A common European approach to the regulatory testing of nanomaterials

NANoREG

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Case study summary report including feasibility check of the proposed answers

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1 Description of task

Task 1.6: Working Groups (addressing Value Chain Case Studies and other R&D related activities)

Value chain case studies (VCCS) and other R&D related activities will be established to support and test the development of answers to the regulatory issues/questions. This may range from testing proposed risk reduction strategies to more detailed aspects of a risk/safety assessment. It is suggested that the case studies are established at an early stage to ensure an iterative development of answers to the regulatory question.

Depending on the available information and relevance, case studies should consider the entire value chain, from R&D and design over production/manufacturing, to use and disposal/recycling. The outcome of the case studies is multifold:

1) Testing the feasibility of suggested answers from WPs 2-6,

2) Gaining insight in remaining bottlenecks in performing safety assessment and management, including knowledge gaps for risk assessment along the value-chain,

3) Contributing to development of the framework to be defined in Task 1.4.

The establishment of case studies and evaluation of their outcome is done to support Task 1.3 and in parallel with Task 1.2 and, thus, in close cooperation with WP2-6. The case studies will inform the work of WPs 2 to 6 and, vice versa, will receive input from these WPs.

In the case studies, an integrated analysis of data as obtained especially in WP2 and WP5 will be made. The case studies will be based on the MNMs tested in WP4. In addition, as an extension of the case studies, a few selected NMs will also be subjected to life-cycle analyses.

This task requires input from risk assessors, EHS researchers from industry, specialists in value-chain analysis. A specific activity in this task is a re-evaluation and ranking of existing toxicity testing data, which will be of use in completing the value chain case studies.

VCCS will be performed initially on already decided materials, and if relevant on materials as suggested based on input from regulators to Task 1.1. In the case of TEKNIKER, case studies will focus on the use of nanoparticles in lubricants. SINTEF will contribute in particular to the CNT VCCS and other case studies as well. ENEA will produce an integrated analysis of a value chain case study on nanosilver and could expand these activities to the interesting NMs for the project purposes.

(Lead: AIT, contributors: RIVM, IOM, ENEA, TEKNIKER, SINTEF, NILU, TEMAS, BNN)

2 Description of work & main achievements

2.1 Summary

NANoREG has developed the concept of SVCCS, i.e. value chain case studies that in addition take safety aspects into account. During the course of the project, procedures for obtaining candidate value chains, internal feasibility testing, and general aspects of the performance of the SVCCS have been developed and implemented. The case studies can cover the entire or specific stages of a given value chain, depending on case specific considerations. Besides the case-specific increase in knowledge that the SVCCS are aiming to produce, it is also expected that these studies can provide support for answering certain of the regulatory questions that NANoREG has formulated.

The procedures developed for initiating and performing SVCCS have been tested in too few instances to justify any conclusions regarding their appropriateness. However, with minor adjustments, they have functioned well in the actual cases that have been studied. A limitation regarding partner involvement may have been the unclear (financial) commitment to this specific task, and that several partners did not have knowledge regarding the nature of the work.

Suggestions regarding additional case studies have been relatively few. Furthermore, their relevance and realism seem not to have been considered in several cases. There is also a lack of interest regarding industry participation, due to unknown reasons.

Future case studies of this type have to consider activities that enhance industry interest. This may be accomplished by specific “calls for interest” or by allowing “organic” processes to rule, and await proper industrial partners.

The GALANT SVCCS (that focused on possible leaking of nano-TiO_2 from coating of glass vials intended for pharmaceutical solutions) has followed plans and provided output compatible with expectations. Importantly, the obtained results were useful for the involved industrial partner. Furthermore, the progress of the study justified the actions foreseen during the planning. The extent of the investigation did not allow to pursue several interesting questions and was also too limited to allow more statistically supported work and further conclusions.

In general, the extent of resources needed for this case study was underestimated, and/or the project was underfinanced. A future effort into this kind of problem needs also to account for resources to meet unexpected challenges and problems. The GALANT was lucky in the sense that the unforeseen problems could be solved without serious negative effect on the SVCCS study.

The SCVVS CNT/Graphene (which focuses on end-of-life exposure scenarios for nanomaterials in electronic goods, in particular batteries) has also followed plans and provided output which was in line with expectations. The results will feed into developing a knowledge base on end-of-life risk management for nano-enabled electronic waste, and will support development of MNM-enabled electrodes by the partner who provided the materials.

The size of the SVCCS project did not allow for further investigation or scale-up of experiments, although this was always understood to be the case. However, despite these issues the experimental work conducted ultimately led to a preliminary set of results and VC which may be further developed and will form a useful tool for the electronics industry and regulators alike. Further development and harmonization experiments to determine release of MNM will be necessary. In addition, it would be useful to carry out investigations into the presence of MNMs in batteries being recycled / handled in facilities across Europe and elsewhere and to follow the trends of time.

