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Human health and environmental exposure assessment and risk characterisation of nanomaterials

Best practice for REACH registrants

Third GAARN meeting
Helsinki, 30 September2013

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1. Objectives

The purpose of the Group Assessing Already Registered Nanomaterials (GAARN) was to build a consensus in an informal setting on the best practice for assessing and managing the safety of nanomaterials (NMs) under the REACH Regulation, and thereby increase confidence and mutual understanding among stakeholders so that NMs can be sustainably developed and used.

The GAARN group consisted of several experts from the Member States, the European Commission, ECHA and industry. The group selected three registration dossiers that include nanoforms or NMs, and reviewed and exchanged views on the challenges faced by registrants in making sure that their registration dossiers meet the REACH information requirements in the areas of physicochemical properties and substance identity, human health and environmental hazards, and exposure and risk assessment, specifically for these nanoforms. GAARN discussed the best practice for each selected registered NM and developed recommendations on how to fill potential information gaps.

This report summarises the outcomes of the third (and last) GAARN meeting. This meeting was held in Helsinki on 30 September 2013 and focused on discussing the approach and challenges faced by participant registrants when documenting the human health and environmental exposure assessment and risk characterisation of their substances while registering them under REACH. The outcomes of this discussion can be viewed as generic recommendations for the exposure assessment and risk characterisation of NMs under REACH, while considering the present scientific knowledge on the field of nanotoxicology and practice, as well as challenges from participating registrants.

2. Setting

Before the meeting, ECHA and the participating lead registrants (LRs) for the three selected registered substances exchanged a number of questions based on the information provided in their registration dossiers for the hazard endpoints. The aim of this exchange of questions was to offer a basis for discussion at the meeting so that both parties (ECHA and the LRs) could be aware of their concerns and limitations related to assessing the hazards of nanoforms, and to focus the discussion on how nanoforms have been addressed in the respective dossiers.

The GAARN plenary sessions included presentations by the three LR representatives, followed by ECHA's responses to the questions received from the corresponding LRs.

3. Best practice

3.1 GENERAL CONSIDERATIONS

3.1.1 Exposure assessment

One of the objectives of REACH is to make sure that chemical substances are being used safely and to identify the hazards and risks of substances irrespective of their form. It is stated in sections 1 to 4 of Annex I to REACH that an exposure assessment shall cover all hazards that have been identified. Registrants should bear in mind that there are three types of identified hazards that may trigger an exposure assessment to ensure the safe use of the substance. These three types are:

- hazards for which there are classification criteria and there is information to establish that the substance meets the criteria and is therefore classified;
- hazards for which there are classification criteria and there is information on these properties of the substance showing that it does have these properties, but the severity of the effects is lower than the threshold criteria for classification;
- hazards not yet classified but for which there is information to show that the substance has specific hazardous properties.

In particular, special attention should be given to endpoints for which no classification is derived based on hazard data (e.g. mutagenicity, soil and sediment ecotoxicity), but where available data show such hazardous effects. Moreover, it is important not to overlook a potential hazard because of (technical) difficulties encountered (e.g. when applying or adapting the current standardised test guidelines for NMs as well as other forms or when implementing sample preparation considerations in OECD TGs).

When registering NMs and bulk substances under the same technical dossier, specific exposure scenarios for NMs (or other forms) should be included in the registration dossiers if these differ from the ones for the bulk materials. It is important that the exposure scenarios describe:

a) how the substance is produced;
b) its life-cycle uses; and
c) how the manufacturer or importer controls the exposure for humans and the environment.

Industry is also encouraged to consider the development of specific environmental release categories (SPERCs) or scenarios for NMs, as they can generate very valuable data that could be used in the near future for modelling purposes (e.g. dissolution rates under different environmental conditions, coating effects on fate).

3.1.2 Risk characterisation

The classical risk assessment framework for chemicals includes four main steps:

1) hazard identification;
2) hazard characterisation including dose-response assessment;
3) exposure assessment; and
4) risk characterisation.

