Sustainable Nanotechnologies

PROJECT FINAL REPORT

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4.1. Final publishable summary report

Executive Summary

Nanotechnology is one of the Key Emerging Technologies identified in the European Union (EU) 2020 Strategy. Its enormous potential for innovation has fostered large investments in developing new industrial applications and consumer products. However, the outlooks for a rapid growth in the sector have raised not only hopes and high expectations, but also societal concerns about the adequacy of nanotechnology regulation. Indeed, despite their clear benefits, engineered nanomaterials may pose environmental and health risks.

The main reason to launch the project SUN was to investigate these risks and find ways to prevent or reduced them. With a budget of over 13.5 million EUR, its ambitious work program involved more than 100 scientists from 35 research and industrial organisations across 12 European member states and became one of the first EU-funded projects to address risks along the entire lifecycles of real industrial products.

The implementation of SUN has been a challenging task due to the overwhelming uncertainties that marked each step of both risk assessments and innovation activities. The challenges that we encountered provoked the need to develop reliable methods for characterization of nanoparticles released from various product matrices into complex biological, environmental and food media, and for the assessment of their human and environmental exposure, hazard and risk. These tools and the newly developed safety by design procedures have become the highlights of SUN. Their integration into a Decision Support System (SUNDS) and practical risk management guidelines provided industries and regulators with the means to streamline effective decision making about safer products and processes.

SUNDS is one of the “flagship” results of SUN. This user-friendly software system can be used by stakeholders from industry, academia and regulatory bodies to assess environmental impacts and/or to identify and manage possible occupational, consumer and ecological risks arising from the manufacturing, handling, use and end-of-life treatment of nanotechnology products. In situations where the risks are not controlled the tool proposes suitable measures to reduce them. In doing this SUNDS also provides information about the costs of risk reduction as compared to the anticipated benefits from the products. This is particularly useful for industries and SMEs for checking supplier risks, competing products, market opportunities, or for performing an internal risk and benefit analysis.

The industrial partners in the SUN Consortium “reality-checked” and evaluated the new methods and tools developed in the project against real nanotechnology applications. The nanotechnology applications were represented by supply chains of real products containing nanoscale Tungsten Carbide (sintered, wear-resistant ceramics), Copper Oxide (antimicrobial/fungal wood preservatives), Silica (food), Titanium Dioxide (self-cleaning ceramic tiles and air purification systems), organic pigment (the red colour of the Ferrari cars), and multi-walled carbon nanotubes (anti-fouling coatings, lightweight plastics). The extensive development and testing of methods and tools for nanomaterials risk assessment and management did not only generate an enormous amount of new scientific data and knowledge on the release, exposure potential and hazard potency of diverse material types, but new insights into key nano-bio/eco interactions, release pathways, modes of action, and adverse outcome pathways. This validation of the SUN approach culminated in guidelines for safer product and process design, which are publically available on the project website: www.sun-fp7.eu.

Context & Objectives

SUN is based on the hypothesis that the available knowledge on the environmental and health risks of manufactured nanomaterials (MN), while limited, can nevertheless guide the nanotechnology industry to avoid future liabilities provided that an integrated approach to their risk assessment and management is applied that addresses the entire lifecycles of nano-enabled products (NEP). To facilitate this, SUN generated environmental, health and safety (EHS) data and methods and integrated them into a Decision Support System for risk control and sustainability assessment of MN and NEP. The goal was that this approach would enable safer manufacturing, use and end-of-life treatment of nanotechnology products; it would result in more solid risk prevention and mitigation strategies, and would be easily applicable to different materials and industrial settings.

This goal was achieved: the project significantly improved the current approaches to risk assessment and lifecycle assessment of MN and successfully combined them into the user-friendly software SUN Decision Support System (SUNDS) for practical use by industries and regulators. The industrial partners in the SUN Consortium evaluated and “reality-checked” SUNDS against real products in terms of costs and benefits. This validation culminated in guidelines for risk management, including safe nanoscale product and process design. As a “by-product” SUN identified needs for future research and assigned priorities for current regulation. We have involved major international stakeholders in implementing the project results into practice and regulation.

To fulfil this, we achieved the following integrated set of objectives within three central themes of nanotechnology innovation:

THEME I. MATERIALS, PRODUCTS AND PROCESSES

- Perform a data gap analysis to prioritise the generation of new information in the project
- Map hot spots release of MN at different stages of NEP supply chains to guide cost-effective strategies for release and exposure estimation
- Assess the environmental impacts arising from each lifecycle stage of the SUN case studies and compare the results to conventional products with similar uses and functionality
- Develop and validate criteria and guiding principles for green nanomanufacturing (low energy consumption, eco-friendly materials) and for setting environmental quality targets

THEME II. RISK ASSESSMENT

- Collect and characterize MN released from NEP in different lifecycle stages for use in (eco)toxicological and behaviour/fate studies
- Model the behaviour/fate of MN and assess their exposure concentrations in the environment (i.e. air, water, sediment and soil compartments)
- Develop and validate methods (incl. high-throughput and content tools) for prediction of long-term effects on humans and ecosystem services in environments subjected to multiple stressors
- Develop and validate a tiered approach for qualitative to quantitative assessment of inhalation and dermal to gastro-intestinal occupational and consumer exposure to MN, based on high-quality collated and project-generated emission rates, exposure measurements and contextual information
- Use the exposure and effects data acquired from other projects and the data newly produced in SUN for quantitative lifecycle-oriented ecological and human health risk assessment

THEME III. SAFE PRODUCT AND PROCESS DESIGN

- Describe best available technologies/practices for reduction of exposure and effects of MN in different lifecycle stages
- Develop the following innovative risk reduction methods and practices and include them in guidelines for safe nanoscale product and process design:
    - safety by design (SbD**)** elimination/substitution and waste isolation practices to reduce the release of MN from products/composites or to induce their accelerated alteration/degradation in order to reduce their environmental persistence and bioaccumulation
    - methods to analyse the evolution of the product quality parameters, process

conditions and interactions, in real-time, to subsequently exercise control over them, increasing both product safety and quality

    - best practices to minimise release and exposure of MN during handling of waste flows containing MN

- Develop and test the user-friendly SUNDS for estimating MN risk for different targets (e.g. workers, consumers, ecosystems) in each lifecycle stage and evaluating to which extent the available risk management measures could reduce this risk (incl. cost-effectiveness analysis)

To succeed in achieving the above objectives, the project adopted an innovative approach following four guiding principles:

I. Study the longer-term effects of MN on both human health and the environment

   SUN substantially advanced the area of environmental nanotoxicology and had an important contribution to the field of human nanotoxicology. The project achieved this through designing longer-term (eco)toxicity tests with lower exposure concentrations and focussing on issues such as biodistribution, inflammation, histopathology, genotoxicity and epigenetic effects as well as transformation, bioaccumulation, bio-transfer, pool/diversity loss and ecosystem services damage/loss.

II. Understand the release, fate and exposure to MN and their risks from lifecycle perspective

   SUN adopted a lifecycle analysis approach, focusing on identification of likely MN emissions and exposures arising from each lifecycle stage of real products, represented by seven overarching case studies.

III. Prevent and control risks from exposure to MN in occupational, consumer and environmental settings

   SUN collated and developed high-quality product and process-specific MN release and exposure data libraries and a three-tier inhalation and dermal-to-oral exposure modelling framework. Moreover, SUN introduced innovative SbD elimination/substitution and waste isolation practices to reduce the release of MN from products or to induce their accelerated alteration/degradation in order to diminish their environmental exposure and the resulting risks.

IV. Achieve safe/sustainable nanomanufacturing

SUN developed safety by molecular design strategies and a nano-specific Process Analytical Technology (nanoPAT) useful to define Process Control Strategies that ensure scale up of safe high-quality products.

SUN implemented a Decision Support System for risk control and sustainability assessment of MN and NEP.

Main Scientific & Technical Achievements

THEME I. MATERIALS, PRODUCTS AND PROCESSES

Portfolio of Data on Real Industrial Materials and Products

SUN developed and maintained an impressive data portfolio, consisting of data generated internally or collected from other sources in regard to seven case studies. These case studies correspond to supply chains of real industrial products (coatings and composites for the energy, transportation and construction industries as well as nanomaterials used in food). The products embed the following MN: Tungsten Carbide-Cobalt (WC-Co), Copper Oxide (CuO), Silica (SiO2) Titanium Dioxide (TiO2), organic and inorganic (Fe2O3) pigments, and Multi-Walled Carbon Nanotubes (MWCNT). Data on the release, exposure and (eco)toxicity of these materials have been collected for different lifecycle stages of these products in a data inventory: Sun.iom-world.co.uk. The physicochemical properties of the MN have been characterised both as powders and in relevant biological media for the purpose of (eco)toxicological testing and fate experiments, activities that ultimately generated results useful for risk assessment.

The SUN case studies represent a balanced portfolio of both legacy and novel NEP. In early 2014, when SUN had just started, the first mandatory reporting requirement for MN was introduced in France. In this context, the project chose to balance its case studies in three categories:

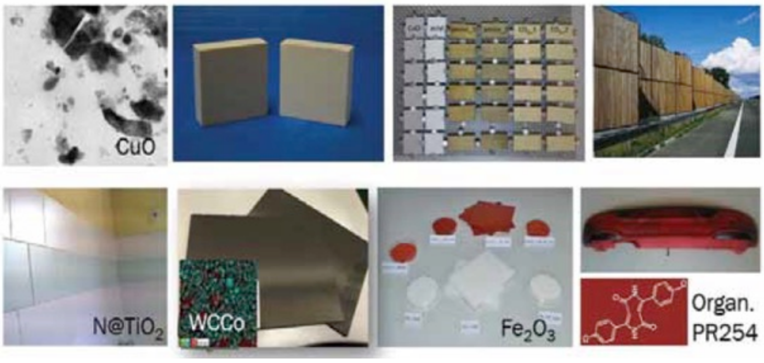
1. Highly studied benchmark nanomaterials, for which the project would generate no or limited experimental data:
    - Nanoscale Silver used in textiles.
    - MWCNT used in marine coatings and automotive parts.
2. Less well-known nanomaterials of high societal relevance. These were chosen from particulates with a history of use, which are now identified as “nanomaterials” in regulatory terms. These case studies had significant data gaps that SUN needed to fill:
    - Organic pigments for automotive parts.
    - Inorganic pigments for automotive parts.
    - SiO2 anticaking agent for use in foods.

