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Analysis of OECD WPMN dossiers regarding the availability of data to evaluate and regulate risk

Executive Summary

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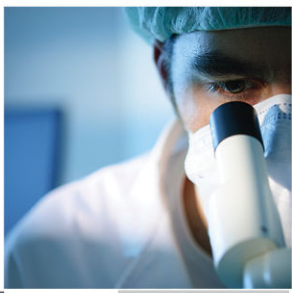

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CONTENTS

1 INTRODUCTION

This study was carried out as part of a wider project sponsored by Velux Foundations to support civil society organisations to ensure the adoption of a precaution-based regulatory framework for the responsible development of nanotechnologies in the EU and beyond, based on adequate risk assessment methodologies and risk management tools. This study focused on the OECD Working Party on Manufactured Nanomaterials (WPMN).

In 2007, the WPMN launched a Sponsorship Programme for the Testing of 11 Manufactured Nanomaterials (MNM), that were in, or close to, commercial use. The resulting dossiers were published[1] in June 2015 as a compilation of datasets presented in International Uniform Chemical Information Database (IUCLID) format, with annexes of original studies, from which the endpoint-related data were derived. The WPMN had not yet drawn conclusions on the data quality and rather suggested that regulators and researchers interpret the data themselves.

However, there were obvious disparities on data availability across the various nanomaterials. Some endpoints seemed poorly addressed, and entire sections of the dossiers were empty. In addition, sources and quality of data varied and the data quality seemed to differ depending on the existence and validity of established testing guidelines and standards.

The Sponsors approached IOM and requested that they carry out a dossier analysis of the OECD data. This is the executive summary describing the most important findings of the study. A detailed description of methods and results is available in a full report.

1.1 OBJECTIVE

This project aimed to look beyond the raw data and to provide a deeper analysis of the dossier data to assess its usefulness for the regulatory risk management of MNM. It had a focus on ecotoxicology and human health aspects, and aimed to supplement existing analysis and studies.

The analysis done within this project provides a horizontal assessment of all 11 dossiers and a more detailed assessment of 3 specific nanomaterials.

2 METHODS

2.1 STRATEGY

The completeness of the OECD nanomaterial dossiers was tested in three steps, an initial analysis that corresponded to a screening of the type of data contained in all the dossiers, a refined analysis that made a detailed

[1] http://www.oecd.org/chemicalsafety/nanosafety/overview-testing-programme-manufactured-nanomaterials.htm. Last accessed on 24 November 2016

assessment of the reported data, and a final step to draw conclusions and write reports. Screening and refined analysis were also recorded in the form of a database to facilitate further analyses of the dossiers at a later stage.

The **initial analysis** provided an understanding of what information was available in the dossiers. All of the OECD dossier documents as well as the associated annex materials [2] were reviewed with regards to:

- Test guidelines used for characterization of physical and chemical properties
- Environmental fate and pathways assessed, including Endpoints, Nanomaterial, Reliability score, Test guideline adopted, Test system/organism, and a Summary of the results.
- Ecotoxicological/Toxicological information, including Endpoints, Nanomaterial, Reliability score, Test guideline adopted, Route of Administration, Test cell/tissue/organism, Type of data, Exposure and dose information, and Phys-chem characterization of the NM
- Manufacture, Use and exposure of nanomaterials
- Human exposure scenarios

The **refined analysis** focused on fullerenes, single-walled carbon nanotubes and zinc oxide, three nanomaterials that are actively researched or widely used in commercial applications that have received relatively lower attention for risk assessment than mainstream nanomaterials such as silver and titanium dioxide. The analysis assessed in more detail ecotoxicological and toxicological information in comparison to literature recommending minimal reporting characteristics for conducting risk assessments.

To understand the general trend of data availability in all the other dossiers, we also carried out a refined analysis on a stratified random sample of about 17% of all the Endpoint Study Records (ESRs) with stratification done along dossiers and second-level endpoint study record numbers.

3 RESULTS

3.1 TEST GUIDELINE ADOPTED IN THE TESTING PROGRAMME

A total of 131 test guidelines (TGs) were adopted in the testing programme. Among these TGs, 65 were from OECD, approximately 50% of all the adopted TGs. Four of the OECD TGs were in draft stage and identified only with a title but not with a TG-number.