It has been acknowledged (e.g. by the OECD chemicals programme on cooperation on risk assessment) that the existing risk assessment paradigm developed for traditional chemicals should also be applied to nanomaterials (OECD, 2012). Nevertheless, these steps need specific considerations in practice when applied to NMs (e.g metric to use, exposure assessment methodology etc.).

3.1.3 Updating IUCLID with relevant and new information

At the moment, there is limited nano-specific exposure information in the registration dossiers submitted to ECHA. Therefore, it is crucial for registrants to update their registration dossiers without undue delay (Article 22 of REACH) when new information becomes available. For instance, the type of identified uses and/or new uses advised against (Section 3.7 of Annex VI); when there is new knowledge available on the risks of the substance to human health and/or the environment, which may lead to changes in the chemical safety report; and when there is an update or an amendment of the chemical safety report or on the Guidance on safe use (Section 5 of Annex VI). Registrants should keep in mind that it is their responsibility to ensure

the safe use of the substance by providing a comprehensive IUCLID dossier and, when required, a chemical safety report to support this. Therefore, ECHA encourages registrants to report any potentially on-going studies in the IUCLID dossier, as this information is relevant for the process of dossier evaluation.

3.1.4 Life-cycle considerations for the exposure assessment and risk characterisation

Occupational, consumer, and environmental exposure to NMs should be characterised during the entire product life-cycle, and particular attention should be given to the potential release of nanoforms at different stages (manufacture, use and disposal). If, in the technical dossier, the registrants describe that NMs are not released at the defined life-cycle stages (not even under extreme conditions) and that a risk characterisation for NMs does not have to be taken into account for the registered substance, they have to provide analytical or/and experimental data to demonstrate and support their "no release" statement.

At the same time, if the registrants consider that aggregates and agglomerates are formed during specific life-cycle stages, and these forms are not relevant for the risk assessment of the substance, they need to provide sufficient and specific data to support this. There should not be an automatic assumption that aggregates are 'irreversibly bound constituent particles'.

It is important to keep in mind that aggregates cannot be treated or considered as bulk, and that the relevance of these aggregated forms, including their potential for dissolution, or disaggregation, also needs to be considered from a(n) (eco)toxicological perspective in the risk characterisation. Indeed, aggregates and agglomerates are not "constituent particles" according to the EU recommendation for the definition of NMs, and as stated in the definition: "*Agglomerated or aggregated particles may exhibit the same properties as the unbound particles. Moreover, there can be cases during the life-cycle of a nanomaterial where the particles are released from the agglomerates or aggregates. The definition in this Recommendation should therefore also include particles in agglomerates or aggregates whenever the constituent particles are in the size range 1 nm-100 nm*".

3.2 SPECIFIC CONSIDERATIONS

3.2.1 Metrics

The EU recommendation on the definition of NMs is based on the size and/or surface area of the constituent particles of a substance. Nevertheless, when reporting toxicological parameters the more appropriate metrics may not necessarily be size or surface area. The metric considered the most appropriate and the one that should be considered for reporting toxicological effects will be the one that correlates better with the effects observed. For instance, the registrants may consider that there are other parameters that may better define the mechanistic toxicity of NMs.

As a general consideration, it was suggested that the number concentration for fibres seems the most adequate metric whereas for insoluble (or poorly soluble) particles the surface area or number might be more relevant.

However, practical considerations, such as information already available, practicability of the toxicological test in other alternative metrics and feasibility of measurement can also influence the final decision on the selection of the best metric.

As already indicated in the RIPoN 2 and RIPoN 3 projects, the results should preferably be presented in several metrics if possible, yet always including the mass metric (if feasible).

3.2.2 Exposure models

Exposure models are a key element of the exposure estimation process. Nevertheless, current research on conventional modelling tools has shown that there is no correlation between the model estimates and the actual measurement data (RIPoN 3). Indeed, the models are not always tuned to and calibrated for NM exposure situations, as they often depend on parameters that are not validated for NMs (e.g. LogKow and Henry's law for EUSES) (Appendix R7a ECHA Guidance, 2012). Hence, the actual model estimates are inaccurate and possibly overestimate the (mass) concentration levels. Therefore, the current alternative is to perform field measurements and use these data in the process of risk characterisation.

