SUN

Sustainable Nanotechnologies Project

A NEW INTEGRATED APPROACH FOR RISK ASSESSMENT AND MANAGEMENT OF NANOTECHNOLOGIES

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SEVENTH FRAMEWORK PROGRAMME

CONTENT

SUN HAS SUCCESSFULLY ACHIEVED ITS GOALS!

Forward By Danail Hristozov, Principal Investigator Of The Sustainable Nanotechnologies (SUN) Project.

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 consumer products and industrial applications. 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 pose environmental and health risks.

The main reason to launch SUN was to investigate these risks and find ways to prevent them. With a budget of over 13 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 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 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 can be used by risk assessors and researchers in industry, academia and regulatory bodies to early identify and manage possible occupational and consumer risks that may arise 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 and their environmental impacts.

The industrial partners in the SUN Consortium evaluated the new methods and tools developed by the project against real nanotechnology applications in terms of cost and benefit. To achieve this, we applied them to supply chains of products embedding nanoscale Tungsten Carbide (sintered, wear-resistant ceramics), Copper (antimicrobial/fungal wood preservatives), Silica (food), Titanium Dioxide (self-cleaning ceramic tiles and air purification systems), organic pigment (the red color 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

Hundreds of stakeholders are engaged in exploiting the SUN results **Worldwide**

ABOUT THE PROJECT

MAIN GOAL

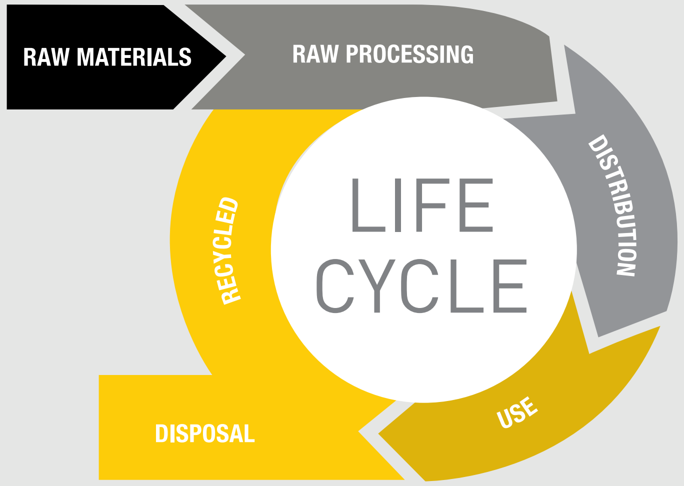
Protect innovation by providing industries with data and tools to streamline effective decision making about safer products and processes.

CONCEPT

Combines the bottom-up development of environmental, health and safety tools, knowledge and data with their top-down integration into a Decision Support System for risk management of nanotechnologies.

HYPOTHESIS

Industries can avoid potential liabilities if they adopt an integrated risk assessment and management approach addressing the entire lifecycle of nanotechnology products.



RISK ASSESSMENT

- Predicting nanomaterial exposure and effects on humans and ecosystems

DECISION SUPPORT

- Integrating the know-how developed in the project to support Industry, regulators and the insurance sector to make informed decisions about nanotechnology

RISK MANAGEMENT

- Designing process changes and technological solutions to reduce hazard and exposure to nanomaterials

OBJECTIVES

- Establish new methods and tools for prediction of longer-term nanomaterials exposure, effects and risks for humans and ecosystems (services).
- Propose implementable practices for risk prevention and control applicable to industrial, consumer and environmental settings.
- Create guidance for safer production, handling and end-of-life treatment of nano-enabled products.
- Develop a risk management Decision Support System for practical use by industries and regulators.

KEY TOPICS

- Real Industrial Materials and Products
- Environmental Impacts
- Lifecycle Release and Environmental Exposure
- Environmental Hazard Studies
- Consumer Exposure
- Workplace Exposure
- Human Hazard Studies
- Health and Environmental Risks
- Risk Management
- Safe Product Design
- Safe Process Design
- End of Life Treatment and Waste Management Practices
- Decision Support System for Risk Assessment and Management of Nanotechnology Products

PARTNERS

ITALY
1. University Ca´Foscari Venice
2. Colorobbia
3. Magneti Marelli
4. Venetonanotech
5. MBN Nanometerialia
6. National Research Council

GERMANY
7. European Research Services
8. BASF
9. PlasmaChem
10. Fraunhofer Institute for Molecular Biology and Applied Ecology
11. RWTH Aaachen University
12. University of Bremen

THE NETHERLANDS
13. Malsch TechnoValuation
14. National Institute for Public Health and the Environment - RIVM
15. Dutch Organisation for Applied Science Research -TNO
16. Foundation for Agricultural Research - Wagenigen
17. VU University Amsterdam

UNITED KINGDOM
18. The REACH Centre Limited
19. Institute of Occupational Medicine
20. Heriot-Watt University
21. University of Plymouth
22. University of Leeds

BELGIUM
23. Nanocyl

SWITZERLAND
24. The Innovation Society
25. Environmental Technical & Scientific Services Gottschalk & Co
26. Swiss Federal Laboratories or Materials Science and Technology - EMPA

DENMARK
27. National Research Centre for the Working Environment - NRCWE
28. Denmark Technical University
29. Aarhus University