The SVCCS 'nano-TiO_2 in ceramic honeycombs' (that aimed at the development of workplace exposure scenarios of NMs in a REACH setting, using primary and real data on the production of ceramic honeycombs activated by nano-TiO_2 applied from a liquid nano-suspension) has also followed plans and provided output that was in line with expectations. The results feed into developing a knowledge base on realistic workers exposure scenarios, in the context of the

manufacturing by specialised industry of air purifiers containing nano-TiO_2. This collaboration of COLOROBBIA srl with NANoREG via the linking partner of T1.6 (ENEA) proved very fruitful for that nano-TiO_2 liquid suspension manufacturer.

The limited size of this nano-TiO_2 SVCCS within NANoREG did not allow for further investigation or scale-up of experiments. However, despite these NANoREG limitations on resources, the experimental work conducted ultimately led to a useful preliminary set of results, as shown in D1.7, which may be further developed and will form a useful tool for that specialised industry.

All SVCCSs can likely provide answers to some selected regulatory questions, but the scope and extent of the case studies limit their impact. Importantly however, the case studies performed according to the NANoREG model can contribute to questions pertaining to characterisation approaches, exposure determination, environmental fate and persistence, life cycle aspects, and risk management. However, a very valuable insight emanating from this work is that SVVCS can feed into discussion/considerations that relate to nano-specific considerations, but also other emerging technologies, among regulators and other stakeholders. Promotion of the usefulness of the SVCCS as such tools would be a useful aspect of NANoREG dissemination activities.

2.2 Background of the task

NANoREG is aiming to perform a number of Safety Value Chan Case Studies (SVCCS; see D1.6 “Assessment of value chain case studies” for definitions and extensive discussions of the concept) on nanomaterials and/or nano-enabled products. This is part of task 1.6, which develops and implements procedures for acquisition of SVCCS, as well as performing and evaluating the case studies. The overall aim for the case studies is to use obtained knowledge for answering the regulatory questions (as produced by T1.1) that are NANoREG's central theme.

The present deliverable is based on the accomplishments with and experiences from the D1.6 and D1.7. D1.6 highlights definitions, value chain characteristics within the NANoREG project, the NANoREG SVCCS process, VCCS on nanomaterials (NMs) and other emerging technologies, risk assessment (RA) of NMs and connections to SVCCS, challenges for NM RA, bringing SVCCS and RA together.
In D1.7, we covered methodology, results, and conclusions of three established case studies: “GALANT” – Glass surface coating to reduce leaching using nano-TiO_2, another SVCCS on CNTs/Graphene – End of life considerations for carbon-based MNM in Li-ion batteries, and a one on the use of nano-TiO_2 – Ceramic honeycomb components used in air treatment units and activated with nano-TiO_2 applied from a liquid nano-suspension.

The analysis in the present document is mainly based on the work with GALANT. This SVCCS was finished on time and provided a useful setting for a first stage evaluation of the NANoREG value chain approach. Furthermore, we employ knowledge about the other SVCCSs to estimate their usefulness in answering the regulatory questions.

2.3 Description of the work carried out

2.3.1 Aims of the deliverable

Deliverable D1.8 “Case study summary report including feasibility check of the proposed answers” aims to:

- Evaluate the internal procedures for acquiring, performing and analysing SVCCSs,
- Evaluate specifically the outcomes and lessons learned from GALANT,
- Indicate compatibilities between SVCCSs in NANoREG and answers to the regulatory questions,
- Conclude on the potential and appropriateness of SVCCSs in providing support for stakeholders regarding safety aspects of NMs and nano-enabled products.

2.3.2 Generic VCSS and SVCCS in NANoREG

The background and rationale for "classical" Value Chain Case Studies (VCCSs) that are used in Business School settings are discussed in detail in deliverable D1.6. There we also introduced the concept Safety Value Chain Case Studies (SVCCSs), including the NANoREG definition for this concept. The traditional value chain can include a number of different activities and processes, as we have outlined in Figure 1. Any kind of NM that is used for integration into a product (nano-enabled product) fits somewhere in such a generic description.

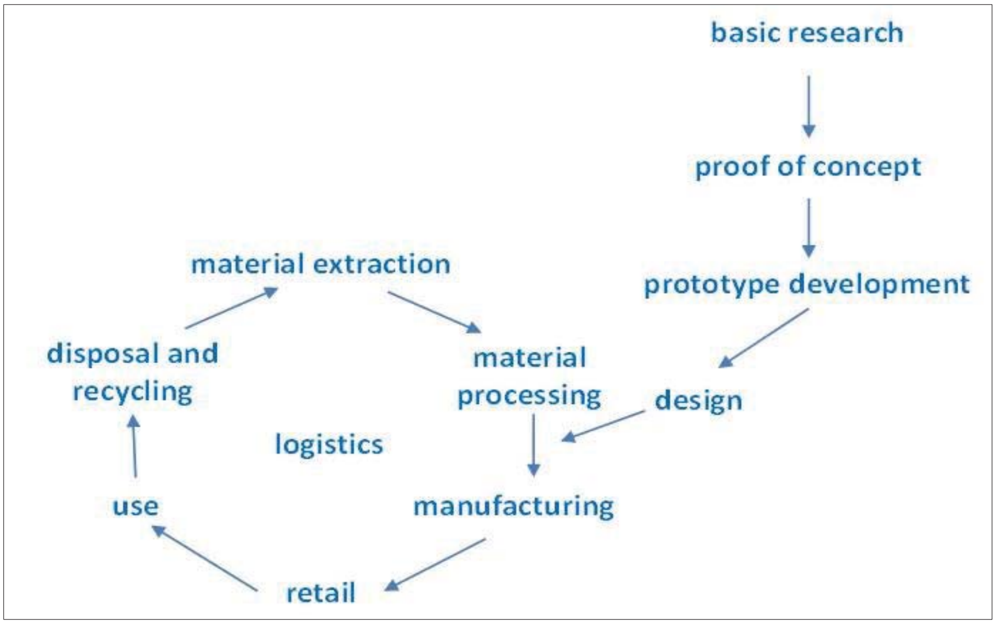

Figure 1. Schematic representation of the steps that constitute a value chain from generation of knowledge to end of life.