3. Innovative nanomaterials of potentially high commercial relevance: SUN essentially had to generate all nanosafety relevant data from scratch:
    - Nitrogen doped Titanium Dioxide for air purification will became a new product enabled by SUN and exploited by the large company Colorobbia.
    - Copper based coating and/or impregnation for wood protection: a product development was re-oriented based on SUN safety assessment, to optimize the balance of performance, costs, safety and sustainability.
    - Tungsten Carbide based coatings on steel for paper mills: This product is marketed based on our results.

Very specific to SUN, for all materials the complete value chain was covered by experiments and modelling. Materials representing each lifecycle stage were provided to partners for testing. In doing so academic and industrial partners collaborated closely together to assess properties, release, exposure, hazards and risks. Of note, all these products were of industrial (product-ready) quality and were derived from pilot lines, actual production lines or batch control labs:

1. SYNTHESIS of nanomaterials (at the premises of the industrial and SME partners Nanocyl, Colorobbia, PlasmaChem, BASF and MBN).
2. FORMULATION into nanotechnology products (by the industrial/SME partners PCMA, Nanocyl, Colorobbia, BASF, MBN).
3. USE in realistic industrial and consumer settings.
4. DISPOSAL / END of LIFE treatment under realistic industrial conditions.

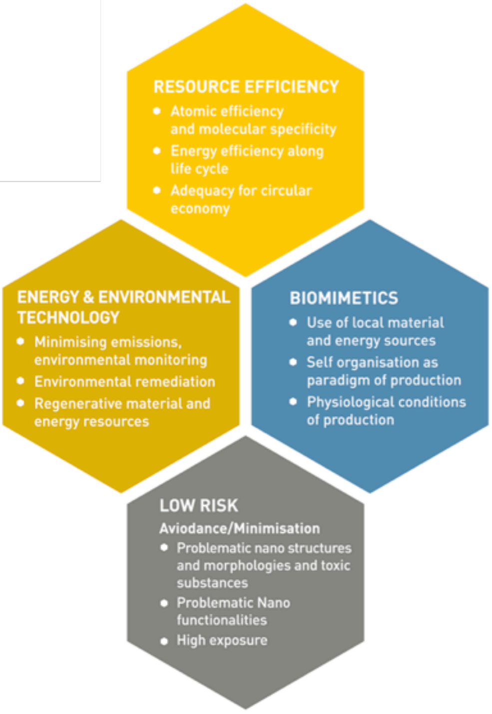
As anticipated back in 2014 when the project started, the “less well studied nanomaterials of high societal relevance” indeed are now registered with large volumes of production in nanoforms (from 100 tons/year to above 100,000 tons/year) according to French reporting. This validates the choices of SUN, in the sense that the project captured many of the nanomaterial application segments, product matrices, material classes that are highly relevant for European consumers. The tools developed by SUN are thus applicable to both established and novel nanomaterials and nanotechnology products.



Environmental Impacts

The environmental impacts of the selected MN and the associated NEP have been investigated by means of the established Life Cycle Assessment (LCA) methodology. To do so SUN developed specific life cycle models and collected/generated Life Cycle Inventory data. These data were used to perform Life Cycle Impact Assessment based on LCA midpoints combined with shadow prices. Since the investigated MNs and their applications were very diverse, this resulted in interesting and informative variety in the details of the LCA case studies. In some case studies the environmental impacts were very low, while in others they were more significant, with the impacts strongly depending on the type of the involved manufacturing process (energy demand, operating supplies, yield, purification rate). It is important to note that the potential for reducing environmental load by nano-enabled products and processes depends on the type and level of innovation (e.g. incremental vs. radical, end-of-pipe vs. integrated). Today most nanotechnology applications are incremental innovations (i.e. improved conventional products), which limits the possibility for redesigning them to meet high environmental standards. To contribute to the future development of “greener” nanotechnologies, SUN developed design principles for entire product portfolios represented by the project’s case studies. One of the key conclusions is that to benefit the environment the future nanotechnology applications should have a combination of following characteristics:

- Use MN as additives leading to better functionality of the NEP.
- Environmental benefit in the use phase (higher resource and/or energy efficiency).
- Long-life (persistent) product.
- Nanomaterials integrated in the product matrix (low release).



Design principles for ‘Green nano’.

THEME II. RISK ASSESSMENT

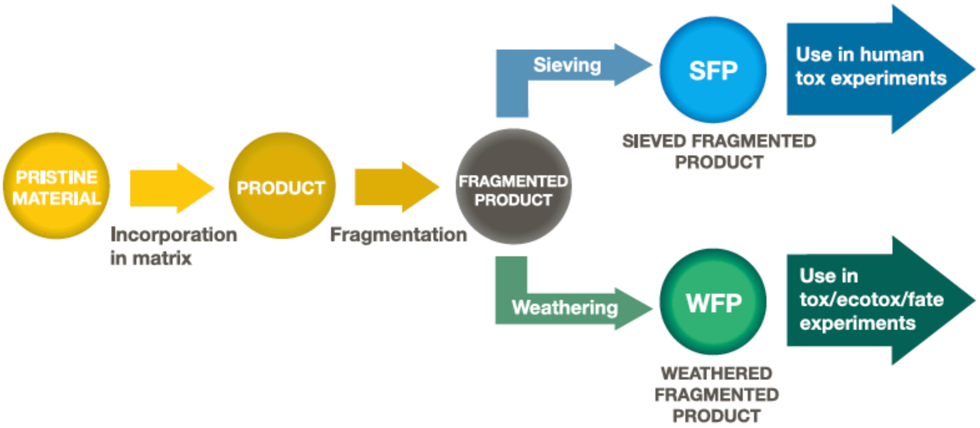
Lifecycle Release and Environmental Exposure

The analysis of the potential risks of nanomaterials has so far been almost exclusively focused on the pristine, as-produced particles. However, when considering a life-cycle perspective, the nanomaterials released from genuine products are far more relevant. The properties of the materials released during the manufacturing, use or end-of-life phases depend on the nature of the matrix and the way the particles are incorporated in it (i.e. surface-bound or internally embedded). Research on release of nanomaterials from products has been growing and the next necessary steps have been to investigate the behaviour and effects of the released materials in the environment and on humans. SUN has been one of the first projects to achieve a considerable progress in these research areas. To do this it was necessary to collect and characterize nanoparticles released from the selected SUN nanotechnology products in different life cycle stages for use in hazard and behaviour/fate studies.

The key requirements identified by our partners for producing such fragments of nano-enabled products have been:

- Use of formulated materials instead of just aging pristine particles.
- The process is reliable and quick.
- The use of samples close to real-world exposure scenarios, such that assays can be prepared for "released" materials.
- They should be available in a sufficient amount (hundreds of grams to kilograms) for testing in hazard studies and with a relevant size distribution.
- A nano-free formulated material is available as a reference.

Based on these requirements, SUN developed an approach to provide materials in hundreds of grams quantities mimicking actual released materials from coatings and polymer nanocomposites by producing what is called "Fragmented Products". These released fragments can further be exposed to environmental conditions (e.g. humidity, light) to produce "Weathered Fragmented Products" or can be subjected to a further size fractionation to isolate "Sieved Fragmented Products" that are representative for *in vivo* inhalation studies.

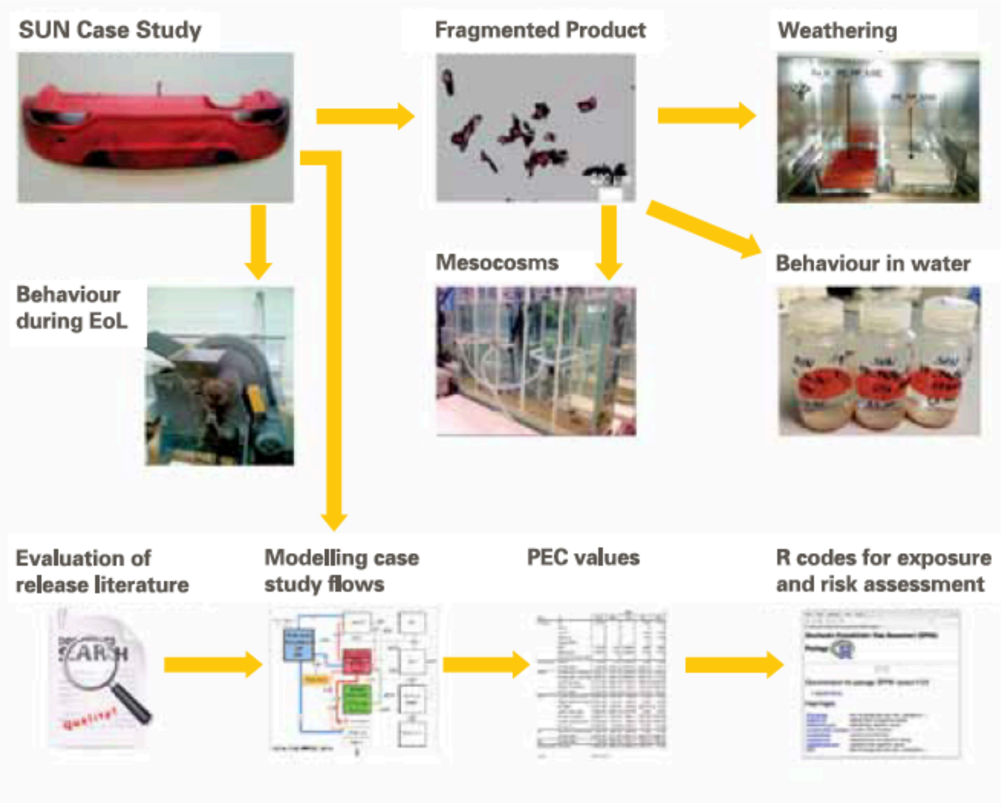


The SUN approach to produce fragmented materials.