SPAIN
30. National Institute for Agricultural and Food Research and Technology

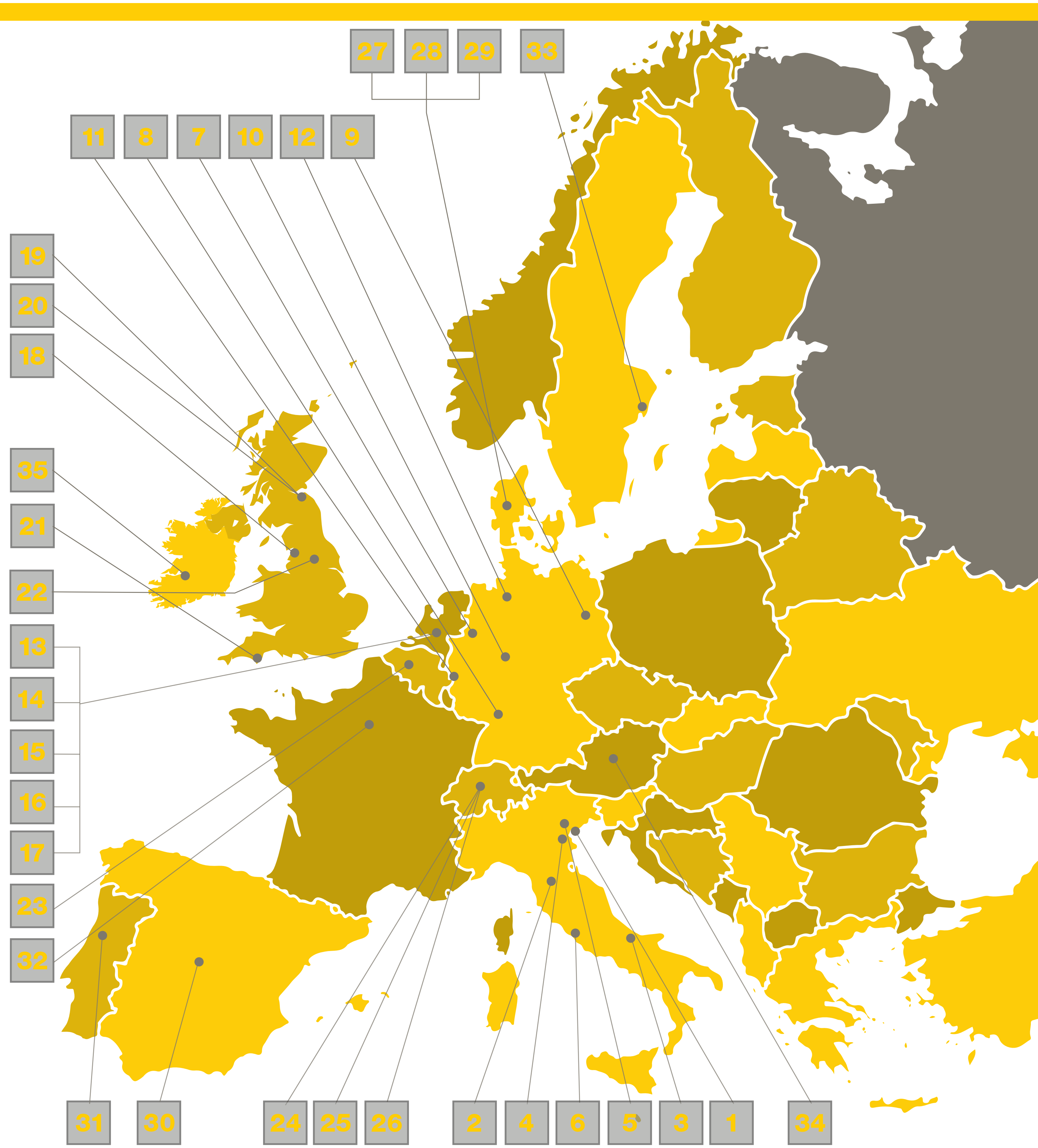
PORTUGAL
31. University of Aveiro

FRANCE
32. National Centre for Scientific Research

SWEDEN
33. Karolinska Institute

AUSTRIA
34. University of Wien

IRELAND
35. University of Limerick



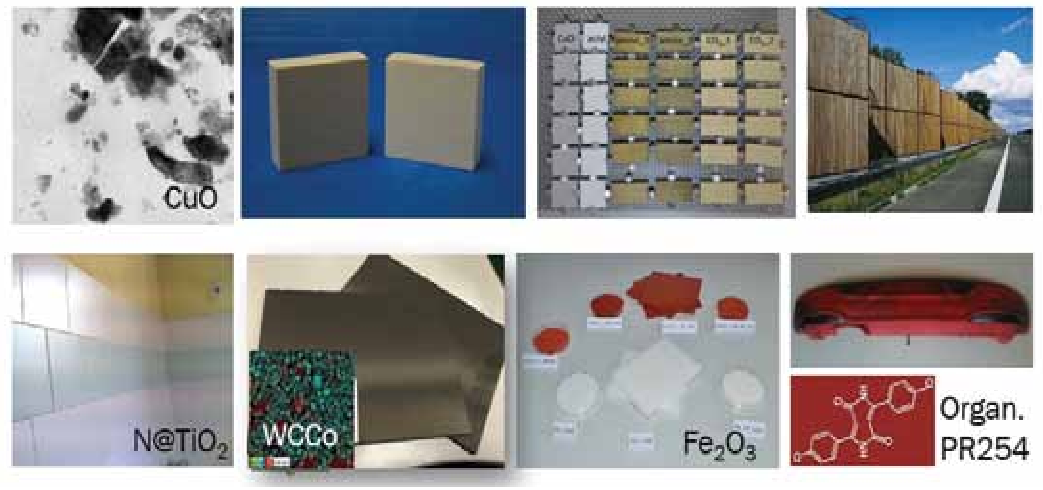
REAL INDUSTRIAL MATERIALS AND PRODUCTS

To test and validate the innovative tools developed in SUN we established a balanced portfolio of both legacy and novel nanotechnology products. In early 2014, when SUN had just started, the first mandatory reporting requirement for nanomaterials was introduced in France. In this context, the SUN 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.
   - Multi-walled carbon nanotubes used in marine coatings and automotive parts.
2. **Less well-known nanomaterials of high societal relevance. These were chosen from particulate materials with a history of use, which are now identified as nanomaterials in regulatory terms. These materials had significant data gaps that SUN needed to fill:**
   - Organic pigments for automotive parts.
   - Inorganic pigments for automotive parts.
   - Silica 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 become 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 SUN results.

Very specific to SUN, for all materials the **complete value/supply chain was covered by experiments and modeling**. Materials representing each lifecycle phase were provided to partners for testing. In doing so academic and industrial partners collaborated closely together to assess their 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 in 2014, 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 as relevant for European regulation by the upcoming 2017 annexes of the European REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulation.

