A common European approach to the regulatory testing of nanomaterials

NANoREG

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Decision tree for risk assessment of MNMs

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1	2016/05/20	Final Deliverable based on the manuscript that was already approved by by the MC.
2	2017/03/16	Project Office harmonized lay-out
3		
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1 Description of task

Task 5.7: Develop decision tree for risk assessment

Partners: RIVM, NIA, LEITAT, TCD, VN-Ecamricert, PToNANO, KI, CNR, IPL, VSB.

This task will develop a decision tree for the risk assessment of nanomaterials. All existing information on exposure, stability and toxicity of the nanomaterials and the possibility of extrapolation from data of similar nanomaterials are used to avoid unnecessary dossier requirements. In addition, the latest developments with respect to (Q)SARs, including the (interim)results from projects within "NMP.2012.1.3-2: Modelling toxicity behaviour of engineered nanoparticles" and results from Task 5.1 will be evaluated with respect to their application within the decision tree. Depending on the expected exposure (WP3), stability and behaviour (WP 2 and WP3, and tasks 5.2 and 5.3) and hazard (WP4 and tasks 5.4, 5.5, 5.6) of a specific nanomaterial and its application and the possibility categorization, read-across, and extra-/interpolation (WP2 and task 5.1), the necessary amount of testing will be determined. This will result in testing strategies, which may include solubility testing (Task 5.2), in vitro testing (Task 5.3, 5.4 and 5.5) and high throughput screening (Task 5.6). The decision tree can be used in the value chain case studies and the development of the regulatory framework/toolbox within WP1 (Tasks 1.4 and 1.6).

Step 1: Evaluation of existing proposals of testing strategies and decision trees. Several research projects have investigated or are investigating this issue (e.g., Savolainen et al. 2010; NanoSafetyVision Report, 2012; Hristozov et al., 2012, FP7 CSA ITS-NANO). An overview of the results of these projects will be made as a starting point of this task.

Step 2: Identify those situations in which no specific risk assessment of the nanomaterial is needed (either from exposure or toxicity point of view) (e.g. high solubility, no exposure, no nanospecific toxicity expected, etc.).

Step 3: Identify those situations (exposure conditions or (categories of) nanomaterials) that need to be prioritized for further (toxicological) research.

Step 4: Identify testing strategies for all other situations Identify testing strategies for all other situations (using categorization read-across, and extra-/interpolation and if applicable also the solubility, in vitro and high throughput screening methodologies developed in Task 5.2, 5.3, 5.4, 5.5 and 5.6).

Step 5: Formulate principles for risk assessment of surface treated and coated nanomaterials, including parameters on the stability of the surface treatment or coating (when the surface treatment or coatings detach from a core particle in 'environmental or human matrices', toxicity data will be needed for the surface treatment or coating, the coated nanomaterials as well as the nanomaterial itself).

2 Description of work & main achievements

2.1 Summary

Nanomaterials have a strong innovative and economic potential, which is illustrated by the recent development of many new applications and the increasing number of consumer products that claim to contain nanomaterials on the market. It has often been indicated that the risks of nanomaterials should be assessed on a case-by-case basis. However, this would require a lot of experimental animals as well as time, effort, and money from both industry and government, given the wide variety of nanomaterials and applications available and the ability of nanomaterial to change during its life cycle, as well.

In the current paper, a new strategy for risk assessment of nanomaterials is described, which builds upon previous project outcomes and is developed within the FP7 NANoREG project. NANoREG has the aim to develop, for the long term, new testing strategies adapted to a high number of nanomaterials where many factors can affect their environmental and health impact.

In the proposed risk assessment strategy, approaches for (Quantitative) Structure Activity Relationships ((Q)SARs), grouping and read across are integrated and expanded to guide the user how to prioritise those nanomaterial applications that may lead to high risks for human health.

