NanoDialogue
of the German Government

Risk research, risk assessment and risk management -- the example of the long-term research project „Nano-In-Vivo“

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Content

1 Background

Since 2006, the German Ministry of the Environment, Nature Protection and Nuclear Safety (BMU) has organised a national stakeholder dialogue on opportunities and risks of the use of nanotechnologies. At the beginning, the dialogue took place in form of a regularly convening Commission that was supported by working groups. Since 2011 the discussion has taken place at two-day ExpertDialogues.

Independent of the stakeholder dialogue, the BMU, together with various federal agencies[1], the company BASF and the Fraunhofer Institute for Toxicology und Experimental Medicine (ITEM), started a 5-year research project to identify long-term effects from exposures via inhalation to low doses of selected nanomaterials. At the beginning, the project was introduced to various civil society groups. As part of the German NanoDialogue, the topic was taken up at the Expert Dialogue on 23rd and 24th of April 2018, thus fulfilling the promise to present and discuss the project results with these groups at an early stage.

The following summary of this ExpertDialogue primarily documents the discussions on the project's context, i.e. the regulatory framework into which the work is embedded and that defines the conditions under which information is generated and used. Communication on the project and its results to the general public as well as the possible consequences for the risk management of nanomaterials were also subjects of the dialogue. As the project was not fully completed at the time of the event, this discussion summary presents the research results only in a general form. A detailed communication is planned for the end of 2018.

2 Workshop Proceedings

On the first day of the ExpertDialogue, the project "Nano-In-Vivo" and its results were presented. Furthermore, several presentations illustrated how a nanomaterial's hazardous properties are identified in different regulatory contexts and which possibilities and limitations exist for risk assessment and risk management.

On the second day, the discussion on the harmonised classification of titanium dioxide were analysed to show the challenges of harmonised classification of solid substances. Thereafter, the participants debated various aspects of risk research, risk communication and risk management in three working groups, considering the experience gathered from the "Nano-In-Vivo" project.

[1] Federal Institute for Occupational Health and Safety (BAuA), German Federal Institute for Risk Assessment (BfR) and German Environment Agency (UBA)

3 The „Nano-In-Vivo“ Project

3.1 Project History and Project Structure

The main aim of the “Nano-In-Vivo” project was to close the, frequently criticised, knowledge gap on the long-term toxicity of selected nanomaterials.

The Federal Institute for Occupational Health and Safety (BAuA), the German Federal Institute for Risk Assessment (BfR) and the German Environment Agency (UBA), the company BASF and the Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM) agreed on a 5-year research cooperation under the auspices of the German Ministry of the Environment. They focused the research questions on the identification of the toxicity of nanoscale cerium dioxide (CeO_2) from long-term inhalation exposure at low concentrations and of barium sulphate at a high concentration. Before the official project start, a method was developed to produce stable aerosol concentrations to expose the rats to the nanomaterials. Furthermore, the concentration ranges that should be analysed in the long-term study were identified in pre-studies.

A “core group” developed the project design which was evaluated by external experts and then agreed upon amongst the partners. The project design was discussed with civil society groups in 2012. An international expert group consulted the project team on the design and implementation of the study. The company BASF carried out the tests and collected in-life data. The BfR analysed the distribution of nanoparticles in the organs. The Fraunhofer ITEM conducted histopathological analyses, which were quality assured by an external expert panel.

The long-term study was conducted according to “good laboratory practice” and according to the OECD test guideline 453[2] with an extended scope to increase sensitivity of tumour detection.

3.2 Granular, Biopersistent Dusts

Granular, biopersistent dusts (GBD) without specific toxicity consist of spherical particles that do not dissolve in the body and hence remain as particles in tissues and body fluids to a large extent. By definition, they should not have a substance-specific toxicity but exhibit their adverse effects through the particle properties as such. Information on the toxicity of one or several representatives of the group of GBDs could be read across to others based on an assumed common effect

[2] Test guideline „Combined Chronic Toxicity/Carcinogenicity Studies“ https://www.oecd-ilibrary.org/docserver/9789264071223-en.pdf?expires=1525152347&id=id&accname=guest&checksum=F978B7D7925EC15EDF74339F56E5B838

mechanism. Based on the above considerations, nanoscale CeO_2 was selected as a representative of the group of GBDs in the "Nano-In-Vivo" project.