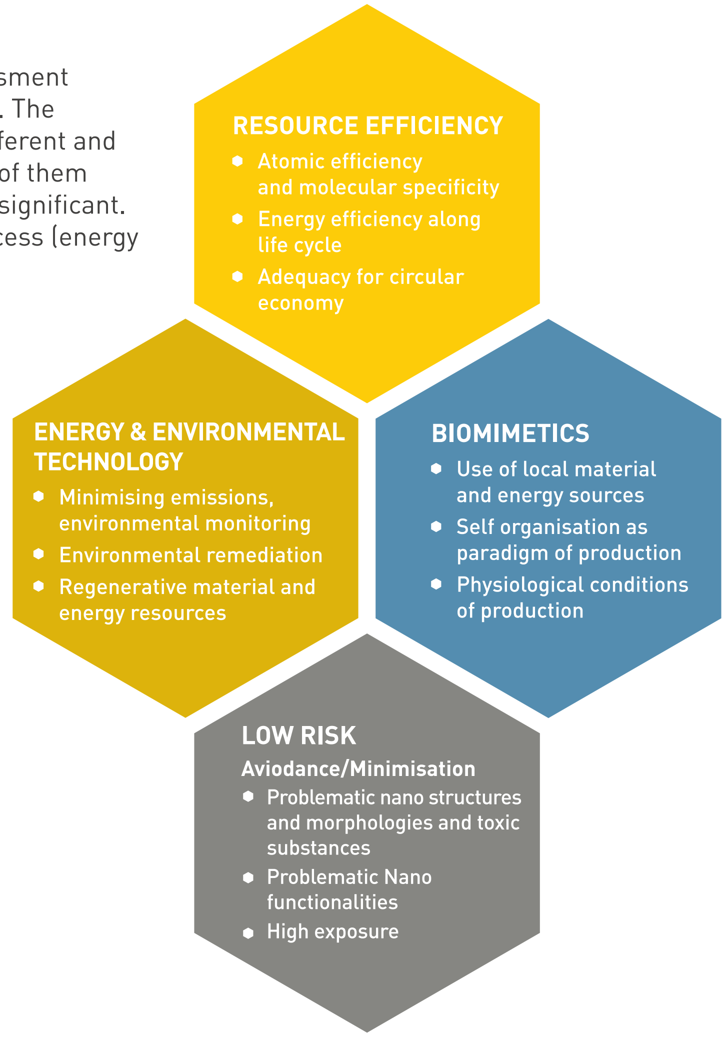
ENVIRONMENTAL IMPACTS

The environmental impacts of the selected nanomaterials and the associated nanotechnology products 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.

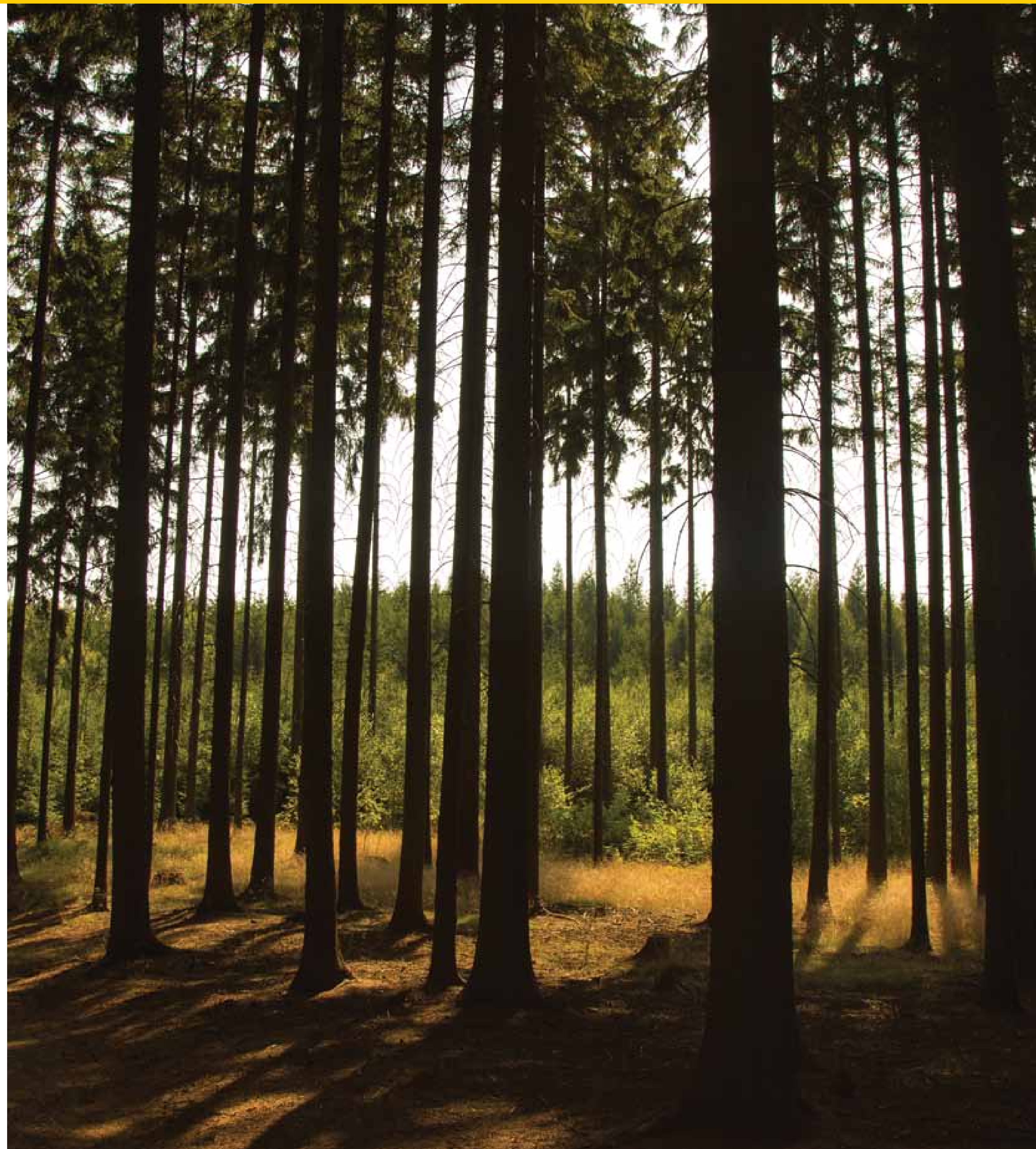
These data were used to perform Life Cycle Impact Assessment based on ReCiPe midpoints combined with shadow prices. The investigated nanomaterials and applications were very different and so were also the results of the LCA case studies. In some of them the environmental impacts were very low, while in others significant. They strongly depended on the type of 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:

- Using nanomaterials as additives leading to better functionality of the nano-enabled product.
- 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'.