SUN significantly advanced the environmental exposure field by contributing methods in a variety of areas. For instance, the project developed tools to analyse MN releases and characterise the released materials in complex matrices. Some examples are the following: 1) sp-ICPMS with reaction cell technology for detection of nanoscale Fe_2O_3 and CuO; 2) combination of AF4 and ICPMS for detection of nanoscale SiO_2 in food; 4) protocols for release of Fe_2O_3 from plastics and SiO_2 from food; 5) climate chamber weathering protocols for: a) Fe_2O_3 in plastics, and b) CuO painted on wood; 6) wet weathering protocols for Fe_2O_3 and organic pigments in plastics; 7) a protocol for studying the release of MWCNT from polymers (based on isotopic labelling - ^{14}C-CNTs); 8) protocols for studying the release of MN from waste during incineration, recycling and landfilling. Moreover, the project has made significant progress in optimizing the above methods so that they can better discriminate MN from background materials. To generate released MN for experimental purposes, manual and mechanical grinding and cryomilling methods were developed. One important focus of SUN was the measurement of MN release during end-of-life treatment (e.g. recycling, incineration) and disposal. In this regard the project 1) developed analytical capabilities for measuring the content of MN in different end-of-life products as well as by-products from waste processes (e.g. leachate); 2) completed tests to assess the recovery of MN during preparation of samples prior to lab analysis; 3) established procedures for leaching tests aiming at assessing the release of MN when NEP come in contact with water in end-of-life scenarios; and 4) performed measurement campaigns targeting the release of MN during pre-treatment of waste prior to recycling processes. The obtained results demonstrated that: 1) the current procedures for sample preparation may be inadequate for dealing with nanowaste; 2) losses of MN during recycling processes are significant and may induce workplace and environmental exposure; 3) leaching tests aiming at assessing release of MN need adjustments compared with the standard protocols and additional tests (e.g. TEM) may be required. Moreover, the environmental transformation of the released particles was investigated using bench scale and mesocosm scale studies in collaboration with our U.S. Advisory Board member Duke University.

The overall concept is visualized in the figure below: starting with the SUN case studies, fragmented products were produced and characterized. These materials were further weathered under environmental conditions and their behaviour in water and mesocosms was studied using methods and approaches developed during the project. The release of nanosized particles from the SUN case study materials was also tested under conditions relevant for the end-of-life treatment. Another line of research used modelling to follow the flows of nanomaterials within the products and after release. This also included assessments of the release literature and development of codes to model environmental exposure, hazard and risk. Using these tools, the nanomaterial flows for the SUN case studies and the resulting environmental concentrations were predicted. Moreover, SUN partners performed modelling of the environmental fate of MN released from solid waste due to recycling and incineration.

Overall, the work performed in SUN presents the most realistic assessment of the environmental exposure of nanomaterials so far because it is based on real-world materials and incorporates release processes. For some case studies such as automotive parts the SUN partners found no significant releases of the nanomaterials, whereas for other case studies such as wood protected with Copper the release was linked to transformation of the nanomaterials and depended a lot on the product formulation.



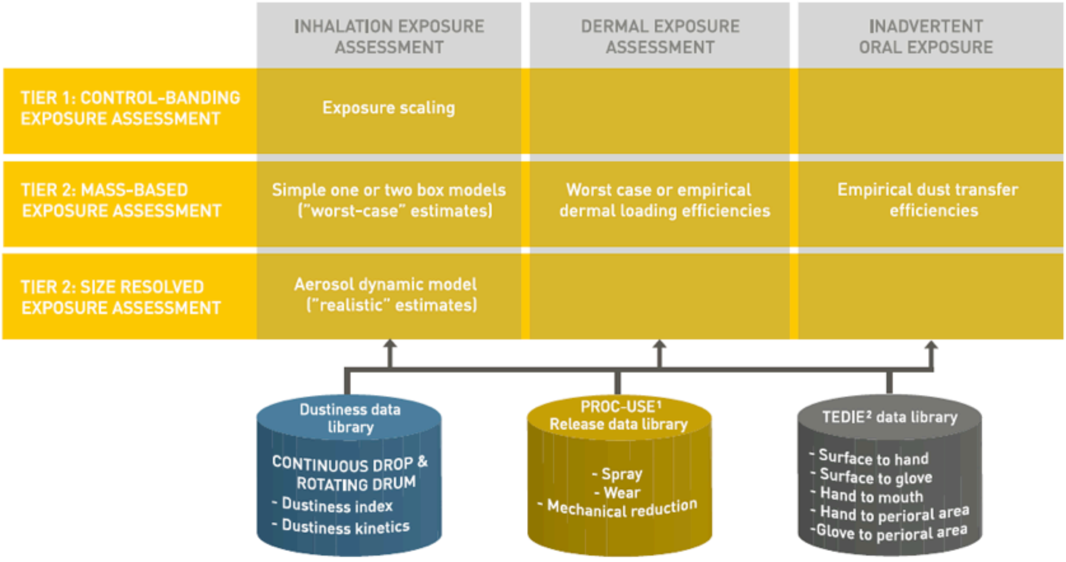
Overview of the environmental exposure research performed in SUN: Starting with the SUN case studies, fragmented products were produced that were investigated with respect to their weathering and fate. Modeling studies complemented the work by quantifying environmental exposure.

Occupational Exposure

The above release work has relevance not only to estimating environmental exposure, but also exposure in occupational settings. In this regard, SUN has significantly progressed in developing a versatile tiered modelling framework for assessing workers’ inhalation, dermal and inadvertent oral exposure to MN. The highlight of this framework is a new aerosol dynamic inhalation model developed in the project. To support the modelling approach, release rate libraries were developed for powder respirable dustiness and different processes based on comprehensive reviews and additional data generated as part of SUN. For assessment of inadvertent oral exposure, dermal to perioral transfer efficiencies were proposed.

The Exposure Control Efficacy Library (ECEL) library on engineered and personal protection equipment was also further developed to include efficiencies against nanomaterial exposure based on data generated in the project.

Five workplace exposure measurement campaigns were completed to establish values for comparison with modelled exposure levels. The measurements were specifically conducted for synthesis of nanoscale CuO, production and handling of WC, production of car bumpers with organic and inorganic pigments, and application of TiO_2 coatings. The results of this work and especially the establishment of the dustiness and release rate data libraries will have a significant impact on the capability and quality of future nano-specific exposure assessments. These libraries will become publically accessible and subscribing laboratories will be able to contribute with further data in the future.



[1] PROC-USE: Process and Product Use

[2] TEDIE: Transfer Efficiencies for Dermal and Ingestion Exposure v. 1.1.3 (provided by IOM). Data are not specific to NM!

The conceptual SUN occupational exposure assessment framework for nanomaterials.

Consumer Exposure

SUN has contributed to the field of nanomaterials consumer exposure assessment through developing realistic scenarios of nanomaterial release from various products. Data from several NEP inventories were analysed to gain information regarding nanotechnology products and their availability, distribution across product groups, and the use of different nanomaterial types. Consumer exposure data libraries were established. Several exposure models were applied to the release data to quantify potential consumer exposure that may arise from using these products. The release of nanomaterials from commercially available articles was experimentally tested, considering conditions relevant for consumer exposure such as leaching from food contact materials, textiles and personal care items as well as dermal transfer from product surfaces. These experiments were designed to allow close to realistic exposure potential estimation.

Overall, the work conducted within SUN regarding consumer exposure provides insight and novel data for both measurements and modelling, with focus on relevant real-world consumer articles and likely exposure scenarios.

Environmental Hazard Studies

SUN took environmental hazard assessment of nanomaterials an immense step forward as it developed a vast array of testing methods that allow us to predict longer-term ecotoxicity of nanomaterials. It is possible to test both pristine MN and such released from products at different lifecycle stages. All environmental media were covered, i.e. sewage sludge treatment plants, soil, sediment and water, with a focus on ecosystem services and key environmental species. The tools include 1) short-term high throughput studies, e.g. *in vitro*, *ex vivo* and *in vivo* omics-related methods, and 2) long-term *in vivo* studies, e.g. longevity, full life cycles, multi-generation and multi-species test methods. The biological endpoints range from omics to population interactions. This includes cell viability, various omics-responses (gene, protein and metabolites expression), individual life stage endpoints, species interactions, and trans-generation effects, including epigenetic effects.

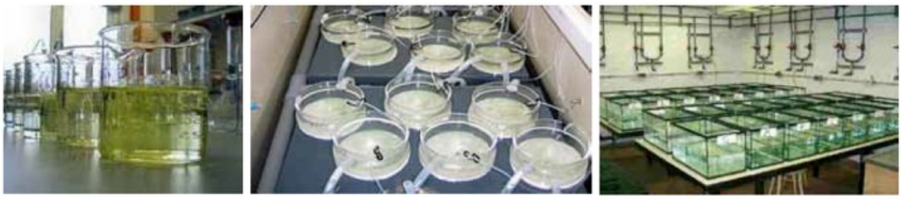
SUN developed new nano-specific testing methods for assessing the effects of MN on ecosystem services, including sewage treatment plant (STP) function and crop production. This has resulted in an array of results for MN effects in sewage treatment plants (e.g. ammonium oxidizing bacteria), terrestrial environments (e.g. *Enchytraeus crypticus*, *Eisenia andrei*), aquatic sediments (e.g. *Lymnaea stagnalis*, *Daphnia magna*), and pelagic parts (e.g. zebrafish embryos). Moreover, longer-term ecotoxicity tests with lower exposure concentrations were performed focusing on transformation, bioaccumulation, biotransfer, gene-pool/diversity loss and ecosystem service damage/loss. In this regard, many long-term *in vitro* and *in vivo* test systems were evaluated or developed *de novo*.