According to the hypothesis on the effect mechanism of GBDs, these are introduced into the lung by macrophages, which normally take up and dissolve particles "foreign to the body" as well as bacteria and viruses. However, due to their biopersistence, GBDs are not dissolved by the macrophages. At high loads of the macrophages, inflammatory reactions and oxidative stress may occur in the lung. Rat studies with titanium dioxide, carbon black and other dusts showed that high GBD concentrations in the lung may cause heavy inflammations and tumours.

The effects of nanoscale barium sulphate ($BaSO_4$) at one, high concentration was assessed as negative control.

3.3 Research Questions

The project aimed at answering the following core research questions:

- How do nanomaterials distribute in the body upon long-term exposure?
- How do nanoparticles impact the lung? Do effects occur outside the lung?
- What is the lung cancer risk from long-term CeO_2/GBD exposure in low doses and can an effect threshold be determined?

3.4 Project Results

Some results from "Nano-In-Vivo" were not yet available and project reports not yet published when this report was written, therefore the summary of the project results introduced at the ExpertDialogue are preliminary. These results are briefly presented here. Detailed results will be available in scientific publications at the end of 2018.

For CeO_2 in the analysed concentration range[3] from 0.1 – 3 mg/m^3, the project partners observed the following:

- Loading of the lung with CeO_2 is independent of the dose and time: the higher the exposure concentration and the longer the exposure duration, the higher was the measured CeO_2 content in the lung. Hence, no steady state[4] could be observed in low-dose exposures.

[3] The observations do NOT refer to barium sulphate and only relate to the tested concentrations. The results were interpreted at the ExpertDialogue but this is not repeated here. Similarly as before, it is referred to the publications expected end of 2018.

[4] A steady-state means that the uptake and the clearance of materials are in equilibrium resulting in a stable concentration in the lung.

- There is a translocation of CeO_2 in the lymph nodes associated to the lungs. This can be explained physiologically, as this is a clearance pathway of particles.
- Cerium was detected in low concentrations also in other organs. It is concluded that cerium and cerium compounds are translocated to other organs at a low level. No changes of these organs were detected in the histopathological analyses (no systemic effects of CeO_2 outside the lungs).
- Also at a low load, the lungs showed a dose-related inflammatory reaction and different tissue changes were observed: the higher the CeO_2 particle concentration in the lung was, the stronger the inflammatory reaction was.
- Despite inflammations in the lungs, no tumour development was observed. The originally assumed relation between inflammation and tumour development was hence not confirmed.
- The strength of the inflammation from nano CeO_2 aerosol exposures cannot be explained only based on the GBD particle properties. Therefore, it appears that an additional, substance-specific toxicity of CeO_2 exists.

4 Context and Cooperation in Risk Research

The following sections summarise the content of the presentations as well as the discussions in the working groups according to topics. The names of presenters and their contributions are indicated. The presentations are partly available on the internet[5].

Various presenters and participants evaluated the project “Nano-In-Vivo” as successful during plenary discussions. In the working group “Research Cooperation” it was also evaluated as successful because it achieved its aims within the time frame and generated important information on the long-term toxicity of certain nanomaterials. The working group highlighted success factors to learn from for similar projects.

According to the working group, an important success factor of “Nano-In-Vivo“ was that it was initiated to answer a specific (and societally relevant) question about the long-term adverse effects of nanomaterials. Also the project was financed through a cooperation of different organisations making it independent of the conditions of the usual research programmes in the field. The working group felt that many research

[5] https://www.oekopol.de/themen/chemikalienpolitik/nanodialog/nanofachdialoge-2016-2017/risikoforschung-bewertung-und-management-am-beispiel-des-langzeitforschungsprojektes-nano-in-vivo/

programmes[6] are too rigid for funding this and similar activities because they would not allow individual project designs, would prescribe application deadlines, topics, project durations and other conditions. In addition, as many research agendas would still assume that nanomaterials are “special”, they would require projects to confirm or disprove such hypotheses. This would be neither necessary nor correct and might even prevent the development of more relevant research aims.