The SVCCS add another dimension to this, as they aim to combine the value chain concept with an assessment and possibly management of safety aspects that the specific material or product can bring on. The safety concerns relate to both environmental and human health, and take possibility for exposure (occupational, consumer, environmental) and hazard potential into account.

Three SVCCSs have been fully performed within NANoREG. The first is the GALANT study, which AIT (lead partner) performed together with the industrial partner Stölzle-Oberglas GmbH, Austria; Graz University of Technology, Austria as external scientific partner; and the NANoREG partners BioNanoNet and SINTEF. The study deals with the question of whether it makes sense from *inter alia* a safety perspective to coat glass vials destined for storage of pharmaceutical solutions with nano-sized TiO_2, since the leaking potential of this approach was not determined properly. This case study as well as other ones that are being performed or considered is described in more detail in Deliverable D1.7.

The second completed SVCCS study is the CNT/Graphene end-of-life study, which IOM (lead partner) performed together with the French Alternative Energies and Atomic Energy Commission (CEA) in France, and the Technical University of Ostrava (VSB) in the Czech Republic. The study considers carbon-based manufactured nanomaterials (MNM) in electronic goods, with particular focus on end-of-life handling and processing of batteries. This study was initiated and supported by the UK National Coordinator, the Department for Environment and Rural Affairs (DEFRA), who were particularly interested in investigating the lack of data for end-of-life of electronic goods. The case study is described and summarised within Deliverable D1.7.

The third case study that we include here focuses on nano-TiO_2 liquid suspension use to 'activate' ceramic honeycombs components used in air treatment units. The study was conducted by T1.6 partner ENEA in collaboration with the industrial NM suspension producer COLOROBBIA Consulting S.r.l. It aimed at the development of workplace exposure scenarios for that NM, using primary and real data on the production of ceramic honeycombs activated by nano-TiO_2 coming from the liquid suspension produced and applied to the ceramics by COLOROBBIA.

How each of these can contribute to activities in NANoREG is depicted in Figure 2. The different SVCCS are shown to “feed in” to different stages along the simplified depiction of a value chain that we have included in the cartoon. Their placement along the horizontal axis based on our assumptions of where the main activities relevant to the SVCCS will take place. Thus, in the case of GALANT, the object of the study is a product that is to use as a consumer product, and not in the manufacturing phase. Any implications for end of life scenarios were excluded in this study, although that could have relevance in an enlarged project. In analogy, the CNTs/Graphene SVCCS is focusing on waste streams, thus the placement of the SVCCS-specific arrows in Figure 2.
The nano-TiO2 in ceramic honeycombs SVCCS is mainly located in parallel to GALLANT (product integration), but ENM manufacturing and end-of-life scenarios were considered, too, when elaboration on the occupational exposure scenarios.

Finally, the knowledge that is generated from the work with SVCCSs strengthens the content that is generated for the NANoREG Framework (D1.11), a central document which provides the theoretical basis for constructing the NANoREG Toolbox (D1.12).