At the same time, and as a result of the lack of validated modelling tools, a number of alternatives have been developed to support temporary solutions in the absence of predictive environmental exposure models that generate quantitative results. Some of these alternatives include the use of evaluation frameworks and adaptive management (Hansen et al., 2008; Metcalfe et al., 2009; Money et al., 2012) . In the case of occupational exposure, some available tools can also provide qualitative assessment for NMs (Brouwer, 2012).

3.2.3 Measuring exposure concentrations

Typical urban air contains anywhere between 10 000 to 40 000 particles/cm3 which come from a variety of sources including, industrial pollution, traffic and domestic emissions.

In **occupational settings**, evidence of technical measurement difficulties related to background nano-aerosols has been reported in several studies (ECHA Guidance, Appendix to Chapter R.14, 2012).

Measurement strategies have been reported to allow the differentiation of background concentrations from those concentrations of the NM under study. For instance, to quantify worker exposure during the various uses, the concentration during different activities can be compared between periods of NM manufacture and non-manufacture. Another alternative is using the background concentration of a geographically similar location where background concentrations can be considered as a baseline for the exposure assessment of sites that are being exposed. These can be complemented with sampling and analysis to confirm that the NM is present. However, the differentiation between background concentrations and the concentrations corresponding to the NM can be very challenging, for instance, in situations of low release of NMs and/or high background concentrations.

ECHA acknowledges that measuring NM exposure is a complicated task and no single approach can currently be used nor recommended, given that the most appropriate choice depends on the substance-specific information and the measuring techniques available. For instance, the availability and type of hazard information (PNEC/DNEL/OEL available and metrics), the ability to measure these PNEC/DNEL/OEL levels (and metric(s)), the contribution from background concentrations, the PEC derivation, etc. It is also important that when performing a risk assessment for NMs, the units of the exposure and the units used for deriving the DNEL must be the same.

At the moment, the majority of reference values available are mass-based, which can hamper the assessment as analytical techniques available might not be sensitive enough to measure very low mass concentrations. Thus, a general recommendation is to follow a multi-metric approach if possible, and use mass as one of the metrics in the overall assessment. For instance, if mass cannot be measured due to low sensitivity of the measurement, it might be possible to estimate the mass concentration by calculation from measurements in another metric (e.g. if certain characteristics of the NM are known) (table R14-4.1 in Appendix 14-4 on "recommendations for nanomaterials" shows devices available for exposure assessment and the exposure metric(s) provided, by direct measurement and by calculation).

Regarding **environmental exposure**, detecting and quantifying NMs from porous media (e.g. soil or sediments) is challenging, particularly for those NMs made of chemical constituents that are highly abundant in the natural environment (e.g. many metals and metal oxide nanomaterials, carbon materials etc.). Current scientific techniques address this challenge through labelling of the NM (e.g. isotopic labelling) in order to provide better exposure estimations.

In addition, there are a number of technical and analytical challenges with measuring NMs in the environment and these include: ambient concentrations below the detection limit of most analytical methods; potential co-existance of natural and manufactured NMs; etc.

In the event that it is not possible to segregate background concentration from the exposed NM concentration, which may be released as a result of their life-cycle use, the total count concentration could be considered in the worst case (RIPoN 3). In the added risk approach, only the concentration added to natural background is considered in the exposure and effects assessment (previous experiences have been gathered with other (non-NM) substances (e.g. zinc compounds under the Existing Substance Regulation (EC 2010)), and generating "Added Predicted Environmental Concentration" (PECadd) and "added Predicted No Effect Concentration" (PNECadd). The added risk approach implies that only an anthropogenic amount of substance (i.e. added to natural background concentration) is considered relevant for effect assessment, and the potential contribution of natural background concentration to toxic effects is not considered.

