**A Thesis Submitted for the Degree of PhD at the University of Warwick**

# Advancing Sustainable Nanotechnology with Multiple Criteria Decision Aiding

**by**

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# *Acknowledgments*

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I want to close these acknowledgments with a quote from the philosopher Friedrich Nietzsche, whose thinking instilled in me the continuous desire to do research (from Human All to Human, 1878):

**“The Cult of genius for the sake of vanity”**

*Because we think well of ourselves, but nevertheless do not imagine that we are capable of the conception of one of Raphael's pictures or of a scene such as those of one of Shakespeare's dramas, we persuade ourselves that the faculty for doing this is quite extraordinarily wonderful, a very rare case, or, if we are religiously inclined, a grace from above. Thus the cult of genius fosters our vanity, our self-love, for it is only when we think of it as very far removed from us, as a miraculum, that it does not wound us (even Goethe, who was free from envy, called Shakespeare a star of the farthest heavens, whereby we are reminded of the line "Do not covet the starts").*

*But, apart from those suggestions of our vanity, the activity of a genius does not seem so radically different from the activity of a mechanical inventor, of an astronomer or historian or strategist. All these forms of activity are explicable if we realise men whose minds are active in one special direction, who make use of everything as material, who always eagerly study their own inward life and that of others, who find types and incitements everywhere, who never weary in the employment of their means.*

*Genius does nothing but learn how to lay stones, then to build, always to seek for material and always to work upon it. Every human activity is marvellously complicated, and not only that of genius, but it is no "miracle”.*

*Now whence comes the belief that genius is found only in artists, orators, and philosophers, that they alone have "intuition" (by which we credit them with a kind of magic glass by means of which they see straight into one's "being")? It is clear that men only speak of genius where the workings of a great intellect are most agreeable to them and they have no desire to feel envious. To call any one "divine" is as much as saying "here we have no occasion for rivalry". Thus it is that everything completed and perfect is stared at, and everything incomplete is undervalued.*

*Now nobody can see how the work of an artist has developed; that is its advantage, for everything of which the development is seen is looked on coldly. The perfected art of representation precludes all thought of its development, it tyrannises as a present perfection. For this reason artists of representation are especially held to be possessed of genius, but not scientific men. In reality, however, the former valuation and the latter undervaluation are only puerilities of reason.*

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Voglio chiudere questi riconoscimenti con una citazione del filosofo Federico Nietzsche, il cui pensiero mi ha stimolato il continuo desiderio di fare ricerca (da Umano troppo Umano, 1878):

**"Il Culto del genio per vanità"**

*Poiché pensiamo bene di noi, ma non per questo ci aspettiamo di poter mai fare l'abbozzo di un quadro di Raffaello o una scena come quella di un dramma shakespeariano, ci convinciamo che una simile capacità sia grandemente meravigliosa, un caso quanto mai raro - oppure, se siamo ancora religiosi, che sia una grazia dall'alto. Così la nostra vanità, il nostro amor proprio incrementano il culto del genio: infatti solo quando è pensato lontanissimo da noi, come un miraculum, esso non ci offende (persino Goethe, privo com'era di invidia, chiamava Shakespeare la sua stella della più remota altezza; e a questo proposito si può ricordare il verso: «non si bramano le stelle»).*

*Ma, a parte queste suggestioni della vanità, l'attività del genio non appare fondamentalmente diversa da quella dell'inventore di meccanismi, dell'astronomo o dello storico, del maestro di tattica. Tutte queste attività si spiegano se ci si rappresentano uomini il cui pensiero è attivo in una direzione, che tutto utilizzano come materiale, che guardano con zelo assiduo alla vita interiore propria e altrui, che dappertutto scorgono esempi e incitamenti, e non si stancano di combinare i loro mezzi.*

*Anche il genio altro non fa che imparare dapprima a porre le pietre, poi a costruire, a cercar sempre materiale e a plasmarlo continuamente. Ogni attività dell'uomo, e non solo del genio, è complicata in modo sorprendente:, ma nessuna è un «miracolo»."*

*Donde proviene dunque la credenza che ci sia genio unicamente nell'artista, nell'oratore e nel filosofo? Che solo costoro abbiamo "intuizione"? (con questa parola si attribuisce loro una specie di occhiale meraviglioso con cui vedono direttamente nell'"Essere"!). Evidentemente, gli uomini parlano di genio solo colà dove i grandi intelletti producono su di loro gli effetti più piacevoli ed essi da parte loro non vogliono provare invidia. Chiamare taluno "divino" significa: "qui non abbiamo da rivaleggiare". Poi: tutto ciò che è finito, perfetto, viene ammirato, tutto ciò che sta diventando è sottovalutato.*

*Ora nessuno può vedere come l'opera dell'artista si è fatta; è questo un vantaggio, perchè dovunque si può vedere il divenire, si prova un sentimento di freddezza. La perfetta arte della rappresentazione elimina ogni pensiero di divenire; essa tiranneggia come una perfezione presente. Perciò gli artisti della rappresentazione sono di preferenza considerati geniali, e non gli uomini di scienza. In realtà questa prima valutazione e questa ultima sottovalutazione sono soltanto una puerilità della ragione.*

# *Declaration*

This thesis is submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. It has been composed by myself and has not been submitted in any previous application for any degree.

# *Publications*

## From Chapter 2:

### Journal paper (non-peer reviewed)

**Cinelli, M.**; Coles, S. R.; Jørgensen, A.; Zamagni, A.; Fernando, F.; Kirwan, K. Workshop on life cycle sustainability assessment: the state of the art and research needs—November 26, 2012, Copenhagen, Denmark. *The International Journal of Life Cycle Assessment (IF: 3.324, Q1)*, 2013. 18(7): 1421-1424.

### Conference presentation

**Cinelli, M.**; Coles, S. R.; Kirwan, K. "Sustainability assessment of nanocellulose and its applications: a critical review and a proposal of an integrated methodology". TAPPI International Conference on Nanotechnology for Renewable Materials, 24-27 June 2013, Stockholm, Sweden (Oral presentation)

## From Chapter 4:

### Journal paper (peer reviewed)

**Cinelli, M.**; Coles, S. R.; Kirwan, K. Analysis of the Potentials of Multi Criteria Decision Analysis Methods to Conduct Sustainability Assessment. *Ecological Indicators (IF: 3.190, Q1)*, 2014. 46: 138-148.

### Conference proceedings and presentations

**Cinelli, M.**; Coles, S. R.; Kirwan, K. Use of Multi Criteria Decision Analysis to Support Life Cycle Sustainability Assessment: An Analysis of the Appropriateness of the Available Methods. in *Proceedings of the 6th International Conference on Life Cycle Management*, 677-680, 25-28 August, 2013. Gothenburg, Sweden.

**Cinelli, M.**; Coles, S. R.; Kirwan, K. "Development of an Approach for the Sustainability Assessment of Nanomaterials". 11th MCDA/M Summer School 2013 Helmut-Schmidt-Universität, July 22– August 2, 2013, Hamburg, Germany (Poster)

**Cinelli, M.**; Coles, S. R.; Kirwan, K. "Multi Criteria Decision Analysis: supporting Life Cycle Sustainability Assessment". 6th International Conference on Life Cycle Management, 25-28 August 2013, Gothenburg, Sweden (Oral presentation)

## From Chapter 5:

### Journal paper (peer reviewed)

**Cinelli, M.**; Coles, S. R.; Sadik, O.; Karn, B.; Kirwan, K. A Framework of Criteria for the Sustainability Assessment of nanoproducts. *Journal of Cleaner Production (IF: 4.959 , Q1)*, 2016. 126: 277-287.

### Conference presentations

**Cinelli, M.**; Coles, S. R.; Kirwan, K. "Development of an Approach for the Sustainability Assessment of Nanomaterials and nanoproducts". 2nd Sustainable Nanotechnology

Organization Conference, 3-5 November, 2013, Santa Barbara, USA (Second place best poster award)

**Cinelli, M.**; Coles, S. R.; Sadik, O.; Karn, B.; Kirwan, K. *"*Moving Sustainable Nanotechnology Forward*"*. "Seminars on Nanotechnology", 09-10 June, 2015, WMG, University of Warwick, Coventry, UK (Oral presentation)

## From Chapter 6:

### Journal paper (peer reviewed)

**Cinelli, M.**; Coles, S. R.; Nadagouda, M. N.; Błaszczyński, J.; Słowiński, R.; Varma, R.S.; Kirwan, K. A green chemistry-based classification model for the synthesis of silver nanoparticles. *Green Chemistry (IF: 8.506, Q1)*, 2015. 17: 2825-2839.

Kadziński, M.; **Cinelli, M.**; Ciomek, K; Coles, S. R.; Nadagouda, M. N.; Varma, R. S.; Kirwan, K. Co-constructive development of a green chemistry-based model for the performance assessment of nanoparticles synthesis. *European Journal of Operational Research (IF: 2.679, Q1),* 2016. Accepted for publication.

### Conference presentations

**Cinelli, M.**; Coles, S. R.; Kirwan, K. *"*Improving the Sustainability of Nanomaterials Synthesis with Multi Criteria Decision Analysis*"*. 1st WMG Doctoral Research and Innovation Conference, 10-11 July, 2014, WMG, University of Warwick, Coventry, UK (Poster)

**Cinelli, M.**; Coles, S. R.; Nadagouda, M. N.; Błaszczyński, J.; Słowiński, R.; Varma, R.S.; Kirwan, K. *"*Supporting Decision-Making for Green Synthesis of Nanoparticles*"*. 22nd Bio-Environmental Polymer Society Conference, 14-17 October, 2014, Kansas City, USA (Oral presentation)

**Cinelli, M.**; Coles, S. R.; Nadagouda, M. N.; Błaszczyński, J.; Słowiński, R.; Varma, R.S.; Kirwan, K. *"*Multi-Criteria Decision Aiding: Supporting Decisions for Green Chemistry-Oriented Synthesis of Nanomaterials*"*. 2nd WMG Doctoral Research and Innovation Conference, 30 June - 1 July, 2015, WMG, University of Warwick, Coventry, UK (Oral presentation)

**Cinelli, M.**; Coles, S. R.; Nadagouda, M. N.; Błaszczyński, J.; Słowiński, R.; Varma, R.S.; Kirwan, K. *"*Multi-Criteria Decision Aiding: A Decision Support Approach for Green Chemistry-Oriented Synthesis of Nanomaterials*"*. 23rd International Conference on Multiple Criteria Decision Making, Hamburg, Germany, 2-7 August, 2015 (Oral presentation)

## From Chapter 7:

### Conference presentation

**Cinelli, M.**; Coles, S. R.; Nadagouda, M. N.; Błaszczyński, J.; Słowiński, R.; Varma, R.S.; Kirwan, K. *"*Multiple Criteria Decision Aiding Moves Sustainable Nanotechnology Forward*"*. 82nd European Working Group on Multiple Criteria Decision Aiding, Odense, Denmark, 24-26 September, 2015 (Oral presentation)

# *Abbreviations*

| | |
|---|---|
| AHP | Analytical hierarchy process |
| ADME | Absorption, distribution, metabolism, excretion |
| ATS | Alternative testing strategies |
| CAI | Classes acceptability indices |
| DM(s) | Decision maker(s) |
| DRSA | Dominance-based rough set approach |
| ECON | Economic performance |
| ELECTRE | Elimination and choice expressing the reality |
| ENVIMP | Environmental impacts |
| ERAM | Environmental risk assessment and management |
| GCP | Green chemistry principles |
| HRAM | Human health risk assessment and management |
| IL | Importance level |
| LCA | Life cycle assessment |
| LCC | Life cycle costing |
| LCSA | Life cycle sustainability assessment |
| MAUT | Multi attribute utility theory |
| MCDA | Multiple criteria decision aiding |
| N | Number of participants who replied to pilot/main survey |
| NP(s) | Nanoproduct(s) |
| PC | Processing conditions |
| PIN | Protocol identification number |
| PROMETHEE | Preference ranking organization method for enrichment of evaluations |
| PV | Point of view |
| RA | Risk assessment |
| RAM | Risk assessment and management |
| RI | Relative index |
| RQ | Research question |
| SA | Sustainability assessment |
| SD | Sustainable development |
| SI | Social implications |
| SLCA | Social life cycle assessment |
| SMAA | Stochastic multi-criteria acceptability analysis |
| TBL | Triple bottom line |
| TP | Technical performance |
| WOS | Web of Science |

# *Abstract*

Nanotechnology is currently emerging as the next industrial revolution. It enables the production of goods (i.e. nanoproducts, NPs) with enhanced functionalities, which have nonetheless caused mounting concerns about the potential implications they can have on the environment, economy and society. This thesis employs Multiple Criteria Decision Aiding (MCDA), one form of decision support, to aid the sustainable development of nanotechnology. The first original contribution of this doctoral research is the development of a framework of sustainability assessment criteria for NPs, through a three-phase procedure based on the MCDA process, including a literature review, a pilot and a main survey. It lead to a comprehensive framework of 68 criteria, ranked according to their relative importance*,* allocated to six main domain areas*:* (i) economic performance; (ii) environmental impacts; (iii) environmental risk assessment; (iv) human health risk assessment; (v) social implications; and (vi) technical performance. All the criteria are reliable and can be used in real case studies to increase the knowledge about the sustainability of NPs. The second original contribution presented in this thesis is a robust model (DRSA-based model) based on green chemistry principles implementation for the classification of synthesis processes of nanomaterials in preference-ordered classes. This tool was developed through knowledge elicitation techniques based on co-constructive MCDA with the collaboration of two experts (the decision makers) in synthesis of nanomaterials. The robustness of the ensuing model was assessed (and confirmed) by means of another model developed ad hoc (ELECTRE-based model), structured on an MCDA method implementing a stochastic multiple criteria classification strategy. The results confirm that MCDA is an effective decision support approach to foster sustainable development of nanotechnology, providing that the analysts who apply it take these considerations into account. They must ensure that (1) multidisciplinary teams are created to perform comprehensive and credible sustainability evaluations; (2) problem structuring and model construction are as important as (if not more important) than the results (i.e. decision recommendations) themselves; (3) identification of the appropriate MCDA method depends on the problem at hand and not vice-versa; and (4) the credibility of the decision recommendations is subject to the preferences of the decision-makers. If these considerations are accounted for, the possibility of advancing nanotechnology on a sustainable path is very concrete and realistic.

# Chapter 1. Introduction

## 1.1 Research context

The future of the next generation depends heavily on the type of development that is adopted nowadays. Guaranteeing a standard of living for all human beings as it is currently available in industrialized countries in the 21st century will require huge coordination in terms of technological advancement, international and national policy structuring and people's attitude change towards their production and consumption patterns. Nanotechnology has been proposed as one of the premier solutions to the current unsustainable exploitation of Earth's resources; in order to achieve this objective its development and advancement must proceed responsibly and sustainably [1-3].

**This thesis tackles this challenge by adopting Multiple Criteria Decision Aiding (MCDA) to develop a framework of sustainability assessment (SA) criteria for nanoproducts (NPs), as well as two models to classify synthesis processes for nanomaterials based on green chemistry principles implementation.**

MCDA is a discipline of Operational Research whose main objective is to provide decision support strategies and tools to aid stakeholders in making informed, transparent and justifiable decisions [4].

Nanotechnology refers to the development of NPs, namely nanomaterials (materials at the nanoscale, i.e. one billionth of a meter, $10^{-9}$ m) and products containing such materials with unique physicochemical properties that do not exist yet or are better when compared to competitive non-nano solutions [5]. More formally nanotechnology is defined by the United States National Nanotechnology Initiative as the [6]

> *"research and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1 - 100 nanometer range; creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size; and the ability to control or manipulate on the atomic scale."*

There are three main aspects that characterize this emerging technology [7]:

i. It refers to the voluntary manipulation, handling, and control of matter at the nanoscale;
ii. The scale of the matter nanotechnology deals with is so small that the comparative surface area becomes very large and determines some of the unique properties of these materials, not normally exhibited by their bulk equivalents;
iii. It enables new and improved applications that can have an important role in supporting sustainable innovation and economic growth.

There are rather corresponding views on the huge potentials of nanotechnology to empower the production of new products with enhanced performance [8-10]. Nanotechnology is currently considered as an enabling technology that has started supporting products innovation in various sectors as a result of their unique characteristics, such as higher chemical reactivity and better optical, electrical and magnetic properties [9-11]. The inclusion of nanomaterials in formulations has been shown to enhance product properties like strength, hardness and electrical conductivity. Table 1-1: provides a (non-exhaustive) list of major industrial sectors employing NPs [1-3, 12], justifying the reason why it is usually considered as having wide prospects for drastically changing our lives.

**Table 1-1: An indicative list of business sectors employing NPs. Adapted from *[1-3, 12]***

| | | | |
|---|---|---|---|
| Automotive Industry | Chemical Industry | Construction | Cosmetics |
| Electronics | Energy and Environment | Engineering | Food and Drinks |
| Household | Biomedicine | Sports/Outdoors | Textiles |

Nanotechnology has the potential to lead to widely available products on the market that span across a variety of areas including thermal insulation, power generation, drug delivery, sensors and building materials. Translucent nanomaterials (e.g. gold, lanthanum) can be used to increase thermal insulation of windows as well as UV protection [13], and the behaviour can be tuned depending on the degree of solar radiation. Lithium-ion batteries are receiving mounting interest as a result of the increased storage performance and efficiency that nanomaterials (e.g. carbon nanotubes, silicon, stannic oxide) enable when embedded in such systems [14]. Carbon dioxide can be transformed into products such as polymers and hydrocarbons through the use of carbon nanotubes [15].

Nanomaterial types are many and those of major commercial interest include metals, metal oxides, fullerenes, carbon nanotubes and compound semiconductors [7, 11].

## 1.2 Research gaps

The pervasive nature of nanotechnology in a wide variety of industrial sectors suggests that the implications it can have on the environment, economy and society are multiple, both from a positive and a negative standpoint [1, 3, 16]. For example nanomaterials can increase the degradation efficiency of pollutants when compared to their bulk formulation while on the other side their life cycle impacts or risks can be higher. Similarly a T-shirt containing nanosilver can improve the antibacterial properties of the textile whilst at the same time the impacts on the ecosystem can be more problematic than a conventional chemical.

The unique physicochemical properties of nanomaterials are due to their very small scale; which is also the reason for their improvement in terms of products functionality [8]. Nonetheless, their small scale is also a source of major health and safety concerns since they can penetrate cell membranes normally not accessible to larger objects thus causing potential threats to humans and the environment [17]. Manufacturing nanomaterials can be highly energy demanding as well as resource inefficient [18], raising concerns about their impact on resource depletion and damaging emissions. NPs can be used for ethical disputable purposes, such as military espionage and data hacking [19, 20]. Nano-enabled applications could be developed to aid tackling illnesses (e.g. HIV) widespread in developing countries, however developed nations drive most of the nanotechnology advancement and they do not primarily prioritize products development for disadvantaged countries [19]. These few examples illustrate how nanotechnology development has to be linked to responsible governance in order to support its widespread accepted use in the decades to come.

Just over a decade ago, the concepts of green chemistry and sustainability were linked with the development of nanotechnology in order to steer its advancement on a more responsible path and to pose the basis for its future widespread acceptance and success [10, 16]. This has led to the emergence of green and sustainable nanotechnology consisting in the application of the principles of green chemistry and sustainability to nanotechnology throughout the whole life cycle [3, 16, 21-27].

The two main objectives that characterize this new concept of nanotechnology are [16, 25, 26, 28-30]:

i. Produce NPs that do no harm the environment and human health;
ii. Use NPs in support of sustainability, for example by creating applications to be used to treat wastewater, produce clean energy or reduce weight of composites.

Currently, there is not an agreed definition of sustainable nanotechnology [21, 31], however a variety of interpretations and proposals for the assessment of its implementation has emerged along the years. These include integration of green chemistry and engineering principles in the development of new nanomaterials and nanomanufacturing processes [23, 24, 32, 33], life cycle assessments to evaluate environmental implications [34-36], health and safety impacts assessments of NPs as well as investigations of their environmental behaviour [37-42], identification of criteria sets for a variety of impacts categories [5, 23, 43-46] and integration of available information with MCDA methods [47-49]. Among the studies and methods cited above, MCDA (a discipline aiming at elaborating recommendations to decision makers) is emerging as a very suitable candidate to further sustainability governance of nanotechnology [47, 48, 50-53]. This results from the flexibility of MCDA in terms of problem formulation, selection of assessment criteria, management of uncertainty, handling of potential criteria trade-offs and disagreements among different stakeholders [49, 52, 54-58].

In order to pose robust basis for the widespread acceptance of nanotechnology, its technological development should be coupled with the understanding and communication of its societal, environmental and economic implications [19, 45, 59, 60]. The adoption of sustainability principles for nanotechnology can contribute to overcoming the burden of current unknown risks and since the development of such technology is at the beginning, this is a good opportunity to implement changes [16, 25, 27, 30, 61]. However, **there are several limitations and obstacles to be solved**, **including** the need to [3, 5, 22, 23, 28, 30, 31, 43, 50, 61-63]:

i. **Define a comprehensive and agreed set of criteria to assess the sustainability of NPs;**

ii. **Elaborate guidelines to assign the label "green" for nanomaterials and their synthesis processes;**
iii. Develop appropriate analysis and characterization tools and also reaction mechanisms to improve and standardize synthesis and production processes;
iv. Improve collaborations with regulatory bodies to support proper regulation efforts based on the envisioned application areas and materials properties;
v. Create collaboration between research institutions and industry.

**This thesis deals with the advancement of nanotechnology on a sustainable path and it is focused on the first and second challenges listed above, which emerged as pressing issues for supporting research, industrial and policy decision-making processes for the sustainable development of nanotechnology.**

Such interest is due to the fact that there is not a clear understanding of the sustainability of NPs [3, 5, 30], which can be related to the lack of a comprehensive and agreed set of criteria to assess their sustainability implications [5, 30, 31, 48, 53, 59, 63]. In addition, design guidelines to aid greener nanomaterials development and production have been advocated by researchers as well as professional organizations and governmental agencies, but they are currently missing [22-24, 26, 29-31, 50, 62, 64].

## 1.3 Thesis objectives

The objectives of the Ph.D. thesis can be summarized as follows:

i. Review the state-of-the-art for SA of NPs;
ii. Evaluate the potentials of MCDA methods to support SAs of NPs. The analysis must show pros and cons of the methods from the main families of MCDA approaches;
iii. Develop a comprehensive set of SA criteria for NPs. This set must provide a reliable and validated set of criteria, with priorities and correlations of such criteria investigated too;
iv. Develop and validate a model for the classification of synthesis processes for nanomaterials on the basis of green chemistry principles implementation. The model must be easily intelligible by non-experts in decision aiding and it shall provide design guidelines for greener nanomaterials development.

## 1.4 Overview of the thesis

**Chapter 1** introduced the importance of nanotechnology in the current economy and described the implications that its products (i.e. nanoproducts, NPs) can have on the environment, economy and society. Following this background, the objectives of the thesis have been defined.

**Chapter 2** outlines the concept of sustainable development and proposes a clustering of the methods that have been used to perform SAs. The cluster provides the background for Chapter 3 to categorize these methods in the area of nanotechnology.

**Chapter 3** firstly presents an overview of the approaches used to assess the sustainability implications of nanotechnology following the grouping presented in Chapter 2. It also highlights the current lack of a comprehensive and reliable framework of criteria to perform a holistic SA of NPs, justifying the work to fill such research gap, described in Chapter 5. Furthermore, the lack of design guidelines for “green” nanomaterials is advanced as the other knowledge gap that this doctoral research filled, as described in Chapters 6 and 7.

The potentials and weaknesses of MCDA methods for sustainability evaluations are surveyed in **Chapter 4**, justified by the wide interest and promises that MCDA has shown both for in general (Chapter 2) and more specifically in the area of nanotechnology (Chapter 3). The outcomes of this review entitled the selection of MCDA process and methods in Chapters 5, 6 and 7.

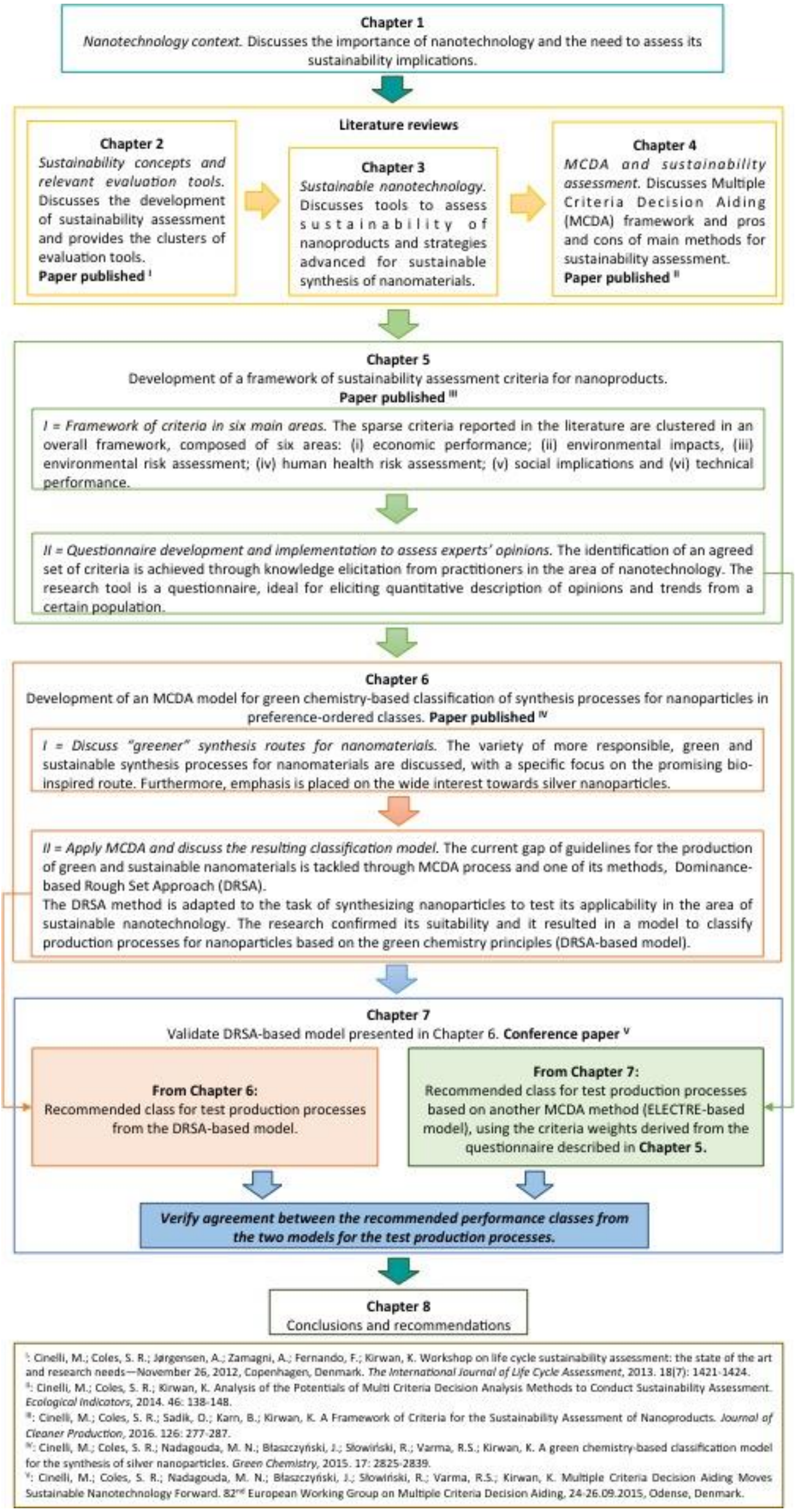
**Chapter 5** describes the framework of criteria that was developed to assess the implications of NPs. The devised methodology, structured on the MCDA process, employs a three-phase procedure including a literature review, a pilot and a main survey. It lead to a comprehensive framework of 68 criteria allocated to six domain-specific areas. All the criteria are reliable and ranked according to their relative importance, which warrants its use in real case studies, as it is demonstrated in Chapter 7.

**Chapter 6** presents a case study where knowledge elicitation techniques, including the MCDA process, one of its methods (Dominance-based Rough Set Approach, DRSA) and concept mapping were employed in collaboration with two experts in synthesis of nanomaterials. This resulted in a classification model (DRSA-based model) for synthesis of nanomaterials in preference-oriented classes according to the implementation of the principles of green chemistry.

**Chapter 7** advances another MCDA-based approach that was devised to validate the model presented in Chapter 6, by evaluating the independency of the classification recommendations from the DRSA-based model from the subjectivity of the decision-makers (DMs) who collaborated in its development. It employed the rankings of a subset of criteria from the framework proposed in Chapter 5 with another MCDA method, namely Stochastic Multicriteria Acceptability Analysis. This resulted in another classification model, whose decision recommendations were used to assess the robustness of the DRSA-based model.