LIFECYCLE RELEASE AND ENVIRONMENTAL EXPOSURE

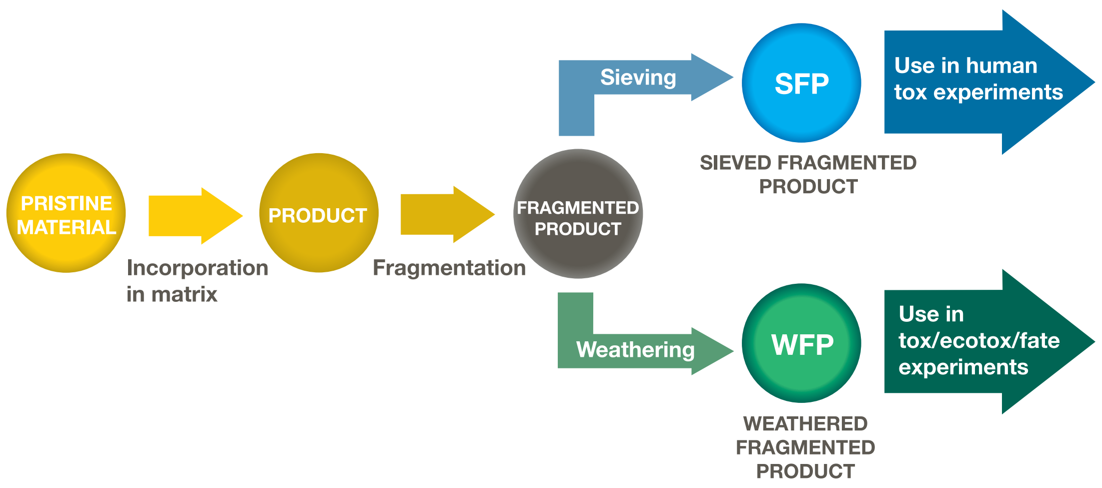
The analysis of the potential risks of nanomaterials has so far been almost exclusively focused on the pristine, as-produced particles. However, when considering a life-cycle perspective, the nanomaterials released from genuine products are far more relevant.

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 behavior 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 behavior/fate studies.

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

- To use formulated materials instead of just aging pristine particles.
- The process is reliable and quick.
- The samples are close to real-world exposure, 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 relevant size distribution.
- A nano-free formulated material is available as reference.

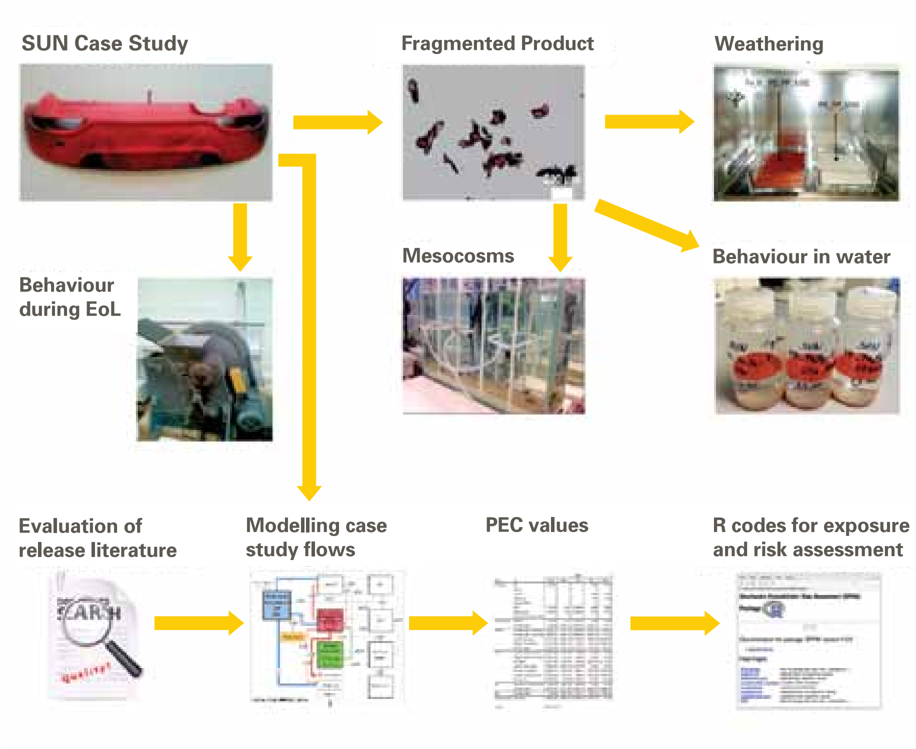
Based on these requirements, the SUN Consortium developed an approach to provide materials in hundreds of grams quantities mimicking actual released materials from coatings and polymer nanocomposites by producing what is called "Fragmented Products". These released fragments can further be exposed to 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 inhalation studies.



The SUN approach to produce fragmented materials.

The SUN Consortium significantly advanced the environmental exposure field by contributing methods and tools in a variety of areas. The overall concept is visualized in the figure: starting with the SUN case studies, fragmented products were produced and characterized. These materials were further weathered under environmental conditions and their behavior 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 modeling 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. Overall, the work performed in SUN presents so far the most realistic assessment of the environmental exposure of nanomaterials because it is based on real-world materials and incorporating 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.

ENVIRONMENTAL HAZARD STUDIES

The SUN Consortium takes environmental hazard assessment of nanomaterials an immense step forward because it has developed a vast array of novel hazard tools. These tools allow us to predict longer-term hazards for nanomaterials. It is possible to test both pristine nanomaterials (NMs) and NMs embedded in products, i.e. from different stages of the material life cycle. All environmental media are covered, i.e. sewage sludge treatment plants, soil, sediment and water, with a focus on ecosystem services and key environmental species.

The tools include (i) short-term high throughput studies, e.g. *in vitro*, *ex vivo* and *in vivo* omics-related methods, and (ii) 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 interaction. This includes cell viability, various omics-responses (gene-, protein and metabolites expression), individual life-stage endpoints, species interaction, and trans-generation effects including epigenetic effects. For example, 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 *ex vivo* method is a highly effective tool to study uptake mechanisms in fish-gut. Uptake studies are important for identifying dietary exposure and bioaccumulation. The tools are 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 allows for Adverse Outcome Pathways (AOPs) to be developed. AOPs enhance the understanding of the mechanisms of toxicity. AOPs also enable designing materials according to a safer by design approaches. Pristine nanomaterial, modified pristine nanomaterials (safer by design), and fragmented nanoproducts have been tested. Reference materials have also been tested, e.g. soluble salts of the respective metal nanomaterial and fragmented products without nanomaterial embedded.

Overall, the work performed by the SUN Consortium 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.



CONSUMER EXPOSURE

The SUN Consortium has contributed to the field of nanomaterials consumer exposure assessment through developing realistic scenarios of nanomaterial release from various products that could lead to human exposure. Data from several nanoproduct inventories were analyzed to gain information regarding nanotechnology products and their availability, distribution across product groups, and the use of different nanomaterial types. Consumer exposure data libraries have been established. Several exposure models have been applied to the release data to quantify potential human exposure that may arise from using these products.

The release of nanomaterials from SUN products and other commercially available articles was also experimentally tested, considering conditions relevant for consumer exposure – such as leaching from food contact materials, textiles and personal care items, and dermal transfer from product surfaces. These experiments were designed to allow close to realistic exposure potential estimation, as they utilize real-world consumer articles and relevant exposure scenarios. All in all, work conducted within the SUN project regarding consumer exposure provides insight and novel data for consumer exposure measurements and exposure assessment, with focus on relevant real-world consumer articles and likely exposure scenarios.