The *in vitro* methods for the terrestrial ecosystem span over more than five species, and the aquatic *in vitro* methods include both single- and multi-generation cell systems. The developed *ex vivo* methods are highly effective tools to study uptake mechanisms in fish-gut.

Uptake studies were important for identifying dietary exposure and bioaccumulation. The tools were integrated so that the results are mutually supportive; this enables the risk assessor to develop a better risk mitigation strategy. The implementation of high throughput tools allowed for Adverse Outcome Pathways (AOP) to be developed. AOP enhanced the understanding of the mechanisms of toxicity and enabled designing materials according to SbD approaches. Pristine MN, modified pristine MN (SbD), and fragmented materials were tested. Reference materials were also tested, e.g. soluble salts of the respective metal MN and fragmented products without embedded MN.

Overall, the work performed by SUN presents the most advanced and realistic assessment of the environmental hazard of nanomaterials so far. It includes real-world materials and deals with long-term highly relevant ecological processes.

The STP tests have shown that the passage through a STP may increase the ecotoxicity of the CuO MN. There is no evidence that microbial toxicity differs following single or repeated exposures to MN, provided the same final concentration. In the terrestrial environment, advanced single species and multispecies long-term tests have shown pronounced CuO toxicity in contrast to lower toxicity of the rest of the MN investigated in SUN. In the aquatic sediment, all MN have been screened in two species (i.e. *Lymnaea stagnalis* and *Daphnia magna*) using short-term tests, while long-term tests have been performed with *Lymnaea stagnalis* only. The results from these tests demonstrate that the toxicity of the CuO MN is dependent on the water pH. Some epigenetic tests have shown low CuO methylation in collembolan and enchytraeids. Methylation of specific genes was also measured. *In vitro* tests with MN on fish and worm cells have shown decreased viability and disturbance of cellular stability. For earthworms, the cells of five species were tested. Repeated exposures have been performed showing effects different from non-repeated long-term exposure. The relevant results were used to perform ecological risk assessment of NEP along their lifecycles.



Human hazard studies

The SUN project began with an ambitious list of nanomaterials for risk assessment, but due to budget constraints and ethical concerns not all were tested for human hazard using animal models. Instead an intelligent testing strategy was implemented that prioritized a set of nanomaterials for which data did not exist in the published literature or existing projects for *in vitro* and *in vivo* toxicity testing. The *in vitro* models included immune (macrophage) and liver (hepatocyte) cell lines. Macrophages were chosen as these cells are responsible for clearing particles from the body, as well as eliciting an inflammatory response that could be indicative of potential toxicity. Hepatocytes were chosen as the liver is a major site of nanomaterial accumulation in the body following exposure via either inhalation or ingestion. Dose-response relationships were generated for each cell type using the SUN panel of nanomaterials, and both identified pristine CuO nanoparticles as being more toxic than the others. The lack of existing data on this material along with this *in vitro* hazard data and potential widespread use in wood treatment products resulted in its prioritization for *in vivo* hazard testing. The protocols used for the *in vitro* toxicity testing were taken from previous projects (e.g. ENPRA) to allow comparison of data across studies. In the ENPRA project both *in vitro* and *in vivo* instillation studies had been conducted. There was therefore a pre-existing understanding regarding the relationship between the *in vitro* dose response relationship and the doses likely to induce inflammation in the lung *in vivo*. This relationship was used to predict the most suitable deposited dose and hence airborne mass concentration ranges to use for short-term inhalation studies (STIS; 5-day exposure, followed by sacrifice on day 6 or day 28). The dose range chosen generated a dose-dependent inflammation (e.g. neutrophil accumulation and cytokine up-regulation) at day 6 which was largely resolved at day 28. The inflammation was confirmed by quantification of inflammatory cell influx into the lung as well as gene, protein and genomic analysis of the lung tissue. The data generated contributed both to risk assessment and the further modification of the pristine CuO using a SbD approach. A panel of modified CuO nanomaterials were tested *in vitro*, again using the macrophage and hepatocyte cell lines in order to prioritise coatings for further testing *in vivo*. Coating with ascorbate decreased *in vitro* toxicity in both models, and was associated with a lower inflammatory response *in vivo* both at day 6 and day 28. It also did not prevent the antimicrobial function of the CuO. This approach therefore demonstrates the usefulness of alternative models in refining animal studies and reducing the number of animals used.

To investigate the effects of the CuO nanomaterials following ingestion, a new short term oral study (STOS) protocol, based upon the STIS protocol was devised. Similar to the STIS study, treatment with CuO nanomaterials for 5 days resulted in a measurable inflammatory response at day 6 which was largely resolved at day 28. This study demonstrates similarities between impacts regardless of the route of exposure for CuO nanomaterials, and furthermore provides a useful protocol for investigating the consequences of oral exposure to potentially toxic substances. The STIS and STOS generated kinetic data suitable for pharmacokinetic (PBPK) modelling and a methodology was developed on this basis to perform *in vitro-in vivo* and animal to human extrapolations for human health risk assessment.

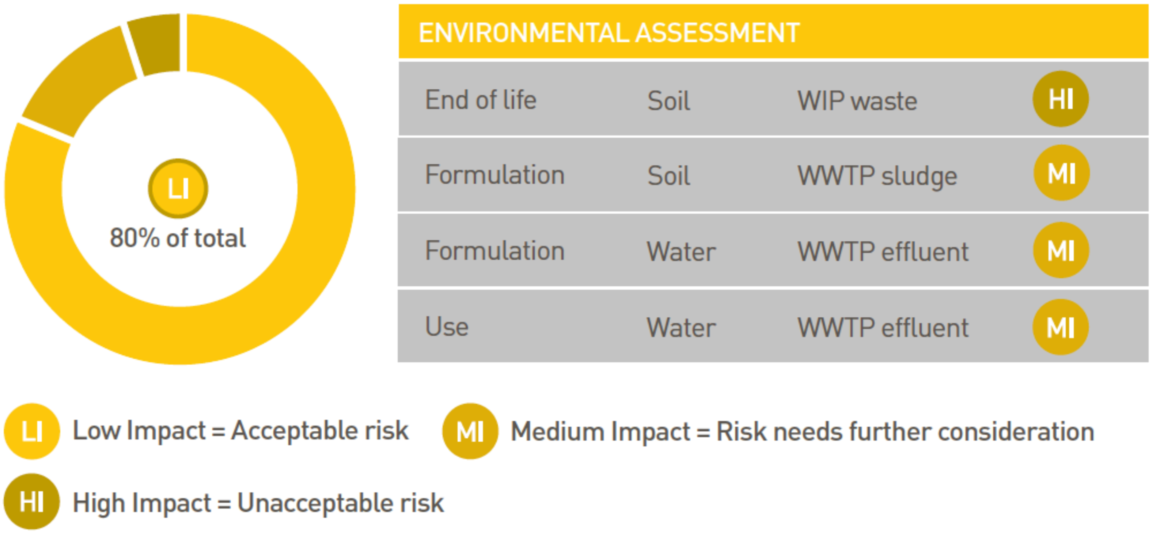
Moreover, *in vivo* epigenetics and transcriptomics tests were performed with the CuO case study in collaboration with Health Canada. In the epigenetic study the levels of gene methylation were found to be low (<1%) overall for all genes, and highly variable. No significant differences between any experimental treatments were observed. The transcriptomics study showed that exposure to the higher dose for 5 days yielded the most significant changes in gene expression, accounting for significantly changed mRNA of about 1000 genes, most of which were up-regulated. In contrast, animals collected after recovery yielded < 20 dysregulated genes, thus indicating return to levels similar to the controls. Most of the deregulated genes related to inflammation and cell proliferation in a dose-response manner, which was reversible after the recovery period.

Health and Environmental Risks

SUN advanced in the field of human health risk assessment of nanomaterials by developing a probabilistic risk assessment methodology, which was implemented as a software module in SUNDS. Hazard and exposure data can be estimated deterministically or probabilistically, depending on data availability. Traditional (deterministic) risk assessment relies on single point estimates of hazard, exposure and risk, and often fails to explicitly report the uncertainties that are needed for robust risk management decision making. In this context, a considerable strength of the developed probabilistic approach is that the estimated risk distributions explicitly communicate these uncertainties and support the identification of the parameters (e.g. exposure conditions, selection and use of assessment factors) that most strongly affect the estimated risks.

Specifically, health risk assessment in SUN was performed considering the entire value chains of the SUN priority nanomaterials and exposure of both workers and consumers via inhalation and ingestion. The estimated probabilistic health risks were then classified as acceptable or non-acceptable. Once risk is estimated for individual targets, activities and routes of exposure, an aggregation step produces a single risk value for each lifecycle stage (synthesis, formulation, use, end of life) as well as for the entire lifecycle of the investigated NEP.