**Chapter 8** provides the general conclusions of the thesis and some recommendations for future research.

**Figure 1.1 below illustrates the graphical layout of the Ph.D. thesis chapters.**



**Chapter 1**
*Nanotechnology context.* Discusses the importance of nanotechnology and the need to assess its sustainability implications.

**Literature reviews**

**Chapter 2**
*Sustainability concepts and relevant evaluation tools.* Discusses the development of sustainability assessment and provides the clusters of evaluation tools.
**Paper published** [I]

**Chapter 3**
*Sustainable nanotechnology.* Discusses tools to assess sustainability of nanoproducts and strategies advanced for sustainable synthesis of nanomaterials.

**Chapter 4**
*MCDA and sustainability assessment.* Discusses Multiple Criteria Decision Aiding (MCDA) framework and pros and cons of main methods for sustainability assessment.
**Paper published** [II]

**Chapter 5**
Development of a framework of sustainability assessment criteria for nanoproducts.
**Paper published** [III]

*I = Framework of criteria in six main areas.* The sparse criteria reported in the literature are clustered in an overall framework, composed of six areas: (i) economic performance; (ii) environmental impacts, (iii) environmental risk assessment; (iv) human health risk assessment; (v) social implications and (vi) technical performance.

*II = Questionnaire development and implementation to assess experts' opinions.* The identification of an agreed set of criteria is achieved through knowledge elicitation from practitioners in the area of nanotechnology. The research tool is a questionnaire, ideal for eliciting quantitative description of opinions and trends from a certain population.

**Chapter 6**
Development of an MCDA model for green chemistry-based classification of synthesis processes for nanoparticles in preference-ordered classes. **Paper published** [IV]

*I = Discuss "greener" synthesis routes for nanomaterials.* The variety of more responsible, green and sustainable synthesis processes for nanomaterials are discussed, with a specific focus on the promising bio-inspired route. Furthermore, emphasis is placed on the wide interest towards silver nanoparticles.

*II = Apply MCDA and discuss the resulting classification model.* The current gap of guidelines for the production of green and sustainable nanomaterials is tackled through MCDA process and one of its methods, Dominance-based Rough Set Approach (DRSA).
The DRSA method is adapted to the task of synthesizing nanoparticles to test its applicability in the area of sustainable nanotechnology. The research confirmed its suitability and it resulted in a model to classify production processes for nanoparticles based on the green chemistry principles (DRSA-based model).

**Chapter 7**
Validate DRSA-based model presented in Chapter 6. **Conference paper** [V]

**From Chapter 6:**
Recommended class for test production processes from the DRSA-based model.

**From Chapter 7:**
Recommended class for test production processes based on another MCDA method (ELECTRE-based model), using the criteria weights derived from the questionnaire described in **Chapter 5.**

***Verify agreement between the recommended performance classes from the two models for the test production processes.***

**Chapter 8**
Conclusions and recommendations

[I]: Cinelli, M.; Coles, S. R.; Jørgensen, A.; Zamagni, A.; Fernando, F.; Kirwan, K. Workshop on life cycle sustainability assessment: the state of the art and research needs—November 26, 2012, Copenhagen, Denmark. *The International Journal of Life Cycle Assessment*, 2013. 18(7): 1421-1424.
[II]: Cinelli, M.; Coles, S. R.; Kirwan, K. Analysis of the Potentials of Multi Criteria Decision Analysis Methods to Conduct Sustainability Assessment. *Ecological Indicators*, 2014. 46: 138-148.
[III]: Cinelli, M.; Coles, S. R.; Sadik, O.; Karn, B.; Kirwan, K. A Framework of Criteria for the Sustainability Assessment of Nanoproducts. *Journal of Cleaner Production*, 2016. 126: 277-287.
[IV]: Cinelli, M.; Coles, S. R.; Nadagouda, M. N.; Błaszczyński, J.; Słowiński, R.; Varma, R.S.; Kirwan, K. A green chemistry-based classification model for the synthesis of silver nanoparticles. *Green Chemistry*, 2015. 17: 2825-2839.
[V]: Cinelli, M.; Coles, S. R.; Nadagouda, M. N.; Błaszczyński, J.; Słowiński, R.; Varma, R.S.; Kirwan, K. Multiple Criteria Decision Aiding Moves Sustainable Nanotechnology Forward. 82nd European Working Group on Multiple Criteria Decision Aiding, 24-26.09.2015, Odense, Denmark.

**Figure 1.1: Graphical representation of thesis chapters**

# Chapter 2. Sustainability Assessment: Origins and Methods

## 2.1 Introduction

Technological development allows the production of a multitude of products that satisfy an increasing variety of needs. In order to guarantee that future generations will be able to have access to such products and develop their own, it is necessary to shape sustainable business models that adopt a different approach towards use and consumption of resources, especially finite ones. This goal is achievable if we are capable of measuring the progress towards or away from sustainability. This chapter provides a comprehensive overview of the tools that are currently available to assess this progress.

## 2.2 The concept of Sustainable Development

The concept of sustainable development (SD) emerged as part of cultural traditions (such as Hawaiian and African ones) whose main viewpoints were that humans should live in harmony with nature and that each human action has a direct impact on the environment [65]. Since the industrial revolution, the exploitation of natural resources in conjunction with advancements in technological developments allowed some countries to increase living standards of their population, usually at the expense of people in other countries, through an uncontrolled impact on the environment.

This imbalanced “progress” fostered the birth of environmental movements and proposals for a different way of development that did not have unconfined growth as its philosophical foundation. In 1972, the UN Conference on Human Environment in Stockholm recognized the importance of environmental management and the role of environmental assessment as a management tool [66] and posed an important step towards the concept of SD. Additionally, the Club of Rome, a pool of experts in responsible development, started in 1968 to highlight the incumbent risk of exceeding ecological limits within decades with their current economic growth [65].

The need to link environment and development together became a major topic of international politics and it was consolidated with the Brundtland Report in 1987, where SD was defined as follows [67]:

> *"Sustainable development is development that meets the needs of the present without compromising the ability of future generations to meet their own needs".*

Two fundamental concepts were included in this definition:

i. Needs satisfaction, specifically those of the poor;
ii. Limitations of the feasible human activities dependent on the finite environmental resources.

SD has since become the basis of environmental discourse and the 1992 United Nations (UN) Conference on Environment and Development in Rio marked another important step [68]. In fact, 27 legally non-binding principles were defined to foster environmental protection and responsible development. Furthermore, concrete questions about how to move towards a more sustainable world and how to evaluate this progress started emerging [65]. The environment represented the first pillar out of the three that will later constitute one of the most well-known definitions of SD, the "triple bottom line" (TBL) [69-71], which also embraces the concepts of economy and society as pivotal components of SD.

Understanding how best to implement the concepts of SD is of crucial importance to allow future generations to flourish. As a result, development of tools and methods to evaluate such implementation are an ethical responsibility that humans have.

## 2.3 Assessing the progress towards sustainable development

The literature about what SA actually represents is steadily growing, with different interpretations and implementations of this concept available so far [72-74]. On one side, there are rather conceptual and holistic proposals based on sustainability principles which introduce frameworks to encompass and combine different values and perspectives [67, 69, 70], while on the other side there are more concrete approaches that try to define and derive measureable sustainability criteria/pillars to make the concept of sustainability operational [69, 75-77].

The underlying philosophy of this thesis has been shaped around these two definitions of SA:

> *‘‘Sustainability assessment is* [...] *a tool that can help decision-makers and policy-makers decide what actions they should take and should not take in an attempt to make society more sustainable’’* [78]

> *“Sustainability assessment can be considered as an umbrella term that embraces a range of processes that all have as their broad aim the integration of sustainability concepts into decision-making* […]*”* [79]

Furthermore, the purpose of SA is [80]:

> *“to provide decision-makers with an evaluation of global to local integrated nature–society systems in short and long term perspectives in order to assist them to determine which actions should or should not be taken in an attempt to make society sustainable”.*

There are two recurrent concepts in the definitions reported above:

i. DMs, those who are in charge of making decisions and in doing so, influencing people’s lives;
ii. Contribution to a more sustainable society, which requires the measurement of sustainability concepts.

This suggests that it is not possible to conduct SA if one of the two concepts above is missing as without DMs there are no decisions being taken and without measurement of sustainability concepts it is not possible to evaluate whether the choices being made are contributing to a more sustainable society.

Gibson proposes a set of leading principles to assess the progress towards sustainability, including [69]:

i. Socio-ecological system integrity;
ii. Livelihood sufficiency and opportunity;
iii. Intra-generational equity;
iv. Inter-generational equity;
v. Resource maintenance and efficiency;
vi. Socio-ecological civility and democratic governance;
vii. Precaution and adaptation;
viii. Immediate and long-term integration.

The need to implement the principles of sustainability and to measure (although not comprehensively) the progress towards a more sustainable society started taking shape with the identification of a variety of pillars or spheres of sustainability depending on the context of the analysis/evaluation to be performed, with each one characterized by individual indicators [69, 72, 76, 77, 81-83]. As mentioned before, one of the most common is the TBL approach, which is based on the environmental, economic and social pillars, having equal importance in the decision-making process [21, 69, 75, 84, 85]. This approach has been widely used as it fits properly with the professional figures and organizational bodies that operate in each of the pillars [69].

Measurement of contribution to a more sustainable society can only be achieved if data is available and reliable criteria can be shaped and used throughout every assessment.

**In this thesis a pragmatic approach towards SA has been adopted, aiming to make the concept of SD operational. As a result, sustainability criteria constitute an essential part of this research.**

The conceptualization of SA should be based on the context of the analysis/evaluation to be performed. In other words, the criteria to be used in evaluating a car cannot be the same of those needed for a transport policy. In fact, the objective of SA can range from a micro to a macro scale, meaning that the inclusion of various processes and mechanisms cannot always be taken into account with the same approaches [81, 82].

Additionally, the spheres or pillars of sustainability considered can vary, which means that some studies can consider only environmental and economic aspects, others only the environmental ones and others environmental, economic and social together [77].

SA has also the role of improving the decision-making process, by [86, 87]:

i. Integrating sustainability spheres and considering their interdependencies;
ii. Including intra-generational and inter-generational considerations;
iii. Supporting constructive interaction among stakeholders;
iv. Accounting for uncertainties and adopting a precautionary approach;
v. Contributing to monitoring and communication of results.

An important methodological consideration that has to be introduced as it deeply affects the possible tools and methods that can be used when assessing the progress towards sustainability is the distinction between the concept of weak and strong sustainability. Weak sustainability is based on the theory that substitution among different forms of capitals (e.g. manufactured, human, natural) can be accepted [88]. As a result, reduction in one form of capital can be counterbalanced by an increase in another one [55]. From a methodological viewpoint this implies that the decrease in the performance of a sustainability criterion can be compensated by the improvement in another one. On the contrary, strong sustainability limits or abolishes the level of substitution mentioned above, since some forms of capital (as the natural one) are considered as crucial and not commutable with others [55, 88, 89]. In this case, sustainability criteria are partially or not substitutable among each other. This methodological consideration has extensive implications on the types of methods that can be used when performing SA, and the issue is discussed in detail in Chapter 4.

## 2.4 Clusters of sustainability assessment methods

Over the past decades a plethora of methods and tools were developed to perform SA studies, focusing on different scopes (i.e. different pillars) and scales/objectives (i.e. micro, meso and macro), with some covering only a certain pillar and object of sustainability (e.g. Life Cycle Assessment (LCA)), and with others widening both (e.g. cost-benefit analysis, MCDA) [73, 81].

Several proposals have been advanced to categorize tools and instruments to perform SA and a general set of categories includes:

i. Biophysical indicators [90, 91];
ii. Monetary indicators [90, 91];
iii. Social indicators [91, 92];
iv. Indicators sets and sustainability dashboards [80, 87];
v. MCDA [55, 80, 90, 91].

An indicator can be defined as an “operational representation of an attribute of a system” [87] and it supports the decision-making processes by converting knowledge in manageable units of information [93]. Indicators represent the basic features for the first three categories shown above, with each one developed to assess a particular aspect of the system under evaluation.

The main driver of biophysical tools is the amount of resources used to produce a good or a service. The building blocks are physical indicators that are expressed in terms of comparable measurement units, aimed to indicate the environmental impacts. Their principal commonality is that they all share an “ecocentric” perspective [74] and their main limitations are that they can explicitly cover only one dimension of sustainability (i.e. environment) and within this they normally focus only on individual domains (e.g. use of water, energy, land), [54, 87, 90, 91]. However, they enforce strong sustainability accounting for the non-substitution of forms of capitals [91]. One example is LCA, a tool that can span the whole life cycle of a product [80, 94]. It is a very powerful instrument to evaluate the environmental impacts that can arise during the life cycle of a certain good, phasing out the problems of shifting negative effects of one life cycle stage to another one [95].

The second category of tools to assess sustainability is the monetary one, based on the concept that a monetary value can be assigned to each form of capital (i.e. man-made, human, social and natural) and on the assumption that substitution between different forms of capital is possible [96]. One of the most well-known approaches is Cost-Benefit Analysis (CBA), which was developed to assess the costs and benefits of a project and to identify the alternative with the best return on capital [97]. Costs refer to all the expenditures incurred by the investor, whereas benefits are all revenues obtained from the project. Acceptable projects must exceed a certain threshold return on investment and all the variables taken into consideration are reduced to a measurement scale which is monetary [96].

The third group of indicators is the one devoted to the social implications of goods and services. There is a wide range of methodologies that has been proposed to investigate a variety of social impact categories, including human rights, labour practices, decent work conditions and product responsibility [98]. One of the most notable achievements in this area, at the product level, is the social life cycle assessment methodology [98], a relatively new approach as compared to its environmental and economic counterparts. It received a lot of interest in the last five years with evaluation criteria being proposed to assess the social implications of products on several interest groups, among which the general public, workers, local communities and regions [99].

Assessing sustainability is a multidimensional and interdisciplinary process, which can be approached using indicator sets and dashboards from different spheres or principles of sustainability [54]. This is the fourth group of tools for SA. One example is the set of 58 indicators proposed by the United Nations Commission on SD [93]. These are grouped into 14 themes that provide an evaluation of countries development by considering economic, social, environmental and institutional indicators. Although linkages among the indicators are identified, they are not aggregated into a score or index, leaving the results rather complex and difficult to interpret by DMs and the general public. This is due to the inability of human mind to consider complex information all at once (e.g. 58 indicators), especially when the relative performance of the alternatives is good on some parameters and poor on others [80]. An example of indicators sets is the life cycle sustainability assessment (LCSA) framework, which tries to integrate under the same umbrella the environmental, economic and social strategies for SA of products by accounting for their life cycle [100]. There is not an agreement yet on how LCSA can be actually implemented, whether as a sum of independent results from LCA, life cycle costing (LCC) and SLCA or as a unique evaluation considering criteria from each sustainability domain. Nonetheless, it is emerging as one of the most comprehensive approaches to study sustainability impacts of products, especially for its capacity of covering each life cycle stage [100].

Indicators sets and dashboards can objectively and transparently represent the sustainability characteristics of a product/project/country and they can be used to employ a strong concept of sustainability [54, 73, 74, 87, 90, 91]. Nonetheless, it is difficult to use these tools for supporting decision-making as the encoded information is unstructured and difficult to assimilate for DMs. What is more, the procedures adopted to identify the assessment indicators (e.g. project participants' preferences), to elicit expertise and knowledge from the stakeholders (e.g. experts' workshops) and communicate the results (e.g. spider diagrams), do not usually follow a traceable, participatory and transparent strategy, which hampers the credibility and acceptance of the delivered results [94]. This leads to the last family of methods and tools for SA, which is MCDA.

MCDA is a process and a group of methods that can be used to structure problems, identify alternatives and assessment criteria and integrate information to provide decision support for DMs [101, 102]. MCDA methods can be categorized as integrative assessments, in other words approaches that try to handle the information from individual indicators in a comprehensive manner, by considering interrelations and interdependencies among them, accounting for the different importance that they might have, and adopting different degrees of aggregation [101, 103-105].

The MCDA definition has clear links with the definitions of SA reported at the beginning of this chapter, where people (i.e. stakeholders) are involved in making or influencing decisions that are going to have an impact on society, economy and the environment. This suggests that MCDA can be a very suitable candidate to support SA, as reported by a variety of authors [55, 56, 87, 90, 91, 104-110]. However, there are a series of unresolved matters in MCDA, including agreement on how to structure a problem into relevant evaluation parameters, the elicitation and the meaning of weights for the assessment criteria and the transparency of the aggregation procedures leading to a comprehensive evaluation of the alternatives [4, 111, 112]. Furthermore, the aggregation of information in MCDA is based on stakeholder or expert knowledge elicitation, which introduces subjectivity in the assessment [111, 113]. This is a sensible matter which needs to be properly addressed by means of sensitivity and robustness analysis to assess the credibility of the recommendation provided by the MCDA models [114].

As far as the level of integration among the sustainability spheres is concerned, sectorial views (one single sustainability sphere) are characteristic of biophysical tools since they focus on individual assessment targets (e.g. water consumption, energy efficiency), whereas monetary and MCDA methods allow for inclusion of a wide spectrum of sustainability implications (e.g. technical, environmental and economic) [90]. Another advantage of MCDA over the other tools is that it can explicitly account for multiple stakeholders' preferences and perspectives. This is particularly beneficial for sustainability evaluations, since they usually necessitate collaborations between stakeholders with different competencies, values and expertise (e.g. engineering, social science, economics, materials chemistry, regulation) [90].

## 2.5 What method to choose for assessing sustainability?

It is not possible to affirm that there is a “perfect” tool or method to assess sustainability, since every evaluation has a specific goal, focus, data availability and stakeholders. Nonetheless, various considerations about the appropriateness of each type of approach are available.

A topic of wide controversy concerns the use of approaches that imply or allow substitutions among different forms of capital (e.g. natural and man-made); monetary tools are among these [88, 96]. The most fervent critique to such methods is that the use of a common measurement unit (as monetary tools do) to assess the progress towards sustainability does not account for the fact that biophysical constrains that are necessary to sustain world ecosystems as water, air, minerals, energy, space and genetic materials are not exchangeable [55, 88].

Due to the complexity of SA and the need to provide a path towards the achievement of a sustainable future, decisions have to be made and this has to take place in a structured, transparent and reliable way. As a result, the process of integrated assessment for SD must follow an acknowledged path. In order to reach this goal, during the EU project named "Sustainability-A" around 50 tools considered appropriate for SA studies were categorized in 7 groups [94, 115]:

i. Assessment frameworks;
ii. Participatory tools;
iii. Scenario tools;
iv. Cost-benefit and cost-effectiveness analysis tools;
v. Accounting tools, physical analysis tools and indicator sets;
vi. Model tools;
vii. MCDA.

One of the main conclusions of Sustainability-A project was that a successful integrated evaluation of sustainability can be achieved only if different methods are adopted. This leads to the need of understanding (and thus knowing) what tools are needed in what situation and how they can be combined in a successful manner [94, 115]. An important methodological note is that MCDA is a process that leads to integration of information from criteria provided by methods and models and it is not to be seen as a tool in competition with them but rather an enabler for the exploitation of their potentials to support decision-making.

Although there is the need to operationalize sustainability and, as a result, to define a series of spheres and criteria to evaluate it, the simple sum of the individual aspects cannot provide us with a satisfactory and even realistic evaluation of how sustainable a product, process, project or policy is. This is due to the many interlinkages amongst the various aspects of sustainability, which determines a network of feedbacks and connections that should to be accounted for [69, 75]. This is the main reason why a need for trans-disciplinary research has been long advocated in the case of sustainability studies, indicating the necessity to switch from a "mode I science" paradigm (i.e. academic, mono-disciplinary, certain and predictive) to a "mode II science" paradigm, where cross-disciplinary work is performed, experts from different disciplines collaborate and methods and models can be effectively linked [83, 94]. The switch to "mode II science" paradigm requires a more open perspective, where many stakeholders are involved, making scientists only one of the components of the process. It is important to bear in mind that the development of the concept of SA is the result of the inappropriateness of the conventional methodology of taking decisions as, along the years, the need for more structured, participated, integrated and science based decision-making has emerged [69, 116].

## 2.6 Summary

The concept of satisfying human needs in conjunction with the preservation of the environment we live in has been embedded in some cultures since the early stages of human civilization and it represents the main philosophical foundation of SD. SD emerged as a pressing need for society during the 1970's when human-centric development started showing its dangerous effects in terms of pollution increase, environmental degradation and depletion of scare resources.

Formal definitions of SD emerged along the years, with the most famous one formulated by the World Commission on Environment and Development, which underlined the necessity to consider the satisfaction of human needs, specifically those of the poor, in conjunction with the limitations of environmental resources to satisfy such needs.

Assessing the progress towards a more sustainable society became a primary concern and many approaches, tools and methods started emerging to achieve this goal. Some of them are based on sustainability-oriented principles, whereas others try to define specific aspects and criteria that need to be implemented to contribute to a more sustainable society.

A general classification of the instruments to be used to perform SA identifies five main categories:

i. Biophysical indicators;
ii. Monetary indicators;
iii. Social indicators;
iv. Indicators sets and sustainability dashboards;
v. MCDA.

The first three categories are indicators, namely individual representations of a part of a system under consideration. They can be useful to provide information about a specific sphere and domain of sustainability, however they are limited in the capacity of accounting for interdependencies and interrelations among different spheres and domains.

Indicators sets and sustainability dashboards are good candidates to transparently represent sustainability-related characteristics of target objects, reporting different forms of capital simultaneously. However, due to the lack of aggregation the information they convey is usually difficult to assimilate for the DM.

The last category of methods and tools for SA is MCDA, which is a process and a set of methods that can be used to support structured decision-making, leading to aggregation of information in a transparent manner. Sustainability evaluations are decision-making processes themselves and as a result MCDA is a good candidate to support such appraisals. This type of assessments involve complex interrelation of impacts, values, indicators and most importantly DMs who are faced with the need of making decisions and have good reasons and explanations for them. In this regard, MCDA can be seen as a very good candidate for SA as it is the only group of tools that can provide such structured support for the DMs and this is probably the reason for such growing interest in it from sustainability analysts' viewpoint.

Chapter 3 provides an overview of the SA methods that have been used to evaluate the sustainability implications of NPs following the clustering proposed in this chapter.

# Chapter 3. Sustainable Nanotechnology: State-of-the-Art

## 3.1 Introduction

Chapter 1 highlighted the importance that nanotechnology can have in shaping the advancement of several industrial sectors through the application of nanoscience into products to enhance their performance. Nonetheless, the governance of this emerging technology must keep sustainability as a main pillar to guarantee a widespread consensus and acceptance of such technology. Chapter 1 also mentioned that there is still lack of agreement on the definition of sustainable nanotechnology and it emphasized that heterogeneous studies emerged to evaluate the implications that nanotechnology can have on the environment, economy and society.

This chapter presents a brief overview of the methods used to assess NPs sustainability, following the clustering of tools proposed in Chapter 2, from the indicators that cover one or more sustainability pillars to integrative assessments based on MCDA.

## 3.2 Sustainability indicators

### 3.2.1 Risk assessment studies

The high reactivity of NPs and their ability to access cells as a result of their small scale raised health and safety implications concerns among the political and regulatory workforce, which reflected in increasing funding for research projects to study these potential impacts in detail [40, 117-120]. The main tool which has been put forward to estimate health and environmental risks of NPs is the risk assessment of chemicals (i.e. hazard identification, dose-response assessment, exposure assessment and risk characterization) [118, 121]. It has been applied to several types of nanomaterials, including fullerenes, carbon nanotubes, metal and metal oxides [118] and each step of the procedure is restrained by substantial limitations:

i. Missing consensus about the most suitable dose descriptors (e.g. mass, surface area, number, concentration or a combination of those) leads to incomparable toxicity results [17, 118, 122-126];

ii. Difficulties in monitoring the concentrations, environmental behaviour and fate of nanoparticles in the environment hampers the environmental exposure assessment [40, 126-130];

iii. Data gaps in regards to the number of workers exposed to materials at the nanoscale, the type of materials workers are exposed to, the pathways of exposure, the concentrations of nanoparticles in the working settings and the effectiveness of risk management measures restrains realistic occupational exposure assessment [17, 124, 126, 127, 129, 131];

iv. Deficient knowledge about the NPs production volumes, numbers of products containing these materials, market penetrations of these products and releases throughout their life-cycles hinders consumer exposure assessment [124, 126, 127, 129, 132].

As a consequence of the limited applicability of quantitative and predictive human health and environmental risk assessment tools, expert driven approaches started emerging to support screening-level hazard, exposure and risk investigations of NPs [38, 52, 127, 133, 134]. An example is the control banding procedure for occupational risk assessment, where exposure and hazard “bands” are used to define the qualitative or semi-quantitative level of risk and recommended risk management measure [135-140]. Such bands go from a low to a high priority depending on the hazard and exposure conditions of the material and activity under consideration. Hazard bands are defined by various information that includes physicochemical characteristics (e.g. size distribution, shape, density, physical state, water solubility, aggregation, dissolution, particles diameter, moisture content) and hazard factors (e.g. persistency, redox activity, stability, bio-persistency, toxicity, carcinogenicity, mutagenicity) [135-139]. The exposure bands are derived from a wide set of occupational-related aspects that include type of emission, physical surrounding, amount of handled material, dustiness, number of employees, frequency of operation, duration of operation, background concentration, material source and type of exposure controls [135-139]. The hazard and exposure bands are then usually combined in a matrix, which provides the recommended risk level and the control measure to be adopted for a certain activity.

### 3.2.2 Environmental impacts studies

LCA has been used to assess the environmental sustainability of NPs, including graphene production processes [141], nano-enabled waste treatment systems [142, 143] and production of metal nanoparticles (gold and silver) from renewable and conventional (e.g. hydrazine, sodium borohydrate) sources [144, 145]. Reviews of the available studies point clearly out that there are challenging limitations that hamper holistic and reliable LCA of NPs, including:

i. Lack of specific inventory data to cover all the life cycle stages, which leads to partial assessments, mostly confined to the cradle-to-gate approaches based on generic data and assumptions [34-36, 64, 146-151];
ii. Lack of reliable nano-specific characterization of emission entities and pathways [34, 48, 124, 150, 151];
iii. Current cut-offs only based on mass are not appropriate for NPs since other properties (e.g. surface area, size, length) are also considered as important determinants of impact and environmental behaviour [34, 152];

LCA is a quantitative assessment tool, based on data that are usually costly to obtain and that companies are rarely willing to share with sustainability analysts. Furthermore, there are currently no reliable and accurate models to estimate the behaviour of NPs once released in the environment as well as in occupational and consumer settings. These limitations lead to modelling assumptions in LCA that are difficult to justify, which hinder the credibility of their results [34, 48, 124, 150, 151].

The solutions that have been advanced to aid environmental impacts assessment studies include accounting for the uncertainty in the data collection stage and use of semi-quantitative and qualitative parameters [48], both capacities supported by MCDA methods (details in section 3.4).

## 3.3 Sustainability indicators lists and dashboards

Holistic sustainability evaluations of NPs are needed because of the complex implications they can have on the environment, economy and society. For instance, a NP employed for composite reinforcement can cause environmental degradation of the wastewater it is directed in and be a health hazard to the workers, but it can also contribute to the business success of the company manufacturing such product. As a result, governmental authorities and research teams expanded the breadth of their assessments by including criteria from multiple subjects to achieve balanced SA frameworks.

An example is the list of parameters, proposed by the German Federal Government, for the assessment of risks and benefits of NPs on the environment, consumers, employees, companies and society [22, 43]. Risks are evaluated with semi-quantitative metrics by indicating whether there can be a concern or not during the life cycle stage of he NP while the benefits are assessed on a qualitative scale based on comparisons with reference products (i.e. non-nano enabled).

A similar approach was taken in Nano-Meter, a tool to support the identification of opportunities and risks of NPs [20]. Areas of evaluation are environmental impacts, health and safety, resources requirements, user advantages, benefits and risks for society.

Researchers from a German Institute (Oko-Institut) advanced an approach, named Nano-Sustainability Check, to assess the strengths, weaknesses, opportunities and threats of NPs [5]. Evaluation parameters include environmental impacts, technical performance, economic and also social implications as well as regulatory compliance.

These initiatives and also similar ones from other research groups such as the LICARA project team [45] are valuable contributions to advance the practice of sustainability research for nanotechnology, however they are always the result of a restrained pool of experts selected ad-hoc. This limits the widespread acceptability and use of such criteria frameworks and it justifies the call for a comprehensive and agreed set of criteria to assess the sustainability of NPs [5, 30, 31, 48, 53, 59, 63].