The “Nano-In-Vivo“ was developed in a differentiated manner at an early time by a “small core group” and quality assured by external international experts. This allowed differentiating the original ideas and translating them into concrete research activities. According to the working group this approach was a further success factor, as it made the work process targeted and efficient. In addition, the external quality assurance increased trust in the results.

According to the working group, another reason for the project’s success was that the partners were selected based only on their competence and not (also) because they belong to a particular stakeholder group. The participation of civil society groups would be particularly important for the evaluation and further use of the results. They were involved through presenting the project at its beginning and discussing the results, among others at the ExpertDialogue. However, they were not involved in the project development and management because a direct translation of societal discussions into research activities would often be hardly possible.

The working group named the complexity and the resulting high coordination efforts as a core challenge of the project. In addition, a high conflict potential was expected due to the participation of different organisations and their various perspectives and research interests. These challenges were met by a stringent project management and a strict separation between research actions, data generation and interpretation of results.

The working group also discussed if and how the societal information need could be determined and integrated into the research agenda. It concluded that stakeholder discussions, like the NanoDialogue, would be a good opportunity to formulate societal questions and provide them to the scientific actors. The Committee on Hazardous Substances (AGS)[7] was seen as formally different but similar in content: it consists of actors involved in worker protection, poses questions on occupational

[6] This was stated for the research programme of the German Ministry for Education and Research as well as the EU programmes. The conditions of the German Research Society (DFG) were stated to be less stringent but more focussed on basic research and therefore less appropriate for applied sciences and related questions.

[7] https://www.baua.de/DE/Aufgaben/Geschaeftsfuehrung-von-Ausschuessen/AGS/Ueber-den-AGS.html

health and safety, introduces them into the scientific community and integrates scientific findings into the practical work.

5 Identification of Toxic Properties of Nanomaterials

Three presentations at the ExpertDialogue dealt with the identification of toxic properties of chemicals, including nanomaterials, according to EU requirements.

5.1 Legal Requirements

Mr. Gebel (BAuA) presented that, among others, REACH (industrial chemicals) and the regulations on biocides and on plant protection products define, which (toxicological) data are to be generated and provided as a preconditions for market entry (registration/authorisation). While for biocides and pesticides the same type of information is generally necessary for each substance, the data requirements under REACH depend on the registered tonnage. At the time of the ExpertDialogue, there was a discussion at EU-level how the respective REACH annexes should be adapted to nanomaterials.

Mr. Gebel explained that substance properties are to be determined based on OECD test guidelines. These are internationally discussed, consented to and partly adapted to nanomaterials. This ensures that data is internationally comparable and accepted and that unnecessary testing is avoided, as there is no need to test a substance for a specific property more than once.

5.2 Classification

Ms Wilrich (BAM) explained that information from hazard testing is compared to criteria of classification classes[8] in order to classify chemicals. The UN “Globally Harmonised System on the Classification and Labelling of Chemicals” (GHS) defines these classes and is implemented in the EU by the “Classification and Labelling Regulation” [9]. Within the classes, categories are differentiated depending on the severity of the effect. Ms Wilrich called the GHS a set of building blocks, which is used differently in the various countries and regions of the world. Therefore, the requirements of the categories are not yet globally harmonised. However, the criteria of the GHS and the EU CLP Regulation would be applicable to nanomaterials.

[8] For human toxicity, the following classes are defined: acute toxicity, skin irritation/corrosion, eye irritation, sensitisation, mutagenicity, reproductive toxicity, carcinogenicity, target organ toxicity (single and repeated exposure), aspiration hazard.

[9] Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures

Ms Darschnik (BAuA) presented that certain properties of substances can be subject to an EU harmonised classification, i.e. they are evaluated in a formal process by an authority based on available data. This so called legal classification should be appropriate and adequate, is legally binding and published in Annex VI of the CLP regulation. Ms Darschnik reported that the classification system seems to reach its limitations with an adequate legal classification of titanium dioxide: titanium dioxide would be carcinogenic only under certain conditions, among others at a specific particle sizes and upon inhalation exposure. According to Ms Darschnik a discussion is taking place at EU level on whether or not the strictly hazard-based classification system is suitable for solid substances, in particular in those cases, where the legal consequences appear to be neither sensible nor appropriate. This could be the case if the conditions causing the hazard do not exist.