The 131 TGs were adopted in 4 first-level endpoints as follows with the number of TGs adopted in each of the first-level endpoints.

- Physical and chemical properties: 26 TGs
- Environmental fate and pathways: 11 TGs

[2] Available at http://www.oecd.org/chemicalsafety/nanosafety/dossiers-and-endpoints-testing-programme-manufactured-nanomaterials.htm. Last accessed on 24 November 2016

- Ecotoxicological information: 54 TGs
- Toxicological information: 42 TGs

Several TGs were adopted *with deviations* as claimed by data submitters. In the endpoints under ecotoxicological and toxicological information, 33 TGs (out of 94 TGs, 35%) were adopted with deviations for 144 endpoint studies in tests of 8 types of nanomaterials, except for dendrimers, gold nanoparticles and nanoclays. Among these TGs, 51 were from OECD, which were adopted for 424 endpoint studies in tests of the same 8 types of nanomaterials.

3.2 INITIAL ANALYSIS OF OECD NANOMATERIAL DOSSIERS

In the initial analysis, we reviewed all the dossier documents, extracted necessary information and compiled it into a database. In total, 6075 pages of dossier documents were thoroughly reviewed and 5279 pages of annex documents were referred to when necessary.

The **information of environmental fate and pathways** was totally unavailable for dendrimers, gold nanoparticles and nanoclays. There are 112 ESRs for the other 8 types of the nanomaterials in the Testing Programme. For most of the third-level endpoints with ESRs, data was only available for less than 4 types of nanomaterials.

The Klimisch score is metric that was developed to assess the reliability of toxicological studies for regulatory purposes under OECD. Studies rated with a Klimisch score of 1 or 2 are considered to be of direct regulatory relevance, while other scores may still be considered as supporting evidence. An assessment of the **Klimisch score availability** showed that approximately 60% of the ESRs did not have a Klimisch score. Only one third of the endpoint studies were conducted according to TGs.

An assessment of the **ecotoxicological and toxicological information** documented 782 ESRs. The number of ESRs at each third-level endpoint for each type of nanomaterials was calculated and shown in a heat map (see Full report).

3.2.1 Manufacture, use and exposure of NMs

In the IUCLID-format, Section 3 allows reporting human exposure scenarios. OECD did not have the intention to systematically collect such information. Consequently, such information was missing for all of the 11 types of nanomaterials in the dossiers. However, in the section on health surveillance and sensitisation, some relevant human exposure related observation was identified for 5 types of nanomaterials.

3.3 REFINED ANALYSIS OF THREE DOSSIERS

The dossier documents of fullerenes, SWCNT and zinc oxide were reviewed in more detail to assess the availability of characteristics in comparison to

recommended minimal data requirements recommended in several leading peer-reviewed journals.

3.3.1 Quality indicators

Less than 40% of the ecotoxicological and toxicological endpoint studies were performed with Good Laboratory Practice (GLP) compliance. Only 1 out of 19 endpoint studies of fullerenes was performed with GLP compliance. Approximately 30% of toxicological endpoint studies of zinc oxide and SWCNT were GLP-compliant, while no toxicological endpoint study of fullerenes was GLP-compliant. Half of ecotoxicological endpoint studies of SWCNT followed GLP compliance while the percentage for zinc oxide was less than 30%. The percentage for fullerenes was also 50% because in total only 2 ecotoxicological ESRs were available for fullerenes.

Of all the 178 ESRs we reviewed in the refined analysis, Klimisch score (indicating usefulness for regulatory purposes) was not available for only 4 ESRs of SWCNT. The availability of Klimisch score in the refined analysis (98%) was significantly higher than that of all the 11 types of nanomaterials in the initial analysis (59%). Approximately 90% of the ecotoxicological and toxicological endpoint studies of SWCNT and fullerenes were assigned either the top rank of 1 (reliable without restriction) or the second rank of 2 (reliable with restriction), while only half of the endpoint studies of zinc oxide were assigned with a Klimisch score of 1 or 2. Ecotoxicological and toxicological endpoint studies of zinc oxide had similar Klimisch score distribution. For SWCNT, more studies with Klimisch score of 1 and 2 were found in toxicological studies than ecotoxicological ones.