## 3.4 Integrative assessments based on MCDA

The availability of assessment criteria is a necessary requirement for conducting sustainability evaluations, though it is not sufficient to provide DMs with straightforward, comprehensible and traceable decision support capabilities. What is more, sustainability information is frequently uncertain and of different type and quality. Consequently, SA tools must support these duties and MCDA provides the relevant competencies, which explains the growing use of its methods to conduct SAs [47, 72, 153]. The interest in MCDA has also emerged in the area of nanotechnology, where all the studies conducted so far integrate the performance of NPs expressed as evaluation criteria to provide decision support for the user, in the form of a performance score, a ranking or classification of the NPs or nanotechnologies under assessment.

The majority of the risk assessment-focused studies propose rankings of nanomaterials and nano-enabled products structured on utility theory methods [154-157], even though classification models based on outranking methodology as well as decision rules have also been proposed [158, 159]. A wide spectrum of criteria typologies were employed as criteria, including physicochemical properties, toxicity, data quality, physical surrounding of the nanomaterial, and exposure characteristics (e.g. type of material handling, duration and frequency of task, type of processing and risk management measures).

Criteria of various sustainability pillars are characterized by different type and scale, such as qualitative, quantitative, fuzzy, continuous or discrete. Such heterogeneous parameters have been aggregated through MCDA approaches as a result of their unique capacities of accepting this typology of input. The methods mostly used for this purpose are the analytical hierarchy process (AHP), Utility Theory and PROMETHEE, whereas the criteria cover several of their technical performance and sustainability implications, including health and environmental impacts, social benefits, stakeholders' preferences, costs, operating conditions, technical feasibility, value chain quality, R&D capability, marketability and government aid [45, 51, 142, 160-172]. The results are rankings and comparisons of nanomaterials, nanosynthesis processes, nano-enabled products (e.g. waste treatment systems, composites) as well as nanotechnologies and related risk management strategies considering perspectives from multiple disciplines in a holistic manner.

The main benefit of using MCDA to aggregate criteria in the form of comprehensive assessments of alternatives, instead of using stand-alone indicators, is that the decision support provided to the DMs can be much more structured and effective since they can easily identify the most and least preferred options (given certain value preferences) without the need of going through all the results for each criterion for each alternative [153].

## 3.5 Summary

This chapter reviewed the scientific literature that emerged during the last decade to evaluate the impacts of nanotechnology on sustainability, as well as its benefits. As sections 3.2-3.4 have shown, the selection of single or multiple indicators/criteria for the evaluation of the implications of nanotechnology on sustainability varies widely, both for the typology of sustainability criteria (e.g. risk-, economics-, environmental- focused), as well as their measurement scale (e.g. quantitative, qualitative). What is more, there is not a comprehensive framework of criteria that is reliable and validated through a wide range of knowledgeable practitioners that can be used to perform a holistic SA of a NP. This Ph.D. thesis fills such research gap and the relevant work is described in Chapter 5.

Due to the pervasive nature of nanotechnology and the extent of its potential implications, the capacity of supporting decision-making for its governance has become a necessity, which poses MCDA in a privileged position, considering that providing structured decision support is its main goal. This could be one of the reasons why many studies emerged in the literature (as discussed in section 3.4) employing MCDA to conduct assessments of NPs by providing rankings or classifications of such materials or related technologies based on specific sustainability criteria. The analysis of MCDA applications for these studies indicates that limited efforts have been devoted to understanding the actual strengths and weaknesses of the employed methods, as well as their limitations and appropriateness depending on the typologies of decision-making problems. This background material confirms the need for an in-depth investigation of MCDA potentials to conduct sustainability evaluations, which is presented in Chapter 4. Furthermore, the analysis of these methods applications has been used in Chapter 5 for the identification of the initial criteria to develop a comprehensive framework of SA criteria for NPs.

# Chapter 4. Assessing Sustainability through Multiple Criteria Decision Aiding

## 4.1 Introduction

Decisions have to be taken in everyday life. They usually involve multiple criteria and represent problems that are important and non-trivial. Such situations are faced by DMs, who need to tackle complex decisional contexts, characterized by objectives and criteria that can be conflicting, so that mere intuitive judgment is not appropriate to handle them.

MCDA consists in a process whose scope is to support DMs in structuring, understanding and solving a problem so that an informed decision can be recommended [173]. The focus of MCDA is not on finding the ultimate best decision, but rather on providing help to the DMs during the whole procedure of identifying the problem, structuring it and achieving the best compromise solution that is not independent from the process that allowed achieving it [102]. The first part of this chapter is devoted to describing such process (sections 4.2-4.4), which was partially used in Chapter 5 to develop a framework of sustainability criteria for NPs and fully implemented in Chapters 6 and 7 to shape two decision support models for green chemistry-based nanosynthesis, respectively.

MCDA has been specifically developed to support decision-making and extensive literature is available, whereas an up-to-date analysis of the practical potentials and limitations of its methods for conducting SA is missing. This current gap was confirmed by the review of the applications of MCDA to conduct SA in general and to assess the sustainability of NPs, as described in Chapters 2 and 3, respectively. Several of its methods were used to evaluate the sustainability impacts of NPs; however the lack of robust arguments in favour of the employed MCDA approach for the specific problem was identified, such as the correspondence between the theoretical framework of the method and the decision context or the practicality of the chosen technique. What is more, an analysis of the strengths and weaknesses of each method rose as another main deficiency in the literature. These represent critical knowledge gaps from a decision support perspective, because the rigorous understanding of the capabilities and limitations of the methods is a prerequisite to avoid the possible misuse and misinterpretation of the decision recommendations that they can provide.

The following chapter fills these research gaps by presenting an analysis of the potentials of methods from main MCDA families used for assessing sustainability (sections 4.5-4.7), which informed the selection process of MCDA methods for the development of a robust classification model, as reported in Chapters 6 and 7, for the green-chemistry based classification of nanosynthesis.

## 4.2 MCDA components and concepts

MCDA process builds upon a methodological paradigm (i.e. decision aiding) and components (i.e. actors, alternatives and criteria) that are core building blocks of this thesis. Consequently their definitions are provided below.

Decision Aiding is an activity that one or more persons perform, by means of explicit and not necessarily completely formalized models, in order to support one or more stakeholders in trying to answer questions and provide recommendations about a certain decision process [173]. The search is not for the ultimate “truth” or for the best option or set of options, but rather it is for a structured approach to facilitate the decision process, so that it can be aligned with the objectives and the value system of whom, or in the name of whom, the decision aiding is adopted [173].

Actors are the people taking part in the decision process. At minimum there are two figures: a DM and an analyst. The DM is the person who is in charge of taking the decision, has knowledge in the field under investigation and does not necessarily need to have competency in MCDA. The analyst is the person referred to as a facilitator or researcher that is in charge of the implementation of the decision aiding process by helping the DMs to structure the problem, investigate their preferences, and develop a MCDA model in compliance with the decisional context.

Alternatives are the products, processes, scenarios, plans and programs that need to be assessed during the decision aiding process. They might not be well defined and implementable a priori, in which case they can be constructed by means of interaction between DM(s) and analyst(s).

Criteria are the parameters that are employed to characterize and also assess the alternatives. They can be regular attributes, which means that no preference is assigned to their domain, as it can be a symptom or a colour or they can have preference-ordered domains, e.g. toxicity, energy consumption or waste production.

A group of criteria is defined as $F = \{g_1, g_2, \ . \ . \ . \ , g_m\}$, where *m* is the number of criteria. They can be of different types, including [174]:

i. Measurable criterion: criterion scale takes into account the entity of the degree of preference and real-valued numbers express the preference difference. Preferential comparison of intervals of the scale used for the evaluation of the criterion is meaningful and can lead to three sub-types:
    - True-criterion: without any threshold;
    - Semi-criterion: with indifference threshold;
    - Pseudo-criterion: with indifference and preference threshold.
ii. Ordinal criterion: the criterion scale does not account for the extent of the difference in preference and the DM uses linguistic terms to compare the alternatives, e.g. low, medium, high;
iii. Probabilistic criterion: the values of the criterion are assigned in the form of probability distributions;
iv. Fuzzy criterion: intervals of the criterion’s scale are used to characterize each alternative.

## 4.3 The MCDA process

The MCDA process aims to support the interaction between the DM and the analyst. The latter uses his methodological knowledge to improve the DM’s interpretation of the decision challenge under consideration. The goal is to reach a consensus between the two figures in terms of correctness and meaningfulness of the problem representation, assessment and final recommendation [175].

This procedure is enabled by MCDA through an integrated assessment where the search is not for an optimal solution, that might not even be available, but for a more transparent evaluation that can suggest a preferable solution, usually a compromise [55, 57]. Such a process is affected by several factors, including the personality of the DMs and the analyst, the context of the decisions and the method adopted [176].

More formally, the decision aiding process can be structured in four main steps that are interdependent [175]:

i. Definition of problem situation;
ii. Problem formulation;
iii. Construction of the evaluation model;
iv. Final recommendation.

### 4.3.1 Definition of problem situation

The first phase consists in the representation of the decisional problem by means of interaction between DM and analyst. It requires the identification of the problem under consideration and the people who are affected by it, who are involved and have an influence on the topic of interest.

Furthermore, it is important to identify the roles, stakes and concerns of all the actors involved in the process. The DMs are encouraged to communicate naturally in order to express their goals and objectives. The role of the analyst is to provide guidance to the DMs so that they can express themselves explicitly.

### 4.3.2 Problem formulation

The next stage is defined as problem formulation which leads to a formal and abstract model which will allow choosing the method to use from the decision theory [175]. Three main components are necessary to achieve the objective. The first one is the identification of the alternatives to be assessed. These might not be readily available and may have to be constructed, or new ones might need to be included if there are not any already available [175]. The next component is the set of points of view (PV) that must defined to characterize, shape and assess the alternatives. There can be several “elementary” PVs which can be clustered to define “fundamental” PVs. Thirdly, a problem statement is necessary to complete the problem formulation, requiring the definition of what decision(s) need to be taken with the set of alternatives. The characterization of the decision problems proposed by Roy includes four typologies that fit with most of real world applications [102, 177]:

i. Sorting problematic: allocating each alternative to a pre-defined category based on the project objectives. This is a classification problem.

ii. Ranking problematic: ordering the alternative in a complete or partial order with possible ties and incomparabilities.
iii. Choice problematic: selecting a preferred alternative or a small set of actions out of the whole set of options.
iv. Description problematic: describing the alternatives.

### 4.3.3 Construction of the evaluation model

The third stage of the decision aiding process is the construction of the evaluation model, where the analyst uses his methodological knowledge to select a model that fits with the problem that was formulated. It is generally composed of:

i. Alternatives to be assessed;
ii. Evaluation parameters for the alternatives: they can include non-preference ordered criteria (defined also as regular attributes) and preference-ordered criteria;
iii. Uncertainty characterization factors that allow handling the uncertainties in place in the decision process;
iv. The method to be used to derive a global relation and /or a function on the alternatives.

The selected method needs to be understood by the DMs and several parameters need to be fixed to reflect their preferences. The procedures available to identify these parameters are discussed in section 4.4.

### 4.3.4 Final recommendation

The final output of the process is a recommendation to the DM for the decision at stake. However, this recommendation must be assessed in relation to its robustness by accounting for the variability in the performances of the alternatives as well as DM's preferences.

## 4.4 Preference representation

Effective decision aiding requires a clear structuring of DM's preferences as this will affect the selection of the method to aggregate the information, as well as the type of preference elicitation technique [101]. Bernard Roy proposed a comprehensive set of

DM's preferences structures, using elementary binary relations when comparing two alternatives (i.e. *a* and *b*) [102]:

i. *a* **I** *b* (indifference situation): *a* is indifferent to *b*;
ii. *a* **P** *b* (preference situation): *a* is strictly preferred to *b*;
iii. *a* **Q** *b* (weak preference situation): there is hesitation between indifference and preference situation;
iv. *a* **R** *b* (incomparability situation): there is hesitation between *a* **P** *b* and *b* **P** *a*.

These relations can be used to model the assessment of the alternatives and a general distinction is in place between the MCDA methods that use only indifference and preference conditions, normally labelled as performance-aggregation based, and those employing all the four preference structures, normally labelled as preference aggregation-based [178, 179].

## 4.5 MCDA aggregation techniques

One of the main strengths of MCDA is that the DM is provided with easily understandable decision recommendation in the form of a rank, class or performance for the alternatives. In order to reach this stage, DM's preferences as well as the performance of the alternative must be integrated. This step in MCDA is called multiple criteria aggregation and four main families of MCDA methodologies have been developed for this purpose. Three of them deal with problems with a finite number of alternatives (relatively small, a few dozen at most) and a fourth one works with problems having an unlimited or large number of alternatives and aims at identifying the one (or the group of those) which satisfy certain constrains (i.e. multi-objective optimization) [101, 180]. The focus of this thesis is on the first three approaches as the challenges this doctoral research dealt with include a discrete set of options to be evaluated.

The grouping in three MCDA aggregation approaches dealing with a finite number of alternatives has been proposed by Greco and Slowinski [181, 182], who distinguish three underlying theories: (i) utility-based, (ii) outranking relation and (iii) rule-based. The utility-based theory includes methods synthesizing the information in a unique parameter (also called performance aggregation-based approaches) and it was introduced during the 1970s by Keeney and Raiffa [183]. Its simplest form is the weighted average approach, where the performance of each parameter is multiplied by its respective weight and added up to provide a score that normally goes from 0 (worst) to 1 (best).

The outranking relation theory involves methods based on comparisons between pairs of options to verify whether "alternative *a* is at least as good as alternative *b*" (also called preference aggregation-based approaches) [184]. The rule-based theory originates from the artificial intelligence domain and it allows derivation of a preference model through the use of scenarios expressed in the form of "*if* condition *x, then* decision *y"* [185].

There are a lot of methods from each of the three families mentioned above and five of them are detailed below:

i. For the "unique parameter" methods: multi attribute utility theory (MAUT) and analytical hierarchy process (AHP);
ii. For the outranking relation theory: ELimination and Choice Expressing the REality (ELECTRE) and Preference Ranking Organization Method for Enrichment of Evaluations (PROMETHEE);
iii. For the rule-based theory: Dominance based Rough Set Approach (DRSA).

The first reason for the selection of these sets of methods is that utility-based (especially MAUT and AHP) and outranking approaches (specifically ELECTRE and PROMETHEE) applied with direct preferences elicitation have been the most widely used MCDA tools in SA research, with a similar trend for nanotechnology implications too, as reported in Chapter 3 and elsewhere [21, 47-49, 113, 134, 153, 180, 186-190]. The rule-based technique has also been proposed as a promising emergent instrument to conduct SAs [191-197], suggesting the usefulness of a deeper analysis of its potentials in this area. A further consideration is that the capacities of rule-based methodologies of providing easily interpretable decision recommendations in the form of "if -> then" connectors highlighted a potential suitable fit with the fourth Ph.D. thesis objective, namely the development of design guidelines for greener nanomaterials as discussed in Chapters 1 and 3.

### 4.5.1 Multi Attribute Utility Theory

Multi Attribute Utility Theory (MAUT) is based on the assumption that there is a utility function $U(x) = U(x_1,x_2,.....,x_n)$ which represents the global performance of each alternative, obtained through the aggregation of utility functions $u_i(x_i)$ for every criterion and respective weights $w_i$ [198].

Utility functions for the criteria represent the marginal increases of utility that the improvement in performance of the alternative can determine [199].

Weights for the criteria indicate the trade-offs that are in place between them, and they represent scaling constants that account for their different importance in relation to the measurement scale of the criteria [200].

### 4.5.2 Analytical Hierarchy Process

AHP was introduced in 1980 by Saaty with the aim of evaluating tangible and intangible criteria in relative terms by using an absolute scale [201, 202] . It also provides a comprehensive assessment of the alternatives in the form a single score as it is for MAUT, though the main difference is that it employs pairwise comparisons to evaluate the alternatives and define criteria weights [101].

All the alternatives and criteria are compared in respect to each other by asking the DM his preference on a scale from 1 to 9, with 1 indicating equal preference and 9 absolute preference for one alternative/criterion over the other [201, 202]. Intermediate values are used to express increasing preference/performance for one alternative/criterion.

This procedure results in a matrix of comparisons expressed as ratios, which is then reduced to a set of scores representing the relative importance of each criterion and performance of alternatives (priority vectors), normally through the calculation of the eigenvector of the matrix [101].

Once the criteria weights and alternatives scores have been derived, overall performance of the alternatives can be calculated by means of a linear additive model [202]. The final result is a value between 0 (worst) and 1 (best), where the weights indicate the trade-offs between the criteria [101].

### 4.5.3 ELimination and Choice Expressing REality

ELimination and Choice Expressing Reality (ELECTRE) methods were introduced by Bernard Roy in order to account for more elaborate modelling of DM’s preferences. In addition to the strict preference and incomparability relations supported by MAUT and

AHP, the concepts of weak preference and incomparability where introduced because the first two relations were not sufficient to represent the complexity of the DM's knowledge modelling in practical case studies [102].

This rationale posed the basis for the outranking approach, with ELECTRE methods proposed as the first implementation [200]. They are based on pair-wise comparisons of the alternatives, so that each one is compared to the other to evaluate whether the outranking relation is in place, in other words to verify if the first alternative is at least as good as the other one on all the criteria [102].

Innovative modelling tools in ELECTRE are the indifference and preference thresholds which allow accounting for the potential hesitation of the DM between strict preference and indifference for the alternatives and uncertainty in the input information [101, 103, 178].

ELECTRE methods were developed in order to account for heterogeneous criteria whose aggregation in a common scale is difficult and to prevent compensation between them [203]. Several ELECTRE methods have been developed to handle different decision problems, namely choosing (ELECTRE I, IS), ranking (ELECTRE II, III, IV) and sorting (ELECTRE TRI-B, ELECTRE TRI-C, ELECTRE TRI-NC) [184, 203].

### 4.5.4 Preference Ranking Organization Method for Enrichment of Evaluations

Preference Ranking Organization Method for Enrichment of Evaluations (PROMETHEE) methods represent the other main stream of outranking approaches, developed by J.P. Brans during the early eighties with the prerequisites of being easily understandable by the DMs, while at the same time employing a methodological framework capable of supporting most of complex real life decision-making challenges [204, 205].

Criteria weights in PROMETHEE are independent form their measurement scales and represent the relative importance of every parameter [206]. A preference function is assigned to each criterion, expressing the outranking relation of one alternative over the other, with six different types to choose from that allow accounting for the preferences that the DM has on every criterion [204].

Once the preference functions for all the criteria and their weights are identified, leaving and entering outranking flows can be calculated, indicating the outranking power and weaknesses of each alternative over the other, respectively. Lastly, the leaving and entering flows can be combined, resulting in the net outranking flow (index) that provides the performance of each alternative [204].

### 4.5.5 Rule-based methods

Rough set theory has been tailored to MCDA in the last decade, becoming a main representative for the third class of multiple criteria aggregation procedures, i.e. rule-based ones. This rough set methodology is called Dominance-based Rough Set Approach (DRSA) and it can handle classification, choice and ranking problems [185, 207, 208].

DRSA is based on an information table whose rows are defined as alternatives, while the columns are divided into condition attributes; namely the criteria that are needed to assess the alternatives and the decision attribute, which represents an overall evaluation of the alternative. This can be a quantitative measure or an expert judgment [209].

DMs provide their preference information either through the assignment of a comprehensive performance class to each alternative under consideration or by comparing one alternative with the others and deciding which one performs better [210].

DRSA approximates the information reported with the decision attributes by considering the knowledge reported in the condition attributes, by means of the dominance relation concept. In order to extract information from these attributes, DRSA defines [211]:

- Objects dominating *x*, i.e. objects that perform better than *x* in terms of the set condition attributes;
- Objects dominated by *x*, i.e. objects which perform worse than *x* in relation to the set of condition attributes.

DRSA provides useful contribution to the decision-making process as from the dominating and dominated sets the approach extracts condensed and structured expert knowledge in the form of *"if … , then …"* decision rules [212]. These rules are simple connections of elementary conditions between condition and decision criteria, and they are exploited to provide the decision recommendation [212].

## 4.6 Preference elicitation

MCDA aggregation procedures require preference information from the DM in order to construct a decision model. Preference elicitation strategies are divided in two groups [182, 213]: (i) direct and (ii) indirect. When using the direct approach, DMs are questioned by the analyst in order to elicit their preferences and then construct the model to derive the comprehensive assessment of the alternative. On the other hand, the indirect approach requires only a partial comprehensive preference on the alternatives from the DM that is then used to infer the aggregation model and the resulting preference parameters by means of a regression approach. These two families are discussed in more detail in the sections below.

### 4.6.1 Direct preference elicitation methods

Direct aggregation procedures need preferences from the DM that can be obtained from an interaction with the analyst where the components of the method are built in a stepwise fashion. For example, when MAUT is used, the individual utility functions and weights expressed as trade-offs must be elicited, whereas in the case of PROMETHEE, the relevant shapes for the preference functions, their thresholds and relative importance of criteria are necessary.

As far as the rule-based methods are concerned, the direct elicitation procedure requires that the decision rules are specified by the DM on an individual basis [192] and a main downside is that the approach can become very laborious and tedious for the DM when a high number of rules is demanded [192, 214-216].

This preference elicitation strategy necessitates the DM to understand the aggregation procedure of the selected MCDA method(s) and the meaning of all the parameters that need to be used to obtain a global comprehensive assessment of the alternatives.

### 4.6.2 Indirect preference elicitation methods

It has been reported that a highly demanding effort is required from the DM to understand the meaning and role of the parameters (e.g. weights, thresholds, rules) required to aggregate criteria and weights to derive the decision recommendation [210, 217-219]. This implies that specific sessions need to be devoted to the explanation and elicitation of such parameters, which can be a daunting procedure for the DMs as they might not have enough time to dedicate to them, or this might even be beyond their cognitive capabilities [220].

As a result, indirect preference elicitation methods have become more popular since they drastically reduce the cognitive effort required by the DM, normally in the form of a comprehensive preference judgment [174, 217, 221, 222]. The approach has been labelled as disaggregation of preferences and it consists in inferring model parameters and aggregation operators from the analysis of decisions made by the DMs on a set of "reference actions" $A_R$ that can be [174]:

i. A set of previous decision actions ($A_R$ – past actions);
ii. A subset of decision alternatives in case the whole set of options $A$ is large ($A_R \subset A$);
iii. A set of fictitious alternatives that can be easily assessed by the DM ($A_R$ – fictitious actions).

The global preference required from the DM can be in the form of (i) a measurable judgment on $A_R$, (ii) a classification on $A_R$, (iii) a ranking on $A_R$, (iv) pairwise comparison of alternatives of $A_R$ and (v) sorting of alternatives of $A_R$ [174, 219].

The disaggregation methods have been advanced to produce different outcomes on the basis of the adopted MCDA method, like weights, value and utility functions, thresholds and decision rules [217, 220]. The decision rule-disaggregation approach has been used to elicit preferences of the two DMs involved in model development as described in Chapter 6.

## 4.7 MCDA methods as a support for sustainability assessment

Conducting realistic SAs requires the identification of evaluation parameters, inclusion of relevant stakeholders and capabilities of communicating the results in a transparent and understandable format. MCDA satisfies these requirements and its use for aiding sustainability research can be traced back to the 1990's with first applications being conducted in the area of environmental planning and management [108, 223]. Since then a lot of this type of research was conducted and published [47, 76, 157, 158, 160, 187, 224-228]. For example, Oman integrated different spheres of sustainability and stakeholders perspectives for the assessment of a "product service system" and the "car road pricing in Austria" [227]. Akadiri used MCDA to evaluate the sustainability of building materials [229] while Buchholz used it to assess bioenergy systems [228].

Practical applications of MCDA-based SAs applied to products have also emerged [230-236]. Furthermore MCDA has been integrated with existing SA tools (e.g. LCA) to enhance the decision support provided to DMs [104, 105].

As it was widely reported in the literature [21, 47-49, 113, 134, 153, 180, 186, 187, 190] as well as in Chapter 3 the MCDA methods mostly used in SA in general as well as nanotechnology are MAUT, AHP, ELECTRE and PROMETHEE. Furthermore, the rule-based techniques emerged as particularly appropriate in the context of the fourth objective of this Ph.D. research, namely the development of design guidelines for the greener production of nanomaterials. They have also already been shown as very promising instruments to conduct SAs [191-197].

In the majority of the available SAs employing MCDA, the selection of the method appeared dependent on the familiarity and affinity with the approach rather than on the decision-making situation under consideration [153, 189, 237]. Furthermore, development of specific guidance for selection of MCDA methods depending on the application context has been advocated [237]. This research gap was partially filled by this doctoral research thorough a review of some of the available MCDA methods with respect to their potentials and limitations when doing SAs, which is discussed in the next sections.

### 4.7.1 Research methodology

A state-of-the-art review of the MCDA methods described above was conducted by employing ten comparison criteria, indicated as fundamental by several authors when dealing with sustainability-related research [54-56, 77, 101, 106, 178, 191, 228, 238, 239], which have been clustered according to the approach proposed by [240] in three domains: (i) "scientific soundness", i.e. capability of handling different type of information and preferences modelling and provide robust results, (ii) "feasibility", i.e. availability of support tools for implementation of MCDA methods; and (iii) "utility", i.e. easily accessible comparison potentials.

The comparison criteria are reported in Table 4-1, together with their description and the rationale for the positive or negative assessment of the MCDA methods in relation to

Table 4-1: Description of comparison criteria and rational for evaluation

| Criteria domain | | Criterion | Criterion description | Rational for evaluation |
|---|---|---|---|---|
| **Scientific soundness** | *Referring to input data* | Use of qualitative and quantitative information | Capability of including information which is qualitative and quantitative in nature | *Weakness:* Only qualitative or quantitative information can be handled |
| | | | | *Strength:* Both qualitative and quantitative information is usable, a common requirement in sustainability-related research |
| | | Life cycle perspective | Possibility of including the life cycle stages of the assessment target | *Weakness:* Limited stages in the life cycle can be included in the assessment |
| | | | | *Strength:* All the life cycle can be included in the assessment in order to avoid impacts shifting |
| | *Referring to calculation method* | Weights typology | Significance of the weights used to assign importance levels to the criteria | *Weakness:* Weights are used as trade-offs which implies compensation and so commensurability |
| | | | | *Strength:* Weights are used as importance coefficients so that compensation is not implied |
| | | Thresholds values | Thresholds represent turning-points values that can be used to model complex preference structures and uncertain information | *Weakness:* No thresholds can be used |
| | | | | *Strength:* Thresholds can be used |
| | | Compensation degree | The level of compensation among sustainability spheres and criteria determines the distinction between approaches based on strong and weak sustainability concepts | *Weakness:* Compensation is an intrinsic feature of the method, allowing only the use of weak sustainability |
| | | | | *Strength:* Compensation is limited or abolished, allowing the use of a strong sustainability concept |
| | | Uncertainty treatment | Capability of handling uncertain, imprecise or missing information | *Weakness:* Uncertain, imprecise and missing information cannot be managed |
| | | | | *Strength:* Uncertain, imprecise and missing information can be treated |
| | | Decision-context dependency | Influence of addition or deletion of alternatives on the decision recommendation | *Weakness:* Results are dependent on addition or deletion of alternatives |
| | | | | *Strength:* Results are independent from new alternatives or deletion of existing ones |

**Table 4-1: Description of comparison criteria and rational for evaluation (cont.)**

| | | | |
|---|---|---|---|
| **Feasibility** | Software support and graphical representation | Availability of tools to implement the method, manage the information and show the results in a clear and multi-perspective manner | *Weakness:* Limited availability of software and poor graphical representation |
| | | | *Strength:* Software available and wide range of graphical potentials that improves the communication with stakeholders |
| | Ease of use | Intelligibility of the method, simplicity of its structure based on users' (i.e. DM) perspective | *Weakness:* The method is perceived as a black-box from the DM and it is highly demanding in terms of cognitive efforts |
| | | | *Strength:* Intelligibility of the method(s) is very simple and the DM is comfortable with the preferences elicitation process |
| **Utility** | Learning dimension | Possibility of re-evaluating results if new information becomes available (e.g. alternatives or criteria) | *Weakness:* No re-evaluation is possible and new software runs need to be performed and independently compared with the previous ones |
| | | | *Strength:* Assessments can be run with new alternatives and compared simultaneously |

each of them. A literature review was adopted as research methodology with the target database being Web of Science (WOS), which includes more than 12,000 journals and 30,000 books worldwide [241]. In addition, the Journal of Multi-Criteria Decision Analysis and Integrated Environmental Assessment and Management were searched individually, as they are excluded from WOS.

### 4.7.2 Results

The results of the performance of the MCDA methods based in relation to ten comparison criteria are shown in Table 4-2. Three symbols have been used to indicate the performance (i.e. **+** = good, indicating strength of the set of methods; ○ = intermediate, indicating a dependence of the specific method within the set or the authors' referenced interpretation; **−** = poor, indicating weakness of the set of methods) of each group of methods in relation to each criterion.