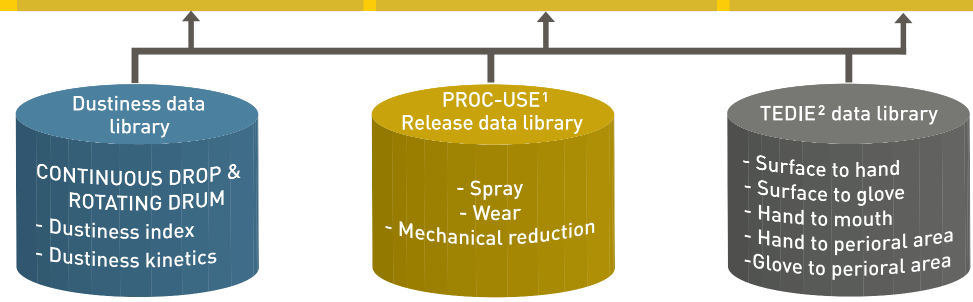
WORKPLACE EXPOSURE

To facilitate the estimation of occupational exposure to nanomaterials SUN evaluated and improved several existing models, and used them to establish the first tiered nano-specific framework that covers inhalation, dermal and inadvertent oral exposure. The highlight of this framework is a new aerosol dynamic inhalation model, which is a major methodological achievement.

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 the project. The ECEL library on the efficiencies of engineered and personal protection equipment was also further developed to include efficiencies against nanomaterial exposures.

For assessment of inadvertent oral exposure, dermal to perioral transfer efficiencies were proposed. Four workplace exposure measurement campaigns were completed to establish values for comparison with modelled exposure levels. The measurements were specifically conducted for synthesis of nanoscale Copper Oxide, production and handling of Tungsten Carbide, production of car bumpers with organic and inorganic pigments, and application of Titanium Dioxide 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 nanospecific exposure assessments. These libraries will become publically accessible and subscribing laboratories will be able to contribute with further data in the future.

	INHALATION EXPOSURE ASSESSMENT	DERMAL EXPOSURE ASSESSMENT	INADVERTENT ORAL EXPOSURE
TIER 1: CONTROL-BANDING EXPOSURE ASSESSMENT	Exposure scaling		
TIER 2: MASS-BASED EXPOSURE ASSESSMENT	Simple one or two box models ("worst-case" estimates)	Worst case or empirical dermal loading efficiencies	Empirical dust transfer efficiencies
TIER 2: SIZE RESOLVED EXPOSURE ASSESSMENT	Aerosol dynamic model ("realistic" estimates)		



[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!

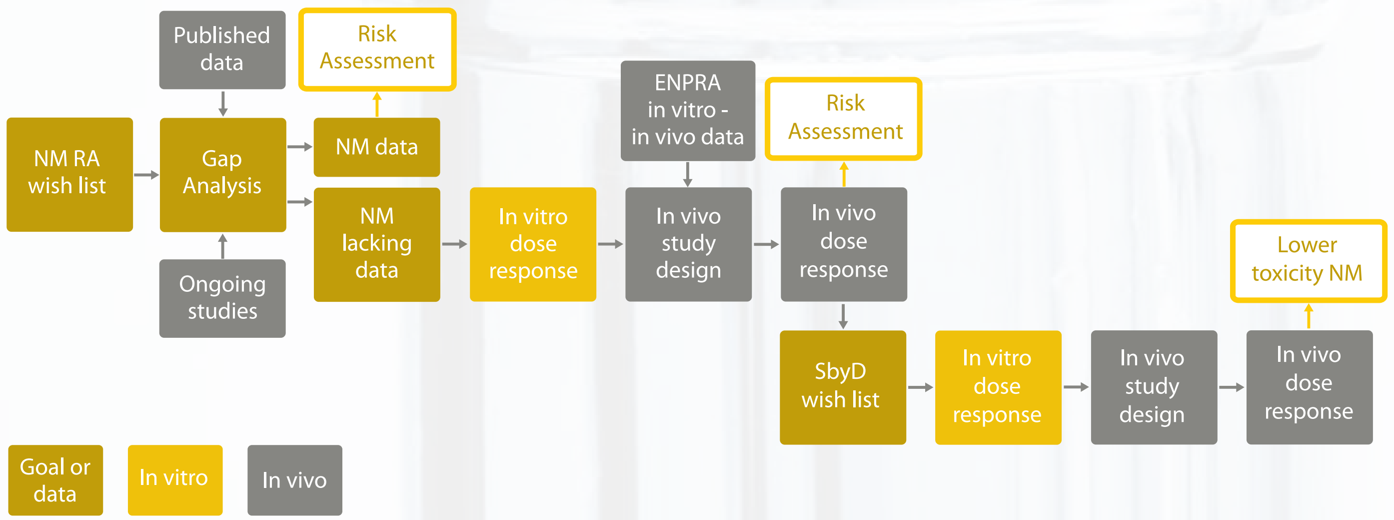
The conceptual SUN occupational exposure assessment framework for nanomaterials.

HUMAN HAZARD STUDIES

The SUN project began with an ambitious list of nanomaterials for risk assessment, but due to 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 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 Copper Oxide nanoparticles as being relatively toxic. The lack of existing data on this material along with this *in vitro* hazard data resulted in the prioritization of this material for *in vivo* hazard testing.

The protocols used for the *in vitro* toxicity testing were taken from previous projects (e.g. ENPRA) in order 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 Copper Oxide using a Safety-by-Design approach. A panel of modified Copper Oxide 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. This approach therefore demonstrates the usefulness of alternative models in refining animal studies, to reduce the number of animals used, as well as for making decisions for strategic development, modification and testing of nanomaterials.

In order to investigate the effects of the Copper Oxide 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 Copper Oxide nanomaterials for 5 days resulted in a measurable inflammatory response at day 6 inflammation which was largely resolved at day 28. This study demonstrates similarities between impacts regardless of the route of exposure for Copper Oxide nanomaterials, and furthermore provides a useful protocol for investigating the consequences of oral exposure to potentially toxic substances.