SUN also advanced in the field of ecological risk assessment of nanomaterials by developing the first methodology and tool for the estimation of risks along the lifecycle of nanotechnology products covering key environmental compartments (e.g. surface water, soil, sediments). Specifically, a probabilistic material flow environmental exposure model developed in the project predicted environmental concentrations (PEC) resulting from flows of nanomaterials released from products in each lifecycle stage. Moreover, Predicted No Effect Concentrations (PNEC) were derived by means of both deterministic and probabilistic (i.e. Species Sensitivity Distributions) procedures compliant with the REACH guidelines on Chemical Safety Assessment. Thus, an ecological risk portfolio along the lifecycle is calculated by choosing the maximum risk for each lifecycle stage:



ENVIRONMENTAL ASSESSMENT			
End of life	Soil	WIP waste	HI
Formulation	Soil	WWTP sludge	MI
Formulation	Water	WWTP effluent	MI
Use	Water	WWTP effluent	MI

Example of the ecological risk portfolio along the lifecycle of a nanotechnology product.

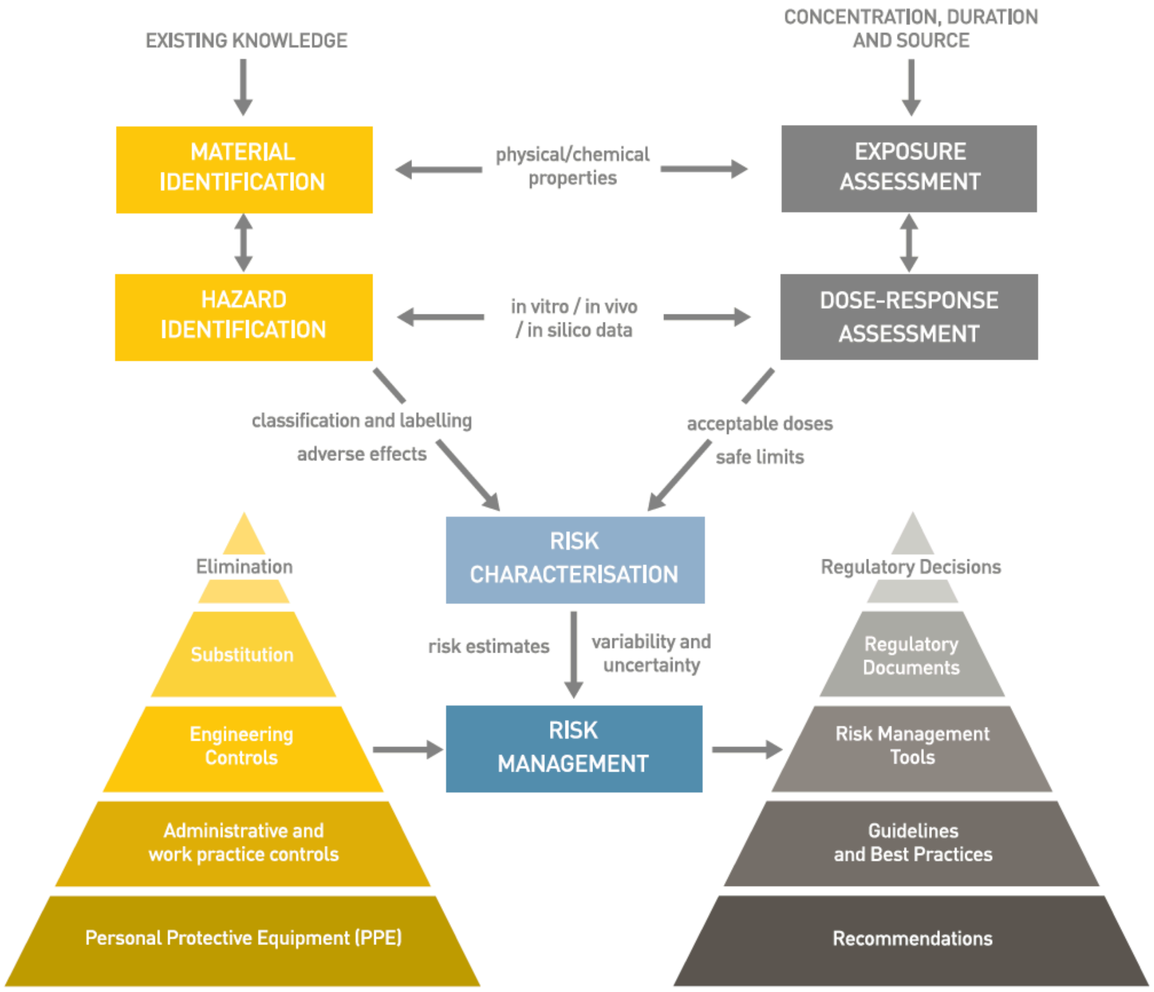
Both the ecological and human health methodologies were tested in the SUN case studies and were implemented as software modules in SUNDS for practical use by industry and regulators.

THEME III. SAFE PRODUCT AND PROCESS DESIGN

Risk Management

The risk management of nanotechnologies has received much attention over the last years and significant data on the efficacy of risk management measures applied to nanomaterials (e.g. local exhaust ventilation, fume hoods, glove boxes) have been generated. To collect these data and information on SbD methods and make them easily available to our industrial stakeholders SUN developed an inventory of Technological Alternatives and Risk Management Measures (TARMM), which was hosted in the ECEL online library. The compiled information was then summarised in easy-to-read guidelines. The analysis of the data showed that engineering controls and protective clothing are more commonly used to reduce risks of MN as compared to SbD practices targeting the elimination, substitution and modification of NEP. This is mainly due to the unknown or unacceptable effects of manipulating the characteristics of the nanomaterials on their desired functionality. Some of the key conclusions drawn by SUN partners for selecting the appropriate risk management measures for nanomaterials are the following:

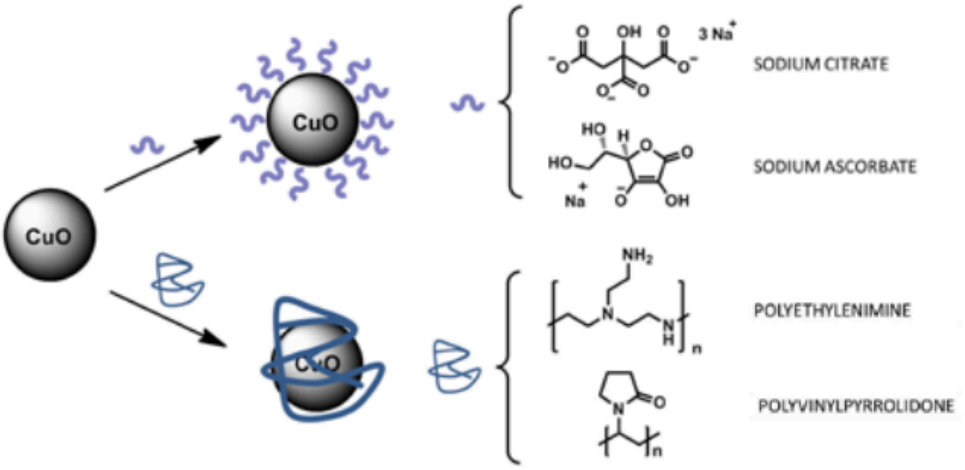
- When the intrinsic safety measures (e.g. elimination and substitution) are not viable, the second-best option for safe handling of MN is to implement engineering control measures.
- The selection of engineering controls at workplaces should be made based on the state of the nanomaterial (e.g. physical form and properties), the level of concern about a hazard (e.g. low, medium, high), the exposure potential (e.g. low, medium, high) and the primary routes of exposure (e.g. inhalation, dermal absorption or ingestion).
- When there is no/low potential for airborne release (e.g. nanoparticles bound in solid matrix), advance engineering controls are usually not needed. This applies also to nanomaterials suspended in liquids, except for the combination of substances of elevated hazard potential (such as CNTs) with processes of high energy input (such as sonication). In any case, drying of suspensions is to be prevented.
- Working with dry nanoparticles of low hazard potential (such as the pigments investigated in SUN) can generate a measurable emission, but the risk can stay in the acceptable limits without enclosure. In general, removing the airborne emissions through local exhaust ventilation is advised nonetheless.
- Working with dry nanoparticles of elevated hazard potential requires very careful attention. When there is high probability of airborne emissions leading to exposure (e.g. nanoparticles in powder form or pellets), the work should be performed in fume hoods or an enclosed system such as glove box or glove bags. To assess the probability of airborne emissions, SUN generated tools and libraries via measurements of the dustiness of powders.



Risk assessment and management process.

Safe Product Design

The design of safer nanotechnology products and processes can prevent risks. However, the selection of SbD solutions is complex and often requires data-intensive validation. SUN developed SbD strategies for the WCCo and CuO case studies. Specifically, for the WCCo micronization techniques (i.e. spray and freeze drying) were developed. In the case of CuO four surface modifying agents were chosen: positively charged (branched polyethylenimine-PEI); neutral (polyvinylpyrrolidone-PVP); negatively charged (sodium citrate-CIT); negatively charged with strong anti-oxidant capacity (sodium ascorbate-ASC). Once the surface was modified we tested the effects arising from the different surface chemistries and charges to identify the most promising design alternatives. The aim was to control surface charge and its direct electrostatic interaction with cell membranes and to test some antioxidant molecules (citrate and ascorbate) for their protective action against free radicals.



Schematic representation of SbyD strategy applied: introduction of surface modifying agents (i.e. CIT, ASC, PEI and PVP) by self assembling.

To validate the above strategies, we adopted a stepwise approach that aimed at providing answers to the following questions:

1) Do the introduced modifications affect the design properties (chemical composition, crystallinity, surface area/chemistry/charge, primary size) that define synthetic identity?

2) Do the modifications affect risk determinant properties (structural alerts) such as properties that define exposure identity (e.g. evolution of synthetic properties in testing and life cycle media, particle size distribution (PSD), ZETA potential, colloidal stability, MN release/mobility and bioavailability, dustiness) and properties relevant for estimating hazard potential because they are driving some of the most established modes of actions (e.g. ROS production; IONS dissolution/speciation/ distribution)?