Another example, where this occurs are explosive substances. For those, the packaging would be taken into account in the classification of substances as it may also be decisive for the explosiveness.

Ms Wilrich presented how a separate annex of the UN GHS was developed in order to circumvent the challenges for the classification of explosive dusts. Explosiveness is derived according to the annex by also including several parameters, which are not intrinsic properties.

At the ExpertDialogue, different opinions were expressed on whether or not exposure aspects should be considered in classification. Many participants particularly valued that the classification system focusses on hazards independent from the use conditions. This would highlight the intrinsic properties and the use context. Potential exposures and risks, could then be considered in a second step. Some actors saw classification without considering the exposure conditions necessary for an effect as problematic as it could confuse consumers, e.g. when tooth paste would have to be classified as carcinogenic due to its content of titanium dioxide in the future. In addition, a classification that considers relevant exposure conditions could prevent inappropriate legal consequences in other legislation.[10]

All stakeholders agreed that it should be unambiguous for the general public where risks lie and where not. The opinions were divided on whether labelling (of consumer products) could sufficiently achieve this or if (and in which form), additional information should be provided.

[10] Various legislation in the field of chemicals, installations, worker health and safety, consumer protection and environmental protection include requirements, which are triggered by a particular classification, such as carcinogenicity, mutagenicity or reproductive toxicity.

5.3 Effect Thresholds

Mr. Gebel (BAuA) and Ms Hartwig (KIT/MAK-Commission) explained in their presentations that ideally toxicity testing would allow defining dose-effect relationships. Based on the resulting curve of this dose-effect relationship, it might be possible to derive a concentration or a dose, below which no negative (adverse) effects on human health are expected (effect threshold). However, they stated the existence of substances that cause adverse health effects also at minimal concentrations or doses and for which no such thresholds could be derived. In these cases, only a (societally) acceptable risk of disease could be defined and a respective maximum acceptable concentration or dose be allocated to the substance.

6 Risk Management of Toxic Nanomaterials

6.1 Worker Protection

6.1.1 MAK-Commission

Ms Hartwig (KIT /MAK-Commission) introduced the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission), which assesses hazardous substances used at workplaces and derives science-based maximum workplace concentrations (MAK-values). The MAK-Commission is based at the Deutsche Forschungsgemeinschaft (DFG), is supported by a secretariat and consists of 35 scientific members and various guests.

According to Ms Hartwig, it becomes more and more complex to derive limit values because more sensitive endpoints are integrated into the assessment (e.g. neurotoxicity and endocrine disruption) and more data are available. A working group of the MAK-Commission had developed criteria to assess nanomaterials in a group approach, e.g. GBDs. The results of the Nano-In-Vivo project would be included in the further development of these criteria as well as in a potential revision of the adequacy of a general exposure limit value for dusts, which should protect from chronic inflammation and tumour risks at the workplace.

6.1.2 Committee on Hazardous Substances

Mr. Pipke (BAuA) explained that the MAK-values are an important basis for the Committee on Hazardous Substances (AGS) to develop workplace exposure limit values. The AGS members are representatives from employers, workers, academics and accident insurance funds as well as from the German Federal States. According to Mr. Pipke, the AGS considers also technical and practical conditions at the workplace in deriving recommendations on the use of hazardous chemical agents at the workplace (Technical Rules for Hazardous Substances (TRGS)).

6.1.3 Risk Management at the Workplace

Mr. Pipke concluded that the results from the "Nano-In-Vivo" project would not suggest an urgent need to revise the AGS's concept for assessing the use of nanomaterials at workplaces, as the existing principles are sufficient, e.g. the Notification 527 "Manufactured Nanomaterials"[11]. However, he recommends reviewing it if the results on CeO_2 are covered by the general dust limit value or if a specific limit value should be derived for it.

In the ExpertDialogue's working group "Risk Management" the expectation was expressed that the relevance of the project results on CeO_2 for the protection of workers are identified and, if needed, additional measures are implemented. Especially the transferability of the results on "all" GBDs would have to be thoroughly assessed.