3.3.2 Data completeness

The data completeness of ESRs in the refined analysis was assessed according to the minimal data requirements recommended by articles from leading peer-reviewed journals. The completeness was calculated as percentage of ESRs with available data (only presence and absence) for each characteristic at third-level endpoint. For a number of characteristics that may undergo significant changes in different conditions (e.g., different degrees of agglomeration and size distributions in various testing mediums or after different periods of time following preparation), only those in endpoint studies that clearly showed relevant characterization had been conducted in the testing system were considered to be available. For example, if an endpoint study had only particle size without showing whether the size had been measured in the testing system by the data submitter, this characteristic would be considered not available in the endpoint study. The results were presented in heat map for zinc oxide, SWCNT, fullerenes and the 3 types of nanomaterials as a whole (Figure 1, see full report for heatmaps of each analysed material and the subsampling of all nanomaterial dossiers).

In the "chemistry" group, degree of purity was available for much more endpoints than other characteristics. No ESR described anything about persistence of the test nanomaterials. Some ESRs described surface chemistry of the tested nanomaterials, such as surface functionalization and coating. Only 1 ERS that clearly mentioned surface charge was measured in the testing system.

Among the characteristics of "nanoscale descriptor", particle mass concentration, which is less nano-specific than the other characteristics in this group, was the only one available in almost all the ESRs. In contrast, in most of the ESRs, data submitter did not well document relevant information or conduct relevant measurements of the other characteristics. Following particle mass concentration, particle size had the second highest availability of "nanoscale descriptors". Morphology was the third one, however, it was unavailable for 18 endpoints in the refined analysis. Only a few ESRs clearly claimed that the data submitter had characterized degree (or size) of aggregation/agglomeration, particle size distribution, surface area and particle number concentration. In particular, particle number concentration was only available for nanomaterial aerosols in studies of repeated dose toxicity via inhalation.

Figure 1. Heat maps showing data completeness for ecotoxicological and toxicological information available in the dossiers of ZnO, SWCNT and fullerenes (combined). Blank space indicates endpoints for which no study records are available.

