, this may lead to a recognized group.

f) Take stock of current knowledge on how certain physical chemical properties may predict certain effects *in vitro* but in particular *in vivo*, potentially pointing to differences in (eco)toxicological effects between (nano)forms of the same chemical composition, with a view to be able to predict toxic effects through read across in a hazard assessment. More concretely, this task relies on assembling scientific input from research primarily related to mechanistic studies. As far as possible, the work will help to list presently known mechanisms and their link to the measurable physico-chemical properties and the adverse effects~~,~~ feeding into the hypotheses generation and verification in Task 4.

g) Provide elements to a roadmap and a realistic timetable for SG-TA and the WPMN, to come forward with OECD guidance, as necessary, on approaches for applying read-across/grouping that can be used for hazard assessment of MN. The expert meeting will take stock of the assessment of the physical-chemical data from the testing programme from the perspective of the useful insights for read across and grouping of MNs (nanoforms), together with the related work performed by partners in the regulatory and research programmes.

[3] Top-down approach: Taking the concepts and procedures developed in the guidance document together with the general understanding on MN properties as a starting point to identify concrete passages that require adaptation. In contrast to bottom-up approach where guidance is applied 'as is' on a concrete NM and the result is analysed, resulting in presentation of cases.

3. PRACTICAL ASPECTS

9. The expert meeting is scheduled to be held over two days in **Brussels on 13-14 April 2016**.

10. The main focus of the expert meeting is on producing practical, concrete recommendations for the best uptake in a regulatory context. Therefore good use of break-out groups will be catered for based on assessment of the existing guidance with indications of matters that have been identified in advance of being particularly relevant.

11. The expert meeting is open to OECD Member Countries, Observers and emerging economies. Delegations will be invited to consider being represented with a good mix of people with expertise in regulatory hazard assessment of nanomaterials and / or read across / non-testing methods applied to 'difficult' chemicals.

12. Approx. 120 participants are expected.

ANNEX

Section 6.9 of the OECD updated its '*Guidance on grouping of chemicals, second edition*', ENV/JM/MONO(2014)4

Initial considerations applicable to manufactured nanomaterials

Nanomaterials are a subset of chemicals that are distinguished by their size (in general between 1 and-100 nm). Most materials described as nanomaterials are solids though there are also liquid nanoparticles such as in some emulsions. Principles and guidance for grouping nanomaterials for the purpose of assessing their toxicological, ecotoxicological and fate properties, are under development. Fundamental research is currently devoted to identifying and characterizing exposure paths, bioavailability and bioactivity of nanomaterial both in vitro and in vivo and the results of this research will provide information that may be useful for selection of appropriate analogues and categories.

Nanomaterials share properties associated with both solutes and separate particles phases, features that complicates the risk assessment of nanomaterials include i) their measurements and characterization in environmental and biological matrices for understanding their fate, transport, and potential impact, and ii) their preparation and testing procedures for the assessment of their bioavailability and effects on organisms (Burello and Worth, 2011; Alvarez et al., 2009; OECD 2012f and 2012g), iii) the many physical-chemical characteristics (e.g. size, coating, shape, surface characteristics, solubility) that can influence fate, behaviour, kinetics and toxicity, and iv) the potentially constantly changing physical-chemical characteristics during the life-cycle of a material. Among initial considerations for characterizing nanomaterials, properties such as structure, size, shape, surface area, surface modification, surface reactivity and electronic properties, agglomeration state and water solubility are certainly relevant to predict their bioavailability, and the mechanism of action potentially leading to effects on organisms and behaviour in the environment. Any guidance likely to be developed in the future will be based on experimental data as well as modelled data and predictions. There are several initiatives in OECD countries to generate good quality data on representatives types of nanomaterials (e.g. OECD sponsorship programme), there are also numerous projects in OECD member countries aiming at developing computational approaches to predict properties of nanomaterials, e.g. oxidative stress potential of oxide nanoparticles (Gallegos Saliner et al., 2009, Burello and Worth, 2011). At present, it seems premature to develop guidance on grouping specifically for nanomaterials. Nevertheless, research efforts will pave the way for common approaches and frameworks to grouping nanomaterials for purpose of hazard assessment in the future and in addition, expand further on why certain properties tend to elicit certain effects in vitro or in vivo and where opportunities may exist to group nanomaterials together to rationalize testing. Section 6.9 will be amended as accepted principles for grouping and read-across of nanomaterials arise from these activities.