In general, the working group supported Mr. Pipke's view on maintaining the current generic assessment approach for nanomaterials. In addition, the participants of the working group supported the proposal to develop a binding dust limit value that covers nanomaterials at EU level.

6.2 Consumer Protection

In her presentation, Ms Schulte (BfR) highlighted deficits she observes in the current (implementation of the) REACH regulation in relation to consumer protection. She pointed to the fact that for substances registered in amounts between 100 and 1000 tpa the ECHA database does not include information on the use in consumer products for the nanoforms. Hence, no communication in the supply chain on these substances could currently exist. The lack of use information for nanomaterials in the ECHA-database would contradict information in product databases, which include various uses. The information deficit could not be compensated via substance evaluation, because demanding such data would only be possible based on a respective "nano-specific" concern. However, this concern could not be formulated without use information.

Ms Schulte reiterated a need to review the criteria of the CLP regulation regarding their appropriateness for nanomaterials because product labelling would be an important consumer protection instrument. According to Ms Schulte, ECHA's guidance documents would address consumer protection insufficiently.

Furthermore, the concentration thresholds of 0.1% and the volume threshold of 1 tpa in all SVHC-related rules would be too high for nanomaterials and the authorisation

[11] https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/Bekanntmachung-527.html

would have only limited relevance for consumers. She named restrictions as an effective instrument, which could also be used for nanomaterials. For consumer products, “precautionary restrictions” for CMRs would enable a quick risk management but would be limited to substances with this type of properties. Ms Schulte mentioned that the use of classified nanomaterials in cosmetic sprays is restricted accordingly.

The working group “Risk Management” at the ExpertDialogue mainly discussed consumer protection in relation to communication aspects. Similarly as in the working group “Risk Communication” and in the plenary discussions, it was identified that consumers assume marketed products are “authorised” and safe. In addition, it was stressed that differentiated information of the general public on potential risks from aerosols would be important, as these may be the most relevant exposure pathway for contained nano particles. For many other products, human exposure to nano particles were regarded as less relevant.

6.3 Environmental Protection

In the discussion of the working group “Risk Management” it was pointed out that the selection of the substance CeO_2 in the “Nano-In-Vivo” project was also justified by the fact that it is used in some car exhaust catalysts, and partly also as a fuel additive. Therefore, it may be present in outdoor air. Data on the exposure of humans from outdoor air are missing, however. Based on the new information on the long term toxicity of GBDs/nanomaterials, a review regarding the environment could be useful.

6.4 Risk Management in Enterprises

The main expectation towards manufactures and importers of CeO_2 and similar materials (GBDs) expressed in the working group “Risk Management” was that they revise their registration dossiers regarding human toxicity data and derived DNELs. In addition, information on consumer uses should be evaluated, potentially complemented and related exposures and risks assessed. It was stressed that updating registration dossiers would not only be important for the authorities’ risk management processes but also to potentially adapt the recommendations on safe use of the manufacturers and importers.

7 Risk Communication on Nanomaterials

In the working group “Risk Communication” it was discussed which information on projects like the “Nano-In-Vivo“ should be communicated to the general public with which aims, in which form and at what time.

7.1 Target Groups and Timing of Communication

The working group named the following target groups as possible addressees of communication on the “Nano-In-Vivo” project or similar research projects:

- the scientific community;
- regulators (e.g. ministries and authorities);
- the critical, interested public;
- the general public, politicians and the media

The target groups would have different knowledge and information needs and would use different channels to inform themselves. According to the working group, it is essential to consider these differences in communication.

For “Nano-In-Vivo” and similar activities, the participants of the working group believed it useful to communicate with relevant (societal) actors at the very beginning of a project in order to integrate their perspectives into the project aims and design. The research results should be introduced early into substance assessment procedures and/or regulatory processes so they can be considered as quickly as possible. However, target groups, which are not involved in the project should be informed only after its end. The general public would need a “translation” of the results and their meaning, which was confirmed in the plenary discussion. Consequently, information would be provided later to this target group than to others.