			Chemistry						Nanoscale descriptor							Circumstance			
			Chemical composition	Purity	Impurities	Persistence	Surface chemistry	Surface charge	Degree of aggregation / agglomeration	Morphology (including aspect ratio)	Particle size (average, range, etc.)	Particle size distribution	Particle mass concentration	Surface area	Particle number concentration	Details on the matrix /dispersant /solvent surrounding the NM	Physical/chemical form of released/detected NPs	Exposure duration	Exposure frequency
Ecotoxicology	Aquatic tox.	6.1.1	100%	67%	44%	0%	0%	0%	0%	22%	22%	0%	100%	0%	0%	89%	100%	89%	89%
		6.1.2	100%	60%	20%	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%	100%	100%	100%	100%
		6.1.3	100%	25%	0%	0%	25%	0%	0%	0%	0%	0%	100%	0%	0%	92%	100%	100%	100%
		6.1.4	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%	100%	100%	100%	100%
		6.1.5	100%	0%	20%	0%	0%	0%	0%	40%	40%	20%	80%	0%	0%	100%	100%	80%	80%
		6.1.6																	
		6.1.7	100%	33%	0%	0%	0%	0%	0%	67%	67%	0%	100%	0%	0%	100%	100%	100%	100%
		6.1.8																	
	Sediment tox.	6.2	100%	33%	33%	0%	33%	0%	0%	33%	100%	0%	100%	0%	0%	100%	100%	67%	67%
	Terrestrial tox.	6.3.1	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%	100%	100%	100%	100%
		6.3.2	100%	100%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%	100%	100%	0%	0%
		6.3.3	100%	100%	25%	0%	0%	0%	0%	50%	25%	0%	100%	25%	0%	100%	100%	100%	100%
		6.3.4	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%	0%	0%	100%	100%
		6.3.5																	
		6.3.6																	
	Bio. eff. Monitoring	6.4																	
	Biotrans. & kinetics	6.5																	
	Addl. ecotox. info	6.6	100%	0%	0%	0%	20%	0%	0%	0%	0%	0%	80%	0%	0%	40%	80%	80%	80%
Toxicology	Toxicokinetics, metabolism & distribution	7.1.1	100%	71%	0%	0%	29%	0%	0%	14%	57%	14%	100%	0%	0%	100%	100%	100%	100%
		7.1.2	100%	50%	0%	0%	25%	0%	0%	13%	13%	0%	100%	0%	0%	100%	100%	100%	100%
	Acute tox.	7.2.1	100%	40%	20%	0%	0%	0%	0%	0%	20%	0%	100%	0%	0%	100%	100%	80%	80%
		7.2.2	100%	0%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%	100%	100%	100%	100%
		7.2.3	100%	50%	0%	0%	25%	25%	0%	0%	25%	25%	100%	0%	0%	75%	100%	75%	100%
		7.2.4																	
	Irritation / corrosion	7.3.1	100%	43%	14%	0%	14%	0%	0%	0%	0%	0%	100%	0%	0%	100%	100%	100%	100%
		7.3.2	100%	60%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%	100%	100%	100%	100%
	Sensitisation	7.4.1	100%	40%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%	100%	100%	80%	80%
		7.4.2																	
	Repeated dose tox.	7.5.1	100%	50%	0%	0%	0%	0%	0%	0%	0%	0%	100%	0%	0%	100%	100%	100%	100%
		7.5.2	100%	63%	13%	0%	50%	0%	13%	13%	75%	13%	100%	0%	25%	88%	100%	75%	75%
		7.5.3																	
		7.5.4																	
	Genetic tox.	7.6.1	100%	78%	35%	0%	22%	0%	9%	4%	4%	0%	100%	0%	0%	52%	100%	78%	78%
		7.6.2	100%	58%	8%	0%	33%	0%	0%	25%	50%	0%	100%	8%	0%	92%	100%	100%	100%
		7.6.3																	
	Carcinogenicity	7.7																	
	Dev. tox. / teratogenicity	7.8.1																	
		7.8.2	100%	0%	0%	0%	50%	0%	0%	0%	50%	0%	100%	0%	0%	100%	100%	100%	100%
		7.8.3																	
	Neurotox.	7.9.1	100%	0%	0%	0%	100%	0%	0%	0%	100%	0%	100%	0%	0%	100%	100%	100%	100%
		7.9.2																	
		7.9.3	100%	47%	47%	0%	6%	0%	0%	12%	12%	6%	100%	0%	0%	76%	100%	88%	82%
	Exp. Related obs. In humans	7.10.1																	
		7.10.2																	
		7.10.3																	
		7.10.4	100%	0%	0%	0%	100%	0%	0%	0%	0%	0%	100%	0%	0%	100%	100%	100%	100%
	Tox. eff. on livestock and pets	7.10.5	100%	0%	0%	0%	33%	0%	0%	0%	0%	0%	100%	0%	0%	67%	100%	100%	100%
		7.11																	
	Addl. tox. info	7.12	100%	14%	0%	0%	7%	0%	14%	29%	50%	7%	43%	0%	0%	36%	86%	43%	43%
	In vitro tox. Info	7.13																	

4 DISCUSSION

The eleven dossiers that were published by OECD document that a considerable amount of endpoint studies were conducted on ENM. In total 113 testing protocols were used, many of these protocols (65) corresponded to OECD testing guidelines. However, only about half of the related endpoint study records were done using unaltered OECD guidelines. Thus, only a small portion of studies would actually meet the rigid criteria according to the mutual acceptance concept by OECD. The reasons for modifications of test guidelines is not clear from the information given in the dossiers. It would be particularly important to understand whether an endpoint study protocol was modified to account for challenges related to nano-specific ENM properties or for other reasons.

At first sight the dossiers seem to document well the toxicity of the materials that were tested. However, the refined analysis reveals that most studies do not provide details about the size or the size distribution of NM test material, characteristics deemed important to understand potential risks of nano-scale materials. It seems that most studies solely relied on the characterisation of the initial raw material as delivered to them, thus without any further assessment of what they used.