3) If no, then hazard assessment through (eco)toxicity testing was performed and different scenarios occurred:

- The tested (eco)toxicity endpoints did not show differences or the differences were not consistent (some results showed a reduction of toxic potential others showed an increase); in this case, further mechanistic investigation was necessary and new design modifications had to be introduced.
- The tested (eco)toxicity endpoints showed a consistent response as the results of the selected modification showed either an increase or a decrease of toxic potency. In this case, we looked for a physically possible compromise between toxicity and requested functionality.

4) If the results from (eco)toxicity testing were useful to consistently predict a reduction of *in vitro* or *in vivo* toxicity along the established modes of action, performance evaluation was

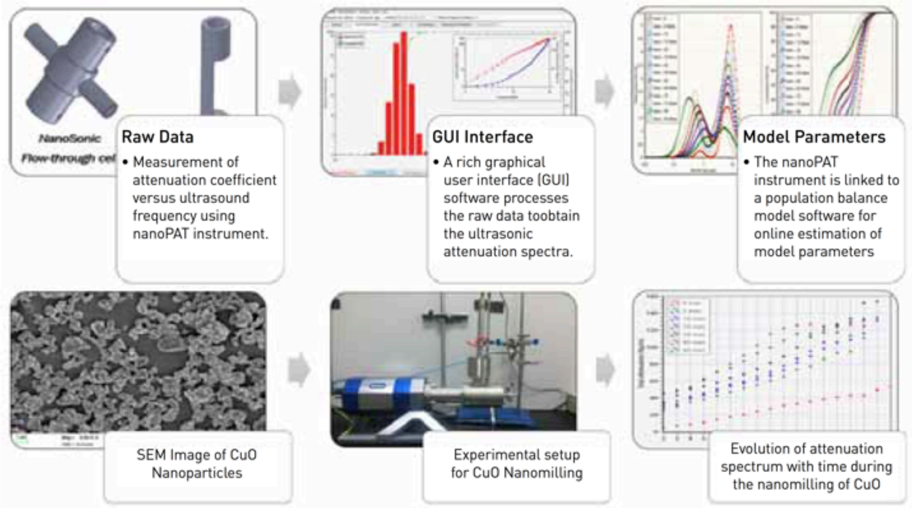
necessary to prove the sustainability of the proposed solutions and a cost-effectiveness evaluation also had to be performed.

The results from the performed activities provided useful data to support the assessment of nano-bio interactions and make hypothesis on mechanisms of toxicity with the real possibility to act on molecular design and drive adverse biological effects.

Safe Process Design

Safe nanomanufacturing is of crucial importance for sustainable nanotechnology, but the dynamic properties of nanomaterials require new analytical and assessment techniques. SUN partners developed a nano-specific Process Analytical Technology (nanoPAT) to measure the real-time evolution of particle size distribution. It is an online particle sizing system based on acoustic spectroscopy. Two different hardware configurations, a flow through cell and a probe, were developed and optimised. The flow through cell operating in transmission mode was designed in a way to ensure easy connection to a flow system while the probe was designed to be inserted into a crystalliser or a reactor. Rich graphical user interface software was developed using Windows Presentation Foundation graphical subsystem to automatically process the raw particle sizing data and to convert the attenuation spectra into the particle size distribution. SUN also developed a new population balance modelling software for online estimation of the process parameters. The nanoPAT instrument was linked to the population balance model software to allow online comparison of the measured and estimated particle size distributions during nano-processing operations.

The nanoPAT system was applied to the processing of α-alumina and CuO. The evolution of particle size distributions during the processing was measured online using the instrument and validated by two other particle sizing techniques, i.e. Dynamic Light Scattering, and Laser Diffraction. The instrument and the software packages have shown great promise in predicting and measuring the evolution of particle size distribution online during nano-processing. Undoubtedly, the ability to dynamically monitor the changes in the particle size distribution of nanoparticle solutions in real time is very significant in the establishment of an effective process control methodology to achieve and maintain desired quality parameters and process specifications.



The nano-specific process analytical technology (nanoPAT) instrument developed in the SUN project and its application to the Copper Oxide nanomilling process.

End of Life Treatment and Waste Management Practices

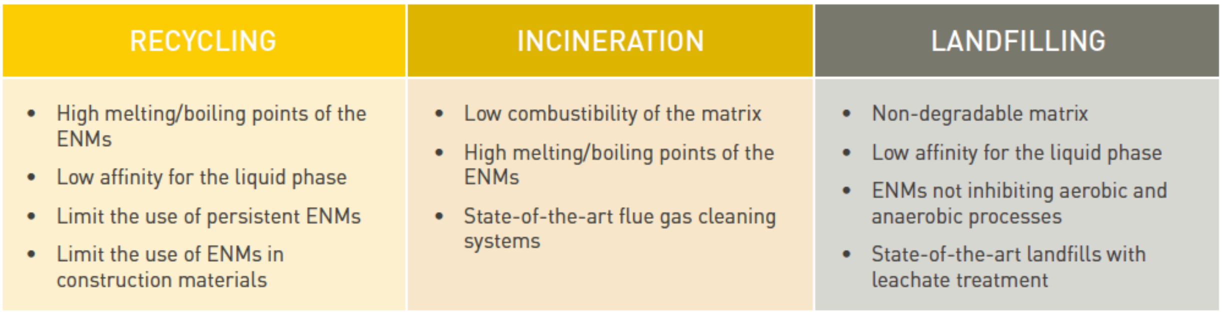
The SUN project specifically addressed the presence of MN in waste streams. The activities focused on three major aspects:

1. Identifying major waste materials and the waste treatment processes.
2. Analysing the factors influencing the release of nanomaterials during waste handling procedures.
3. Developing guidelines for safe handling of waste streams containing nanomaterials.

Using independently maintained websites such as nanodb.dk as centre of evidence, we identified waste plastic as the waste stream where nanomaterials could be found more frequently, while Silver is the nanomaterial most frequently present in this website. It is interesting to note that the legally required reporting of nanomaterial production or import in France prioritizes other nanomaterials much higher (as reflected by the SUN case studies).

The apparent contradiction is evidence of the challenges to understand and regulate nanomaterials. For the three scenarios analysed (i.e. Denmark, United Kingdom, and Europe), we estimated that recycling would be the end-of-life treatment option mostly involved in handling of MN, followed by either incineration (e.g. Denmark) or landfilling (e.g. United Kingdom). When analysing factors determining the release of nanoparticles during waste handling, we found that a range of different aspects should be considered in assessing the potential release, which depend on both the process under consideration (e.g. recycling, incineration, landfilling) and the specific waste material (e.g. plastic, paper, glass, metals). For recycling processes, we identified the following aspects: 1) hardness of the matrix, 2) temperature reached during the process, 3) the affinity of nanoparticles towards the air, solid, or liquid phase. For incineration processes, we assessed that release to the environment would be affected by the 1) combustibility of the matrix, 2) the melting/boiling/degradation points of nanomaterials in relation to the combustion temperature, and 3) the overall performance of the flue gas cleaning system as well as 4) the treatment of the solid residues (e.g. bottom ash, fly ash) from the system. With respect to landfilling, important aspects are: the degradability of the matrix, the affinity of the nanomaterials for the solid/liquid/air phases, mobility/aggregation of the nanomaterials, and finally the presence of a treatment system for landfill leachate.

Based on the identified factors, we developed waste treatment recommendations, which can be used for development of SbD products. These recommendations come along with the general need to better understand the streams of nanomaterials in products.



RECYCLING	INCINERATION	LANDFILLING
• High melting/boiling points of the ENMs • Low affinity for the liquid phase • Limit the use of persistent ENMs • Limit the use of ENMs in construction materials	• Low combustibility of the matrix • High melting/boiling points of the ENMs • State-of-the-art flue gas cleaning systems	• Non-degradable matrix • Low affinity for the liquid phase • ENMs not inhibiting aerobic and anaerobic processes • State-of-the-art landfills with leachate treatment

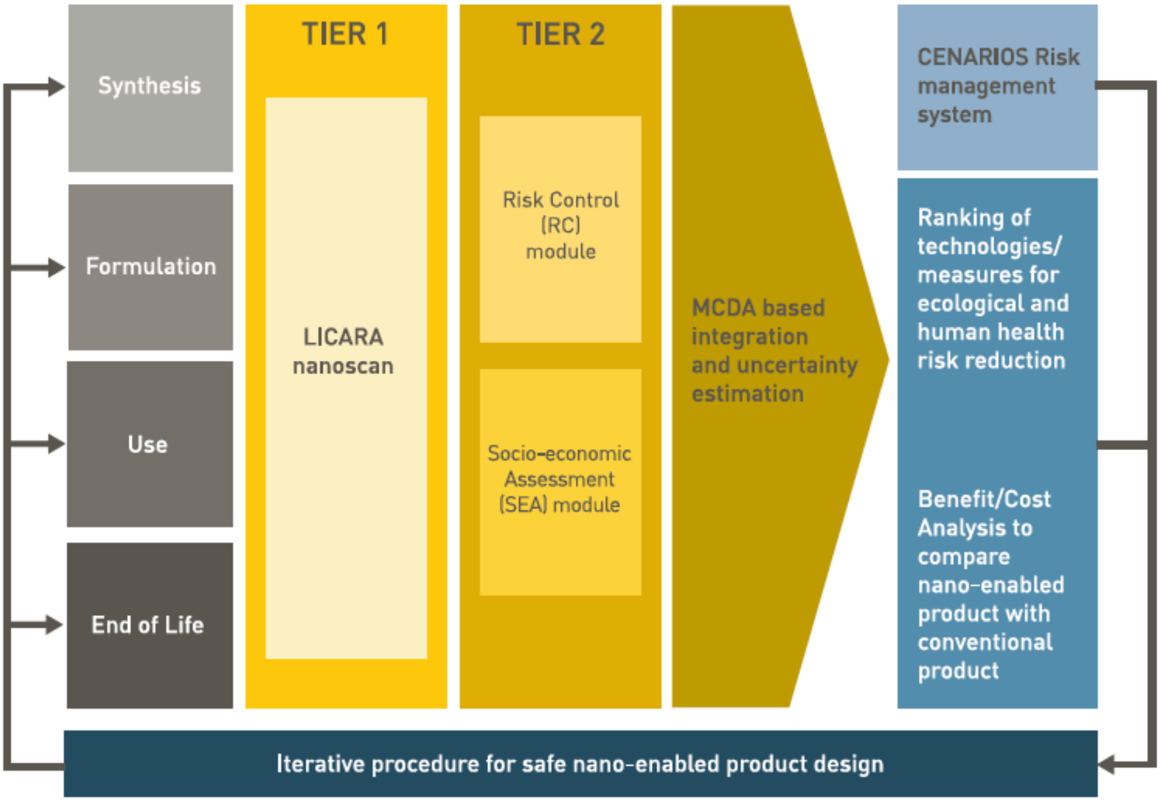
Overview of safe-by-design recommendations in relation to major waste treatment processes.