#### *4.7.2.1 Scientific soundness*

**Use of qualitative and quantitative data**

All the MCDA methods can handle information that is qualitative and quantitative in nature, with the qualitative being reduced to point scales for MAUT and AHP [54]. In the case of ELECTRE, PROMETHEE and DRSA no data transformation is necessary and the only requirement is the preference direction of the criteria scale, either ascending or descending [110, 185, 242].

The flexibility on the input side is one of the main upsides of MCDA, since it does not pose restrictive requirements on the analyst in terms of problem structuring, as may happen with more data intensive techniques (e.g. Life Cycle Assessment, Risk Assessment) that necessarily need quantitative input to operate.

**Life cycle perspective**

There is no pre-defined set of criteria that can or should be used in MCDA. Their number and typology is driven by the steps of problem formulation and model construction, so that all the life-cycle stages of a target object can in theory be accounted for. The number of criteria can rather be driven by data availability on the life cycle stages, a recurrent issue in emerging sectors, such as nanotechnology [63].

### Weights typology

Importance coefficients and trade-offs are the two weights typology that MCDA methods can employ [243]. MAUT and AHP are based on an additive/multiplicative aggregation model and the weights represent the “gain with respect to one variable allowing to compensate loss with respect to another” [55], in other words they are the trade-offs than can be accepted among the criteria [56, 239, 244]. They depend on the criteria measurement scale, as well as on their range, implying that if one changes, the other has to change accordingly [101, 106].

On the other hand, weights as important coefficients can be used for the representation of the intrinsic importance of one criterion over the others; in other words they are the measurement of the psychological concept of importance of each parameter [243]. This is the case for outranking approaches, where the weights are the voting power of the criteria; they are expressed with an ordinal meaning and are representative of non-compensatory methods [55, 101, 103, 105, 110].

This criterion is not applicable to DRSA because the approach works without direct weights elicitation from DMs and it extracts this type of information indirectly from the reduced set of criteria (which maintain the quality of the approximations as the whole set of criteria) that derive from the comprehensive preference provided by the DM [185, 219].

### Thresholds values

Thresholds can be used for two main reasons, the first one being that they allow accounting for indifference and preference when two alternatives are compared [245] and the second one being that they affect the degree of compensation among the different criteria [228].

The basic MAUT and AHP methodologies described above do not allow the use of thresholds [54, 228] although their inclusion has emerged in new MAUT-based software for example within the DecideIT one [228, 246].

The assessment is highly different for ELECTRE and PROMETHEE, which handle effectively different thresholds as they constitute the basic structure the methods are based on. ELECTRE require three types, namely indifference, preference and veto, while PROMETHEE needs only the first two [58, 178, 203, 204].

**Table 4-2: MCDA methods performance with reference to the sustainability-related criteria: + = good, strength of the set of methods, o = intermediate, depends on the method within the set or the author's judgment − = poor, weakness of the set of methods. *: Superscripts report references**

| Comparison criteria domain | | Comparison criteria | MAUT | AHP | ELECTRE | PROMETHEE | DRSA |
|---|---|---|---|---|---|---|---|
| **Scientific soundness** | *Related to input data* | Use of qualitative and quantitative data | + Possible[5,6,11] | + Possible[5,6,11] | + Possible[5,7,11,14] | + Possible[1,5,7] | + Possible[27,28] |
| | | Life cycle perspective | + Possible[4] | + Possible[4] | + Possible[4,17] | + Possible[4] | + Possible[25,27,28] |
| | *Related to calculation method* | Weights typology | – Trade-offs[1,3,4,7,8,9,10,11,12] | + Importance coefficients[11]<br>– Trade-offs[3,4,7,8,12] | + Importance coefficients[3,4,7,8,11,12,13,14,17,20] | + Importance coefficients[4,7,12,15,16,40]<br>– Trade-offs[8,41] | + Not needed[27,28] |
| | | Threshold values | – Not possible[5,8]<br>+ Possible[6,18] | – Not possible[5,6] | + Possible[1,5,7,11,12,13,14,17,20] | + Possible[1,5,6,7,10,12,15] | + Possible, obtained from the decision rules[25,26,28] |
| | | Compensation degree | – Full[1,2,3,5,7,8,9,12] | – Full[2,3,5,7,8,12] | + Null[1,2,3,5,7,12,13,20] /<br>o Partial[1,2,8] | o Partial[1,5,7,8]<br>– Full[2] | + Null[26] |
| | | Uncertainty treatment | + Possible[4,5,6,7,10,11] | + Possible[9,21,39]<br>o Partially possible[4,5,6] | + Possible[4,5,7,13,14,20,35,43] | + Possible[4,5,7,10,13,19, 36, 37]<br>o Partially possible[6] | + Possible[28,29,30,31] |
| | | Decision-context dependency | + No rank reversal is possible[5,8] | o Rank reversal can occur[5,8] | o Rank reversal can occur[5,8] | o Rank reversal can occur[5,8] | o Possible for the choice and ranking problems[27,28] |

**Table 4-2: MCDA methods performance with reference to the sustainability-related criteria (cont.)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Feasibility** | Software support and graphical representation | + Software available with good graphical capabilities[5,6,11,19,39,42,44] | + Software available with good graphical capabilities[5,6,9,11,19,21,39] | - Software available, but with very poor graphical capabilities[5,13,22,35,39]<br>o Software available with some graphical capabilities[17,20,35,42,43] | + Software available with good graphical capabilities[5,6,15,19,23,36,37,39,42] | o Software available, but with some graphical capabilities[33,34] |
| | Ease of use | + High[6,19,44]<br>– Low[7,8] | + High[6,19]<br>o Medium[5]<br>– Low[7] | – Low[1,4,5,7,8,11]<br>o Medium[17,20,35] | o Medium[1,5,6,7,8,19,23] | + High[25,26,27,28,38] |
| **Utility** | Learning dimension | – Difficult[5,6] | – Difficult[5,6]<br>+ Possible[24] | – Difficult[5] | + Simple with scenario analysis[5,6,23] | – Difficult[31,32] |

*:([1]: [178], [2]: [238], [3]: [55], [4]: [101], [5]: [54], [6]: [228], [7]: [56], [8]:[239], [9]: [247], [10]: [248], [11]: [200], [12]: [106] [13]:[203]; [14]: [110]; [15]: [204]; [16]: [205]; [17]: [105]; [18]: [246]; [19]: [47]; [20]: [58]; [21]: [249]; [22]: [250]; [23]: [251]; [24]: [252]; [25]: [209]; [26]: [210]; [27]: [185]; [28]: [219]; [29]: [253]; [30]: [254]; [31]: [255]; [32]: [256]; [33]:[257]; [34]: [258]; [35]: [259]; [36]: [260]; [37]: [261]; [38]: [226]); [39]:[262]; [40]: [263]; [41]: [264]; [42]: [265]; [43]: [188]; [44]: [266])

DRSA extracts thresholds from the decision rules expressed as *if* and *then* conditions, where the *if* part indicates the threshold values that the criteria must have in order to satisfy a certain assignment, being it a class or a position in a ranking [209, 210, 219].

**Compensation degree**

MAUT and AHP use weights that are substitution rates among the criteria, imply the logic of compensation and convey the existence of trade-offs [243]. Trade-offs allow offsetting the underperformance of an alternative to a criterion by a certain improvement to another one. Consequently, MAUT and AHP score badly on this indicator since they assume that criteria performances are “exchangeable” and substitutable and as a consequence they can be used only to enforce a weak sustainability concept, which converts all the resources in a unique evaluation scale [55, 106].

On the contrary, preference aggregation based methods (i.e. ELECTRE, PROMETHEE and DRSA) do not combine criteria into a single score and do not reduce criteria scales to a unique measurement unit, which limits or reduces the compensation among sustainability criteria and spheres and consequently allow the use of a strong concept of sustainability [55, 58, 105, 110, 178, 210, 238, 239] (Table 4-2).

DRSA also scores positively as the rules represent minimum values of performance that need to be achieved by the alternative to satisfy the decision that the rule recommends [210]. This implies that the conditions of the rule are not exchangeable and consequently DRSA is a non-compensatory approach.

**Uncertainty treatment**

Uncertainty can be accounted for in the case of (i) criteria weighting and (ii) performance assessment of the alternatives (i.e. scoring) [57, 228].

MAUT scores well in this case, as it was developed to deal explicitly with uncertain information [101]. In the input stage it can manage random and probabilistic input and, in the case of sensitivity analysis, it can cover both the uncertainties of weighting and scoring [228].

AHP cannot accept ranges of criteria weight or alternatives performance at the input stage while at the output stage the uncertainty can be accounted for the weighting [228].

ELECTRE and PROMETHEE methods explicitly account for uncertain input criteria scores through the use of the pseudo-criterion model that introduces indifference and preference thresholds [56, 106, 110, 188, 203, 204]. ELECTRE and PROMETHEE methods have been widely extended during the last decades, and the treatment of uncertain inputs (e.g. for alternatives performance, criteria weights, classes profiles, preference thresholds) is handled very efficiently by the IRIS [58], JSMAA [259] and SMAA software [260, 261].

In the case of risk and uncertainty, DRSA can operate with the concept of stochastic dominance so that probability scores are assigned to the values that the criteria can have [253, 267], whereas scores intervals rather than precise values are accepted in the case of imprecise datasets [254].

### Decision-context dependency

MCDA methods are considered as context-independent when their decision recommendations are unaffected by the addition or deletion of alternatives. Such independency is considered as a desired feature in most of the MCDA literature because it provides a degree of independency from the framing of the problem and the alternatives under consideration [268-272]. Out of the five methods under assessment, only MAUT satisfies this requirement since the final score of every alternative is unaffected from the performance of the other alternatives [54, 239], leading to its positive evaluation in Table 4-2.

Conversely, the other MCDA methods do not satisfy this independence to third alternatives, which implies that the ranks can be affected by the other alternatives and possibly result in the phenomenon known as *rank reversal* [239, 273].

Saaty, the founder of AHP, provides a different perspective on the issue, stating that rather than being a problem this phenomenon is a need since each decision-making is context-specific and consequently highly influenced by the alternatives at stake [274]. This implies that the evaluation of the alternatives is contingent on all the others, so that the addition of new alternatives or deletion of others determines the restructuring of the decision problem, thus creating a new one [268, 274].

Similar considerations apply to ELECTRE and PROMETHEE which are based on pairwise comparisons and so they are dependent on the overall set of alternatives as is

AHP [271]. Main representatives of the outranking community, such as Bernard Roy, Jose' Figueira and Bernard Mareschal, ascribe the rank reversal to the poor quality of the information available, which implies that more input data is needed, rather than to the poor performance of the methods [268-270].

The recommendations provided by DRSA are dependent on the relative support of rules; namely the number of alternatives that follow the rule in relation to the whole number of alternatives in the information table [209]. This implies that similar considerations as those for AHP, ELECTRE and PROMETHEE apply also to DRSA which suggests that it could suffer from rank reversal too.

#### *4.7.2.2 Feasibility*

**Software support and graphical representation**

Table 4-3 contains the list of some of the available software that can be used to implement the MCDA methods analyzed here. DecideIT, DECERNS, VIP, JSMAA support MAUT and they allow visualizing alternatives rankings with easily interpretable diagrams [47, 228, 259, 266]. The software report the results in a clear and intelligible format, which helps their understanding and communication. Overall scores are shown with bar graphs and each score of the alternatives is well marked. Sensitivity analysis on weights allow a simple and powerful visualization of the effect of relative ranking as a consequence of changes in weighting. JSMAA implements probabilistic MAUT, showing as a major outcome rank acceptability indices, namely the contribution of the parameters values granting to each alternative a certain rank.

Software packages for AHP are Super Decisions, Criterium Decision Plus and Expert Choice and DECERNS, which support a very good set of results representation, including the partial share of each alternative to the total scoring, the evaluation of the effect of different trade-offs (i.e. sensitivity evaluation) and also uncertainty analysis [47, 249, 275].

ELECTRE methods have different software support on the basis of the type of method adopted. ELECTRE IS, III-IV are freely available [262, 276] and their graphical representation is very low as limited to a diagram (i.e. kernel) representing the ranking or sorting of the considered alternatives [250, 277, 278]. Nonetheless, new software is emerging in the case of ELECTRE TRI, such as IRIS and JSMAA, which provide the analyst with much more intelligible and communicable results, such as the range of categories for each alternative to sort [58] and categories acceptability indices, i.e. the probability that each alternative is assigned to each category [259].

PROMETHEE methods are the most widely software supported approach. Management and representation of the results are very good, supporting comparisons of scenarios, visualization of the influence of different weights, criteria, and preference functions [204, 251, 279, 280].

DRSA is supported by two freely available software developed by the Laboratory of Intelligent Decision Support Systems at the Poznan University of Technology [257]. JMAF software supports DRSA for classification problems, it is available as a Java application, its interface is user friendly, the results are easily obtained and the manual is accessible for novice users [255]. Decision rules are shown in the form of "*if* conditions, *then* decision", distinguishing between those that recommend the assignment to 'at most' and 'at least' classes.

JRank is a command line Java application (making its use quite challenging for not experts in the programming area) which supports DRSA for choice and ranking. Its graphical representation is limited to the recommended ranking and the kernel that derives from the exploitation of DRSA approach [256].

Lastly MAUT, ELECTRE and PROMETHEE are also supported by a very flexible platform named Diviz, which allows constructing the evaluation in a stepwise manner, that provides a good insight in the working procedure of the methods [265].

**Table 4-3: Available software for the MCDA methods under consideration**

| MAUT | AHP | ELECTRE | PROMETHEE | DRSA |
|---|---|---|---|---|
| DecideIT | Super Decisions | ELECTRE IS | Decision Lab | JMAF |
| DECERNS | Criterium Decision Plus | ELECTRE III-IV | Visual PROMETHEE | JRank |
| JSMAA | Expert Choice | ELECTRE TRI | DECERNS | ------- |
| VIP | DECERNS | IRIS | D-SIGHT | ------- |
| Diviz | ------- | JSMAA | SMAA(-TY) | ------- |
| ------- | ------- | Diviz | Diviz | ------- |

**Ease of use**

MAUT does not score well from a practical viewpoint as the process of elicitation of the criteria trade-offs and the construction of the utility functions can be time consuming and challenging for the DM [54, 56, 239, 281]. However, there are MAUT-based approaches that significantly reduce such limitations as it is in the case of VIP methodology, which accepts imprecise information on the criteria trade-offs [266]. On the other hand, MAUT application is supported by software (i.e. DecideIT, DECERNS, JSMAA, VIP and Diviz) with simple and intuitive interfaces to structure the assessment [47, 228] and similar considerations apply to AHP as well [47, 228, 249, 252].

ELECTRE methods score low in this case, primarily due to the high number of parameters to be defined, including the thresholds (i.e. preference, indifference and veto), classes' profiles and outranking cutting level (i.e. lambda coefficient). The DM is posed with an intellectually challenging task, especially because these parameters do not always have a practical meaning. Furthermore, the evaluation procedure based on concordance and discordance indexes, the distillation process and the results representation based on the Kernel graphs are difficult to comprehend for a non-MCDA practitioner [56, 200, 239]. However, as far as ELCETRE-TRI is concerned, there are some variants that limit the cognitive burden posed on the DMs, by allowing definition of intervals for weights, classes' profiles, thresholds as well as for the lambda coefficient [58, 105, 259]. These latter characteristics improve the applicability of the ELECTRE-TRI methods which justifies a medium score for the relevant criterion in Table 4-2.

PROMETHEE approach is also affected by the time-intensive thresholds identification, but overall it is regarded as easier to understand and employ than ELECTRE [56, 239]. This is due to the use of easily understandable preference functions and the relatively simple aggregation procedure based on the entering and leaving flows. Furthermore, the software are convenient to use, with a very user-friendly interface [228, 251, 259].

DRSA scores very well in this case as it is characterized by a variety of appropriate features for structuring the decision problem, exploiting it and interpreting the results [185, 209, 210, 219, 226]:

i. It does not require direct elicitation of cognitive demanding information (weights, thresholds) from the DMs, as it is for other MCDA approaches. The indirect preference elicitation procedure limits severely the cognitive burden placed on the DM, who actually feels more comfortable in expressing comprehensive evaluations on a set of reference alternatives;
ii. The decision model is composed of decision rules expressed in the form of *"if …, then ..."* conditions, which are transparent and easily understandable by the DM. The rules are related to specific decision alternatives, which allow tracing and improving the decision process.

#### *4.7.2.3 Utility*

**Learning dimension**

Dynamic reevaluation of results consists in the possibility of comparing simultaneously the results from different software runs, in order to ease results representation, comparability and communication. MAUT, ELECTRE and DRSA software do not permit simultaneous comparisons of the evaluations based on different inputs and, as a result, it is required to re-run the software and obtain independent outcomes [47, 54, 228, 249, 255, 256].

Expert Choice (supporting AHP) allows comparisons of scenarios with different input so that dynamic reevaluation is supported [252].

Decision Lab, Visual PROMETHEE and D-SIGHT (supporting PROMETHEE) offer the widest potentials with the "Multi-Scenarios Analysis" that permits visualization of the various scenarios as 'would-be' alternatives, so that action profiles and walking weights are allowed in a multi-representation setting [251, 279, 280].

### 4.7.3 Discussion

MCDA methods have been widely used to conduct SAs, though an up-to-date analysis of their potentials and limitations was currently missing. This research gap was partly filled by reviewing the performance of the MCDA approaches mostly used in SA in general and also in the area of nanotechnology (i.e. MAUT, AHP, ELECTRE, PROMETHEE). Furthermore, DRSA was included because it emerged as suitable to achieve the fourth objective of this Ph.D. (i.e. green-chemistry based classification model for the production of nanomaterials).

A broad literature review of published studies was adopted as the research methodology, employing ten performance criteria that tools focusing on the assessment of sustainability should embrace. Some of the analysed papers considered one or more of the ten comparison criteria, whereas others did not specifically take this into account and the information was extracted herein. The analysis of the MCDA methods did not rely on expert judgement resulting from the studying of the method as some comparative work on indicator-based method did [282] or on a implementation of the method [240].

The review has shown that the available literature can be clustered in a rather coherent and comprehensive scheme which is summarized in Table 4-2. However, different schools of thought sometimes lead to a lack of agreement among authors concerning some comparison criteria. Nonetheless, several considerations can be derived starting from the positive fact that all the methods can conceptually include all the life stages of a target object, being it a product, process, service or policy.

The use of qualitative and quantitative information in SAs is fundamental as a wide variety of data typology has to be accounted for. In fact indicators can be of quantitative nature (e.g. kWh for energy consumption, kg for materials usage), though there are also many that have a qualitative domain (e.g. level of risk, health benefit), making this criterion a very important requirement for sustainability evaluation tools. From the review it emerges that all the methods can satisfy it, however, the explicit inclusion of qualitative or mixed information for the utility and outranking based methods is questioned by some researchers due to the need of manipulating the information at the input stage (e.g. transformation of qualitative data in a points scale) [191].

MAUT and AHP can only use a weak sustainability perspective with criteria trade-offs as the norm, whereas ELECTRE, PROMETHEE and DRSA enforce a strong one, by limiting or abolishing the compensation among/within sustainability spheres. From a practical viewpoint, utility-based approaches render exchangeable constrains that are actually not negotiable to sustain world ecosystems, such as water, air, minerals, energy, space and genetic materials [88], highlighting methodological inappropriateness of these methods when strong sustainability is the philosophical foundation of the assessment.

The identification of trade-offs from DMs can be difficult and time consuming, as they may feel uncomfortable about expressing their compensation acceptances among the criteria, they might not have enough time to dedicate to the lengthy elicitation procedure, or they might simply not have this type of information in mind. Contrarily, weights in outranking methods represent the intrinsic relative importance of the individual indicators, a much easier type of information to be elicited from the DMs. As a result, outranking techniques as well as DRSA, which does not use any weights, perform better from this preferences elicitation perspective.

What is more, there has been a misuse of weights in many studies, by eliciting them as importance coefficients when they should have been treated and derived as trade-offs [55, 101, 243]. This is due to the fact that DMs are usually comfortable to express the relative importance of criteria via a semantic scale that indicates ratios among them, but this implies that the derived information represents the importance that they assign to the criteria rather than the trade-offs among them [101]. As a result, if weights want to be used as importance coefficients, non-compensatory approaches must be selected [243]. DRSA overcomes this weights elicitation process, because the identification of the relative importance of the parameters is performed indirectly, from the information table, in the form of the reducts. Reducts are subsets of criteria that guarantee the same quality of evaluation of the alternatives under consideration, but possibly with a smaller number of criteria, highlighting the parameters that do not exert any influence in the evaluation and those which do excel in this (through their frequency in the rules). This reduces consistently the cognitive load for the DM and it is thus a very positive feature of DRSA from a practitioner’s viewpoint.

Dealing with imprecise data and managing the level of compensation that the method implies are success factors for SAs, because input data are rarely punctual in value and the compensability can have sensible impacts on the model recommendations. These important capabilities can be treated by means of thresholds and ELECTRE and PROMETHEE perform very well in this case as they are inherently based on them to lead the decision aiding process. On the other hand, AHP and MAUT are not directly adapted to work with thresholds, which limit their flexibility in terms of data management. However, new extensions of MAUT included this feature, showing how real-life decision problems can shape the development of decision aiding tools. It must nonetheless be noted that the identification of exact values for the thresholds is a difficult procedure, specifically due to the fact that the DMs are required a considerable cognitive effort during the elicitation process [56]. DRSA is in an advantaged position, because the method supports the indirect identification of thresholds, without the need of eliciting them directly from the DMs. In fact they are extracted from the decisions that were made and are summarized in the conditions part of the decision rules.

All the methods analyzed in this review are capable of managing uncertain information in the form of probability distributions and/or analysis of sensitivity to the input data. MAUT, ELECTRE and PROMETHEE can consider imprecise input with probabilistic approach and support sensitivity analysis on weights as well as on criteria scores. DRSA can handle uncertainty by assigning scores with a certain probability to every possible value or by defining intervals within which the “real” values of the criterion can reside.

Software support is provided for all the MCDA methods discussed, although the features of each of them are different and affect the potentials of data communication, analysis and re-evaluation. MAUT, AHP and PROMETHEE are among the most widely applied MCDA techniques, which resulted in various software with simple user interfaces and straightforward results representation capabilities. Former ELECTRE software are limited to the representation of the resulting ranking, choice or class in the form of a simple diagram. However, more advanced software that improve the user interface, the intelligibility of the method and relevant parameters, such as IRIS and JSMAA for ELECTRE-TRI, have been developed. DRSA scores poorly in this case as its Java-based applications only convey the decision rules in a simple list format. It must be noted that DRSA is a much younger technique when compared to the other analyzed in this review, which somehow justifies the limited status of its software advancement.

Direct comparison of results from various software runs is only possible with AHP and PROMETHEE, since the other software do not provide such capability. This limitation can nonetheless be easily surmounted by saving separate files of the various runs independently, which can later on be opened in separate windows and compared.

Independency from the decision context has been advanced as a desired feature of MCDA methods, even though this has been heavily questioned by the practitioners within the outranking community. Only MAUT satisfies this requirement and its decision recommendation cannot be affected by the rank reversal phenomenon as each alternative is assessed in absolute terms. On the other hand, all the other reviewed methods can suffer from rank reversal. The literature is divided on this topic as some authors see it as a major problem, whereas others consider it as acceptable and legitimate. The crucial peculiarity for AHP, ELECTRE and PROMETHEE and DRSA is that they are all based on the structure of the problem that has been tackled, which is completely dependent on the whole set of the alternatives. As a consequence, there is no "right" or pre-defined classification or ranking to be identified, but the decision aiding process is rather based on the situation at stake, and it is consequently context dependent. When the alternatives to be evaluated are changed, this affects the relative scoring in the AHP, the credibility degree in ELECTRE, the outranking flows in PROMETHEE and the dominance relations in DRSA, thus resulting in a new decision situation that cannot be considered as the same as the previous one.

The easiness of use is a fundamental aspect in the MCDA process, specifically when the DMs are not experts in the field. For what concerns MAUT and AHP, a discrepancy has been identified in the literature between the lengthy and cognitive demanding processes of value/utility functions development, pairwise comparisons and trade-offs identification, in contrast with the easy-to-use and straightforward software that have been developed to support them. ELECTRE scores low, since they are the most sophisticated class of methods which requires several parameters to be identified (e.g. three types of thresholds, discordance and concordance indexes), some of which do not have a clear and practical meaning, and the exploitation procedures is perceived as somehow obscure. The limited graphical potentials aggravate the evaluation even more. PROMETHEE, although based on the outranking approach as ELECTRE, is easier to understand for the DM, it is more flexible as it handles different preferences structures through different preference functions and is supported by a variety of powerful and simple-to-understand software, very powerful in terms of results representations, understanding and communication.

Overall, DRSA scores the highest in terms of easiness to use, because it is easily intelligible by the DM through the concepts of global preference which limits severely their cognitive effort. Furthermore, the decision model in the form of *"if … , then ..."* decision rules can be easily understood, especially because they can be traced back to the decisions that originated them, justifying the definition of "glass box" tool when compared to other MCDA methods [212].

As a general recommendation, researchers should take into account two important features when selecting an MCDA method. Firstly, they should verify that the axioms the method is based upon are respected. Secondly, the data quality and properties should drive the search for the method that best fits the decision-making challenge, and not vice-versa.

## 4.8 Summary

The progress towards sustainable development is challenging because of its multidisciplinarity and multidimensionality nature. Consequently, a huge variety of data must be handled and stakeholders involved. MCDA emerges as an excellent process and set of methods that can help shaping and completing decision-making for sustainability evaluations.

The MCDA process is structured into a series of steps that help decision analysts and stakeholders framing each SA in a transparent and apprehensible form, starting from problem representation to problem formulation, moving to the construction of the evaluation model until a final decision recommendation.

Several methods belong to the MCDA family and for each one specific requirements must be verified. A general clustering of MCDA methodologies distinguishes them in utility-based, outranking-based and rules-based approaches. Each methodology requires DM's preference elicitation to perform the information aggregation. This elicitation process can take place in two forms: (i) directly and (ii) indirectly. Direct elicitation procedures are time-consuming and require highly cognitive efforts from the DM whereas indirect elicitation procedures are much more intuitive and are emerging as preferable solutions for preferences identification.

MCDA methods have been indicated as very suitable to perform assessments of sustainability, by accounting for different spheres/pillars, perspectives, stakeholders, values, uncertainties and intra and inter-generational considerations. For this reason, a variety of SAs based on MCDA have emerged during the last decades, ranging from micro level (e.g. products comparisons), to meso level (e.g. organization performance), up to macro level (e.g. biofuel policy choices). Overall, a comprehensive analysis of the strengths and weaknesses of the methods used in case studies and also comparisons of different approaches when applied to the same problem appeared as a major research gap, which can hamper the rigorous and long-term application of MCDA in the area of SA. These considerations suggested the need for a review of the available MCDA methods with respect to their potentials and limitations when doing SAs, which was conducted throughout this doctoral research. This resulted in a comparative analysis of five MCDA methods (MAUT, AHP, PROMETHEE, ELECTRE all applied with direct preferences elicitation and DRSA) belonging to the three MCDA methodologies mentioned above. The major reason for such methods selection is that they have been widely used or have considerable potentials for SA of NPs and a clearer understanding of their actual pros and cons was considered paramount to shape the future steps of the research activities.

The methods were assessed through a literature review with specific reference to ten criteria that emerged as crucial for tools aimed at sustainability-related evaluations. The review comprehensively confirms that MCDA methods are outstanding tools for performing SA and they can all manage quantitative and qualitative information as well as support a life cycle perspective. The flexibility in terms of input data and inclusion of criteria are actually two characteristics that distinguish them from other tools to evaluate sustainability. MAUT is demanding in terms of DM's efforts, since the utilities for each criterion and the trade-offs between the criteria must be assessed with a variety of cognitive demanding questions. However, the approach is widely used, can handle uncertain information very well and is not affected by rank reversal.

AHP is the easiest approach from a conceptual viewpoint, since the relative scale from one to nine is easily understood by the DMs. However, the number of comparisons can grow very fast and this might affect the DM's willingness to perform the assessment and more importantly their judgements inconsistencies, which can heavily reduce the credibility of the results or even the practicability of the method.

ELECTRE allows the most sophisticated preferences modeling, but is also the most difficult approach to adopt and use to communicate with the DM, also due to the poor graphical representation of the results. PROMETHEE is easier than ELECTRE, as the preference modeling is more intelligible. PROMETHEE also has a very good software support, which provides an easy and effective interaction with the DM. DRSA is a relatively recent methodology compared to the previous ones, it is less demanding in terms of information elicitation from the DMs and it is the easiest approach. It is particularly appealing because it allows straightforward tracking of the preferences and indirect identification of critical criteria and thresholds.