Furthermore, those aspects of exposure, kinetics and hazard assessment that are most likely to be influenced by the nanospecific properties of the material under assessment are identified. These aspects are summarised in six elements, which play a key role in the strategy: exposure potential, dissolution, nanomaterial transformation, accumulation, genotoxicity and immunotoxicity.

With the current approach it is possible to identify those situations where the use of nanospecific grouping, read across and (Q)SAR tools is likely to become feasible in the future, and to point towards the generation of the type of data that is needed for scientific justification, which may lead to regulatory acceptance of nanospecific applications of these tools.

The proposed approach, including the type of information linked to the various elements and endpoints, is based on the current state of knowledge and is flexible enough to accommodate future insights and knowledge of nanomaterials. Further elaboration and refinement is needed based on experience with case studies and newly generated systematic sets of high quality data to identify verify and validate which nanomaterial characteristics influence which aspect of the exposure, kinetics or toxicity. Although the current approach focusses only on the human risk assessment of nanomaterials, the approach can be expanded to environmental risk assessment in the future.

2.2 Background of the task

This task gives direction to where and how a more efficient risk assessment of nanomaterials (e.g. across multiple nanoforms) can be performed and what type of information could be used for scientific justification. It uses the current **scientific insights** in the specific **properties** that are **crucial** in the **behaviour and toxicity** of nanomaterials. In addition it uses information from many other tasks within the NANoREG project, including concepts from work package 3 (on exposure), task 5.1 (grouping and read-across) and methods from work package 2 (SOPs to determine physicochemical properties) and work package 5 (SOPs for in vitro assays).

The approach developed within this task is applicable to nanomaterials that are **already on the market**, while the safe innovation approaches developed in work package 6 are applicable to new nanomaterials that are still in the **research and development phase**. However, s**everal elements**, such as use of grouping and read-across methods and aspects that are most important to address the nanospecific issues within the risk assessment, are **applicable in both approaches.**

The approach developed within this task **facilitates** further development of a **more efficient risk assessment** for nanomaterials in the future and **accelerates** the rate at which **information** needed for risk assessment can be **generated, by identifying:**

a) those **applications of nanomaterials** that have the **highest potential to cause human health effects** (due to high exposure and/or toxicity)

b) those **aspects of exposure, kinetics or hazard** that are **most important** to address in the human health risk assessment of nanomaterials,

c) those **situations where** the use of **nanospecific grouping, read across and (Q)SARS** is likely to become **feasible** and potentially regulatory acceptable in the **near future**, and

d) the **type of information needed** for this regulatory acceptance.

Link to regulatory questions and needs:
This task will identify which information and test methods (obtained and developed within the different tasks) are most relevant to prioritize and assess nanospecific risks (RQ5 and 14).

2.3 Description of the work carried out

See Chapter 4 with reference to the final manuscript

2.4 Data management

Not applicable.

3 Deviations from the work plan

In the DoW it is stated that a decision tree would be developed. However, during the development and specification of the different branches and elements within the decision tree, it became clear that it was difficult to combine the different aspects of each element into one decision tree in a logical and comprehensive way. Furthermore, it was not yet possible to define benchmarks or cut off values for each box in the decision tree, so the term decision tree might be misleading. Therefore, the name of the developed approach (decision tree) was changed into flow chart. This allowed for a more flexible way to structure the different elements in such a way that the most important aspects for the risk assessment of nanomaterials are addressed first.

4 References / Selected sources of information

Dekkers, S., Oomen, A. G., Bleeker, E. A., Vandebriel, R. J., Micheletti, C., Cabellos, J., Janer, G., Fuentes, N., Vázquez-Campos, S., Borges, T., João Silva, M., Prina-Mello A., Movia, D., Nesslany, F., Ribeiro, A. R., Emílio Leite, P., Groenewold, M., Cassee, F. R., Sips, A. J. A. M., Dijkzeul, A., van Teunenbroek, T., Wijnhoven, S. W. (2016). Towards a nanospecific approach for risk assessment. Regul Toxicol Pharmacol, 80, 46-59. doi:10.1016/j.yrtph.2016.05.037