Nevertheless, the relevance of the chosen approaches always needs to be demonstrated for NMs.

3.2.4 PNEC derivation

When deriving PNEC values, it is important to consider the relevance of potential indirect effects that may contribute to the adverse effects observed at environmentally-relevant concentrations or at concentrations that are considered to be safe for the environment. When the indirect effects are relevant for the risk characterisation, they should be considered in the PNEC derivation (e.g. local PEC/PNEC scenarios). Nevertheless, it is important to keep in mind that in such situations, the use of assessment factors may not be suitable for PNEC derivation (e.g. physicochemical properties of the substance). If indirect effects are not considered in the PNEC derivation, the approach chosen should be justified.

3.2.5 Risk management measures

In an occupational environment, conventional risk management methodologies and hierarchy of controls are adequate for NMs and should provide some levels of protection for workers from exposure to NMs. Several publications support the effectiveness of risk management measures (RMMs) to reduce the concentration of nanoparticles (Vogel et al., 2014, ISO 2012, ISO 2008).

Therefore, performance and efficiency of the RMMs should be verified, as it is affected by several factors such as particle size, maintenance and (in)adequate use. The control technologies used to handle dusty materials are applicable to NMs and provide good control if implemented and maintained correctly.

3.2.6 Improving justifications for safe use claims

To instil confidence in safe use claims under REACH, registrants are encouraged to provide explicit and transparent documentation of the scientific assumptions made during their assessments (hazard, exposure and risk characterisation). Registrants are invited to consider a worst case approach and address the

remaining uncertainty though experimental and scientific data in a transparent manner. Registrants are reminded that a lack of (hazard) data does not automatically mean there is a lack of specific hazards or risks for a substance or NM.

4. Conclusions

During the GAARN meetings, the representatives from the European Commission, the MSCAs and ECHA indicated the importance for the registrant to describe the scope of the registration dossier, in line with the current NM definition (2011/696/EU). The IUCLID dossier should include a detailed physicochemical description of the substance registered, including the different forms of the substance as well as any additive/capping/surface treating agent used in the manufacturing process.

The provisions that apply to the registration of NMs under REACH are the same as those that need to be fulfilled for any other chemical substance. However, in line with scientific developments, there are specific considerations that registrants should report in specific endpoint sections, as this information will facilitate the evaluation of the adequacy of the tests performed and data obtained with regard to the safety assessment of NMs (e.g. sample preparation, solubility/dispersion, use of stabilisers etc.).

The registration dossier should contain a comprehensive physicochemical characterisation of the registered nanoform(s) (First GAARN meeting best practices report, http://echa.europa.eu/documents/10162/5399565/best_practices_physiochem_subst_id_nano_en.pdf). Only when well-characterised nanoforms are reported in the dossier, can a read-across approach or use of existing data (e.g. weight of evidence) be considered for the purpose of hazard assessment. Generating data on toxicokinetics might also be considered for grouping substances in relation to read-across approaches, or extrapolating from in vitro to in vivo situations. The recommendations for the environmental and human health hazard assessment of NMs discussed during the GAARN, can be found in the Second GAARN meeting best practice report, http://echa.europa.eu/documents/10162/5399565/best_practices_human_health_environment_nano_en.pdf.

Registration dossiers including NMs and bulk substances under the same technical dossier should include specific exposure scenarios for NMs (or other forms) if these differ from the exposure scenarios developed for the bulk materials. It is crucial for the registrants to update their registration dossiers without undue delay when new information on NMs becomes available.

In principle, the existing risk assessment paradigm developed for traditional chemicals should also be applied to NMs. Currently, comprehensive risk assessments for NMs present challenges both for human health and the environment. At present, the following conclusions in this respect can be drawn.

Regarding the risk assessment for workers, due to the lack of validated modelling tools for nanomaterial exposure, field measurement data are currently preferred to support the risk assessment. If possible, the risk assessment should follow a multi-metric approach. The use of qualitative approaches is allowed to support measured or estimated exposure data. Concerning RMMs, the conventional control technologies to handle dusty materials are applicable to NMs and provide good control if implemented and maintained correctly.