Concerning sustainability-specific aspects, the analysis has shown that most of the requirements are satisfied by the MCDA methods, although at different extents, with the exclusion of management of mixed data and adoption of life cycle perspective, which are achieved by all.

ELECTRE, PROMETHEE and DRSA score better than MAUT and AHP in terms of enforcement of a strong sustainability approach together with thresholds management. The weights in MAUT and AHP express the trade-offs between the criteria, imply the logic of compensation and are dependent on the measurement scales. On the other hand, ELECTRE, PROMETHEE and DRSA limit heavily or abolish the compensation degree among sustainability criteria and spheres. This implies that (i) weights must be used as importance coefficients and not as trade-offs when strong sustainability is chosen as the driving paradigm and (ii) only non-compensatory MCDA methods (e.g. ELECTRE, PROMETHEE, and DRSA) can be used when such sustainability concept is enforced. It is important to stress that only weights as importance coefficients indicate the intrinsic importance of one criterion over the others, and they are independent from the measurement scale of the criteria.

SAs are multiple criteria based evaluations, which necessitate the inclusion of a wide variety of data typology with various certainty degrees. MAUT, ELECTRE, PROMETHEE and DRSA can handle uncertain information very well by means of robustness analysis as well as preference thresholds. Each method has dedicated software that support uncertainty management, which can be conducted by all the approaches to investigate the variability of the results depending on the input data.

Rank reversal consists in the change of results (e.g. ranking of options A and B) due to the addition or deletion of alternatives (e.g. C and D) or criteria. AHP, PROMETHEE, ELECTRE and DRSA can suffer from such phenomenon, which has caused several debates about its interpretation and management. On the whole, this is an issue to be handled with care in the evolving area of sustainability where new information and alternatives become continuously available and need to be included in the assessments. An important consideration that analysts must account for during their analysis is that decision-making processes are heavily influenced by the procedure that leads to the formulation of the decisional problem, the identification of the evaluation criteria and the selection or creation of the alternatives. Consequently, it can be argued that it might be difficult to consider a problem as well defined if the alternatives are not accounted for along the MCDA process, which places AHP, PROMETHEE, ELECTRE and DRSA in a better position regarding this controversial issue.

The review showed that there is a growing interest in the adoption of MCDA methods to conduct SAs. A major consideration that emerged is that the success and failure of the methods will heavily depend on two important features, the easiness of use of the techniques and the technical support (i.e. computer scientists and software tools) that is available to implement them. The success of MCDA methods for SAs will depend on two factors. The first one is the capacity of sustainability analysts to interact efficiently with the DMs to construct a fair representation of the problem without overloading them with mathematical modeling requirements. The other one is that easily interpretable results, especially from a visual perspective, need to be provided by software tools. This can be successfully achieved if sustainability analysts team up with computer scientists to develop synergistic partnerships.

Overall, the review achieves the second objective of the Ph.D. thesis by highlighting the wide potentials of MCDA in supporting an emerging and heterogeneous area as SA. Firstly it confirms the invaluable contribution that the MCDA process can have in structuring these types of evaluations, which are normally ill-defined decision-making problems, with unclear definition of the alternatives to be compared and the assessment criteria to be employed.

Furthermore, the review demonstrated how MCDA methods offer decision support for analysts interested in performing sustainability evaluations by issuing a decision recommendation in the form of a comprehensive assessment of the alternatives under analysis. This is normally achieved by conveying a lot of information in a clear and understandable format, such as a ranking or a classification in preference-oriented classes for the alternatives of interest. The review also highlighted that the selection of a certain MCDA method has to be based on an appropriate knowledge of the basics of the approach and the evaluation to be performed as well. This implies the recognition that some types of SAs can be performed only by certain methods and modeling paradigms and not by others, so that the adoption of the approach is tailored to the decision-making situation at stake and not vice-versa.

These methodological considerations have been of paramount importance to shape the doctoral research described in the next chapters. Chapter 5 partially adopts the MCDA process to define a comprehensive group of criteria to assess the sustainability of NPs, Chapters 6 and 7 adopt the whole MCDA process to develop and assess the robustness of a model for the classification of synthesis routes for silver nanoparticles in preference-oriented classes.

# Chapter 5. A Framework of Criteria for the Sustainability Assessment of Nanoproducts

## 5.1 Introduction

Nanotechnology is emerging as one of the next industrial revolutions, enabling enhanced functionality of current products as well as creating new products in a broad set of application areas, including environmental remediation, UV filters, energy production, hydrogen storage, composites reinforcements and drug delivery [1, 10]. For this reason, the assessment of the implications of NPs must be accounted for in order to guarantee a responsible and sustainable development of this technology [48, 50].

Chapter 3 showed that several approaches and criteria have been used to evaluate the implications of NPs on sustainability. Such analysis has shown that there is a clear need for the definition of a shared concept of "sustainable nanotechnology" and the criteria required for implementing it, including their relative priorities as well as the correlations in place between them [22, 30, 43].

In order to perform holistic evaluations of sustainability of NPs it is necessary to develop comprehensive approaches that can cover every sustainability implication. Chapters 2 and 4 highlighted that the attainment of this goal is possible if a clear structuring of such approaches is firstly performed, followed by the identification of assessment criteria. Nowadays there is no comprehensive and agreed criteria set available for evaluations of sustainability of NPs [5, 16, 30, 48] and considering that this Ph.D. thesis aims at advancing the sustainability research on NPs implications, this became the third objective of the research project. Chapter 4 also stressed the role that DMs, namely those with "knowledge in the field under investigation", have in shaping a certain problem and contributing to achieving recommendations in such area. For this reason, the inclusion of experts' knowledge resulted as an appropriate solution to resolve the following questions:

i. Is it possible to obtain a comprehensive and reliable list of sustainability criteria for NPs?

ii. Are there criteria more important than others in affecting the sustainability impacts of NPs?

iii. Are there any correlations between the sustainability criteria that would allow identifying links among them?

This chapter provides answers to these questions by integrating literature review outcomes from Chapters 2, 3 and 4 with a questionnaire developed to investigate knowledge of experts in the area of sustainable nanotechnology. The MCDA process has been used as a solid methodological basis for achieving this objective.

## 5.2 Research methodology

The literature review on SA tools for nanotechnology (Chapter 3) showed that during the last decade various and rather broad-focus studies emerged, though none providing a complete set of assessment criteria. The first consideration leading the definition of the research methodology is that this gap was due to the lack of rigorous problem definition and formulation. Furthermore, the absence of an internationally agreed concept of sustainable nanotechnology and the fact that research on its sustainability implications is spread across multiple areas of competency and expertise, whose practitioners do not generally cooperate, appeared as two additional reasons for a missing comprehensive set. The challenge would thus have been providing a common platform for this knowledge sharing and capturing to happen. The MCDA process has interestingly been developed for this specific typology of problems (see Chapters 3 and 4 for details), which offered solid grounds for its use in the development of the assessment criteria.

Even though the MCDA process is structured around four main steps, there are no mandatory guidelines and standards to apply it in practice. In this research, the MCDA process was adapted in a 3-phase procedure to achieve the research objective and answer the research questions (RS) (Figure 5-1).

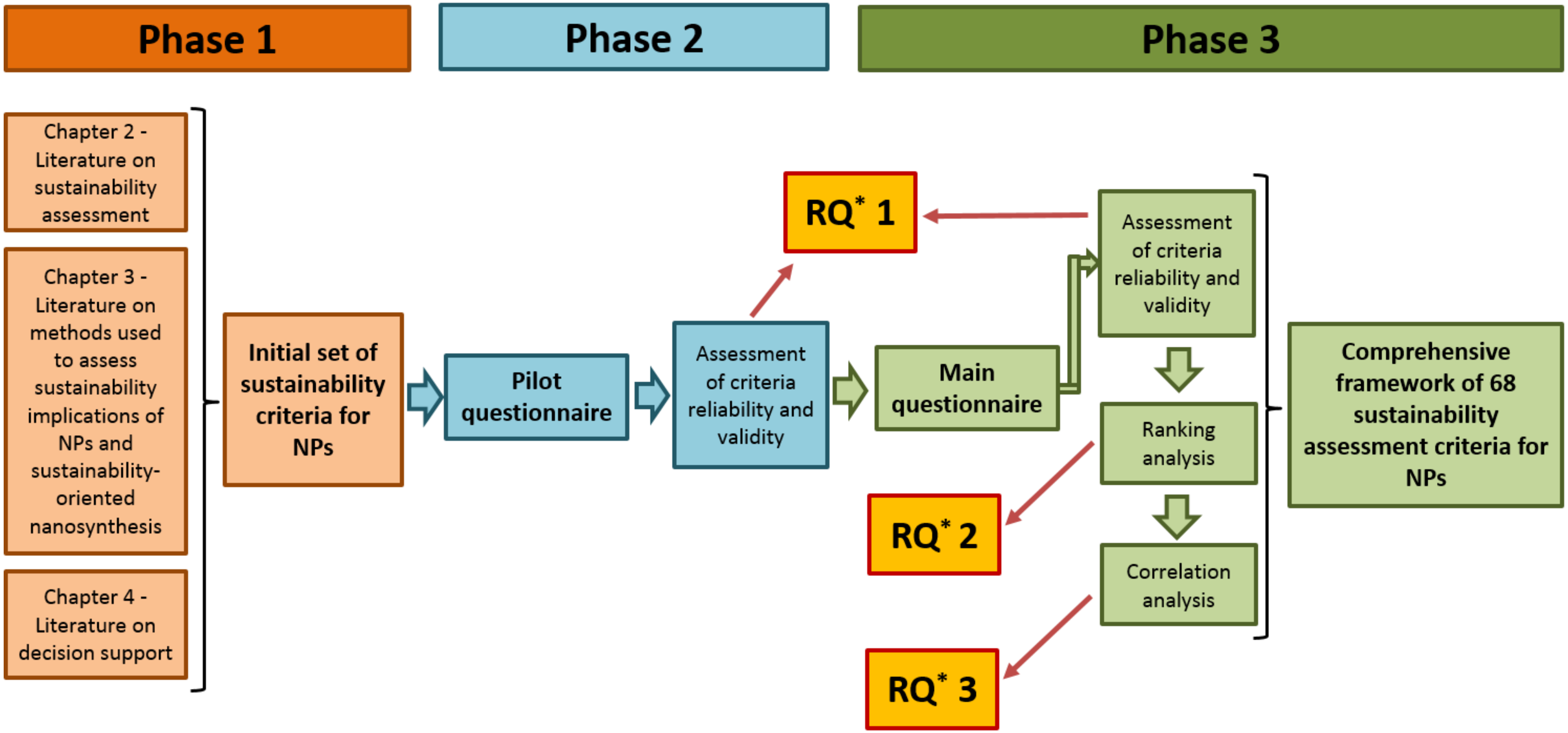


**Figure 5-1: Research methodology adopted for development of SA criteria for NPs (* = Research question)**

### 5.2.1 Phase 1 – Initial set of sustainability criteria for NPs

Phase 1 led to the identification of an initial set of SA criteria for NPs. This was achieved through three sub-phases, which did benefit from the extensive literature review reported in Chapters 2 and 3, where the shaping of the broad context of SA in general (as well as the one of nanotechnology) was performed. The first sub-phase was the problem definition, where an elaboration of the findings from Chapters 2 and 3 lead to the identification of six established sustainability-related research themes that drew from the triple bottom line definition of sustainability. Each researcher in every research theme was envisioned as the DM from the MCDA perspective.

The second sub-phase was the problem formulation, which started with the alternatives selection. The studies in Chapter 3 showed that there is not a unique assessment target when evaluating the outputs of nanotechnology at the product level. In fact, they span from nanoparticles to nanomaterials up to nano-enabled applications. In order to be as comprehensive as possible, the reference alternative that was considered as appropriate in this case was the concept of NP, namely any nanomaterial and product containing such material [5]. The problem formulation was completed by determining the problem statement. Following the types of decision problems that are typical in MCDA (see Chapter 4 for a list of common decision problematics), the one the practitioners in this area focused on from a decision aiding perspective is the description of the implications of NPs, being it from a social, economic as well as an environmental standpoint.

The last sub-phase of Phase 1 was the identification of evaluation parameters of the alternatives (i.e. NPs), which from the MCDA viewpoint is part of the construction of the evaluation model. These parameters did actually represent the individual criteria that had been used by the practitioners with the various methods (Chapter 3) to provide a description of the NPs in terms of their sustainability implications. In order to identify and develop the initial set of criteria, the tools and strategies for sustainable nanotechnology discussed in Chapter 3 were screened to select the criteria following the guidelines developed by [229, 283]:

i. Comprehensiveness: all the implications on sustainability should be covered in order to assure a complete evaluation list. As discussed in Chapter 2, the TBL definition of Sustainable Development can be seen as a broadly accepted starting point [65, 69, 70, 284], which lead the search for criteria in the environmental, economic and social domains literature. The appropriateness of this approach finds confirmation also in the specific literature on sustainable nanotechnology [21, 48].

ii. Applicability: the criteria had to be generally applicable to a NP, without any additional specification in terms of potential application.

iii. Transparency: the criteria had to be easily understandable and selected in a traceable manner, so as to avoid misunderstandings and misinterpretations;

iv. Practicability: the criteria must be implementable and operational. This does not mean that they must necessarily be measured as current but that it is possible to foresee the implementation in a practical setting if resources and time become available for analysis and assessment.

Figure 5-2 (details in Appendix A.1) shows the evaluation criteria selected as a starting list. They have been grouped in six main areas, distinguishing along established research themes. Economic performance was identified as an area by itself (*framework area I*), whereas the environment was split into two areas, one referring to the environmental impacts (*framework area II*) caused by the NP during its lifecycle, while the other targeting the environmental risks assessment and management (*framework area III*). In a similar fashion, societal issues were divided in two major themes; the human health risk assessment and management (*framework area IV*) and the broader ethical, legal, governance and social implications (*framework area V*). Lastly, the area of technical performance (*framework area VI*) completed the domains of research. The latter was included in the framework of sustainable nanotechnology since the emergence of NPs is strictly dependent on the performance of such goods when compared to conventional products [63]. As a consequence, products that do not meet technical specifications would not even be considered for production, which would render any effort to identify sustainability criteria in other areas worthless [5].

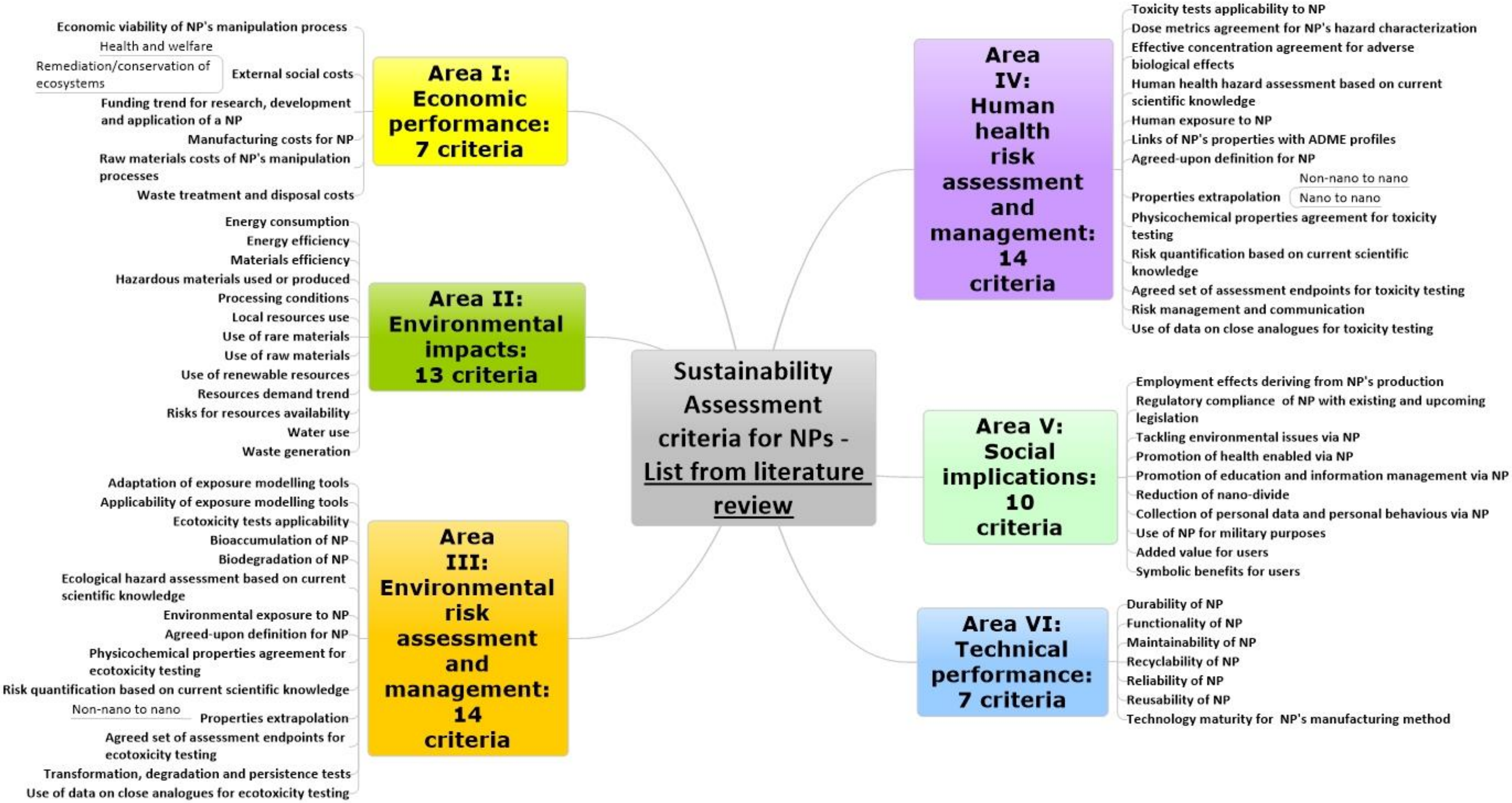


**Figure 5-2: SA criteria selected for the pilot survey from the literature review**

### 5.2.2 Phase 2 and 3 – Questionnaire development

Inclusion of experts' knowledge in unstructured research and professional domains is regarded as a promising solution for identifying agreement on research lines, as well as their priorities [285-290]. As mentioned above, the domain of sustainable nanotechnology is characterized by practitioners from multiple areas of competency that leads to a fragmented provision of SA criteria. In this regard, MCDA places a strong focus on the inclusion of the DMs, those who have a competency in the area under analysis, in the development of the assessment of the alternatives (see details on the role of DMs in the decision process in Chapter 4). This strengthened even more the adoption of MCDA philosophy in this research project, which was achieved in Phase 2 and 3 of the research methodology. This consisted in iterative implementation of the last sub-phase of Phase 1 described above, using a survey questionnaire, through the integration of experts' knowledge in order to aid the identification and selection of the comprehensive set of assessment criteria, which was the third objective of the thesis.

Questionnaire was used as a research method since it allows eliciting quantitative description of trends, opinions and attitudes from a sample of a certain population [291]. Questionnaires are very efficient instruments to collect information from a large group of people, either by means of closed or open-ended questions [291]. In line with the aim of answering the three research questions presented in the introduction, the survey (Appendices A.2 and A.6) was developed to collect the following information from the respondents:

i. Specification of professional expertise and geographical area of operation;
ii. Evaluation of importance of each criterion in relation to the assessment of implications of NPs in the area of concern (on a 5-point Likert scale from very low to very high);
iii. Addition of missing criteria and comments.

The questionnaire was developed as an online assessment through the software Questionmark Perception[1], licensed to the University of Warwick, UK.

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[1] https://www.questionmark.com/content/questionmark-perception

#### *5.2.2.1 Phase 2 - Pilot questionnaire*

Comprehensibility and feasibility of the questionnaire was assessed through piloting, which was conducted to test the appropriateness of the questions wording, the reliability and validity of the criteria used in each area and to include further criteria that might have been excluded during the literature review [292]. The results from the pilot survey were also used to modify the main questionnaire by improving accuracy through re-wording of questions.

In this research, the respondents' sample was composed of key informants in the areas of nanotechnology and assessment of its sustainability implications (see Appendix A.3 for selection strategy of experts). Such an approach was adopted since expert opinion analysis is regarded as an excellent tool for investigation of unstructured knowledge [293] and it was successful in tackling similar issues related to the safety of NPs [294-296].

#### *5.2.2.2 Phase 3 - Main questionnaire*

The main survey was conducted with the collaboration of the only organization available that gathers people working worldwide in the area of sustainable nanotechnology, namely Sustainable Nanotechnology Organization (SNO)[2], as well as the Nanotechnology Knowledge Transfer Network of Innovate UK (Nano-KTN)[3], the UK's innovation agency committed to accelerating economic growth. The final questionnaire was submitted to all the members of these organizations.

This phase provided the answers to the three research questions listed in the introduction of this chapter. Firstly, reliability and validity of the questionnaire were confirmed. Secondly, the relative ranking of the criteria was derived in order to define research priorities and lastly the correlations between the criteria were investigated. Details on the data analysis techniques are provided in section 5.2.3.

#### *5.2.2.3 Recruitment of participants*

The recruitment of participants took place in three stages, both for the pilot and the main survey:

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[2] http://www.susnano.org/

[3] https://connect.innovateuk.org/web/nanoktn

i. Firstly an e-mail with a cover letter explaining the background of the project was sent to each expert providing a link to the online survey;
ii. A reminder e-email was sent ten days after the first e-mail;
iii. Another reminder e-email was sent ten days after the first reminder.

The results were collected through the online platform of Questionmark Perception, stored in Excel files and analyzed with SPSS software[4] version 22, operating with the extension bundle developed to handle ordinal data analysis [297].

### 5.2.3 Data analysis

The information obtained from the questionnaire consisted of primarily nominal and ordinal data. As far as ordinal data is concerned, it comprised five preference-ordered categories from very low (1) to very high (5), with the addition of the "I do not know" option. Likert-type replies are thus the major components of the results, which do not allow for parametric statistics, unless "precarious and, perhaps, unrealistic assumptions are made about the underlying distributions" [298]. On the contrary, ordinal data type is well suited for non-parametric statistical tests, which is ideal for rank-ordered scales (as Likert-type is) [283, 298-302].

The analysis of the replies from the respondents included descriptive statistics, reliability assessment through ordinal alpha, content validity analysis, ranking analysis based on relative index (RI) and correlation analysis by means of gamma coefficient.

#### *5.2.3.1 Descriptive statistics*

Descriptive statistics was used to describe the background of respondents who participated in the survey, their length of practice in the field(s) and choose their scale of operation on a four-choices base (i.e. local, national, supranational and global). Frequencies and percentages were utilized to summarize and present the results.

#### *5.2.3.2 Reliability assessment*

Reliability was assessed first as it is a necessary pre-requisite for the analysis of data from questionnaires based on closed questions [303, 304]. The reliability was evaluated through internal consistency which allows assessing whether the items (criteria) selected

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[4] http://www-01.ibm.com/software/uk/analytics/spss/

for the areas do actually belong to each one. It represents a necessary test of questionnaire psychometric properties since it has major implications in the process of developing the main questionnaire, including questions rewording or elimination of unreliable criteria [303, 304].

A reliable scale is ideally composed by all the items that make it comprehensive while it does not include the parameters that do not actually measure the underling construct the scale aims at representing (e.g. environmental impacts). Internal consistency was assessed by means of ordinal alpha coefficient (α) proposed by Zumbo et al. [305] as the appropriate measure to be used with ordinal data [297, 306, 307]. A scale goes from 0 to 1 and values greater than 0.7 are usually required to indicate acceptable internal consistency, but scores above 0.8 are preferable [306, 308]. Items that correlate low (under 0.300 as a rule of thumb) or even negatively need to be deleted or the relevant question(s) rephrased [303, 304, 308], as the reliability tests indicate that they are not measuring the target scale.

#### 5.2.3.3 Validity assessment

Validity is another mandatory component of survey evaluation as it indicates whether the scale measures what it is supposed to measure [304, 309]. In the questionnaire content validity of the scales was assessed by asking two specific questions to the pilot experts, whether there were any missing criteria and if there were any doubts about the clarity and organization of the questionnaire [303].

#### 5.2.3.4 Relative index

Priorities in the criteria lists were derived by means of RI, which was used to aggregate the scores rated on ordinal scales and derive rankings for the criteria. RI allows identifying the most important parameters based on participants replies and it has been shown as a powerful tool in similar studies, to prioritize the parameters rated on Likert-type scales [283, 299, 310].

The formula of the RI is the following [283, 299]:

$$\mathrm{RI} = \sum_{\mathrm{i}=1}^{\mathrm{i}=5} \frac{\mathrm{w_i f_i}}{\mathrm{N}} \qquad (1)$$

where $w_i$ is the weighing factor obtained from dividing the rating score by the highest score (i.e. 5), $f_i$ is the frequency of responses and N is the total number of responses. It must be noted that the RI was only used to derive an ordinal ranking of the criteria and not to extrapolate a relative importance score on a percentage basis.

Furthermore, importance levels (IL) clustering an equal number of criteria (wherever possible) were assigned according to this qualitative approach: first, second and third sub-group of parameters. This strategy resembles risk-based approaches where high, medium and low risk factors are identified within a given group to set research or/and funding priorities.

#### 5.2.3.5 Correlations between criteria

The correlations between the criteria have been assessed by means of Gamma, $\gamma$, which is an appropriate measure of association for ordinal variables [301, 311, 312]. Its value derives from the assessment of paired observations of the variables and is calculated as follows [312]:

$$\text{Gamma} = \frac{\text{SOP} - \text{IOP}}{\text{SOP} + \text{IOP}} \qquad (2)$$

where SOP stands for “same order pairs”, and IOP stands for “inverse order pair”. SOP considers the cases where the higher the rank is for one variable the higher it is for the other as well, whereas IOP considers the cases where the higher the rank is for one variable the lower it is for the other. Gamma values vary between − 1 and + 1, with values close to 0 indicating lack of correlation between the variables and values close to $|1|$ indicating strong positive (+ 1) and negative (− 1) correlation between the variables. The threshold limit of $\pm$ 0.5 (or higher whenever indicated) was used as an indication of a substantial/strong relationship between two variables [294, 301, 312].

## 5.3 Results and discussion

### 5.3.1 Pilot questionnaire

A total of 54 experts replied to the pilot survey, covering one or more sustainability areas. Table 5-1 shows the number of replies received from the experts (i.e. N), varying from 9 to 17 per area, together with their years of experience and the reliability of each sustainability area. Almost 800 years of cumulative expertise were collected in the pilot survey, which can be seen as a notable amount of information when accounting for the lack of a recognized population to sample the respondents from. In fact, the pool was composed of people with a recognized reputation in the area of sustainable nanotechnology, having published extensively in this domain and holding positions of relevance in organization and institutions that aim at fostering the responsible development of this technology (see Appendix A.3).

**Table 5-1: Results summary of pilot survey for each individual sustainability area (*: RAM = risk assessment and management)**

| Statistics | Economic performance | Environmental impacts | Environmental RAM* | Total |
|---|---|---|---|---|
| Replies | 9 | 16 | 17 | |
| Overall years of experience | 69 | 119 | 117 | |
| Reliability of scale (α) | 0.370 | 0.883 | 0.827 | |
| Criteria based on literature review | 7 | 13 | 14 | |
| Changes applied following analysis of pilot survey results | 2 criteria added | - | 1 criterion deleted and 2 added | |
| | **Human health RAM*** | **Social implications** | **Technical performance** | |
| Replies | 17 | 14 | 14 | |
| Overall years of experience | 144 | 125 | 208 | |
| Reliability of scale (α) | 0.781 | 0.823 | 0.844 | |
| Criteria based on literature review | 14 | 10 | 7 | |
| Changes applied following analysis of pilot survey results | 1 criterion deleted and 1 added | 1 criterion deleted | 2 criteria added | |
| Cumulative years of experience | | | | 782 |

The results of the piloting have been used to assess the reliability and content validity of the questionnaire. Table 5-1 show that out of the six areas under investigation the reliability is good or very good for five of them, with the exclusion of economic performance. The comments from the respondents have been important to increase the clarity of the questions and to add the parameters that had not been accounted for. Furthermore, the statistical tests and the respondents' comments were necessary to understand what criteria had to be rephrased or removed and the reasons for such choices. A summary of the changes that were applied following from the pilot results are presented in Table 5-1 and Table 5-2, while details can be found in Appendices A.4 and A.5.