Less than 2% of the study records document size distribution to be assessed in the actual test media (aerosol, dispersion, feed) as part of the experiment. Instead, most studies use mass rather than number or size distribution (thus not following scientifically recommended reporting practice), which is more pronounced even in inhalation studies. However, for many of the studies reporting mass concentrations, it is not certain that the presence of the nanomaterial was confirmed qualitatively or quantitatively in the final preparation (aerosol, dispersion, feed) used for testing. This leaves only a minute number of studies that provided a full nano-specific characterisation of nanomaterials in the actually delivered material preparation (aerosol, liquid, feed, etc).

Information about impurities is often missing. Although it would be good to document impurities in all ESRs, it is understandable, to some extent, that information about impurities are not available if the degree of purity is high (e.g., ≥98%). However, in principle, even purity as high as 98% is not a sufficiently "safe" level because a trace amount of toxic impurities can dominate the overall toxicity of the tested nanomaterial and thus mislead the risk assessment. Therefore, the approach to report impurities should be assessed. One approach could define a threshold above which it is not necessary to report impurities as long as one can prove that at the tested level, all of the possible impurities are far below levels able of causing toxic effects to the test organism.

Considering documented challenges in preparing materials for delivery in test systems and organisms, most of the endpoint study records in the dossiers are therefore associated with two important uncertainties:

a) Whether the expected *amount* of nanomaterial was delivered (risk of loss of material during the preparation)

b) In what *form* the material was delivered and thus which if any nano-characteristics may have influenced the outcome of the tests.

In addition, for soluble materials, it is in most cases undocumented in the records whether the material was still in particular form or in ionic form.

These uncertainties lead to several problems for interpreting the dossiers as a whole.

First, assuming that the material was actually delivered to the test cells or organism in the intended quantities and that the test guidelines do work with the nanomaterials, the dossiers document the toxicity of these tested materials delivered in this form. However, due to the lack of nano-specific data, it is not possible to make any statements about the influence of individual nano-specific characteristics to the observed toxicity.

Second, the absence of nano-specific characterisation of the material as it was presented to the biological test system means that it is problematic to understand whether the tested form represents material properties as they can be found in real life, i.e. in industrial production or consumer products.

OECD assigned study records with a Klimisch score. The Klimisch score aims to reflect the degree of reliability for regulatory purposes (from 1 as very reliable to 3 as not reliable and 4 as not assignable). Usually, only studies with scores 1 and 2 are considered suitable for European regulatory purposes such as REACH. The Klimisch Score of the assessed studies was not well correlated to the degree of details provided. Actually, many Klimisch 1 score studies gave very few details about what they did and even less details with regard to nano-specific data. Thus, the Klimisch score, while usually informing about the reliability of a study for regulatory purposes, does not inform whether a study in a dossier can be used to improve our understanding of nano-specific aspects of the material.

The dossiers contain very little human exposure data and environmental fate. This existence of these sections stems from the decision of OECD to adopt the IUCLID format. However, OECD did not have the intention to collect this type of data, which is stated in a footnote of the OECD nano-dossier website, "*For the sake of completeness, the spreadsheet identifies all of the endpoints available in IUCLID. Not all of the IUCLID endpoints were addressed in the Testing Programme, nor were they intended to be addressed.*" Unfortunately, OECD does not further specify which of the data was intended to be systematically collected, which was occasionally available and which of the not available data was not intended to be collected. It would be very useful if OECD could include this information also in the actual dossiers, e.g. by writing under the relevant section headers in each dossier "These endpoints were not addressed in the Testing Programme, nor were they intended to be addressed."

It is regrettable that OECD had decided to **not** collect exposure and environmental fate data, because one of the biggest challenges in assessing the risks of nanomaterials is the absence of sufficient information to develop scenarios about typical worker, consumer and environmental exposures. These scenarios would also be helpful to understand whether concentration ranges used in toxicological studies were in an exposure-relevant range.

5 CONCLUSIONS

The initial question of the presented study was to assess whether the data in the dossiers would allow for a risk assessment, which may be used also for regulatory purposes. However, the dossiers contain insufficient data informing about exposure to workers, humans and ecosystems, which allows the conclusion that the dossiers alone are insufficient to assess the RISK of nanomaterials in the sense of risk being a function of exposure and hazard. Furthermore, even when exposure information is known by regulators, they still cannot draw conclusions about nano-specific risks because nano-specific information on the hazard side is mostly missing. Thus, our analysis confirms the statement made by OECD when publishing the dossiers that they should not be used for regulatory risk assessment.