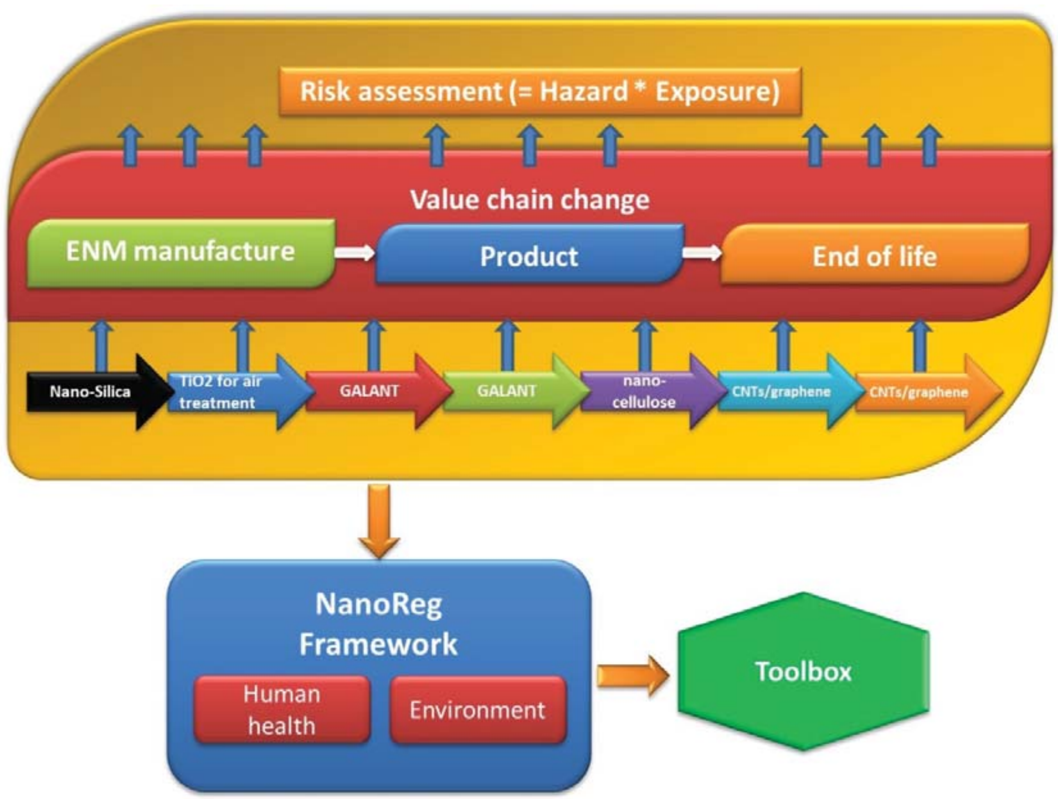

Figure 2: An elaborated version of the NANoREG SVCCS concept taking the focus of specific case studies into account. The chart has developed organically over the project time and is here presented in a version that harmonizes with the current status of project. Further modifications can be made according to the progress. The nano-TiO_2 in honeycombs SVCCS, which was added at a time the above figure could be updated

anymore, is mainly located in parallel to GALLANT (product integration scenarios), but ENM manufacturing and end-of-life scenarios were considered, too.

2.4 Results and Discussion

This section provides a summary of the activities and outcomes that are relevant for the different sub-headings. The analytical discussion is included here instead of in a separate chapter.

2.4.1 The NANOREG SVCCS procedure

Two major activities belong to this subsection. The first one deals with the initiation of the project. A detailed description is provided in deliverable D1.6. The initiation relied heavily on the drive and dedication of a partner, often promoting the SVCCS to the end, such as, for instance, BioNanoNet in the case of GALANT. The acquisition is initiated by local/national activities that bring attention to a suitable subject for study to the NC, who, in turn, mediates the candidate proposal to the attention of other relevant actors which leads to an approval/rejection decision by the MC.

This process has been tested only twice, since other candidate proposals have stopped short of submitting proposals. The foundation for any evaluation is thus extremely thin, and has to be considered more as individual case reports rather than process evaluations based on substantial input. One lesson learned is that personal interaction between industrial and scientific partners contributed significantly to the successful implementation. This was the case, for example, in GALANT with BioNanoNet as 'driving force', and in the nano-TiO_2 in ceramic honeycombs with ENEA's sponsoring. In summary, the application processes for all three SVCCSs went smoothly and do not justify any revisions to the protocol. It is however noted that SVCCS application and execution decisively benefit from a 'sponsor' investing seriously own resources.

The suggestions regarding further projects have been relatively few. Some candidate case studies were suggested at an early stage, of which a few have been evaluated regarding their relevance and realism. However, beyond that, surprisingly few suggestions have been brought to our attention. Of these, some showed initial promise, but were not further pushed by the involved partners. The reasons for this are unknown. One possible factor regarding the modest activity can possibly reside in the (lack of) interest from possible industrial partners. Our own experience from several encounters with industrial representatives is that they were not obviously willing to participate. The reasons for their scepticism can be many, possibly including proprietary and/or financial concerns, not seeing the need for the exercise in question etc. No systematic effort has been made to investigate this further, since it was not within the initial mandate and also not foreseen at an earlier stage of the entire project.

The second aspect deals with the actual study on SVCCS. The procedures include general value chain mapping, identification of the NMs used or produced, (physicochemical properties, forms, quantities etc.) and how these change along the value chain, identification of relevant industrial (or other appropriate) processes and how they relate to possible exposure scenarios. Depending on the specific questions, further work includes appropriate experimental approaches, data gathering and analysis, and feed-back of conclusions into the value chain and to the interested parties.

This has been performed in full extent in the GALANT case study. The industrial partner showed exemplary readiness in sharing existent knowledge and gave good support for the analytical aspects of the project. An initial concern was the identification and recruitment of partners with necessary competence and also with dedicated resources to take part in the practical work. We have suggested using the competence matrix developed in task 1.3 for this purpose. However, due to the limited amount of work foreseen, this was not needed in this case. Relevant competence was already available as partners with resources ready and interest in participating in T1.6.

The CNT/Graphene case study also identified a relevant industrial partner via the project partner CEA. Initial investigation as part of this VCCS revealed a significant lack of information available in the public domain relating to the presence or otherwise of MNMs in the waste stream. Following initial issues with identifying nanomaterial-enabled batteries, liaison with this partner via CEA provided the resources required to undertake the practical experimental aspects of the VCCS. However, it is notable that further investigation on whether (and which) MNMs enter waste streams, as well as prediction of future trends, is required.