**Table 5-2: Changes applied to main survey based on pilot survey responses**

| Sustainability area | Changes introduced in the main survey |
|---|---|
| **Economic performance** | • Rewording of main introductory question for this area to account for the fact that the criteria are not always about impacts, but rather about conditions for NPs to emerge<br>• Addition of criteria: (i) "collaboration embedment of stakeholders along the value chain", and (ii) the business capital investment for "public perception of NPs" |
| **Environmental impacts** | • The concept of functional unit of the NP was emphasized in the main survey so that selection of importance of criteria is requested in comparison to a non-NP with the same functionality |
| **Environmental risk assessment and management** | • Rewording of questions to account for the need of a case-by-case (i.e. NP specific) consideration when indicating the importance of the criteria<br>• Deletion of criterion "properties extrapolation from non-nanoscale to nanoscale materials" due to lack of correlation and supportive relevant literature<br>• Addition of criteria: (i) "use of alternative ecotoxicity testing strategies" and (ii) "development of media specific ecotoxicity tests for NPs" |
| **Human health risk assessment and management** | • Rewording of questions to account for the need of a case-by-case (i.e. NP specific) consideration when indicating the importance of the criteria<br>• Deletion of criterion "properties extrapolation from non-nanoscale to nanoscale materials" based on expert judgement<br>• Addition of criterion "use of alternative toxicity testing strategies" |
| **Social implications** | • Deletion of criterion "added value for users" due to lack of correlation and consistency with the whole scale of assessment |
| **Technical performance** | • Addition of criteria: (i) "method of manufacturing for the NP" and (ii) "reproducibility of NP characterization technique" |

All the considerations reported and discussed above have been used to improve the survey by rephrasing questions and deleting or adding criteria in order to shape the final survey (see Appendix A.6).

### 5.3.2 Main questionnaire

65 practitioners, with a variety of expertise across the sustainability areas, responded to the main survey (Table 5-3). Replies for each one varied from five for the economic performance of NPs up to 22 for their environmental impacts and environmental risk assessment.

**Table 5-3: Results summary of main survey for each individual sustainability area (*: RAM = risk assessment and management)**

| Statistics | Economic performance | Environmental impacts | Environmental RAM* | Total |
|---|---|---|---|---|
| Replies | 5 | 22 | 22 | |
| Overall years of experience | 59 | 194 | 158 | |
| Reliability of scale (α) | 0.756 | 0.835 | 0.936 | |
| Number of criteria in each area | 9 | 13 | 15 | |
| | **Human health RAM*** | **Social implications** | **Technical performance** | |
| Replies | 18 | 12 | 16 | |
| Overall years of experience | 145 | 80 | 161 | |
| Reliability of scale (α) | 0.962 | 0.912 | 0.734 | |
| Number of criteria in each area | 14 | 9 | 8 | |
| Cumulative years of experience | | | | 797 |

Cumulative years of expertise ranged from 59 years for the economic performance up to 194 for the environmental implications, with a total of 797 years for all the experts. This is a substantial number of years considering that nanotechnology itself is less than two decades old. All the areas overcome the threshold limit for the acceptable level on reliability, which is actually excellent for environmental and human health risk assessment as well as social implications, very good for the environmental impacts

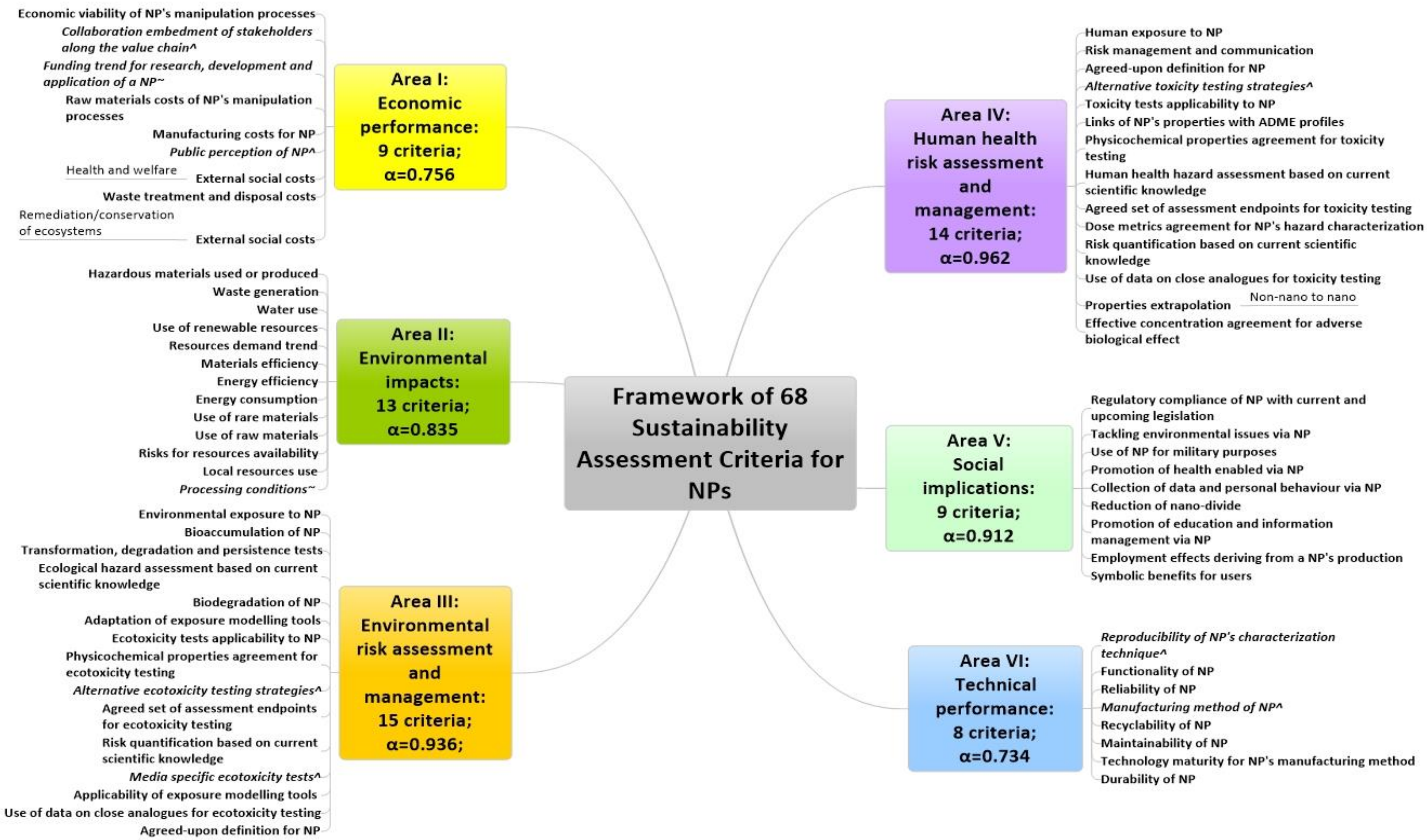

**Figure 5-3: Comprehensive criteria set clustered in the relevant domain areas and ranked according to their relative importance (^ = criterion added based on respondents' recommendation from pilot survey; ~ = unreliable criterion based on internal consistency check)**

and good for the economic and technical performance (Figure 5-3). Reliability assessment of scales was a very important step since it validated the criteria selected for the framework and allowed all the further analysis that the next sections present [313, 314].

#### *5.3.2.1 Economic performance*

**Demographics, reliability and validity**

The demographic of the respondents from the main survey is summarized in Table 5-4. The economic performance area received relatively few replies (i.e. 5) compared to the other domains, however 80% operated at a global level and three of them had more than ten years of experience, with a total expert knowledge accounting for 59 years.

**Table 5-4: Years of experience and scale of operation of the respondents for economic implications criteria (N = number of participants who replied), main survey**

| N | Years of experience | % | N | Scale of operation | % |
|---|---|---|---|---|---|
| 5 | ≤3 | 0.0 | 5 | Local | 0.0 |
| | 4-6 | 20.0 | | National | 20.0 |
| | 7-9 | 20.0 | | Supranational | 0.0 |
| | ≥10 | 60.0 | | Global | 80.0 |

The economic performance area exceeds the 0.700 acceptance threshold for a reliable scale [306] and all the criteria show acceptable correlations, with the exclusion of the criterion “funding trend for research, development and application of a NP” (Figure 5-4).

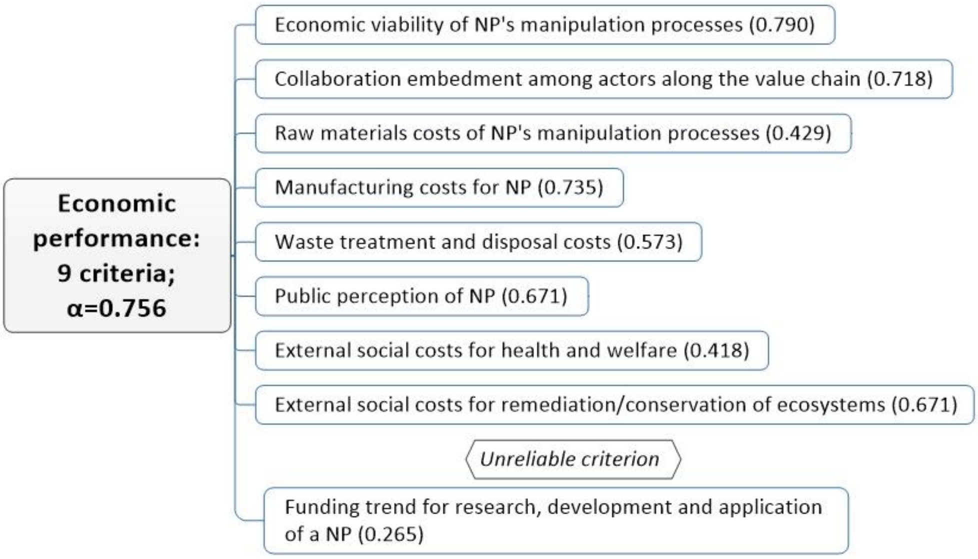

**Figure 5-4: Economic performance criteria, α and relevant correlation with scale reported within brackets**

The reliability of the economic implications area (α = 0.756) is a primary improvement when compared to the pilot survey outcome, where the α was very low (i.e. 0.370). Such findings confirm the crucial importance the pilot survey had to (i) understand which questions were wrongly phrased and (ii) what considerations where missing when respondents were asked about the economic implications of NPs. In this regard, the addition of “conditions for emergence of NP in the market” and “comparison of the NP to a non-NP” in the main questionnaire seem to have played the role in results improvement. Furthermore, the addition of two criteria recommended by pilot respondents, namely “collaboration embedment among actors along the value chain” as well as business capital investment for “public perception of NPs”, contributed to completing the reliable criteria set.

This final set of criteria covers three major sub-sets. The first one is the type of market and value chain the NP is embedded in, exerted by the economic viability of manipulation processes, the embedment of collaboration among the various actors, the funding available for research, development and application and the raw materials costs. The second is represented by more technical aspects namely the costs for manufacturing and for waste treatment and disposal. Lastly, the broader implications related to socio-economic aspects complete the group, being public perception and external social costs for health and welfare as well as for remediation and conservation of ecosystems.

The relatively low correlation for the funding trend criterion renders the belonging of such parameter to the scale questionable. However, three considerations apply. The first one is that the 0.300 limit is arbitrary in nature and thus somehow flexible [315] and the second one is that the number of replies is relatively low when compared to the other areas. Furthermore, funding trend has been indicated as a very important component for the success of NPs which would suggest a rational belonging to this area [5]. These considerations recommend that a cautious approach should be adapted and consequently this parameter is kept in the framework, though the evaluation of its appropriateness to this area of the assessment could be a focus of future studies.

As far as the validity of this domain is concerned, the respondents did not indicate any missing criterion.

## Relative index and correlations

The economic viability of processes that involve NPs manipulation (ECON 1) ranks at the top for the economic implications criteria and it correlates completely with raw materials costs (ECON 4), confirming the importance that a stable materials market has to foster economic sustainability of NPs [59] (Table 5-5). This consideration is of remarkable importance for nanotechnology as there are various rare earth materials (e.g. gallium, germanium, tellurium) that are crucial in the development of NPs and suffer from limited availability and almost monopolized offer, which is subject to unpredictable prices fluctuations and consequently limited raw materials costs stability [59]. A stable marketplace with limited prices fluctuations has a determinant role in securing long-term development and investments in this emerging technology [316].

**Table 5-5: IL, RI and correlations of economic performance criteria (N varies between 4 and 5)**

| Criteria | IL | RI | Positive correlation | Negative correlation |
|---|---|---|---|---|
| ECON 1 = Economic viability of NP's manipulation processes | I | 0.800 | ECON 4, 5 | ECON 7 |
| ECON 2 = Collaboration embedment among actors along the value chain | | 0.720 | ECON 3 | |
| ECON 3 = Funding trend for research, development and application of a NP | | 0.720 | ECON 2, 6 | |
| ECON 4 = Raw materials costs of NP's manipulation processes | II | 0.680 | ECON 1, 5 | ECON 7 |
| ECON 5 = Manufacturing costs for NP | | 0.640 | ECON 1, 4, 9 | |
| ECON 6 = Public perception of NP | | 0.640 | ECON 3, 7 | |
| ECON 7 = External social costs for health and welfare | III | 0.600 | ECON 6 | ECON 1, 4 |
| ECON 8 = Waste treatment and disposal costs | | 0.550 | | |
| ECON 9 = External social costs for remediation-conservation of ecosystems | | 0.440 | ECON 5 | |

Collaboration embedment among various actors in the value chain (ECON 2) emerges as a very important parameter since nanotechnology business is cross-sectorial, it depends on multidisciplinarity and it necessitates integration of several types of organizations such as university spin-offs, start-ups and small and medium enterprises (SMEs) [2]. This type of development needs to find financial support, which is confirmed by the strong correlation between this criterion and the funding trend available for research, development and application of a NP (ECON 3), thirdly ranked in this domain.

The funding for such type of activities can play the role of glue among the various actors and place the basis for the nano-markets to be realized.

Raw materials and manufacturing costs occupy the fourth and fifth positions respectively in terms of relative importance, they are very highly correlated and a lot of literature confirms this, indicating that such costs are major interlinked players for investors and developers of this emerging technology [2, 44, 51, 317-324]. New manufacturing processes labeled as more sustainable also from an economic perspective are being investigated [325] and they involve the selective addition of materials at the nanoscale so that substantial reduction in the amount of raw materials employed, the number of processing steps and the waste produced can be achieved. Appealing characteristics from a sustainability perspective are that the processes are performed at room temperature and pressure, resulting in lower equipment, energy and maintenance costs. Furthermore, the processes are simple (primarily dip coating and spinning-based processes) which reduce tools and operating costs. Some examples of these techniques involve templates used to direct the assembly (through electrophoretic force) of nanoparticles [326] and carbon nanotubes [327].

Public perception of NPs and the funds required by companies to influence it (ECON 6) is another reliable aspect to be accounted for the economics of NPs. In fact, as stated by a participant in the pilot survey, “most businesses exert a lot of money and effort in controlling public perceptions” (see Appendix A.7). Information available to individual purchasers can affect the success or failure of a NP, as they have the power of choosing whether to buy or not a certain good [60]. As one respondent reported in his comment (Appendix A.7), public perception is a very sensible topic that can be subject to manipulation from both standpoint groups, those pro-nanotechnology and those against it. In order to avoid a backlash on such technology (as has happened with genetically modified organisms), companies need to be as transparent as possible on their activities involving NPs, inform the public about them and collaborate with relevant institutions to develop safe and responsible products [328]. Currently, the label of ‘nano’ is used as a strong business point in China as it was in Europe during the early 2000’s, while in the latter nano-labeling is seen nowadays as a concern rather than an advantage. These research findings indicate that only the engagement of all interested parties, including universities, industry, governmental organizations and the general public can effectively contribute to a widespread and agreed deployment of nanotechnology.

Lastly, external social costs that society has to bear for health and welfare maintenance (ECON 7) and remediation and conservation of ecosystems (ECON 9) are part of the scale and represent the hidden economic impacts of NPs [43]. They are relegated to the least important level, probably because of the current unreliability and limited applicability of human health and environmental costs monetization techniques [2]. What is more, customers that buy nano-enabled products with increased functionality (e.g. more reliable and accurate medical devices) might be willing to pay a premium for such benefit. On the other side, the considerations about broader implications of the production and end-of-life might or might not be of influence at the point of purchase, which adds rationality to the lower ranking of the external social costs criteria. Nonetheless, public perception (ECON 6) and social costs for health and welfare (ECON 7) are highly linked as show in Table 5-5, which confirms that robust and reliable information about risks and impacts of NPs can have direct influence on customers' willingness to pay for a NP, consequently driving its success or failure. This stresses the need for accurate development of monetization techniques for the externalities caused by NPs along the life cycle.

#### *5.3.2.2 Environmental impacts*

**Demographics, reliability and validity**

Half of the respondents for the environmental impacts area had more than 10 years of experience and just below 50% had a global operational scale (Table 5-6).

**Table 5-6: Years of experience and scale of operation of the respondents for environmental impacts criteria (N = number of participants who replied), main survey**

| N | Years of experience | % | N | Scale of operation | % |
|---|---|---|---|---|---|
| 22 | ≤3 | 4.5 | 21 | Local | 4.7 |
| | 4-6 | 22.7 | | National | 19.0 |
| | 7-9 | 22.7 | | Supranational | 28.6 |
| | ≥10 | 50.0 | | Global | 47.7 |

Good internal consistency was achieved for the environmental impacts area, whose α is 0.835 (Figure 5-5). All the items correlate relevantly with the scale, with the exception of processing conditions (PC) criterion.

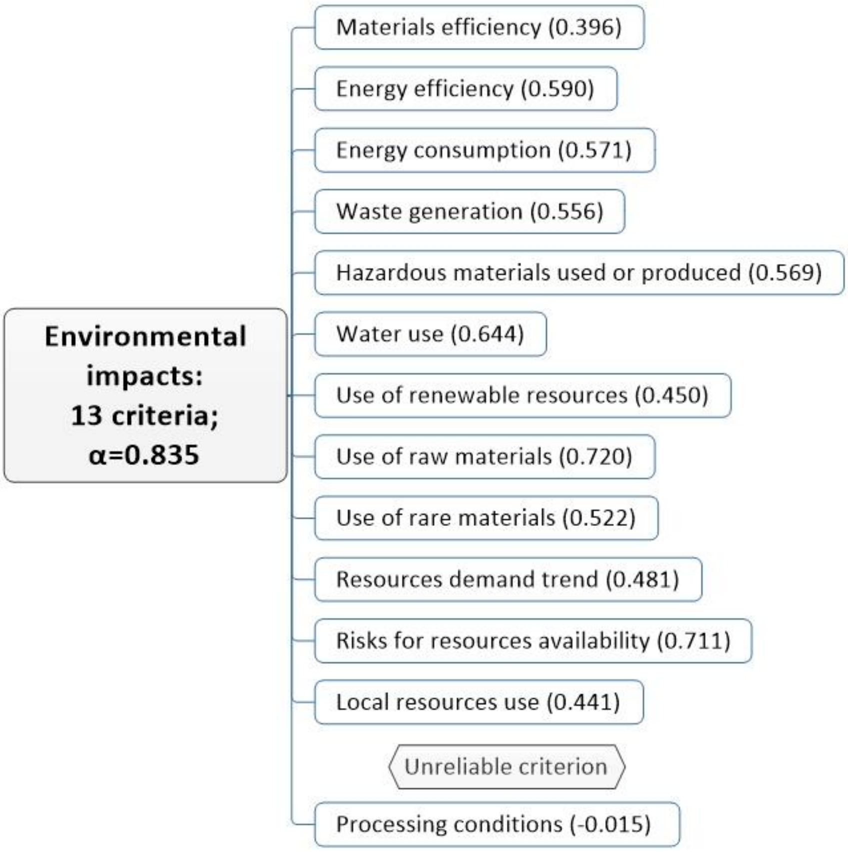

**Figure 5-5: Environmental impacts criteria, α and relevant correlation with scale reported within brackets. All criteria refer to the manipulation processes of NP over the entire life-cycle**

The characteristics of the processes that involve manipulation of NPs constitute a first cluster of parameters driving the environmental implications of NPs, including their materials and energy efficiency, the consumption of energy and the PC (e.g. temperature, pressure, time). Two further indicators that are dependent on the type of employed process include the production of waste and also the use of hazardous materials. Environmental impacts of NPs heavily also depend on the types and amounts of materials employed, which are covered in the framework by the criteria use of water and other renewable resources and the use of raw and rare materials. Dynamics of resources employed during the life cycle are covered by the criteria resources demand trend, the risks for resources availability and the use of local resources.

The internal consistency of the PC criterion in the environmental impacts area indicates that the parameter as it was used in the main survey did not show consistency among the respondents. Nonetheless, PC are indicated as crucial drivers for impacts on the environment [22, 23, 28, 61] which suggests an inconsistency between survey respondents and the literature. A possible explanation of this mismatch is that the wording of the question was ambiguous, leading the participants to respond in a way that was not reflecting the true meaning of the parameter [329]. The reasonability of this explanation is substantiated by the different interpretation that the term PC can have for practitioners; the respondents of this area might have had a limited understanding of this concept, in fact a high percentage (50%) indicated medium importance, a sign of possible hesitation.

From the survey validity standpoint (Appendix A.7), four respondents questioned the potential widespread applicability of the criteria, suggesting that the target NP has to be known before any recommendation can be made and distinctions among life cycle stages have to be accounted for individually. Although these are well-grounded comments, the idea behind the survey was to remove the application-specific domain and select criteria that were free from such expectation. This is in line with the principle of widespread applicability that the guidelines for selecting the criteria was based on [229, 283]. In addition, the possibility of dividing each question in several sub-sections considering the different life cycle stages was part of the initial design of the questionnaire. However, such choice would have caused a huge increase of questions that would have rendered the whole survey impractical. Nonetheless, starting from a high level framework that this survey allowed to develop, the consideration of the life cycle stages could be a focus of further studies as well as a clear definition of LCA metrics that identify/quantify the implications of NPs while also addressing uncertainties.

**Relative index and correlations**

Use and production of hazardous materials (ENVIMP 1) tops the ranking for the environmental impacts area (Table 5-7). Hazardousness of materials is a complex concept that requires integration of a wide variety of characteristics of the materials, including flammability, toxicity, mobility in different environmental compartments, tendency to agglomerate, biodegradation resistance, bioaccumulation and large-scale impacts on the environment such as climate change caused by greenhouse gas emissions [18, 20, 317, 330].

Risks for resources availability (ENVIMP 11) shows strong correlations with the use of raw (ENVIMP 10) and rare materials (ENVIMP 9), as well as the hazardous materials used and produced (ENVIMP 1) and the waste generation along the life cycle (ENVIMP 2) (Table 5-7).

**Table 5-7: IL, RI and correlations of environmental implications criteria (N varies between 18 and 22)**

| Criteria | IL | RI | Positive correlation | Negative correlation |
|---|---|---|---|---|
| ENVIMP 1 = Hazardous materials used or produced | I | 0.735 | ENVIMP 10, 11 | ENVIMP 13 |
| ENVIMP 2 = Waste generation | | 0.700 | ENVIMP 11 | |
| ENVIMP 3 = Water use | | 0.690 | ENVIMP 10, 12 | |
| ENVIMP 4 = Use of renewable resources | | 0.678 | ENVIMP 5, 8, 12 | |
| ENVIMP 5 = Resources demand trend | | 0.670 | ENVIMP 4 | |
| ENVIMP 6 = Materials efficiency | II | 0.658 | ENVIMP 7 | |
| ENVIMP 7 = Energy efficiency | | 0.648 | ENVIMP 6, 8, 12 | |
| ENVIMP 8 = Energy consumption | | 0.646 | ENVIMP 4, 7, 12 | |
| ENVIMP 9 = Use of rare materials | | 0.646 | ENVIMP 10, 11 | |
| ENVIMP 10 = Use of raw materials | III | 0.637 | ENVIMP 1, 3, 9, 11 | |
| ENVIMP 11 = Risks for resources availability | | 0.620 | ENVIMP 1, 2, 9, 10 | |
| ENVIMP 12 = Local resources use | | 0.550 | ENVIMP 3, 4, 7, 8 | |
| ENVIMP 13 = Processing conditions | | 0.545 | | ENVIMP 4 |

With the increasing request for materials to produce NPs [9], the organization of the supply chains will become a pressing issue in the near future, particularly those with a regional concentration of mining, with constrained physical offer and with structural and technical burdens that could limit the widespread availability of relevant resources. Efficient use of materials and their criticality have also been proposed as pillars for the sustainable management of NPs in a recent evaluation framework [46]. Criticality is a function of material’s supply risk and its (economic) importance, affected by the influence of supply interruption on the value chain, the possible substitution of the materials, as well as their recyclability.

From a large scale production perspective, the waste production during the life cycle of a NP can have huge impacts on the environment specifically in cases where hazardous materials have been employed. As a result this issue has also been regarded as a major focus of analysis and improvement of environmental sustainability of NPs [20, 24, 43, 44, 331]. Furthermore, several nanomanufacturing processes have very low materials efficiency, which causes high amounts of waste generation in relation to the end product [18]. These major environmental concerns find confirmation in the main survey, where the waste generation criterion receives the second place rank.

Potential environmental benefits, as well as the economic ones discussed in section 5.3.2.1, can be achieved through nanomanufacturing techniques based on direct assembly and transfer approaches, where selective addition of nanomaterials can be achieved as well as reduction in the use of raw materials, waste production, processing steps, energy consumption and increase in materials and energy efficiency [325].

The trend for resources demand (ENVIMP 5) and the use of renewable feedstocks (ENVIMP 4) are highly correlated and complete the first IL group. In addition, the latter (ENVIMP 4) is linked with the energy used during the life cycle of a NP (ENVIMP 8) and the use of local resources (ENVIMP 12). These results suggest that the future of sustainable nanotechnology with limited environmental implications has to rely on an interlinked management system where the controlled development of local renewable resources demand is combined with reduced energy consumption and highly energy and materials efficient processing along the life cycle. A relevant example in this regard is a recent LCA study investigating the possible application of CNT switches to current cellular phone flash memory [332]. The study found that energy-intensive processes during the life cycle are the foremost contributors to the environmental implications of the CNT switch under study, leading the authors to recommend the improvement of energy efficiency of manipulation processes of NPs as a pressing priority.

Trend of resources demand (ENVIMP 5) is an important aspect to be accounted for, because economic interests for scarce resources (e.g. rare materials) can outweigh environmental protection concerns and cause severe stress on areas that have localized concentration of the relevant resources [5, 59, 331]. What is more, the use of certain materials which are highly resource-intensive and necessitate disproportionate amounts of unrefined material to be mined and processed to yield one unit of target raw material need specific attention from a sustainability perspective. Confirmation emerges in the above mentioned LCA study, which found that the major contributor to the environmental burdens was the mining and refining of gold to be used for the production of the CNT-based switch [332].

Environmental implications of NPs represent also the impacts caused by these products due to the limited efficiencies of the processes that involve the manipulation of NPs themselves [5, 20, 22, 61, 117]. The second IL group accounts for these factors in three interlinked criteria, being materials efficiency (ENVIMP 6), energy efficiency (ENVIMP 7) and energy consumption (ENVIMP 8). For instance, low material utilization are reported for chemical vapour deposition processes, molecular beam epoxy, ion implantation, due to incomplete conversion of reactants, limited geometrical coverage of the wafers on the target surface, loss of precursor materials through the exhaust system and the deposition of reactants on the reactor ceiling [18].

#### *5.3.2.3 Environmental risk assessment and management*

**Demographics, reliability and validity**

The demographics of environmental risk assessment and management area shows rather peculiar patterns to the previous area, with more than 60% of the years of experience between seven and nine and at least ten, and more than 50% of the scale of operation either supranational or global (Table 5-8).

**Table 5-8: Years of experience and scale of operation of the respondents for environmental risk assessment criteria (N = number of participants who replied), main survey**

| N | Years of experience | % | N | Scale of operation | % |
|---|---|---|---|---|---|
| 22 | ≤3 | 13.6 | 22 | Local | 27.3 |
| | 4-6 | 22.7 | | National | 18.2 |
| | 7-9 | 27.3 | | Supranational | 13.6 |
| | ≥10 | 36.4 | | Global | 40.9 |

The reliability of the environmental risk assessment scale showed a considerable improvement from the pilot to the main survey, with the α that increased from 0.781 to

0.936 (Figure 5-6), an excellent value for the internal consistency. What is more, all the criteria correlated with the other ones as a whole. It can thus be affirmed that the rewording of the risk quantification criterion, the addition of the criteria (i) "alternative testing strategies" and (ii) "media specific ecotoxicity tests" recommended by the pilot questionnaire respondents and the lack of validity challenges from the main survey respondents lead to a very reliable and exhaustive scale.