HEALTH AND ENVIRONMENTAL RISKS

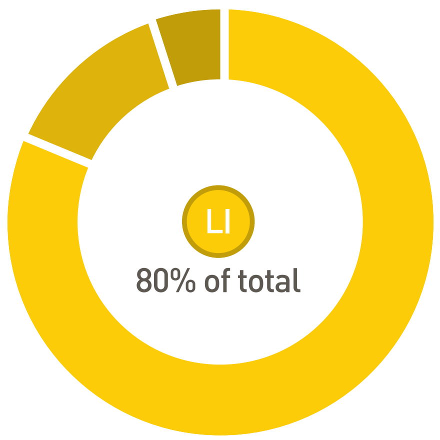
The SUN Consortium advanced in the field of Human Health Risk Assessment (HHRA) of nanomaterials by developing a probabilistic risk assessment methodology which integrates the outputs of human hazard assessment and exposure models. Hazard data and exposure data can be estimated deterministically or probabilistically, depending on data availability. Traditional (deterministic) HHRA 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 distribution explicitly communicates these uncertainties and supports the identification of which are the parameters (exposure conditions, selection and use of assessment factors, etc.) that most strongly affect the estimated risks.

Specifically, HHRA in SUN is performed considering the life cycle stages of the SUN priority nanomaterials (synthesis, formulation, use, end of life) as well as targets, activities and routes of exposure. The estimated probabilistic human health risks are then classified as acceptable or non-acceptable.

Once risk is estimated for each relevant combination of life cycle stages, targets, activities and routes of exposure, an aggregation step produces a single risk value for each lifecycle stage as well as for the entire lifecycle. Particularly novel features of the SUN HHRA approach are its abilities to differentiate the risks specific to the nanomaterials released from the products from the ones caused by the fragments of the embedding matrix and to estimate realistic rather than worst-case scenarios.

Moreover, SUN advanced in the field of Ecological Risk Assessment (ERA) 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, waste water treatment plants effluent and sludge, waste incineration plants waste). Specifically, a probabilistic material flow environmental exposure model developed in SUN was able to predict environmental concentrations (PECs) resulting from flows of nanomaterials released from products in each lifecycle stage (synthesis, formulation, use, end of life). Moreover, Predicted No Effect Concentrations (PNECs) could be derived by means of both deterministic and probabilistic Species Sensitivity Distributions procedures compliant with the REACH guidelines.

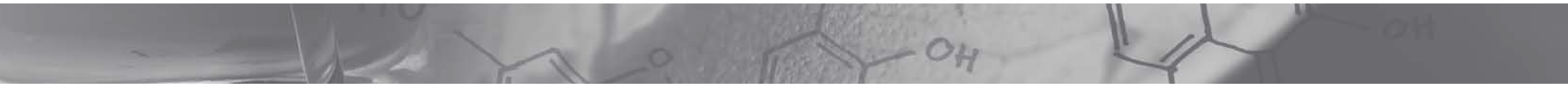
Thus, an ecological risk portfolio along the lifecycle is calculated by choosing the maximum risk for each lifecycle stage to characterize it. The resulting ecological risk is either deterministic (i.e. PEC/PNEC) or probabilistic. Both the ERA and HHRA methodologies were applied to the SUN case studies and were implemented in the SUN Decision Support System for practical use by industry, regulators and insurance companies.



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

LI Low Impact = Acceptable risk
MI Medium Impact = Risk needs further consideration
HI High Impact = Unacceptable risk

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



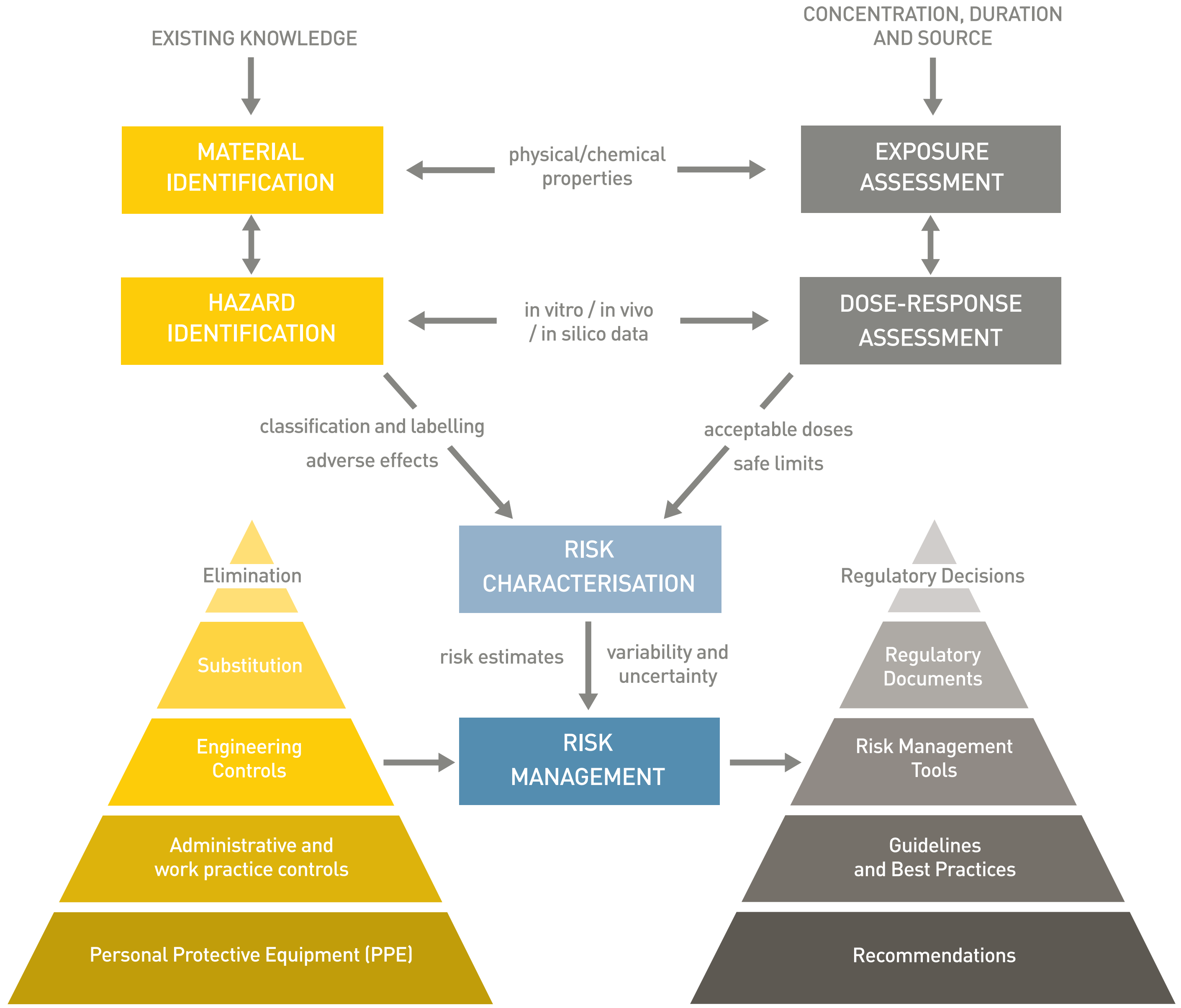
RISK MANAGEMENT

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 of safe by design 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 Exposure Control Efficacy Library (ECEL).