Decision Support System for Risk Assessment and Management of Nanotechnology Products

SUNDS is one of the highlights of the project. It is a user-friendly software system that estimates occupational, consumer and environmental risks from nanomaterials in real industrial products along their lifecycles. In situations when the risks are not acceptable SUNDS proposes suitable risk management measures, including information about their costs compared to the benefits of the nanotechnologies. SUNDS has been tailored to the needs of key stakeholders from e.g. industry, regulation and insurance who were engaged in a series of interviews and workshops to discuss its design and functionality.

SUNDS comprises Risk Control (RC) and Socioeconomic Analysis (SEA) modules. RC can be demonstrated by reducing risk to below threshold levels or by investigating feasible alternatives to the substance. If risks are not adequately controlled and no feasible alternatives to a substance are found, SEA is used to demonstrate that benefits of using a certain MN significantly outweigh the risks/costs.

SEA analyses all environmental, economic and social impacts, at both micro and macro levels. Integrating RC and SEA within the SUNDS allows its users to be guided on the technical and economic performance of risk management along the lifecycles of NEP.

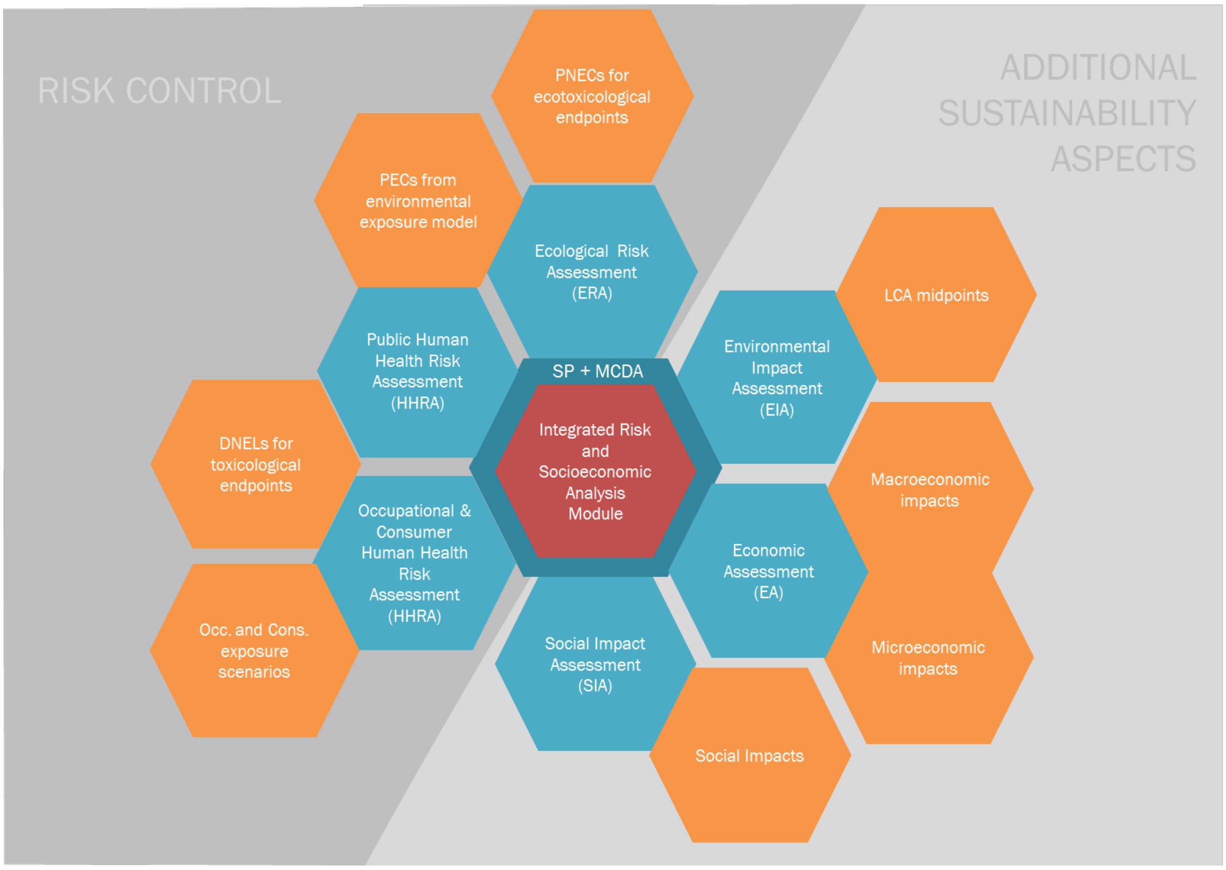


SUNDS Conceptual Framework

In addition to the two tiers shown in the figure above a stand-alone module based on CENARIOS (Certifiable Nano-specific Risk Management and Monitoring System) standard was developed and included in SUNDS.

Tier 1 of the decision support system comprises of the NanoSCAN developed within the FP7 LICARA project specifically for SME that often do not have the resources and expertise to apply complex decision support systems. Therefore, NanoSCAN is a very user-friendly screening-level tool with relatively low data requirements that provides a semi-quantitative evaluation of the environmental, social and economic benefits and the ecological, occupational and consumer health risks of MN in products from lifecycle perspective. In addition, NanoSCAN can assist SMEs in checking supplier risks, competing products, market opportunities or making an internal risk and benefit analysis.

SUNDS Tier 2 implements an integrated RC and SEA module, in which the RC module comprises of three risk sub-modules (in blue, with dark grey background the figure below) and SEA comprises of all the sub-modules (in blue in the figure below).



SUNDS Tier 2.

The *Ecological Risk Assessment (ERA)* sub-module derives ecological risk quantitatively by integrating outputs from: a) an environmental exposure model that estimates PEC in different environmental compartments (e.g. water, soil), and b) deterministic procedures or Species Sensitivity Distributions that estimates PNEC for various species in these compartments. Both models were developed in SUN based on work in previous projects.

The Public Health Risk Assessment sub-module estimates the risks for humans exposed to nanomaterials via the environment by integrating outputs from: a) the environmental exposure model described above, and b) deterministic and probabilistic procedures for dose-response assessment and intra/inter-species extrapolations (developed in SUN). The resulting estimation of human health risk will be always quantitative, but either deterministic (Exposure dose/Derived No-Effect Level (DNEL) >1) or probabilistic (i.e. 5% of the population has at least a 10% response with 95% confidence) depending on the nature, quantity and quality of the input exposure and effects data.

Occupational and Consumer Human Health Risk Assessment (HHRA), which derives occupational and consumer health risk by integrating outputs from: a) Human health exposure model (developed in SUN), that assess relevant occupational and consumer exposure scenarios according to three tiers (i.e. qualitative, semi-quantitative and quantitative) and taking into account the effect of applied risk management measures, and b) the above deterministic and probabilistic procedures for dose-response assessment and intra/inter-species extrapolations.

Environmental Impact Assessment (EIA) sub-module, which accepts LCA midpoints calculated as per explicitly specified LCIA methodology (e.g. ReCIPe, CML, etc.). The conduction and interpretation of LCA requires specific expertise; therefore in order to protect the user-friendliness of SUNDS it was decided not to program an LCA software and database within its platform, but to link it as external software to estimate impacts such as climate change, ozone depletion, terrestrial acidification, eutrophication, photochemical oxidant formation, particulate matter formation, ionising radiation, land use, water resource depletion, resource depletion, human toxicity and ecotoxicity.

Economic Assessment (EA) sub-module, which assesses microeconomic impacts due to NEP. Microeconomic impacts are at the individual company level, and implement a cost evaluation methodology for nanomanufacturing. BASF contributed to developing this module based on their SEEBALANCE tool, which is based on lifecycle costs from a consumer perspective.

Social Impact Assessment (SIA) sub-module, which assesses social impacts due to NEP. It focusses upon impacts due to workplaces, products and regional contexts. Social indicators are normalized to suitable impact classes and expressed in absolute terms. The company BASF contributed also to developing this module based on their SEEBALANCE tool.

In the Risk Control (RC) Module outputs of the ERA and HHRA sub-modules are integrated with the TARMM inventory by means of Multi-Criteria Decision Analysis (MCDA).

The Socioeconomic Assessment (SEA) module in Tier 2 which integrated outputs of ERA, HHRA, EIA, EA and SIA sub-modules, each classified by the user as benefit or cost, to compare NEP to conventional products.