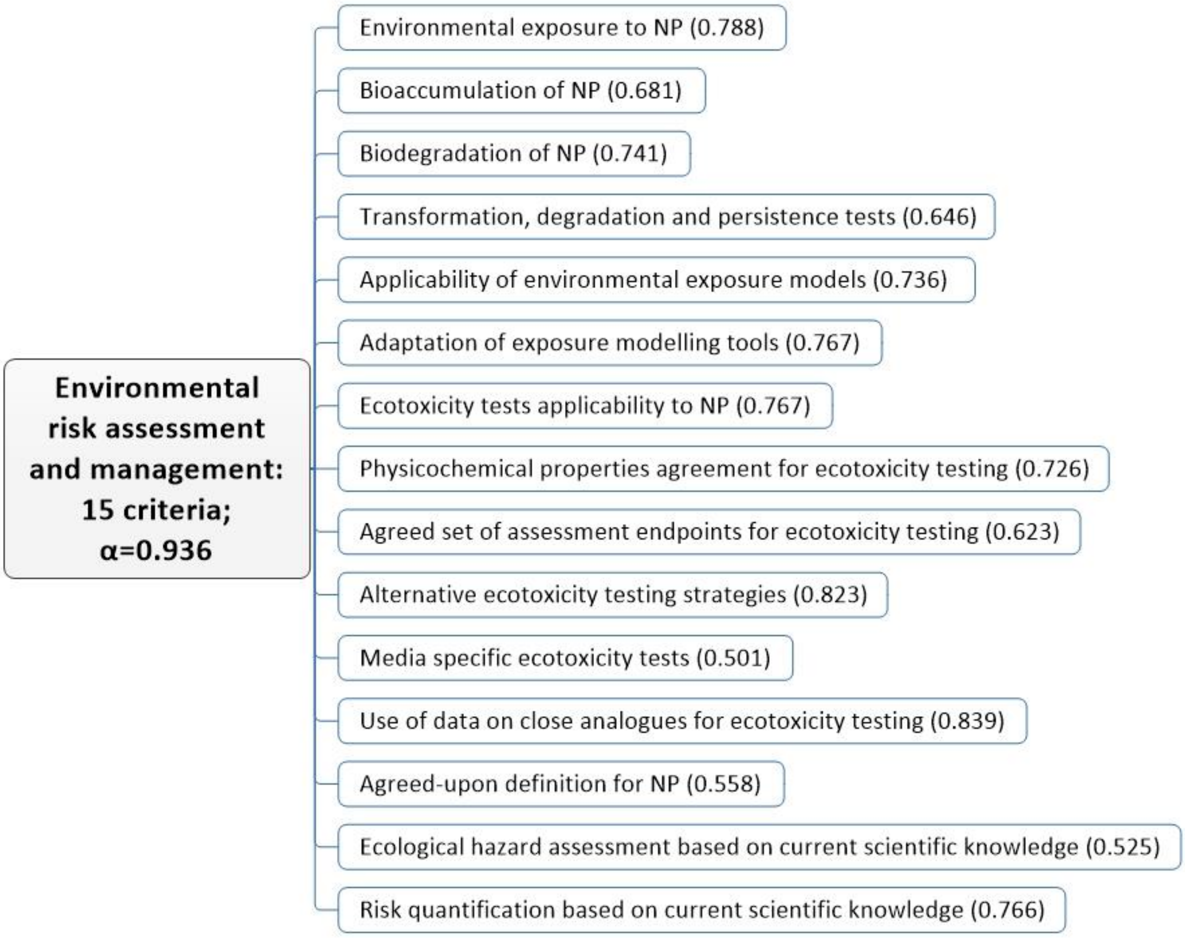

**Figure 5-6: Environmental risk assessment and management criteria, α and relevant correlation with scale reported within brackets**

This research domain covers both components of risk assessment, the hazard identification and exposure characterization. As far as the environmental exposure is concerned, there are six criteria that target it specifically, namely the knowledge about the levels of exposure to a NP, the understanding of the bioaccumulation, biodegradation, transformation, degradation and persistence of the NP, and lastly the applicability and adaptation of exposure modelling tools.

As far as the hazard identification is concerned, the criteria are characterized by the search for consensus among practitioners on the applicability of the available ecotoxicity tests, the physicochemical properties and assessment endpoints to be used for such testing, the use of alternative testing strategies, the need for media specific ecotoxicity tests and lastly the possible use of ecotoxicity data from close analogues. The agreed definition of a NP, the available ecological hazard assessment and the risk quantification based on current scientific knowledge complete this set of criteria.

**Relative index and correlations**

The risk assessment and management area received primary attention from the scientific community, as NPs have unique properties that allow production of new goods but also cause risk concerns as nanoscale materials behave differently from a toxicity and exposure standpoint when compared to their macroscopic counterparts [118, 333].

Knowledge about the environmental exposure to a NP (ERAM 1) is the first criterion, whose high rank is justified by the fact that there is currently no knowledge about actual concentrations of NPs in environmental media mainly due to the lack of appropriate measurement techniques [334, 335]. Bioaccumulation (ERAM 2) and agreed-upon tests for transformation, degradation and persistence of target object (ERAM 3) share the second position and the knowledge about the ecological hazard assessment based on the current information (ERAM 4) ranks fourth while biodegradation (ERAM 5) completes this major important criteria set. All these parameters correlate strongly as reported in Table 5-9, showing the crucial importance that experts in this area report for the need of investigating in a reliable manner the interdependent mechanisms that cause NPs modifications once released in the environment and the realistic exposure concentrations. These considerations have also been stressed in recent reports of the OECD, where these criteria were ranked as priorities [129, 334], and are connected with the necessity of developing database about actual environmental exposure levels to NPs [128]. Regarding the environmental fate assessment, the applicability of available tests for “conventional” materials is very limited and controversial because their properties change with the media, dispersant use and presence of environmental ligands, which justifies the need for specific guidance on sample preparation. Furthermore, the transformations that the NPs face during the aging in natural conditions have to be included in future guidelines [334].

**Table 5-9: IL, RI and correlations of environmental risk assessment criteria (N varies between 19 and 22; Discrimination threshold for criteria correlations was raised to 0.6 in order to aid data management)**

| Criteria | IL | RI | Positive correlation |
|---|---|---|---|
| ERAM 1 = Environmental exposure to NP | I | 0.764 | ERAM 2, 3, 4, 5, 6, 7, 12 |
| ERAM 2 = Bioaccumulation of NP | | 0.717 | ERAM 1, 5 |
| ERAM 3 = Transformation, degradation and persistence tests | | 0.717 | ERAM 1, 8, 9 |
| ERAM 4 = Ecological hazard assessment based on current scientific knowledge | | 0.713 | ERAM 1, 5, 8, 11, 14 |
| ERAM 5 = Biodegradation of NP | | 0.691 | ERAM 1, 2, 4, 11 |
| ERAM 6 = Adaptation of exposure modeling tools | II | 0.686 | ERAM 1, 8, 9, 10, 11, 13, 14 |
| ERAM 7 = Ecotoxicity tests applicability to NP | | 0.682 | ERAM 11, 13, 14, 15 |
| ERAM 8 = Physicochemical properties agreement for ecotoxicity testing | | 0.675 | ERAM 3, 4, 6, 9 |
| ERAM 9 = Alternative ecotoxicity testing strategies | | 0.666 | ERAM 3, 6, 8, 10, 11, 12 |
| ERAM 10 = Agreed set of assessment endpoints for ecotoxicity testing | | 0.648 | ERAM 6, 9 |
| ERAM 11 = Risk quantification based on current scientific knowledge | III | 0.635 | ERAM 4, 5, 6, 7, 9, 13, 14 |
| ERAM 12 = Media specific ecotoxicity tests | | 0.630 | ERAM 1, 9 |
| ERAM 13 = Applicability of environmental exposure models | | 0.626 | ERAM 6, 7, 11, 14, 15 |
| ERAM 14 = Use of data on close analogues for ecotoxicity testing | | 0.600 | ERAM 4, 6, 7, 11, 13 |
| ERAM 15 = Agreed-upon definition for NP | | 0.582 | ERAM 7, 13 |

Bioaccumulation (ERAM 2) and biodegradation (ERAM 5) studies are two important criteria to support environmental risk assessment of NPs. Studies are required to evaluate the behaviour of a NP once it is released in the environment, especially how and if it is degraded, what paths characterize its exposure to organisms, how it can cross cell membranes and in what tissues it can accumulate [336-339]. Limited research has been conducted on the biodegradation of NPs [338, 339], whereas various studies emerged on their bioaccumulation [337]. They found that the NPs tend to accumulate more in daphnids rather than in fishes, possibly due to their uptake behaviour. However, it is stressed that the lack of standardized ecological accumulation test is a major hamper for data comparability. International efforts are in progress to fill these methodological problems and they are showing that the existing OECD test guidelines for bioaccumulation and biodegradation are not applicable to NPs, thus suggesting the need for new ones [334, 340]. This is due to the fact that some parameters only relevant at the nanoscale are not considered (or not enough in detail) in the existing guidelines, such as dissolution, heteroaggregation (i.e. agglomeration of NPs with naturally-occurring particles) or target species that might be more nano-relevant.

The hazard assessment based on current scientific knowledge (ERAM 4) ranks high due to the pressure for the identification of the ecotoxic principle, namely the constituent or the substructure that causes the ecotoxic effect, such as the surface area, the presence of impurities or the surface functionalization [119, 340]. Unfortunately, the identification of critical parameters that drive ecotoxicity is not close to achievement due to the lack of understanding of toxic behaviour of NPs and relevant measurement (characterization) techniques [334, 341].

The need for adapting the exposure modeling tools (ERAM 6) to tackle NPs uniqueness is the first parameter of the second importance sub-group and it is also correlated with all the higher ranked criteria (Table 5-9). Similar considerations emerged also in three recent relevant review articles [34, 149, 342]. Crucial aspects that future generation models need to be able to account for are the actual environment the NP can get in contact with (e.g. ionic concentration, the organic carbon content, pH, fulvic acid concentration) [42]. Experimental modeling results can fill several data gaps, since the use of expensive and time-consuming measurements equipment cannot be employed for all the potential exposure scenarios [335].

Applicability of the ecotoxicity tests (ERAM 7), the agreement on physicochemical properties for such testing (ERAM 8), the possible use of alternative testing strategies (ATS, ERAM 9) and the agreement on assessment endpoints (ERAM 10) are widely linked and complete the second importance sub-group (Table 5-9). Ecotoxicity testing methods for NPs are a topic of wide interest and debate since there is still limited scientific information about the interactions mechanisms of NPs with living systems, the influence of aggregation and agglomeration phenomena on NPs' physicochemical properties, the effects of different environments on their reactivity and the assessment endpoints for ecotoxicity testing, from the entities to be protected to the concerns or effects to be protected from [126, 334, 335, 341, 343, 344]. However, many international guidelines for toxicity testing in soil/sediment and water are considered as generally applicable to NPs, though specific amendments are missing due to limited knowledge on a variety of factors, including NP aging, dose metrics agreement (e.g. particle number, mass, surface area), nano-sensitive endpoints (e.g. uptake rate, internalisation rate, attachment efficiency), variability of tests results and tests applicability across different media types [334, 340, 345].

In order to aid the categorization of nanomaterials risk potential, alternative testing strategies (ATS) to NPs can be a viable solution. ATS include reduction of whole animal testing with in vitro and in silico approaches to generate data for hazard and risk assessment. In this regard, a recent categorization system has been proposed to support preliminary grouping of NPs to screen those of concern [346]. In the advanced decision-tree, adapted to carbon nanotubes, in vitro tests are the first Tier proposed to identify potential pulmonary toxicity. In the positive case, Tier 2 testing is undertaken to assess short-term lung injury potential. Lastly, if (and only if) the results of Tier 2 are positive, Tier 3 should be adopted, consisting in a 90-day inhalation study. This decision-tree based on ATS represents a cost-efficient and quick screening tool that has the potentials of reducing lengthy and expensive long-term testing for each NP that is developed.

The third criteria cluster incudes two indicators that account for the usability of available data, namely the risk quantification based on the current scientific knowledge (ERAM 11), and the applicability of available exposure modeling tools (ERAM 13) (Table 5-9). Risk quantification that relies on available information (ERAM 11) can be seen as a complementary tool to be aligned with the specific assessment under performance. A crucial issue in this case is the actual comparability of the results which is regularly hampered by different exo-toxicity tests, media conditions and target endpoints as well as physicochemical properties [121]. On the other side, current exposure modeling is based on parameters not tailored to NPs (e.g. dispersion, agglomeration), which leads to lack of correlations between the actual exposure levels to these products and the modeled ones [347, 348].

The development of ecotoxicity tests that account for the specificity of the environmental medium (ERAM 12) is another low importance parameter, with an RI of 0.630. Current review of OECD testing strategies is confirming the need for such tests since the stock dispersions preparation can result in NPs' properties modification (e.g. agglomeration, settling, surface chemistry, dissolution) and consequent incomparable ecotoxicity results [334, 340, 341]. However, the harmonization process for the pre-treatment procedures seems rather complex and far-away to come [334, 340], which justifies the position in the set.

#### *5.3.2.4 Human health risk assessment and management*

**Demographics, reliability and validity**

Similarly to the previous two areas more than 60% of the respondents had between 7 and 9 or more than 10 years of experience, with the scale of operation being either supranational or national for over 50% of this people pool (Table 5-10).

**Table 5-10: Years of experience and scale of operation of the respondents for human health risk assessment and management criteria (N = number of participants who replied), main survey**

| N | Years of experience | % | N | Scale of operation | % |
|---|---|---|---|---|---|
| 18 | ≤3 | 0.0 | 17 | Local | 11.8 |
| | 4-6 | 27.8 | | National | 29.4 |
| | 7-9 | 38.9 | | Supranational | 23.5 |
| | ≥10 | 33.3 | | Global | 35.3 |

The human health domain showed improvements from the pilot to the main questionnaire too. Firstly, the α increased from 0.827 to 0.962, but more importantly all the criteria reached a very satisfactory level of inter-item correlation, confirming that the 14 parameters that make up the scale can be seen as a cohesive set to move the human health risk assessment and management of NPs forward (Figure 5-7).

A similar distinction of criteria coverage shapes this risk research area as well. The exposure assessment is characterized by two crucial criteria, namely the knowledge about the exposure to the NP, as well as the risk management and communication strategies that are employed to limit it. The toxicity assessment-related criteria include several indicators that seek agreement among experts, being the relevant dose metric(s) and effective concentration, the physicochemical properties, assessment endpoints and applicability of existing and alternative approaches for toxicity testing, the possible use of data on close analogues and the properties extrapolation from non-nano to nanoscale. Furthermore the capacity to link NPs properties with ADME behavior, an agreed-upon definition of NP, the available hazard assessment and risk quantification based on current scientific knowledge complete the criteria set.

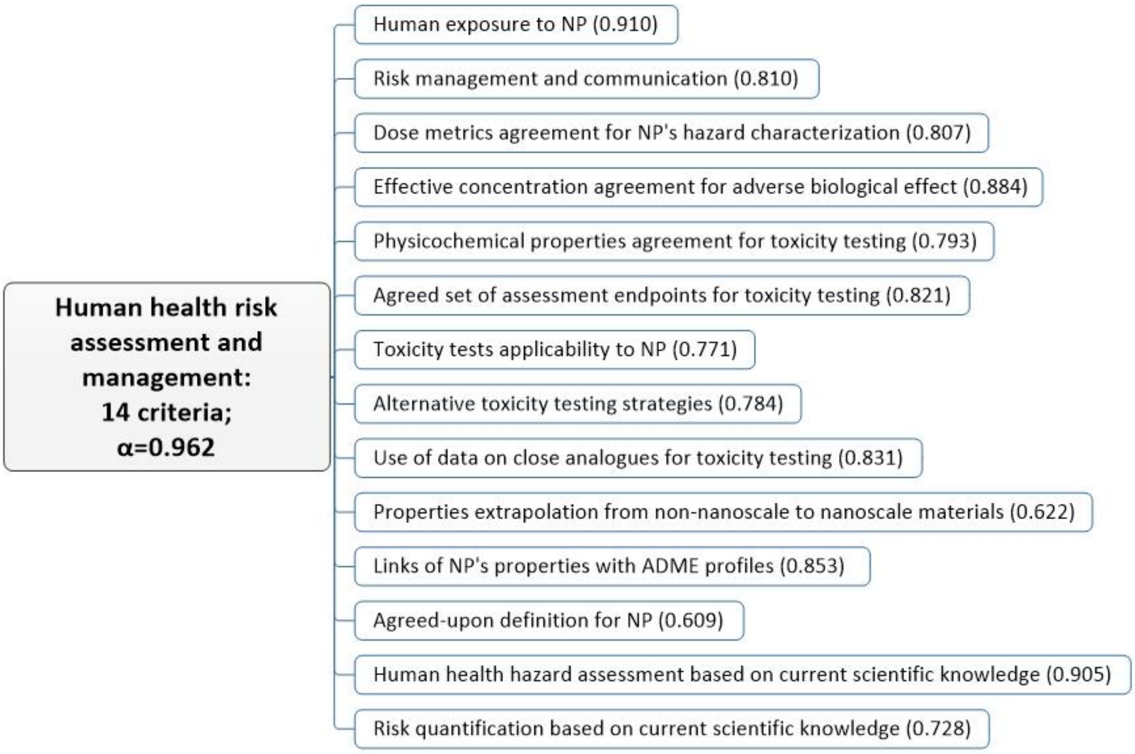

**Figure 5-7: Human health risk assessment and management criteria, α and relevant correlation with scale reported within brackets**

One respondent highlighted two issues that can be the focus of further study. The first one is the assessment of the impacts, named as indirect, on safety of materials and systems in contact with the NP. As an example, the possibility that nanomaterials enable toxins to enter into other parts of the body or undergo biochemical transformations that affect their toxicity and bioavailability should be a matter of investigation. The other aspect of interest is the effect of the impurities and the transformations that the NP is subject to during the life cycle stages. The practitioner stressed the fact that nowadays there is no information on the transformations that affect the NPs when they are produced with scaled up equipment, as well as how this influences the purity, durability and stability of the end products or byproducts at the nanoscale.

**Relative index and correlations**

Exposure of humans to the NP (HRAM = 1) and risk management and communication strategies (HRAM 2) are the first criteria in this area and they are highly correlated (Table 5-11), confirming that these assessments can be accurately conducted only if information on the exposure of the target organism is known and reliable. The achievement of such objective is hindered by the lack of agreement on the properties of interest from a nanotoxicological perspective (e.g. mass, particle number, surface area, surface charge, particle size distribution), which hampers the development of appropriate exposure measurement as well as health protection equipment and techniques [340, 349].

What is more, risk management and communication measures, including adoption of technical solutions and precautionary schemes to limit exposure play a discriminant role in human exposure settings. As far the occupational exposure is concerned, a lot of research is currently underway to verify the appropriateness of current technical and personal protection measures to NPs, confirming that a lot of fume hoods and respirators have good efficiencies and provide reliable protection, as well as gloves and aprons [350-352]. On the other hand, consumers' exposure research is more unstructured, due to the fact that information on the content of nanosized materials in products is usually not publicly known, which causes several difficulties in identifying the products to test and to track the potential concern to a specific good.

The development of an agreed-upon definition of NP (HRAM = 3) is ranked third, confirming its usefulness both from a risk assessment and a regulatory perspective, including the properties needed for the characterization [349]. There are currently several definition of NP intended as nanomaterial, which indicates that international bodies need to agree on a common definition to help harmonizing the understanding among practitioners in various parts of the world and help regulatory processes. This necessity is remarked by the experts working on the development of OECD guidelines for the identification of size and size distribution of NPs, who indicate the development of a well-understood and harmonized vocabulary as a first priority [341].

**Table 5-11: IL, RI and correlations of human health risk assessment and management criteria (N varies between 17 and 18; Discrimination threshold for criteria correlations was raised to 0.7 in order to aid data management)**

| Criteria | IL | RI | Positive correlation |
|---|---|---|---|
| HRAM 1 = Human exposure to NP | I | 0.718 | HRAM 2, 5, 6, 7, 8, 11, 12, 14 |
| HRAM 2 = Risk management and communication | | 0.700 | HRAM 1, 5, 6, 8, 12, 14 |
| HRAM 3 = Agreed-upon definition for NP | | 0.689 | HRAM 7, 9 |
| HRAM 4 = Alternative toxicity testing strategies | | 0.689 | HRAM 7 |
| HRAM 5 = Toxicity tests applicability to NP | II | 0.678 | HRAM 1, 2, 8, 11 |
| HRAM 6 = Links of NP's properties with ADME profiles | | 0.678 | HRAM 1, 2, 7, 8, 14 |
| HRAM 7 = Physicochemical properties agreement for toxicity testing | | 0.667 | HRAM 1, 3, 4, 6, 8, 9, 10, 12, 14 |
| HRAM 8 = Human health hazard assessment based on current scientific knowledge | | 0.646 | HRAM 1, 2, 5, 6, 7, 9, 11, 12, 13 |
| HRAM 9 = Agreed set of assessment endpoints for toxicity testing | | 0.643 | HRAM 3, 7, 8, 10, 11, 12, 14 |
| HRAM 10 = Dose metric agreement for NP's hazard characterization | III | 0.632 | HRAM 7, 9, 14 |
| HRAM 11 = Risk quantification based on current scientific knowledge | | 0.632 | HRAM 1, 5, 8, 9 |
| HRAM 12 = Use of data on close analogues for toxicity testing | | 0.632 | HRAM 1, 2, 7, 8, 9, 14 |
| HRAM 13 = Properties extrapolation from non-nanoscale to nanoscale materials | | 0.610 | HRAM 8 |
| HRAM 14 = Effective concentration agreement for adverse biological effect | | 0.567 | HRAM 1, 2, 6, 7, 9, 10, 12 |

The first IL group is completed by the ATS (HRAM = 4), which confirms the necessity for quick and testing-parsimonious categorization framework aimed at reducing expensive and time-consuming testing for every NP. ATS for human RA is strongly lined with the agreement on physicochemical properties for toxicity testing (HRAM = 7) as well as the endpoints agreement (HRAM = 9), once again underlying how these congruities are a necessity, not only to guarantee reliability of the approaches but also the comparability of the results [121]. Physicochemical properties that have received specific attention for supporting risk assessment are state of dispersion, aggregation and agglomeration of NPs, their size and size distribution, surface area and porosity and surface reactivity [341]. Development of guidelines for dispersion, aggregation and agglomeration and zeta potential of NPs are indicated as priorities by OECD. Particle size and particle size distribution measurements are a necessity for the reliability assessment of NPs and also for their toxicological assessment. A detailed analysis of the available methods has demonstrated that TEM and SEM are best candidates for spheroidal and non-spheroidal, agglomerated or aggregated nanoparticles. Regarding the surface area, a reliable method (i.e. Brunauer Emmett teller) is available, even though further testing with reference materials is required, together with transformed NPs that underwent modifications after release into the environment.

As far as the applicability of toxicity testing protocols is concerned (HRAM = 5), OECD test guidelines are considered to be applicable to NPs, although additional properties that can be of notable influence at the nanoscale must be accounted for too (e.g. surface area, surface charge, ADME profiles) [344]. Consequently, an evaluation of the adaptation of these guidelines is of paramount importance for risk assessment [341]. Furthermore, the fact that preparation of samples can affect the activity of a NP lead to the development of a specific guidance on the sample preparation and dosimetry [353]. Features of nano-relevance include: presence of impurities, surface functionalisation, nanomaterial changes during storage conditions, chemical composition of the media (i.e. ionic strength, calcium concentration and hardness, pH, dissolver organic matter, alkalinity and dispersing agents), samples characterization prior to administration (e.g. volumes used, sonication times, time lag between sonication and administration) [353].

The relatively high position of physicochemical properties (HRAM = 7) is justified by the fact that NPs toxic and exposure behaviour seems to be affected by properties that are commonly irrelevant or of limited influence for their macro-scale counterparts, which leads to the emergence of the need for identifying properties that can be insightful in the mechanisms of NPs interactions with organisms and that can help understanding the distribution and transformation of the materials under different exposure conditions [354, 355]. Number, surface area and mass are currently put forward as the properties of interest from a toxicological viewpoint [353]. Table 5-11 shows that a strong link is in place between this criterion (HRAM = 7) and the one a rank higher, the capability to link NP-specific properties to ADME effects (HRAM = 6), two conditions that would considerably advance the understanding of NPs behavior, effects and consequently the hazard assessment. The latter (HRAM = 8), based on available data, is a challenge for toxicologists due to the limited comparability of available studies (mainly caused by different toxicity tests and endpoints) and the difficult understanding of NPs behaviour in target organs and extrapolation of the findings to whole organisms [124]. This aspect has been pointed out especially in the nanomedicine area, stressing the fact that ADME profiles are very important but difficult to define even for specific NPs due to the transformations the nanomedicines go through in the body [333]. Furthermore, the properties of a NPs such as shape, size (distribution) and surface chemistry can be selective in the process of uptake in the human body [356, 357], and must be consequently accounted for during risk evaluation.

The group with the least important criteria includes two that are strongly correlated and still characterized by fervent discussion among practitioners, namely the agreement on dose metric for hazard characterization (HRAM = 10) and the agreement on the effective concentration for adverse biological effects (HRAM = 14). Currently, there is still no consensus on what metrics should be adopted to assess the concentration-dose-response functions and together with it the effective dose that determines an adverse biological effect [124, 126]. In the face of uncertainty NP number, surface area and mass are indicated as properties to be measured for the dose-response analysis [353]. The relevant dose depends also on the assessment endpoints to be selected (HRAM = 9), which must be agreed and standardized to guarantee results comparability. The strong correlations between these parameters confirm such viewpoints (Table 5-11).

In this importance set there are three other criteria that are still characterized by ambiguity and lack of clarity in terms of their practical usefulness for human health risk assessment. They are the risk quantification based on current information (HRAM = 11), the utilization of read across approach (HRAM = 12) and the extrapolation of properties from non-nanoscale to their nanoscale counterpart (HRAM = 13). These three criteria are limited by the lack of studies comparability to support risk quantification, understanding of physicochemical properties responsible for hazard, exposure or risk potential that can support extrapolations from different nanomaterials, as well as from the macro-form of the NP to its nano-form.

#### *5.3.2.5 Social implications*

**Demographics, reliability and validity**

The area of social implications gathers practitioners who are mainly focused on a supranational scale (i.e. 41.7%) and out of the twelve respondents 33.3 % have between seven and nine years of expertise and 25% at least 10 years (Table 5-12).

**Table 5-12: Years of experience and scale of operation of the respondents for social implications criteria (N = number of participants who replied), main survey**

| N | Years of experience | % | N | Scale of operation | % |
|---|---|---|---|---|---|
| 12 | ≤3 | 25.0 | 12 | Local | 25.0 |
| | 4-6 | 16.7 | | National | 16.7 |
| | 7-9 | 33.3 | | Supranational | 41.7 |
| | ≥10 | 25.0 | | Global | 16.7 |

α for social implications criteria is highly satisfactory, with a score of 0.912. What is more, all the criteria correlations (Figure 5-8) indicate relevant measurement of the same psychological variable.

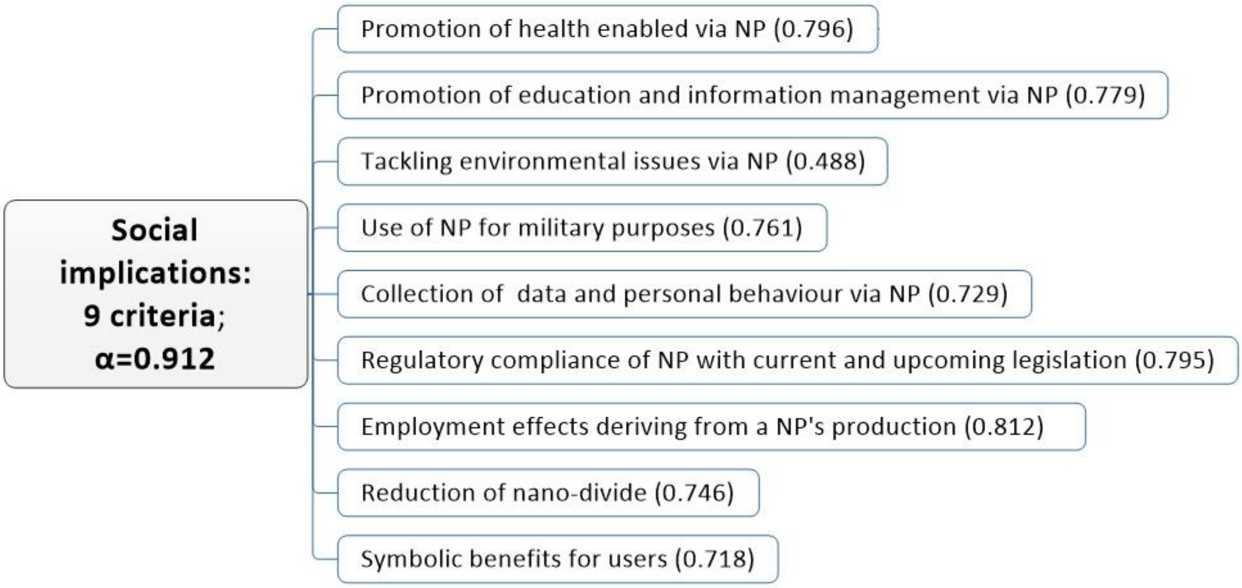

**Figure 5-8: Social implications criteria, α and relevant correlation with scale reported within brackets**

The widespread use of NPs in many industrial sectors is reflected in various criteria assessing their social implications, including the promotion of health, education and information management as well as the advancement of tools to tackle environmental problems. There are also more controversial implications that NPs can have on society and these are accounted for by the criteria considering the use of NPs for military purposes and also to collect private information as well as track individual behavior.