The compiled information was then summarised in easy-to-read guidelines for practical use by industries and regulators. The analysis of the data showed that engineering controls and protective clothing are more commonly used to reduce nanomaterials risks as compared to safer by design practices targeting the elimination, substitution and modification of substances. 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 as follows:

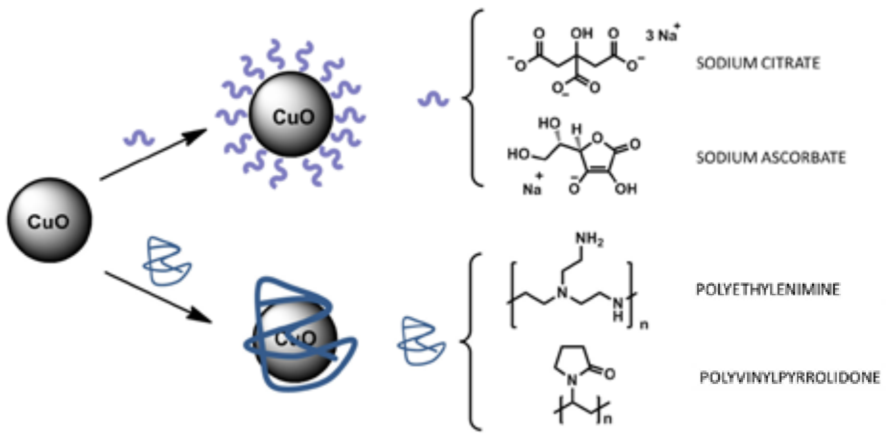
- When the intrinsic safety measures (e.g. elimination and substitution) are not viable, the second-best option for safe handling of nanomaterials is to implement engineering control measures.
- The selection of engineering controls at workplaces should be made based on the state of the nanomaterial (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 and 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 specific 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 safe by design solutions is complex and often requires data-intensive validation. To address this challenge SUN adopted a stepwise approach for validation of such strategies and applied it to the Copper Oxide and Tungsten Carbide case studies. Specifically, in the case of Copper Oxide four surface modifying agents were chosen: positively charged (branched polyethylenimine); neutral polyvinylpyrrolidone); negatively charged (sodium citrate); negatively charged with strong anti-oxidant capacity (sodium ascorbate). 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 that 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. 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.



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

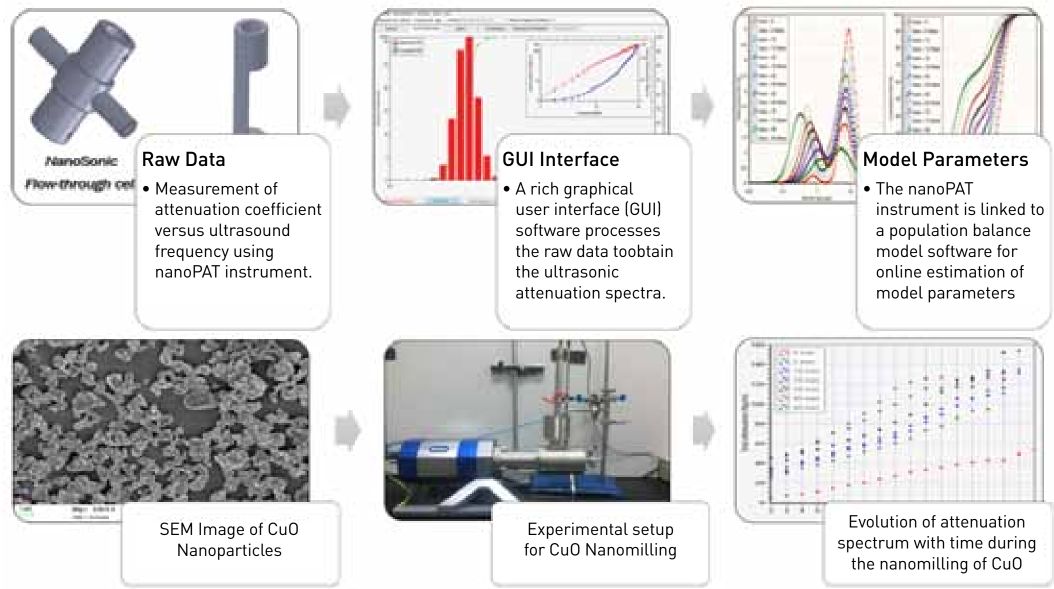
SAFE PROCESS DESIGN

Safe nanomanufacturing is of crucial importance for sustainable nanotechnology, but unique properties of nanomaterials require new analytical and assessment techniques. The SUN Consortium members investigated the development and application of a nano-specific process analytical technology (nanoPAT) to measure the real-time evolution of the key product quality parameters such as particle size distribution.

A new online particle sizing system based on acoustic spectroscopy was developed in the SUN project. Two different hardware configurations, a flow through cell and a nanosizer 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.

As a next step, the nanoPAT particle sizing system was applied to the nano-processing of α-alumina. Evolution of particle size distributions during nano-processing was measured online using the developed instrument and validated by two other particle sizing techniques, Dynamic Light Scattering, and Laser Diffraction. 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 developed and fully tested nanoPAT system was applied to the project case-study nanomaterial Copper Oxide.

The instrument and the software packages have shown great promise in predicting and measuring the evolution of particle size distribution online during nanoprocessing. 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 engineered nanomaterials in waste streams. The activities focused on three major aspects:

1. Identifying major waste materials and the waste treatment processes.
2. Analyzing 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 center of evidence, we identified waste plastic as the waste stream where nanomaterials could be found more frequently, while nanoscale 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.