The dossiers do not contain sufficient information that would allow a risk assessment.

Knowing about how many people are exposed to approximately what levels, what nanoforms and in which situations is important not only to calculate the risk but also to identify where the biggest needs are for regulatory efforts and to identify the most suitable regulatory tools.

Now, the OECD website on which the dossiers are published suggests that "The outcomes of this Testing Programme provide information on the "intrinsic properties" of nanomaterials, that is, on properties of nanomaterials which are unique to the nanoscale dimension of these materials." It further states that "Understanding the intrinsic properties of nanomaterials is crucial to choose existing, adapt or create appropriate risk evaluation and management strategies for Manufactured Nanomaterials.".

However, because of the deficiency of the dossiers to document the actual delivered form of nanomaterials to the testing organisms, it is very challenging to make any firm statements regarding the nano-specificity of the observed hazard data and the extent to which the endpoint changes were linked to different nano-scale properties.

The lack of characterisation of actual used nanomaterial preparations is a serious challenge.

The lack of characterization of actually used dispersions, aerosols and feed is a serious challenge to risk assessment. It is one that is difficult to overcome *post-hoc* because most studies do not indicate dispersion protocols used. This prevents assessment *post-hoc* whether the final dispersion was likely to contain the intended mass concentration, how much agglomeration may have occurred, and how the preparation protocols may have influenced the size-distribution, functionalisation or other properties of the nanomaterial as it reached the target.

Can the OECD dossiers at least inform about nano-characteristics of the raw material that influence their toxicology? Unfortunately, there is not enough nano-specific information in the dossiers to answer this question, though having this information would be highly desirable for regulators as well as companies that are interested in a "safe by design" approach. Also read-across may be very challenging on the basis of the current dossiers.

The dossiers do not allow conclusions on the appropriateness of current Testing Guidelines for assessing ENM hazards.

Could the dossiers be used as a basis for testing the tests, thus to assess if the existing TGs may need adaptations when testing nanomaterials? The dossiers do not contain a systematic testing of the influence of nano-specific characteristics on the outcome, nor do they provide data that would allow assessment of the effect of nanoscale features on the test guidelines. It also would be important to systematically test how and why nano-properties can lead to artefacts, and what can be done to avoid or at least recognise them. Thus, the dossiers in their current format do not allow making statements on the quality of the TGs for nanomaterial testing.

Absence of observed toxicity does not need to equal no toxicity.

One could be tempted to state that for substances that were identified as low toxicity, it is not necessary to do a very detailed additional assessment of the influence of the nanoscale characteristics, because the risk will be low anyway. However, most endpoint studies did not characterize the finally used test-solution or aerosol, thereby leaving the doubt that artefacts in the preparation could have resulted in a partial or total loss of material or toxicologically relevant properties. It is also not clear whether suitable protocols were used for creating the preparations used to expose the test organisms. Thus, in a worst case assumption, hazardous material may not have been recognized as such. A major challenge to many of the endpoint study records is that they do not document any characterisation work done on the used nanomaterial preparations (aerosol, dispersions, feed) and that they do not mention whether the possibility of artefacts was assessed. Together, this implies that no *observed* toxicity does not necessarily equal no toxicity.

6 RECOMMENDATIONS

While the dossiers in their current format have clear deficiencies, they still represent an impressive amount of data. We recommend to complete the dossiers where easily possible and to use the lessons gained in the previous efforts of the WPMN to create data, databases and protocols that provide a support for regulatory risk assessment and management.