Integrating RC and SEA within SUNDS allows its users to be guided on the technical and economic performance of risk management along the lifecycle of NEP. This is particularly interesting for industry and SME as it will enable them to easily perform regulatory safety assessment and to make decisions concerned with product innovation. This can reduce their R&D&I costs and can enable them to compete more effectively.

To explore SUNDS go to http://sunds.dais.unive.it.

Impact

The large-scale production and commercialization of nanotechnologies require an understanding of their environmental, health and safety impacts, and must develop strategies for their safe production, use and disposal. Today we still face challenges to understand and mitigate the potential risks from nanotechnologies. One of the main reasons for this is the fact that MN undergo complex transformations when incorporated in products and when released from them in occupational, consumer and environmental settings. The overall impact of SUN is to provide industries and regulators with data and tools to address these challenges. The project achieved this through development and application of methods for: 1) prediction of release of MN from industrial processes, consumer products, end-of-life processing and waste; 2) estimation of the longer-term effects of released and weathered MN in ecosystems and in humans; 3) occupational and consumer exposure and risk assessment; and 4) risk prevention and control. The project has covered the entire lifecycles of MN and has developed safer by molecular and process design strategies.

We carefully scoped the data generation in SUN to achieve high impact by addressing key concerns of industries and regulators. The markets covered by the SUN case studies TiO_2, SiO_2 and organic pigments used in plastics and fillers are large: 235,000,000 tons/year of plastics worldwide, thereof € 295 billion worth sales and 1,450,000 jobs in Europe; pigments: 317,000 tons, worth €4 billion; and nano-fillers: 242,000 tons. Because the highest profit margins for material producers are in the formulation and synthesis of compounds we have focused the SUN activities on these steps of the supply chains. The sintering ceramic material WC was selected to ensure the applicability of the methods developed in the project also to the impressive portfolios of the cement/concrete and fillers industries. The rest of the materials were selected less for their commercial impact, but because of their very considerable consumer and environmental safety impact: CuO, Ag: fewer than 1,000 tons/year, but of high ecological concern; MWCNT: less than 300 tons, but of high human health concern.

In addressing the risks from some of these materials (i.e. CuO and WC), SUN has shifted the research focus from risk assessment to risk prevention by developing safer by molecular and process design strategies. To increase the safety of these materials without compromising their successful scale-up we also assessed their performance and tried to keep it in commercially viable ranges. In addition, we developed approaches for Inherently Safe Process Design based on a nano-specific Process Analytical Technology, which was improved in SUN and applied to case studies to analyse the evolution of key product quality parameters and process conditions in real time. The obtained results were useful to establish mechanisms to control these parameters in order to increase the safety of production.

To ensure that the above risk prevention and management solutions will effectively guarantee the MN fate, we studied the release of MN from industrial and waste products. The obtained results helped us to partially answer the question of regulators whether the processes studied in the laboratory have relevance to the real-world situations, which has had impact in the implementation of the REACH regulation for MN. The release and exposure data produced in SUN have been also very important for industries to analyse the overall risk and environmental impacts of their products in order to understand where they stand in terms of safety and environmental performance and therefore refine their R&D investment and marketing strategies. Specifically, our industrial partners have used these results to benchmark the environmental performance of their nanotechnology products against conventional alternatives. This has already had a huge impact on their product development, resulting not only in reduction of environmental burdens but also on developing innovative technological solutions. These results are also valuable for regulators to help them estimate the risk-benefit ratios of these technologies.

To base the above mentioned innovative solutions for risk prevention and control on robust experimental data, SUN has completed the development of tools to analyse the long-term effects of pristine, released and aged MN on humans and ecosystems. In doing this SUN has targeted some of our most vulnerable ecosystems and extended environmental risk assessment to cover longer-term realistic scenarios of ecosystems subjected to multiple stressors, including accumulation and contaminant transfer in the food chain up to humans. SUN also studied several important ecosystem services that are essential to public health and society, including the effects of MN on sewage sludge treatments (e.g. aerobic and anaerobic treatment before agricultural use), which provided data of great benefit for utility companies and regulators. These tools enable a fast and direct estimation of risks as well as ability to alter production in time to minimise them. The coverage of the three main environmental media (water, sediment and soil) deals both with the media receiving MN and with vital ecosystem services such as wastewater treatment, food production and genetic pool/variation. The obtained results have had a significant impact on developing the field of ecological risk assessment in general and on the implementation of the REACH Chemical Safety Assessment guidance for MN.

The (eco)toxicity testing in SUN has been to a great extend based on existing standards (e.g. OECD, ISO), often aiming at improving them and contributing to the development of new standards. Specifically, regarding the newly developed *in vivo* test protocols (e.g. STOS, tests for enchytraeids and fish) we have looked for compliance with the existing standards that industry and regulatory agencies are already familiar with (e.g. OECD 407: Repeated Dose 28-day Oral Toxicity Study in Rodents; OECD 220: Enchytraeids test; OECD 210: Fish, Early-Life Stage Toxicity Test). Similar approaches were adopted for the terrestrial multispecies test systems to support the development of OECD guidance also for them. Our partners (e.g. INIA, UNIVIE and IME) have been involved in the OECD WPMN and have contributed to the adaptation of various OECD test guidelines based on results from SUN. Specifically SUN contributed to the OECD Technical Guidance (TG) document on multigenerational tests with Enchtraeids, forming the basis for long-term toxicity tests covering epigenetic effects. In this regard, a Standard Operating Procedure (SOP) enabling validated markers for methylation status (correlated with phenotypic/reproductive toxic consequences) and high-throughput tools for gene expression were developed. Moreover, the SUN results were used to develop the OECD TG on testing dispersion stability and dissolution (kinetics) as well as the OECD environmental fate decision tree and the corresponding guidance document.

In addition to contributing to standardisation activities SUN generated high-impact results in the areas of human health hazard and risk assessment. For instance, SUN focused on investigating the epigenetic effects of MN both *in vitro* and *in vivo*. In this regard, we established a strong collaboration with Health Canada, who dedicated their own resources to testing an array of samples from SUN. This provided an excellent opportunity to gain epigenetic information and guidance on how to use this information for risk assessment. This and the newly developed *in vivo* protocols (e.g. STOS, tests for Enchytraeids and fish) will have a significant impact on the regulatory risk assessment of MN.

SUN significantly progressed beyond the state of the art of workers' and consumers' inhalation, dermal and dermal-to-oral exposure assessment by developing an exposure assessment and modelling framework and toolbox. This toolbox will have major impact on the risk assessment of MN for regulatory purposes and the implementation of the ECHA guidance on Chemical Safety Assessment for MN.

The knowledge acquired in the project and derived from other sources has served as the basis for developing SUNDS. This decision support system will be of significant practical value for both industries and regulators since it would make it possible to integrate technical data about the risks, benefits and costs of MN into a sustainability portfolio to make informed decisions about how to address their safer production, handling and end of life treatment. It can also aid industries in making decisions whether to invest in developing new nanotechnology products. In addition, SUNDS will have practical impact on the work of regulators as it will enable them to prioritize MN based on their risk profiles and select the most adequate risk mitigation measures. In cases when this is impossible, SUNDS will help regulators to compare the risks of MN to their potential benefits. The decision support system is also particularly relevant for SME as it will enable them to easily perform regulatory safety assessment and to make decisions concerned with risk management and product innovation. This will reduce their R&D&I costs and will enable them to more effectively compete with larger industries. Moreover, the application of SUNDS and its underlying tools will reduce uncertainty in the early stages of innovation and will improve risk communication. This will lead to a more positive market interpretation and the perception of safe/responsible innovation will result in better business cases. The application of the decision support system and the risk prevention strategies developed in the project will help industries by providing input into the design of safer products and processes. This will lead to safer workplaces and products, and will facilitate compliance with regulations.

The pressure to assist companies in making technically challenging decisions about safety of their products has increased proportionally to the evolution of regulations. While there are a small number of consultancies providing safety assessment support to businesses, those are limited in terms of the analytical tools they can use, and in terms of the scope and the materials for which they can provide advice. The SUN strategies, methods and the SUNDS could be used by these consultants or directly by the businesses for risk analysis and/or innovation decision making. The same also applies to researchers working in academia who design, develop or use MN or NEP. In addition, regulators in a variety of sectors (e.g. consumer products, cosmetics, food, medicines, chemicals and substances) can use the SUN tools to do their own safety assessments and decision-making.

One barrier to nanotechnology innovation is the relatively slow but constant evolution of relevant regulations and standardisation activities. These processes require input/agreement from multiple stakeholders across national borders. Involvement of key players from ECHA OECD, U.S. EPA and Health Canada in our Advisory Board and the organisation of several workshops with regulators has ensured that the SUN results contribute to regulation. By working closely with representatives of regulation, standardisation, industry and research communities we transparently integrated their input into our research processes, and worked to develop trust in our research products. In addition, the respective skills needed to implement these scientific approaches were developed through training activities targeting these communities. Intensive dissemination of the project’s results raised safety awareness and promoted a debate on how the SUN results can help companies in bringing their products faster to the market while complying with regulatory requirements. This will eventually speed up the evolution of the nanosafety regulations and will increase the market confidence in these technologies and their acceptance by businesses and consumers.

SUN has had a significant impact on research cohesion and integration with other nanosafety projects. For instance, intense collaboration has taken place with NANoREG, eNanoMapper, GUIDEnano, NanoSolutions, NanoMILE and caLIBRAte to avoid overlaps, strengthen complementarities and create synergies among the projects. This has led to the organisation of major international conferences, workshops and initiatives in the areas of nanosafety data management, risk assessment and governance of nanotechnologies. Moreover, SUN partners are leading and/or have been actively engaged within all working groups of the European Nanosafety Cluster and the EU-U.S. Communities of Research. SUN has also considerably contributed to strategic research roadmaps in the nanosafety area.