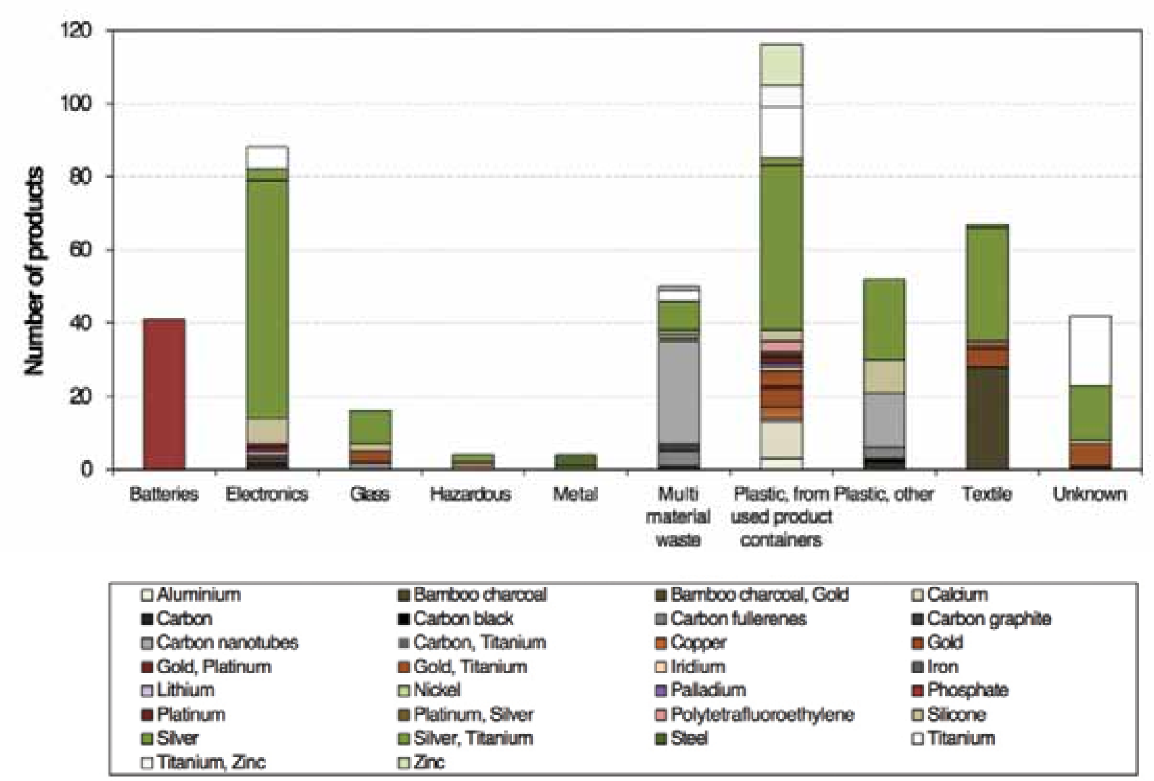
For the three scenarios analyzed (i.e. Denmark, United Kingdom, and Europe), we estimated that recycling would be the treatment option mostly involved in handling of nanoparticles, followed by either incineration (e.g. Denmark) or landfilling (e.g. United Kingdom), depending on the geographical context. When analyzing 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: hardness of the matrix, temperature reached during the process, 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 combustibility of the matrix, the melting/boiling/degradation points of nanomaterials in relation to the combustion temperature, and the overall performance of the flue gas cleaning system as well as 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 safer by design 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.

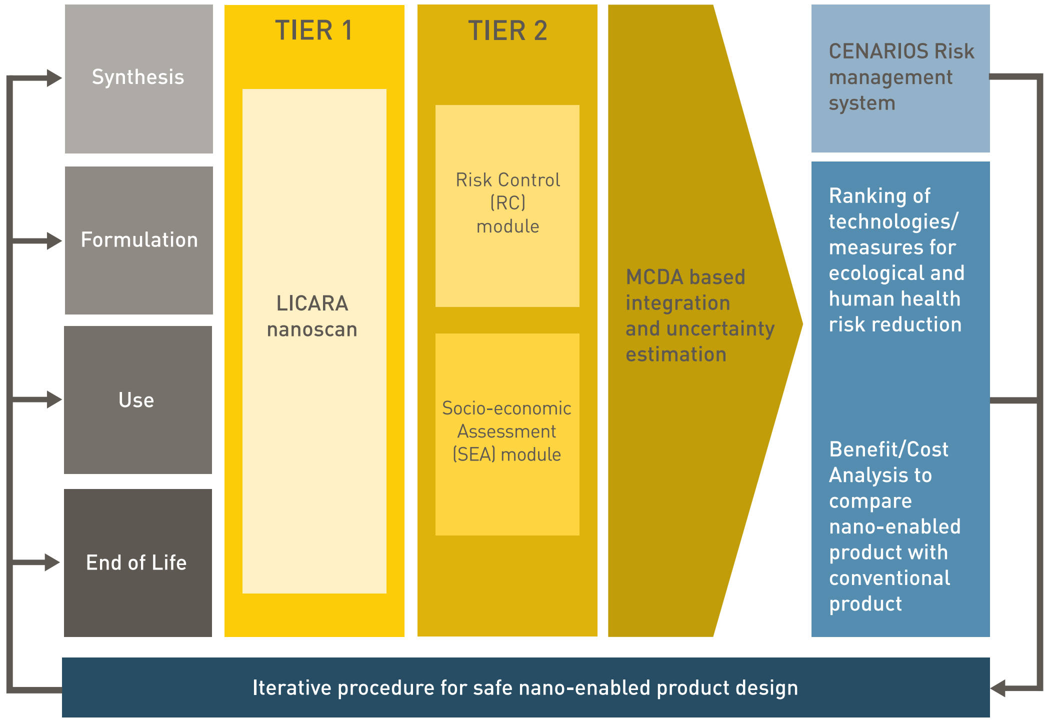


Distribution in the different waste material fractions according to data from nanodb.dk. The Y-axis represents the number of products containing a certain NOAA (taken from (Heggelund et al., 2016)).

DECISION SUPPORT SYSTEM FOR RISK ASSESSMENT AND MANAGEMENT OF NANOTECHNOLOGY PRODUCTS

The SUN Consortium developed an online software Decision Support System - SUNDS. It estimates occupational, consumer and environmental risks from nanomaterials in real industrial products along their lifecycles. In situations where the risks are not acceptable SUNDS proposes suitable Risk Management Measures, including information about their costs compared to the benefits of the nanotechnologies. SUNDS implements a tiered approach. Tier 1 comprises of the NanoSCAN tool developed within the EU FP7 LICARA project specifically for Small and Medium Enterprises (SMEs), who often do not have the resources and expertise to apply complex decision support systems. Therefore, NanoSCAN is a very user-friendly screening-level approach with relatively low data requirements that provides a semi-quantitative risk-benefit analysis from lifecycle perspective.

SUNDS Tier 2 implements an integrated Risk Control (RC) and Socioeconomic Analysis (SEA) modules. RC is 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 the benefits of using a certain nanomaterial significantly outweigh the costs of managing its risks. SEA analyses all environmental, economic and social impacts, at both micro and macro levels. 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 nano-enabled products. In addition to the two tiers, a stand-alone module based on CENARIOS (Certifiable Nanospecific Risk-Management and Monitoring System)® standard was included in SUNDS. To explore the SUNDS go to sunds.dais.unive.it



SUNDS Conceptual Framework

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