Conclusions and recommendations

The procedures developed for initiating and performing SVCCS have been tested in too few instances to justify any conclusions regarding their appropriateness. However, with minor adjustments, they have functioned well in the actual cases that have been studied. A limitation regarding partner involvement may have been the unclear (financial) commitment to this specific task, and that several partners did not have knowledge regarding the nature of the work. On the other hand, active partners exhibited substantial flexibility regarding their contributions, and in 'sponsoring' a SVCCS, and this is an example of a significant success factor.

Suggestions regarding additional case studies have been relatively few. Furthermore, their relevance and realism seem not to have been considered in several cases. There is also a lack of interest regarding industry participation, due to unknown reasons.

Future case studies of this type have to consider activities that enhance Industry interest. This may be accomplished by specific "calls for interest" or by allowing "organic" processes to rule, and await proper industrial partners.

2.4.2 Results and lessons from the GALANT SVCCS

The GALANT study was initiated according to the foreseen procedure within NANoREG. Thus, contacts with the Austrian NC BNN led to further discussions and evaluations of the scope and realism of the proposal, which was submitted to the MC. Prior to that, other participants had been recruited and the work schedule, involved experimental procedures, and financial (and time) commitments were already drafted and agreed upon.

The practical investigation was performed as foreseen, content wise. However, adjustments were needed during the course of the work, and technical problems arose. This led to that the study was taking longer time than expected, but the initial ambition that this project could be concluded by the end of 2015 was fulfilled.

The study itself addressed the problem of possible leaching of TiO_2 nanoparticles out of nano-coatings on the inner surface of glass containers that are used for storage of pharmaceutical solutions. The GALANT partners investigated, and improved on the coating process; analysed leakage during different conditions; and provided suggestions for improving the processes at the industrial partner. Furthermore, since the suggested actions led to that leakage was minimised, there was no rationale to expand the studies to include investigations into environmental fate and behaviour of the used and created materials or to perform specific hazard determination experiments.

Taken together, the initial goals and the scope of the case study were fulfilled, and the results provided to the industrial partner must be considered valuable. However, the extent of the study was limited from the outset. Few samples were investigated, additional possibly relevant conditions were not possible to investigate, and the statistical power in the experiments is low. The reason for this is simple, the involved partners had very limited resources to invest and could not go beyond that although the project as such was found very interesting and rewarding.

Since this case study touched upon a short part of a longer value chain, a number of further interesting questions have appeared. They deal primarily with issues related to waste disposal and recycling. This was brought to the attention of the industrial partner, but received no interest since these issues were not primarily within their remit.

Another aspect of the placement of the study along a limited part of the value chain is that any impact GALANT can have on answering the regulatory question is limited to aspects partly related to the manufacturing process and certain aspects of use of the product (see also Figure 1 above).

Conclusions and recommendations

The GALANT SVCCS has followed plans and provided output compatible with expectations. Importantly, the obtained results were useful for the involved industrial partner. Furthermore, the progress of the study justified the actions foreseen during the planning.

The extent of the investigation did not allow for pursuing several interesting questions and was also too limited to allow more statistically supported work and further conclusions.

In general, the extent of resources needed for this case study was underestimated, and/or the project was underfinanced. A future effort into this kind of problem needs also to account for resources to meet unexpected challenges and problems. The current project was lucky in the sense that the unforeseen problems were possible to solve without any serious negative effect on the project.

2.4.3 Results and lessons from the CNT/Graphene SVCCS

The CNT/Graphene study was initiated according to procedure within NANoREG. Initial contact with the NC led to further discussions and agreement on an angle of approach for the proposal, which was submitted to the MC. Alongside this, other participants were recruited and the work schedule, experimental procedures, and financial (and time) commitments were drafted and agreed.

The initial part of the investigation was performed as foreseen, content wise. However, adjustments were needed during the course of the work, and additional work was undertaken which was not in the original project proposal (namely the exposure related experiments using electrode material). This meant that the VCCS took longer than predicted to undertake, but it was concluded by the end of 2016 in line with NANoREG's requirements.

The VCCS addressed the lack of information available around carbon-based nanomaterials in electronic goods, with a particular focus on end-of-life handling and processing of batteries. Following a literature review and scoping study to elaborate a VC for batteries and identify critical exposure scenarios for human and environmental risk, the CNT/Graphene VCCS partners investigated the potential for nano-object release and occupational exposure during: collecting and sorting electronic waste; recovery of materials from the electronic goods, and disposal of waste.

Overall, the initial goals and the scope of the case study were fulfilled, and the results provided are of value to both the electronics industry (including the VCCS' industrial partner) and those involved in regulatory aspects and risk management. However, the breadth of the study was limited, meaning that only one sample of nano and non-nano enabled electrode material were available for investigation rather than multiple samples of fully packaged batteries, and all of the experiments were undertaken at lab or pilot plant scale. As such, more work would be required to provide data with real statistical power. However, the experiments provided useful and interesting information on the behaviour of nanomaterial enabled products at critical end-of-life stages for batteries which could be built upon and scaled up into larger pilot or plant scale studies.

This case study considered a specific part of a larger value chain, as such there is potential for a number of further interesting questions to be addressed should the opportunity arise. They deal primarily with issues related to manufacture. However, it is likely that as battery construction is undertaken within highly controlled environments, the risk of exposure will be minimal.