7.2 Content of Communication

There was unanimity in the working group “Risk Communication” that the various target groups should be informed why a research project is carried out, which methods are used and which limits it will have. In addition, the findings should be presented and the remaining knowledge gaps should be explained. The integration of the results into regulation and societal contexts should be a separate step which, however, was regarded as lying outside the scope of (risk related) research projects. The clarification of a project’s implications on expert discourses, e.g. the influence of the findings on cerium dioxide on the “nano discussion”, could be part of the communication. In the case of “Nano-In-Vivo” it should also be communicated that enterprises took their responsibility for risk assessment and that governments attended to societal needs, in this case the knowledge gap on long-term effects of nanomaterials.

7.3 Information of the Public

The plenary took up and extended the discussions in the working group “Risk Communication” with regard to the communication content: All stakeholders believed it important that the difference between “hazard” and “risk” is highlighted in any communication. If this differentiation were missing, the public could not prioritise topics and all issues (related to nanomaterials) would be equally important. Communicating this difference would not only challenge research projects but also scientific committees had often difficulties in understandably communicating their decisions and definitions[12]. Some stakeholders critically remarked communication to the general public should not aim at updating it on the scientific state of play. According to their opinion, the majority of consumers is not interested in factual information but rather wants to be sure it can trust those institutions/authorities responsible for their protection.

Overall, all participants saw communication on hazards and risks of chemicals and nanomaterials respectively as a core challenge, with a significant influence on the acceptance and trust in new technologies and products. However, it was pointed out that risk debates frequently only mask other, more fundamental issues. This would be the case, for example, in the discussion on glyphosate, which actually would be a discussion about the type of agriculture society wants to see implemented in the future.

8 Summary

The discussions at the ExpertDialogue, highlighted the project “Nano-In-Vivo” as a good example that risk research carried out in a cooperation of enterprises, science and authorities could generate societally relevant and trustworthy information. The project was evaluated as successful, among others, due to a profound, externally supported and transparent planning and organisation. The results are considered trustworthy due to the external quality assurance, the participation of different authorities and the information and involvement of civil society groups. Furthermore, the project results would be particularly relevant due to the extended scope of the study compared to the OECD test guideline.

According to the project partners’ presentations, it is an important observation that CeO_2, which was selected as a representative of the group of respirable granular biopersistent dusts (GBDs), despite inflammatory reactions in the lung, does not

[12] The Commission for Indoor Air Hygiene was named as a positive communication example. It consists of members from different groups, discusses and evaluates recent research results and then agrees and develops jointly supported press releases.

cause tumours. A translocation of cerium at a low level was measured in different organs, but no adverse effects were observed there.

Communication about risks of nanomaterials in general and the results of risk research in particular, such as those of the “Nano-In-Vivo” project, is still a core challenge for all actors. Considering the various target groups and a potential “translation” of results to the general public requires resources and competence.

The usual procedures of risk assessment and management of nanomaterials in worker protection was regarded as feasible and sufficient by the participants, also in light of the new results of the “Nano-In-Vivo” project. However, there was a consensus on the need for a clear distinction, which substances fall under the definition of GBDs and which do not.

In the area of consumer protection, new/ further information on the use of nanomaterials are necessary to better identify and control risks.

Overall, stakeholders evaluated the experiences from the research project “Nano-In-Vivo” positively. As success factors for the generation of relevant, reliable and broadly accepted risk information as the following aspects were named: orienting on important societal questions, profound planning in a “small group” and feedback to project design and implementation by external experts, selection of competent partners, transparency and involvement of stakeholders as well as external quality assurance and conducting studies according to internationally accepted standards. The participation of authorities in the “Nano-In-Vivo” and similar projects also ensures that risk information is suitable for use in regulation.

Communication of results should be target group oriented and conducted at a sensible time. Information for the general public should be “translated” and brought into a day-to-day context. In addition, one should decide which level of information detail is needed; because the majority of population would rather rely on the diligence of the authorities with regard to product safety than to inform themselves more thoroughly. All participants confirmed that a clear communication including the differences between hazard and risk is very important. The project partners will, at the end of the project, prepare a target-group oriented communication for the general public.

The separation of data generation and the societal evaluation of the results, including a potential derivation of risks management measures, were regarded necessary and useful to prevent mixing of scientific and political argumentation. This would include a clear communication on (remaining) knowledge gaps and a decision by all actors if resources should be invested in their closure.