In particular, we recommend that the following options are considered:

- Expand the currently ongoing programme to systematically test the appropriateness of Testing Guidelines, including how to identify and prevent artefacts
- Develop Testing Guidelines for making nanomaterial preparations such as aerosols, dispersions and feed
- Define a minimum set of characteristics to be reported when testing nanomaterials following OECD TG
- Support the build-up of widely accessible exposure registries and databases
- Fill the gaps of current dossiers

6.1 SYSTEMATICALLY TEST THE EXISTING TESTING GUIDELINES

A large number of research studies have already developed protocols that are suitable within the frame of their study for work with nanomaterials. A series of scientific articles also described how endpoint assessments can be falsified by the introduction of nanomaterials. Large projects in the EU such as QNano, MARINA, NanoValid and Nanoreg have developed and used strategies to improve testing protocols with round robin approaches. This experience should be used for testing the OECD testing guidelines and to improve existing guidelines (if needed) to make them suitable for nanomaterial testing. It is likely that most TG will not require a complete re-work, but that it will suffice to address reporting of nano-specific characteristics and preparation methods (e.g. dispersion protocols), as outlined in the following two sections.

6.2 DEVELOP TG FOR MAKING DISPERSIONS AND OTHER TEST PREPARATIONS

Preparation of dispersions and other test preparations containing nanomaterials is challenging. It is a field where many research groups have already assessed possible strategies. It therefore seems feasible to develop in a reasonable time under OECD guidance, a set of protocols that meet strict requirements made by OECD for its TGs.

6.3 DEFINE A MINIMUM OF NANOMATERIAL CHARACTERISTICS TO BE REPORTED

If a laboratory reports data according to current TG, it will inform about the tested materials but will not be required to inform about nano-specific characteristics of the preparation of nanomaterials in the form it was given to the test organisms. Not having these characteristics in a laboratory report represents a major roadblock for using the reports to assess whether the preparation was free of artefacts and whether nano-specific characteristics that can pose problems were sufficiently assessed.

To address the problem of modification (thus change of the material-type) or ionisation (thus disappearance of the nano-form) of non-persistent materials, it would be also useful to check whether the ENM is stable in the test solution for the duration of the experiment. Ideally, one would also characterize the ENM in the actual test system (cell, animal) during and at the end of the test, though for many materials this may not be possible at reasonably low exposure concentrations.

Finally, considering that it is time consuming and costly to make a full physico-chemical characterization, it would be useful if OECD could support efforts to identify key metrics that allow to assess if (and what) further more detailed assessment of ENM characteristics in the actual preparation seem warranted.

6.4 SUPPORT THE BUILD-UP OF EXPOSURE DATABASES

Having more information about occupational long-term exposure together with a description of health and cause of mortality is critical to confirm that exposures believed to be safe are actually not associated to elevated ill-health, thus that risk management efforts are effective (this is actually valid for chemicals in general). While it may seem difficult to follow workers for decades, following them for a few years will enable identification of most health effects that develop over time. A comparison with air pollution effects could be especially useful because for air pollution, both, public health as well as occupational health dose-response data exists.

There are several governmental bodies collecting such data and bodies such as PEROSH (in regard to workers' exposure) are trying to build up databases. It would be useful if OECD at least endorsed such efforts, if not support them actively by helping define international guidelines for exposure data collection and sharing. This would allow regulators and risk managers world-wide to profit from knowing about observed levels and situations where unhealthy exposure concentrations can be reached. It will also help knowing if large parts of the population can be exposed (even at low levels) to a situation or if it concerns only a few individuals.

6.5 FILL THE GAPS OF THE CURRENT DOSSIERS

The dossiers lack information about nano-specific characterisation, preparation protocols and exposure data.

Characterisation: It is possible that some of the labs actually characterised the dispersion and aerosol before or while exposing the test organisms, but that this information did not make it into the dossiers. We recommend to assess if this is likely to be the case for many of the tests. If so, this information should be retrieved and added to the dossiers.

Preparation protocols: Protocols on how to create nanomaterial preparations (aerosol, dispersion, feed) for these experiments should be collected and made available. This will allow an assessment of the potential for artefact generation during the preparation steps, and thus will allow differentiating between endpoint study records that are more or less reliable with regards to actual exposure concentration and the presentation of nanomaterial characteristics.

Exposure data: Human and ecosystem data is not well represented in the dossiers. However, it would be useful if the OECD WPMN could build upon the testing Programme by including exposure as an important area where information should be collected. Such information will be very useful to develop scenarios of exposure and to define priorities. (see also *6.4 Support the build-up of exposure databases*).

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