Another aspect of the placement of the study along a limited part of the value chain is that any impact CNT/Graphene SVCCS can have on answering the regulatory question is limited to aspects related to end-of-life for the product concerned.

Conclusions and recommendations

The SVCCS CNT/Graphene followed plans and provided output compatible with expectations. Importantly, the obtained results were useful for the involved industrial partner and the NC who requested the direction of the research.

The parameters within which the investigation was undertaken did not allow pursuit of upscaling of the work, or investigation of a wider range of samples. However, the information generated remains of use to both the industrial partner and the wider scientific community.

2.4.4 Results and lessons from the nano-TiO_2 in ceramic honeycombs SVCCS

The SVCCS and the results are described in detail in D1.7. The nano-TiO_2 in ceramic honeycombs study by ENEA and COLOROBBIA S.r.l. was initiated according to procedure within NANoREG. However, initial plans described in the NANoREG DoW to study a case on nanosilver were revised in agreement with the MC to address instead a much more relevant case on nano-TiO_2 in ceramic honeycombs, which could provide useful insights in a real-life application of a liquid NM suspension to industrial components. Alongside this, the details of the collaboration in the NANoREG context between ENEA and COLOROBBIA were discussed during the last year of the project and the work schedule, experimental procedures, and financial (and time) commitments were drafted and agreed.

The VCCS addressed the lack of information available around occupational exposure scenarios when applying nano-TiO_2 from liquid suspension. The SVCCS partners investigated the potential for nano-object release and occupational exposure, using primary data and real acquired data, during: production and application of the liquid suspension to the ceramic honeycomb components, and also during their disposal at end-of-life.

Overall, the initial goals and the scope of the case study were fulfilled: simulation and analysis of the entire value chain in a Life Cycle prospective (production of NM, application in specific products, use and maintenance of products and their end of life). The results provided are of value to NM pigments or coatings industries (including the SVCCS industrial partner) that manufacture and apply liquid NM suspensions, and to those involved in regulatory aspects and risk management.

Though the resources available in the NANoREG context were rather limited, the breadth of the study was good. It allowed for the use of multiple samples on production to collect data, the subsequent elaboration of the data by ENEA in order to evaluate exposure scenarios (occupational) with a REACH approach. The experiments were undertaken at pilot plant scale, with COLOROBBIA that had successfully committed to build an experiment of production and application of the nano-suspensions on the ceramic honeycombs. As such, the work allowed to generate and elaborate very close to real life data with real statistical power.

The main outcome of this SVCCS is that in no one of the analyzed environment (ambient) and personal samples gathered in contributing scenarios (CSs) – production, application, exercise, maintenance and end-of-life – was the TiO_2 exposure level higher than the limit value.

Conclusions and recommendations

The SVCCS followed plans and provided output compatible with, if not beyond, expectations. Importantly, the obtained results were useful for the involved industrial partner and industrial technological field linked to the SVCCS (pigments, coatings applied to components using liquid nano-suspensions of typical NMs, such as nano-TiO_2).

Though the parameters within which the investigation was undertaken in the NANOREG context did not allow pursuit of upscaling of the work to a full production line, data was acquired and information generated (assessment of REACH-based scenarios) in a pilot line type of context, according to the

SVCCS industry partner's specifications. This SVCCS work hence delivered a very realistic vision of key aspects in occupational exposure in an industrial production context. It was verified that in all instances (contributing exposure scenarios) the exposure levels to nano-TiO_2 were lower than the reference limit thresholds.

2.4.5 Answering regulatory questions

A backbone component in NANoREG is the questions addressing regulatory concerns that are formalised and made public in D1.1. The SVCCS were not intended to answer these questions, although the ambition has been to perform case studies that have the potential to answer at least some aspects of some of the questions.

Based on several assumptions regarding scope, activities, and outcome of the performed and suggested SVCCS, we try to come up with a "forecast" to what extent the SVCCS will be successful in this respect. This is presented as "potential of the SVCCSs to answer the proposed refined set of key questions from a regulatory perspective" in table 1. We have also taken into account which kind of experimental activities will be used as far as we know and can reasonably assume.

Although we have made assumptions in our interpretations of how the different SVCCS can impact on the possibility to answer the listed questions, we consider this to be a realistic view on what the available SVCCS can produce in that sense. More substantiated interpretation is coming from the experiences from GALANT, the CNT/Graphene and the nano-TiO_2 applied in air treatment components SVCCSs. In general however, SVCCSs of this type will not likely provide input to questions that have a large component of method/technique development, validation and implementation as inherent characteristics. It is also less likely that problems related to hazard, and fate and behaviour in organisms will be addressed. However, we definitively see a potential for the SVCCSs to provide support for the questions related to fate persistence and long-term effects, as well as certain aspects of exposure determinants, exposure and life cycle analysis. The need for risk assessment can be addressed by the SVCCSs, although risk assessment advances themselves will not be a topic for a SVCCS. Finally, in the specific case, SVCCSs can provide valuable input regarding risk management issues and actions.

Interestingly, these areas are where we primarily see all three SVCCSs as contributing. There are few instances where we have concluded that either SVCCS really provides significant input. Most strikingly though, is that the results nevertheless can be translated into procedural changes at the enterprise and thus eliminate several safety and risk-related issues.