With regards to the environment, the lack of specific hazard data complicates the risk assessment. Moreover, there are significant limitations in the applicability of conventional exposure assessment models. Registrants are advised to collect information on environmental release when possible (RIPoN 3). The current report proposes best practice to achieve realistic exposure data that can be used in environmental risk assessments.

In general, it is important to conclude with the reminder of the legal obligation that registration dossiers need to be updated with new nano-specific studies as scientific developments are progressing. Safe use claims under REACH should be based on explicit and transparent documentation supporting the hazard, exposure and risk assessment of NMs. Registrants are reminded that a lack of (hazard) data does not automatically mean that there is a lack of specific hazards or risks for a substance.

5. References

OECD 2012, ENV/JM/MONO(2012), Important issues on risk assessment of Manufactured nanomaterials, Series on the Safety of Manufactured Nanomaterials No. 33
http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2012)8&doclanguage=en

Guidance on information requirements and chemical safety assessment
Appendix R14 Recommendations for nanomaterials applicable to Chapter R14 Endpoint specific guidance
http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

Guidance on information requirements and chemical safety assessment
Appendix R7a Recommendations for nanomaterials applicable to Chapter R7a Endpoint specific guidance
http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

Guidance on information requirements and chemical safety assessment-Chapter R13: Risk management measures and operational conditions)
http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

REACH Implementation Project on Nanomaterials: Specific Advice on Fulfilling Information Requirements for Nanomaterials under REACH (RIPoN 2)
http://ec.europa.eu/environment/chemicals/nanotech/pdf/report_ripon2.pdf

REACH Implementation Project on Nanomaterials: Specific Advice on Exposure Assessment and Hazard/Risk Characterisation for Nanomaterials under REACH (RIPoN 3)
http://ec.europa.eu/environment/chemicals/nanotech/pdf/report_ripon3.pdf

First GAARN meeting Best Practices Report, ECHA 2012.
http://echa.europa.eu/documents/10162/5399565/best_practices_physiochem_subst_id_nano_en.pdf

Second GAARN meeting Best Practices Report, ECHA 2013.
http://echa.europa.eu/documents/10162/5399565/best_practices_human_health_environment_nano_en.pdf

Hansen SF, Michelson ES, Kamper A, Borling P, Stuer-Lauridsen F, Baun A. 2008. Categorization framework to aid exposure assessment of nanomaterials in consumer products. Ecotoxicology 17 (5), 438-447

Metcalfe C, Bennett E, Chappell MA, Steevens JA, Depledge M, Goss G, Goudey S, Kaczmar S, O'Brien N, Picado A. 2009. SMARTEN: Strategic management and assessment of risks and toxicity of engineered nanomaterials. In: Linkov I, Ferguson E, Magar V, editors. Real time and deliberative decision making: Application to risk assessment for non-chemical stressors. Amsterdam: Springer. pp 95–108.

Money E S, Reckhow KH, Wiesner MR. 2012. The use of Bayesian networks for nanoparticle risk forecasting: model formulation and baseline evaluation Sci. Total Environ.426, 436– 445

Vogel U, Savolainen K, Wu Q, van Tongeren M, Brouwer D H, Berges M. Handbook of Nanosafety. Elseiver 2014.

Brouwer DH. 2012 Control Banding approaches for Nanomaterials. Ann. Occup. Hyg., Vol. 56, No. 5, pp. 506–514, 2012

ISO TS/12901-1:2012. Nanotechnologies — Occupational risk management applied to engineered nanomaterials —Part 1:Principles and approaches.

ISO 2008 TR/12885 Nanotechnologies — Health and safety practices in occupational settings relevant to nanotechnologies.

EC 2010, European Union Risk Assessment Report ZINC METAL, JRC Scientific and Technical reports, EUR 24587 EN – 2010.
http://publications.jrc.ec.europa.eu/repository/bitstream/111111111/15064/1/lbna24587enn.pdf

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