Table 1: The <u>potential</u> of the SVCCSs to answer the proposed refined set of key questions from a regulatory perspective (addressed in NANoREG D1.1, p.15).

	Question	GALANT	CNT/ Graphene	Nano-Cellulose	TiO_2 - air treatment
1	Measurement and characterization - Identification: How can MNMs be identified according to the EC recommendation for a definition of MNMs and for regulatory purposes (i.e. the implementation of the EC definition in e.g. REACH, CLP, cosmetics, novel food, etc.), including other jurisdictions (global harmonisation)? Can we develop robust measurement protocols which enable assessment of whether a NM falls under, or not, the EC definition? Are there robust measurement protocols available (and for which matrices) that enable identification?	*	*	*	n.r.
2	Measurement and characterization: Could an "intelligent characterisation strategy" be defined? What is a minimal set of physical (and/or chemical) characteristics that should be available for risk assessors within the context of regulatory toxicology? What are the relevant features to characterise MNMs, e.g. size, form, aspect ratio, rigidity, flexibility and coating? What methods (SOPs) should be developed / used to determine the physical chemical characteristics of MNMs throughout their different life cycle stages within the context of regulatory toxicology? These questions (closely related to Q1) refer to developing cost effective standard methods, detailed protocols and reference materials both for calibration and analysis of both pristine materials and materials in relevant media or complex matrices throughout the complete life cycle of the nanomaterial. they also refer to whether different categories of characterisation methods (varying e.g. in precision and accuracy) can be defined: Could an "intelligent characterisation strategy" be defined?	n.r.	n.r.	n.r.	n.r.
3	Characterisation/Transformation: What testing should be performed to identify surface modifications that occur once a MNM has been released into the environment or taken up into the body? How can transformation, including agglomeration surface modification, dissolution and incineration, be determined and considered in the exposure and hazard assessment and how do they change the intrinsic toxic properties and biodistribution Do we need to know the details of such surface modifications or of what is bound, or do we need some simple test systems that actually determine the behaviour and transformation of MNM in relevant media throughout all life cycle stages? Is a nano-derived material still nano when it becomes agglomerated? Take into account relationship with questions 7-9.	**	n.p.	n.p.	n.r.
4	Metrology and dose metrics: Which metrics (metrology) should be used for MNMs in regulatory toxicology? As recommended by several committees and guidance, notwithstanding e.g. the OECD GSPD, NANoREG should use mass, particle numbers and surface area (as far as possible) to characterise dose. The data generated within the project will contribute to the development of a body of comparative data (e.g. shape and aspect ratio should be examined when appropriate for the MNM). Using this comparative data, NANoREG should examine which metrics are the most appropriate depending on the different types of materials and media involved, as well as the (eco)toxicological effects and exposure to be assessed in the Risk Assessment process.	n.p.	n.p.	n.p.	n.p.
5	Extrapolation and grouping: What guidance can be provided on how to decide when information from different forms of MNMs (or from the bulk material) can be "re-used" in the sense of read-across, categorisation and grouping? Should / could guidance be based exclusively on physical-chemical properties or could exposure related (eco)toxicological and mechanistic information (as Mode of Action) be used as well and how? Take into account the relation with the following questions.	n.p.	n.p.	n.p.	n.p.
6	Fate, persistence and long-term effects: Can effective in vitro and alternative models to understand long-term effects be developed? Will MNMs accumulate in humans, the environment, environmental species and the food chain and what are the driving	n.p.	***	n.p.	n.p.

	forces? Is this mechanistically different from bulk materials? Will nanomaterials present long-term and/or cause deferred effects? How will coatings or surface modifications or the bio-based nature of the MNM affect biopersistence / biodegradability rates?				
7	Kinetics and fate, determination: How and when should information on absorption from the various routes of exposure, on deposition (e.g. lung burden), on biodistribution, on potential persistence and bioaccumulation, and on internal exposure (taking into account dose, duration, coating and interaction with biological systems) be generated and used? Relate the information with, for instance, the following objectives: • To perform more accurate risk assessment, • To decrease uncertainty (safety factors), • To select, if needed, a second route for acute toxicity testing, • To design additional tests – that are 'affordable' – or to relate to studies that involve exposed workers, such as in the silica industry, • To decide on a strategy for further testing (carcinogenicity, reproductive toxicity, etc.).	n.p.	n.p.	n.p.	n.p.
8	Kinetics and fate, extrapolation: How and when can information on kinetics and fate be used to justify grouping / read across or testing triggering / waiving and for building knowledge on the relationship between physical-chemical properties and toxicity? In other words: to what extent are the kinetics and fate of MNMs (e.g. environmental distribution or deposition and biodistribution in the lung) different from the bulk material? Are there ways to extrapolate this information from the bulk material or from several forms (size, shape, coating, etc.) of the same chemical and how should this extrapolation be made?	n.p.	n.p.	n.p.	n.p.
9	Mode of action: What are the physical and chemical properties driving exposure and (eco)toxicity of MNMs at all stages of their life cycle? How is MNM interaction with biological systems affected? What are critical characteristics of MNMs that need to be considered and included / excluded when developing MNMs to ensure they are safe and which materials have a known increased toxicity in the nanoform vs. the bulk form, and why? How will this facilitate the regulatory safety assessment of new nanomaterials?	n.r.	n.r.	n.r.	n.r.
10	Hazard: Which methods should be used to assess the human and environmental toxicity? What is the applicability of conventional testing methods for nanomaterials? Is adaptation of the conventional methods needed, for example by including nano-specific endpoints or additional guidance on sample preparation? What testing is relevant at all stages of the nanomaterial life cycle?	n.r.	n.r.	n.r.	n.r.
11	Exposure: What are the main determinants for occupational and consumer exposure to MNM and what are the duration and type of exposure?	n.p.	**	n.p.	***
12	Exposure: How should human and environmental exposure be assessed in practice (determining exposure scenario, quantify input parameters for models, assumptions and use of proxy indicators, background and uncertainty estimation)? Consider both measuring and specific modelling for nanomaterials and evaluate the needs for standardisation and validation.	n.r.	n.p.	n.p.	***
13	Exposure and life cycle analysis: Which scenarios could denote potential exposure and what information do we have on them? Can we develop standardized and efficient testing procedures for estimating release of nanoparticles (NP) from powders and NPs in matrices? What are situations in which MNM exposure is expected to be negligible / high? Are the amount and the nature of releases of MNM similar to regular chemicals, when common recycling and end-of-pipe techniques are used? How to minimise and structure LCA to avoid ending up with a '1:1 model of the world'? In other words: what is the exposure probability throughout the different life cycle stages of the MNM: production process of the NM itself, releases during the production process of products in which MNM are used, waste treatment, consumer articles, wearing, abrasion, etc.? Do waste treatment / recycling processes lead to exposure to NMs that can be hazardous to health and environment? If so, are additional risk management measures required? Do the recycled product / residues loose some value /usefulness due to undesired characteristics?	*	**	n.p	***

14	Risk Assessment: What are the no-adverse-effect or benchmark dose levels of long-term (low dose) exposures and can they be derived from short-term exposures (acute and sub-acute)? If not, what kind of information should be generated?	n.r.	n.r.	n.r.	**
15	Risk Management: How can exposure to MNMs be minimized / eliminated? Are risk management measures (RMM), in particular existing personal protective equipment, effective and sufficient when hazards and/or risks are high, uncertain or unknown? Should the RMM be different from bulk powders? Are currently available control banding tools appropriate for NPs or will these need to be further evaluated, improved (related to exposure assessment, too)?	***	***	***	***
16	Health surveillance: What are the triggers to indicate that biological monitoring or health surveillance of (occupational) exposed individuals is needed? Can an 'intelligent strategy' be developed?	n.r.	n.r.	n.r.	n.r.

*** very good potential / ** good potential / * medium potential / n.p. no potential - unclear yet / n.r. not relevant

As repeatedly stated, our present knowledge about the outcomes (and also the specific planned actions) of the other SVCCSs necessitates very speculative assumptions. With these caveats in mind, we expect the SVCCSs dealing with CNTs/Graphene and the occupational exposure scenarios in the nano-TiO_2 applied in air treatment components to have more impact on exposure and life-cycle related questions.

Conclusions and recommendations

The SVCCSs referred to here can likely provide elements of answers to some selected regulatory questions, but the scope and extent of the case studies limit their impact. Importantly, the SVCCSs performed using to the NANoREG model can contribute to questions on characterisation approaches, exposure determination, environmental fate and persistence, life cycle aspects and risk management.

2.5 Evaluation and conclusions

NANoREG T1.6 has produced a number of valuable outcomes. These include: the definition and conceptual understanding of what SVCCSs imply, the procedures for obtaining candidate value chains, internal feasibility testing and general aspects of the performance of the SVCCS. Furthermore, the studies specifically performed as part of the GALANT and nano-TiO_2 applied in air treatment components SVCCSs have provided results that addressed concerns raised by the industrial partner. These results were then useful for actions that *inter alia* have risk management consequences.

The case studies also provide knowledge that can be used to answer some aspects of the key regulatory questions, although the contributions from SVCCSs will be very minor, compared to contributions from other activities within NANoREG. However, a very valuable insight emanating from this work is that SVVCS can feed into discussion/considerations that relate to nano-specific considerations, but also other emerging technologies, among regulators and other stakeholders. Promotion of the usefulness of the SVCCSs as tool would be a valuable aspect of NANoREG dissemination activities.

The concrete interest from stakeholders, particularly Industry, to participate in the SVCCS has been very modest. This has exerted a drag on the recruitment of appropriate case studies. The dedicated resources from some NANoREG partners for performing the SVCCSs have been insufficient. The initial commitment indicated in the DoW was not always mirrored in the performed activities.

2.6 Data management

Not applicable.

3 Deviations from the work plan

The work linked to D1.8 has been performed according to the outline provided by the DoW.

The deliverable has been delayed. The main reason is the delay which T1.6 has experienced in general. That, in turn, has several reasons, including initial problems in receiving the national funding for NANoREG, subsequent delays in personnel recruitment, and reorganization within the T1.6 leading partner organization.