A lot of research and discussion has been placed on the need for rendering the use of NPs as responsible and reliable as possible, a topic considered in the framework by the criterion assessing regulatory compliance of NP with the current or upcoming legislation. The broad spectrum of social implications criteria is completed by the employment effects that can be determined by a NP production, the possible reduction of technological imbalance between developed and developing countries (i.e. nano-divide) and the symbolic benefits that users can obtain from the use of a NP, such as prestige.

The validity of this area was confirmed by comments of the main survey respondents (Appendix A.7). As possible complementary criteria one of them indicated that the general public knowledge and awareness of nanotechnology, its products and possible social, environmental implications is very important. In order to achieve this objective, it is primarily the task of public and governmental organizations to gather such information and make it easily available to the public. In addition, another viewpoint was proposed by a respondent, who stressed the importance of looking at NPs from a balanced perspective in terms of net gain or impact that each one can have on society. As an example, in the case of diesel vehicle emission, use of nanomaterials as cerium [358], reduce the amount of certain high-concern gases (such as greenhouse ones) but result in higher emission of other air pollutants, confirming the need for additional studies to evaluate the overall benefits and risks of using NPs for tackling environmental and health and safety-related problems.

**Relative index and correlations**

From a social perspective, nanotechnology has remarkable potentials of improving the way we live and providing us with tools to tackle problems that humanity can face in a much more effective manner. Nanomaterials are used in a lot of products nowadays and are expected to be even more influential in many sectors including agriculture, electronics, construction, cosmetics, medicine and environmental remediation [9, 10]. These nano-enabled products affect (and will increasingly do so in the future) society. In order to render this process as responsible and reliable as possible the legislation has to be efficient, effective and appropriate for the type of these new goods [41]. This priority finds confirmation in the responses from the experts, placing the regulatory compliance of NPs (SI = 1) at the top. This shows the relevance and importance of this topic as well as the mounting discussion at the global level, with main international bodies in the process of developing and adapting existing legal frameworks for these new types of materials with unique properties. A major European example is the REACH regulation for NPs, for which best practice guidance for registrants has recently been issued [347]. One main initiative that can aid the regulatory efforts is the use of reference materials to develop the assessment tests [341]. Furthermore, regulatory needs include (i) methods that are relevant, sensitive and accurate for specific measurands (e.g. number, size, surface area, volume); (ii) tailoring statistics appropriate for the measurand and its uncertainty; and (iii) adopting well-understood and harmonized vocabulary.

**Table 5-13: IL, RI, and correlations of social implications criteria (N varies between 9 and 12)**

| Criteria | IL | RI | Positive correlation |
|---|---|---|---|
| SI 1 = Regulatory compliance of NP with current and upcoming legislation | I | 0.850 | SI 3, 4, 5, 6, 7, 9 |
| SI 2 = Tackling environmental issues via NP | | 0.782 | SI 6, 7 |
| SI 3 = Use of NP for military purposes | | 0.764 | SI 1, 5, 8, 9 |
| Si 4 = Promotion of health enabled via NP | II | 0.682 | SI 1, 6, 7, 9 |
| SI 5 = Collection of data and personal behavior via NP | | 0.673 | SI 1, 3, 6 |
| SI 6 = Reduction of nano-divide | | 0.600 | SI 1, 2, 4, 5, 7 |
| SI 7 = Promotion of education and information management via NP | III | 0.582 | SI 1, 2, 4, 6, 9 |
| SI 8 = Employment effects deriving from a NP's production | | 0.556 | SI 3, 9 |
| SI 9 = Symbolic benefits for users | | 0.435 | SI 1, 3, 4, 7, 8 |

At the second rank there is a criterion that represents the potentials of nanotechnology to support tackling major problems that humanity faces (SI = 2), in fact nano-enabled applications can be used for pollutants degradation, pollutants monitoring and energy production [359-361]. Some of these applications can also reduce the "nano-divide" (i.e. technological imbalance between developed and developing world) (SI = 6) since they can be seen as primarily tailored for the developing world rather than the developed one, such as off-grid photovoltaic panels and drugs relevant to illnesses in emerging countries (e.g. HIV) [19, 20]. This link is sustained by the correlations between these criteria in the survey (Table 5-13).

NPs can cause risks not only from a toxicological standpoint, but also from a broader societal perspective, considering that nano-enabled applications are developed for military purposes (SI = 3) [19, 20, 22, 43, 362], an unquestionable matter of ethical controversy [60, 363, 364]. An interesting link emerges in Table 5-13 between this criterion (SI = 3) and the one referring to the contribution that NPs can make in collecting personal data or tracking individual behavior (SI = 5), ranked fifth and belonging to the second importance sub-group. Products enabled through nanotechnology can aid retrieving highly sensible personal information that might support military operations, such as espionage activities, terrorism control or more precise targeting (with less collateral damage) [328]. The management of information that this technology supports can lead to social concerns also in the medical field, where data retrieved from devices for medical diagnosis can be misused and cause ethical issues in medical insurance, employment or prenatal diagnosis [20], or support undetectable surveillance of average citizens [328].

Another criterion that received a relatively high position is the promotion of health via NPs (RI = 0.682; SI = 4). Nanomedicine is a main branch of nanotechnology with huge number of applications in use or under development, from nanodrugs to high-resolution microscopes [333]. Many of these products have concrete social benefits, with two examples being more effective cures for diseases as HIV [365] and Alzhemier [366].

In the least IL there is the one considering employment effects determined by the NPs production (SI = 8), a parameter difficult to measure due to the huge complexity that underpins the understanding of the number of jobs that are created directly and indirectly as a result of a certain NP [2, 22, 43, 367]. This issue emerged in a recent project (i.e. SUNPAP) that tried to account for the employment effects determined by nanocellulose production and application along the value chain [318].

Lastly, from an “individual” perspective, nanotechnology can bring symbolic benefits such as prestige and identify creation, resulting from the possession and use of NPs, as it can be an antibacterial T-shirt embedded with nanosilver or a tennis racket reinforced with carbon nanotubes [5, 22, 43]. This is the least important parameter in the list (SI = 9), however it is linked with many others in the set, suggesting that the large scale benefits of NPs can mirror their effects on the single individuals.

#### *5.3.2.6 Technical performance*

**Demographics, reliability and validity**

The last sustainability area of the framework, technical performance, had 56.3% of technical performance respondents with at least 10 years of experience and out of the whole set operational scales were primarily supranational (26.7%) and global (46.7%) (Table 5-14).

**Table 5-14: Years of experience and scale of operation of the respondents for social implications criteria (N = number of participants who replied), main survey**

| N | Years of experience | % | N | Scale of operation | % |
|---|---|---|---|---|---|
| 16 | ≤3 | 6.2 | 15 | Local | 20.0 |
| | 4-6 | 12.5 | | National | 6.6 |
| | 7-9 | 25.0 | | Supranational | 26.7 |
| | ≥10 | 56.3 | | Global | 46.7 |

This domain reached a satisfactory level of internal consistency (Figure 5-9) as well, with only one parameter resulting as an outlier (i.e. reusability) and no further criteria suggested as missing. The criteria that compose this area are focused on one side on the technical properties of the NP and on the other on the processes employed for the manufacturing of these products. In the first sub-set the properties are the durability, functionality, maintainability, recyclability and reliability of the NP. In the other sub-set the method of manufacturing as well as its stage of technological maturity complete the reliable set of criteria together with the quality of reproducibility of characterization technique.

The internal consistency test indicates that the concept of reusability cannot be included as a characteristic of general technical performance for NPs. This can be explained by the fact that there are some application areas, such as the biomedical or the electronic ones, where such type of performance is not considered at all. This indicates that reusability does not satisfy fully one of the selection criteria requirements adopted to identify the framework parameters, which was the wide applicability of the criteria to the whole set of target objects.

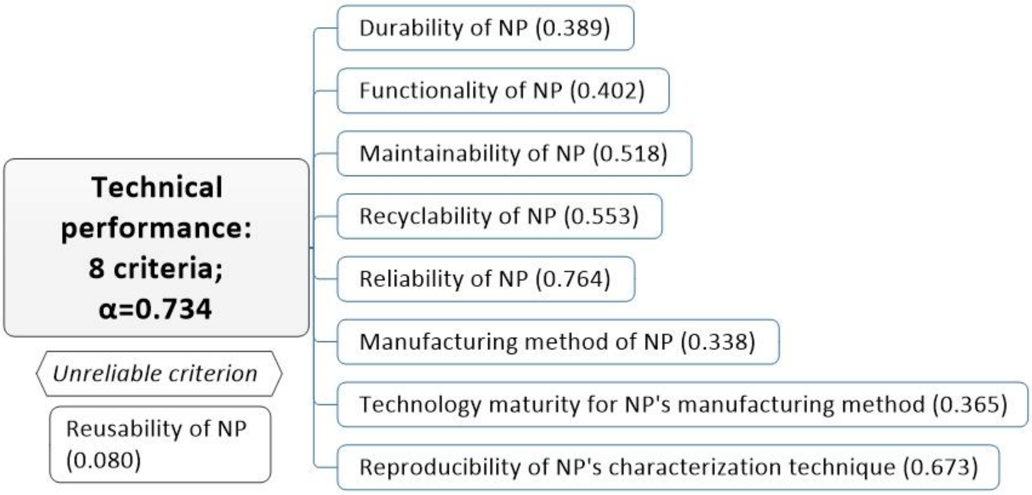

**Figure 5-9: Technical performance criteria, α and relevant correlation with scale reported within brackets**

### Relative index and correlations

Characterizing NPs in a reproducible manner (TI = 1) and manufacturing them with reliable properties (TI = 3) stand at the summit of ILs for this scale, with a very high correlation too (Table 5-15). Due to the uniqueness of NPs, re-assessing current instrumentation suitability for their properties understanding is a pressing priority. This is an international effort currently under way, with the interdependence of these two concepts confirmed by the OECD too [341]. In fact, reproducibility of characterization techniques has a straight effect on the reliability of NPs, driving the quality assurance that nanotechnology has to focus on. Priorities in this regard are the validation of the methods by means of reference materials, including techniques for handling measurement uncertainty. Issues to be tackled in order to provide reproducible characterization techniques and consequently reliable NPs include (for particle size studies) [341]:

- Effect of particle shape on measurement results (spheroidal vs non-spheroidal);
- Method capability of discerning between single particles and agglomerates or aggregates;
- Influence of sample preparation, including test concentrations;
- Identification of complementary method for confirmation check;
- Influence of biological, environmental and toxicological tests on methods' results;
- Applicability to mixtures of particles.

SEM and TEM emerge as favorites both for spheroidal, non-spheroidal and aggregates.

“Functionality” criterion (TI = 2) also receives a high RI, supporting the literature that stresses the need of producing NPs that perform a certain function comparable with the one that a product without the nanomaterial does equally [5, 20, 22, 43, 44, 368, 369]. In fact, the tremendous interest in nanotechnology-enabled products has been the improvement in properties that the materials at the nanoscale can determine [5, 9].

**Table 5-15: IL, RI and correlations of technical performance criteria (N varies between 12 and 16)**

| Criteria | IL | RI | Positive correlation |
|---|---|---|---|
| TP 1 = Reproducibility of NP’s characterization technique | I | 0.880 | TP 3, 7 |
| TP 2 = Functionality of NP | | 0.875 | |
| TP 3 = Reliability of NP | | 0.867 | TP 1, 8 |
| TP 4 = Manufacturing method of NP | II | 0.772 | TP 9 |
| TP 5 = Recyclability of NP | | 0.754 | |
| TP 6 = Maintainability of NP | | 0.743 | |
| TP 7 = Technology maturity for NP’s manufacturing method | III | 0.713 | TP 1 |
| TP 8 = Durability of NP | | 0.700 | TP 2 |

The method of NP manufacturing also received a relatively high rank (TI = 4), which is a driving factor for the widespread diffusion of NPs. A plethora of manufacturing methods are currently emerging for NPs, varying for the type of the target object, such as one-dimensional, two-dimensional and three-dimensional and also the type of techniques, bottom-up and top-down [10]. Their development stage is largely uneven, with some being available commercially as it is for atomic layer deposition, laser ablation, lithography, while others still at a laboratory phase stage, such as microwave irradiation and electrospinning [18, 370]. The success of failure of most of these methods in the long term will depend on the ability to manufacture products that meet the stringent requirements of reliable functionality and increased processes yield [18]. Furthermore, the technology for the manufacturing of a NP is of paramount importance for the possibility of scaling up the production on an industrial scale [371]. This perspective is the driving force for the activities of the Centre for High-rate Nanomanufacturing at Northeasterner University [372], a facility focused on developing high-rate and high-volume manufacturing of NPs based on direct assembly and transfer techniques. Additional factors that affect the performance of manufacturing methods are also the processes safety, the simplicity of operation and the length of each reaction.

“Recyclability” (TI = 5) scores in the middle-importance set in the list and it received a lot of attention in the literature [5, 20, 22, 23, 25, 44, 51, 117, 331]. Potential options to aid the recyclability are [23]: (i) limiting the number of employed materials, (ii) adopting segregation/modular waste collection, and (iii) minimizing use of additives and contamination with impurities. Recycling of NPs is seen with concern, because they add complexity to the products which causes additional problems during recycling, both from a technical and economic perspective [46].

Maintainability (TI = 6) and durability (TI = 8) of NPs have also emerged as reliable technical criteria, but relatively less important than the ones discussed above. Its rationality resides in the fact that applications need first to improve the functionality compared to the non-nano enabled product, be reliable and if possible, improve longevity and reduce upkeep [5, 20, 44, 317]. Likewise, reliability and durability are statistically correlated (Table 5-15), an interdependence that can be a synergistic success factor for NPs. The maturity of manufacturing methods is in the least importance group (TI = 7), suggesting that practitioners consider the type of method adopted together with its reliability of higher interest rather than the development stage it is at.

## 5.4 Summary

Nanotechnology encompasses a wide range of sectors at different advancement stages in the value chains. However, its widespread development is hindered by technological hurdles and by the unclear and pervasive implications that it can cause on society, economy and the environment. Assessing sustainability implications of NPs is inherently dependent on the availability of a comprehensive and reliable set of assessment criteria to evaluate the implications of NPs. Such set was currently missing and the third objective of the thesis became its development.

The MCDA process was used as a methodological basis and it was implemented through a three-phase procedure to achieve the research objective. Extensive literature review from Chapters 2-4 was used to shape and define an initial set of assessment criteria (phase 1) and then a questionnaire was developed to collect opinions of experts and practitioners in the area of sustainable nanotechnology about the relevance and importance of the criteria that can be used to understand the implications that NPs have on sustainability (phase 2 and 3). This procedure allowed developing a comprehensive and reliable framework of 68 sustainability criteria for NPs, based on the integration of literature review findings and the knowledge of 119 experts and practitioners in the sustainable nanotechnology domain, which accounted for more than 1,500 years of cumulative experience.

The framework is divided in six areas, the research domains studying implications of NPs that emerged in the last fifteen years: (i) economic performance; (ii) environmental impacts; (iii) environmental risk assessment and management; (iv) human health risk assessment and management; (v) ethical, legal and social implications; and (vi) technical performance. For each area the reliability of the criteria was assessed through internal consistency check and the validity by means of content analysis. Furthermore the criteria ranking and their correlations were derived with RI and gamma coefficient techniques, respectively.

The economic performance domain (*framework area I*) is composed of nine criteria, with the economic viability of manipulation processes as well as manufacturing and raw materials costs rated as highly important and strongly interrelated. This is due to the fact that many of these processes rely on materials that suffer from limited availability and almost monopolized offer, which causes unpredictable prices fluctuations and consequently limited raw materials costs stability. An additional aspect of high priority is the collaboration embedment among various actors along the value chain of NPs, especially due to the multi-sectorial nature of nanotechnology.

The survey also highlighted the importance that companies place on their financial investments to handle the public perceptions of NPs, a very sensible topic that can be subject to manipulation from those pro-nanotechnology and those against it. As a matter of fact, much of the success and failure of products depends on their publicity, which justifies the attention of companies to provide the “right” image to their goods. On the contrary, the external social costs on human health and the environment are ranked low, possibly due to current unreliability and limited applicability of such monetization techniques.

Assessment of environmental impacts of a NP (*framework area II*) requires particular attention on the organization of the supply chains, especially when hazardous materials are used or produced during these processes, since many have a constrained availability of raw materials and are thus facing risks for resources availability. Waste generation is also a chief priority, mainly due to the low efficiency of processes that involve manipulation of NPs and consequently cause inefficient use of resources.

Environmentally friendly nanotechnology must be based on a management system where the evolution of local renewable resources demand is aligned with reduced energy consumption and highly energy and materials efficient processing along the life cycle. Reduced energy consumption and high materials and energy efficient processes must be a focus due to the fact that several NPs production processes go in the opposite direction due to highly incomplete conversion of reactants caused by the loss of precursor materials through the exhaust system and their deposition on the reactor ceiling.

The third area of the framework is the environmental risk assessment and management (*framework area III*), with the need for a reliable characterization and understanding of the environmental exposure to NPs emerging as highest importance, an aspect strongly correlated with the capacity to study the interdependent mechanisms that cause NPs modifications once released in the environment (e.g. biodegradation, bioaccumulation). Another topic of major interest is the identification of critical parameters that drive NPs ecotoxicity, currently an open issue due to the lack of understanding of ecotoxic behaviour and relevant characterization techniques. The respondents confirm that in order to start prioritizing NPs of high toxic concern, alternative testing strategies based on tiered testing approaches can be employed, thus providing cost-efficient and quick screening tools with the potentials of reducing lengthy and expensive whole animal testing with in vitro and in silico approaches to generate data for hazard screening assessment.

A further priority for environmental risk assessment is the development and adaptation of exposure modeling tools. This would provide invaluable support for this research area, since the use of expensive and time-consuming measurements equipment cannot be expected in all the potential exposure scenarios that will involve NPs.

The human health risk assessment area (*framework area IV*) shows similar patterns as the environmental one, especially in terms of the need for developing reliable strategies to quantify the exposure to NPs. Such objective can be achieved only when a broader consensus on the exposure metrics (i.e. properties of interest also from a toxicological perspective) will be reached, since the development of sensitive and reliable analytical instrumentation is expensive and time consuming, suggesting that companies might not be willing to invest high capitals in tools that could not have a wide market. A strong correlation emerged with the use of risk management and communication measures, which confirms the necessity of continuing verifying the appropriateness of current technical and personal protection measures to NPs and the effectiveness of precautionary approaches.

Respondents for the human health risk assessment domain rated at a relatively high position criteria related to agreements among practitioners, namely applicability of toxicity tests, capability to link NP-specific properties to absorption, distribution, metabolism and excretion effects, physicochemical properties for toxicity testing, hazard assessment information available as of current knowledge and a granted cluster of endpoints for toxicity evaluation. The achievement of such goal is drastically relying on the comparability of the results, which is in this case dependent on the preparation of samples. In fact, there are several nano-specific factors that can alter the NP properties and behavior, hampering any results comparability, such as the presence of impurities, the surface functionalization, effects of storage on nanomaterial, chemical composition of the media and samples characterization prior to administration.

Broad ethical, legal and social implications of NPs are covered in the fifth area (*framework area V*), which sees the role of regulatory compliance of NP as the first prerogative, with three specific needs that include (i) reliable, sensitive and accurate methods for specific measurands, (ii) reliable statistics for such measurands and (iii) an agreed-upon vocabulary for nanotechnology.

Another foremost prerogative for evaluating the social implications of NPs is the development of nano-enabled solutions to tackle environmental issues, especially for the reduction of technological imbalance between developed and developing countries. Successful examples include off-grid photovoltaic panels, HIV-specific drugs, pollutants degradation and monitoring devices.

Additional issues of primary interest from a societal perspective are the contributions that NPs can make in the area of military equipment and personal data management, from high precision weapons to very efficient targets tracking instruments. The survey also highlighted the high expectations that reside in the contribution of NPs to health promotion, including the development of drugs much more efficient and safe than the current ones and also the improvement of microscopies resolution capacities.

The technical performance area completes the criteria set (*framework area VI)*, with the quality assurance leading the set, including functionality and reliability of NP together with reproducibility of characterization techniques. Top precedence emerges for the latter criterion since accurate characterization is paramount for guaranteeing NP reliability. Strategies to aid this process include the investigation of particle shape on measurement results, capability of discerning between single particles and agglomerates or aggregates, identification of complementary characterization methods, effect of biological, environmental and toxicological tests on techniques' suitability and applicability to mixtures of particles.

The functionality of the NP ranks second, indicating that it is really the performance of the target function which will determine the success or failure of this emerging technology. Nonetheless, the reliability and functionality of NP needs to be ensured by the type of production processes, another criterion that received a relatively high rank. This is salient from a scalability perspective, as there are many nanomanufacturing techniques that are still at a laboratory phase stage and their large-scale production potentials has still to be demonstrated.

On the whole, this study demonstrates that a three-phase research procedure based on the MCDA process was a powerful and effective research tool for the analysis, both from a quantitative and a qualitative viewpoint, of the knowledge and opinions of key informants in the area of sustainable nanotechnology. The pilot questionnaire phase was crucial for testing the appropriateness of the organization of the framework in six areas, the identification of the criteria that needed rephrasing or elimination and those that were missing to complete the evaluation set. The main questionnaire was then used to validate the consistency of the criteria in each sustainability area, to rank the criteria according to their relative importance and to identify the correlations between each other.

The present study has two limitations that can be seen as proposals for future research. First, the pool of respondents could be expanded by including additional experts in each area of the framework in order to increase the credibility of the results and further verify the completeness, reliability and validity of the criteria. Second, the survey could be structured in order to include the perspectives of other stakeholders such as single individuals, NGOs and governmental agencies, to study which criteria they would consider worthy of analysis.

The research described in this chapter fulfilled the third objective of this Ph.D. thesis, by developing a reliable and comprehensive framework of SA criteria that those who work in nanotechnology can use to move its development on a sustainable and responsible path. However, DMs in this area struggle in making informed choices without appropriate decision support tools, considering the complexity of the information conveyed by the variety of assessment criteria and the difficulties in integrating the wide array of information they represent. Following such reasoning the construction of evaluation models and provision of decision recommendations are needed to offer complete decision aid for DMs in this domain, which aims to be a focal contribution of this Ph.D.

Consequently, the next two Chapters (6 and 7) are devoted to this goal which is also the last objective of the thesis; i.e. the development of design guidelines that can be used as a classification model to support the greener synthesis of nanomaterials. The MCDA process is used as the underlying framework to achieve such objective through the integration of fragmented published information with experts' knowledge.

# Chapter 6. A Green Chemistry-based Classification Model for the Synthesis of Silver Nanoparticles

## 6.1 Introduction

The third objective of this Ph.D. thesis, namely to advance a comprehensive set of SA criteria for NPs, was achieved in Chapter 5. This contribution to knowledge is important considering that such a set was missing and practitioners can now choose reliable and internationally agreed evaluation parameters for their studies. However, the standpoint adopted in this research project is that the sustainable development of NPs is also dependent on the availability of decision support tools to help those who are responsible for making decisions in the respective domain.

In this regard, in order to aid practitioners in the area of sustainable nanotechnology, there have been specific calls for (i) the development of lists of sustainability-oriented design practices and standards to define products as “green nano” [16, 29, 30, 373] and (ii) design rules for new classes of nanomaterials that have desired properties in conjunction with the implementation of the principles of green chemistry [24, 30, 32].

These requests can be interpreted as the need for a robust classification model from the MCDA perspective, where the fulfilment of certain synthesis conditions (i.e. design rules) trigger assignment of a “green” label (i.e. class) for the NP synthesis. This research gap is in line with the goal of supporting responsible development of NP, which is also the aim of this Ph.D. thesis. Consequently, the development of such a robust model became the fourth objective of this research project. This chapter (6) describes the development of the model while its robustness assessment is reported in detail in Chapter 7.

One of the life cycle stages that received mounting attention in nanotechnology over the last decade is synthesis, as the need to steer its development on a more sustainable path has grown as a pressing issue [16, 24, 25, 30, 33, 373-375]. Presently, a lot of synthesis protocols for nanomaterials are based on existing industrial processes, which were developed with little consideration for sustainability. Typical conditions include the use of high pressures and temperatures and the use of toxic chemicals [374]. Laser ablation, hydrothermal and solvothermal processes and colloidal methods are some popular choices [376, 377]. A wide variety of techniques have been proposed to produce metal nanoparticles, including chemical reduction [378-380], electrochemical and photochemical reduction [381-383], sonochemistry [384] and heat evaporation [385]. Chemical reduction has been the most common route due to the convenient operation, simple equipment, cost effectiveness and process control [377, 386, 387].

There have also been calls for the development of nanomaterials on the basis of the principles of green chemistry [388] and engineering [389], and a variety of studies have consequently emerged [24, 388, 390-392]. Some of the proposed solutions are based on the substitution of reagents with more benign counterparts such as supercritical fluids and solvent-free techniques [16, 24]. In this regard, a lot of interest has been placed on developing more environmentally friendly synthesis for silver nanoparticles, due to the wide variety of potential applications that these nanomaterials can enhance, including biosensor materials, composites, cosmetics, antimicrobial applications and electronic appliances [393, 394]. The next section outlines the synthesis methods for nanomaterials that have been developed to include the principles of green chemistry [388] into this life-cycle stage.

### 6.1.1 Targeting sustainability with nanosynthesis

The synthesis step has a pivotal role in determining the properties of the ensuing nanomaterial, its reliability and also the impacts that it can have from a sustainability perspective [18]. The development of nanomaterials fabrication is in continuous growth and the processes that received major attention in the last decade are those performed with more responsible, green and sustainable approaches [32, 370, 374, 390, 395-397]. These emerging protocols integrate the principles of green chemistry, green engineering and sustainability in the nanosynthesis practice. The following sub-sections summarize some of these emerging approaches, emphasizing how the bio-inspired routes employing plants are the most promising from a scale-up viewpoint.

#### *6.1.1.1 Template methods*

1-D nanostructures can be prepared with templates or scaffolds that allow tailoring the size and shape of the desired materials [398]. Precursors are mixed in customized structures where reactions take place in confined spaces so that the resulting nanomaterial has the same size and morphology of the template. The templates provide a delimited space where to grow the nanomaterial, without the need of surfactants and capping agents, leading to reductions of materials use and waste [390]. Environmental benefits of this technique are that reactions can be performed at room temperature, ambient pressure, require short reaction times and do not employ toxic and hazardous chemicals [390].

#### *6.1.1.2 Ultrasound-based methods*

Hazardless ultrasound irradiation is a versatile nanosynthesis technique that is used to produce nanomaterials of various size, shape, morphologies and cristallinity [399]. The ultrasounds cause the formation, growth and collapse of bubbles during the reaction in the solution. Chemical bonds are broken due to the very high temperature (4,700-25,000 °C) created during the irradiation period, which is followed by a very fast cooling rate (over $10^{11}$ °C/s) that leads to the production of crystalline and amorphous nanoparticles [399]. Successful preparation of monodispersed noble metal nanomaterials has been reported for Au [400], Ag, Pd, and Pt [390].

From a green chemistry perspective, sonochemistry is a viable opportunity since it uses energy much more efficiently than conventional wet chemistry heating techniques, it improves product yields and reduces waste [390].

#### *6.1.1.3 Microwave-based methods*

Microwave (MW) was introduced as alternative source of energy for the rapid synthesis of well-defined nanosized particles. Microwaves have frequencies between 300 MHz and 300 GHz which are used to drastically increase reactions speeds compared to conventional heating techniques [401]. MWs are used to evenly heat a reaction solution, resulting in uniform nucleation and growth conditions [395]. Nanomaterials with various shapes and sizes can be produced with MW by varying the metal precursor concentrations, the reaction time, the temperature and the reducing (and capping) agent [375, 395, 396]. Silver nanomaterial production with microwave technique has been widely investigated [402].

Microwave has several advantages compared to conventional heating techniques, leading to reduction in energy consumption, waste prevention and elimination of hazardous chemicals [395-397, 401, 403-405].

#### 6.1.1.4 *“Enhanced” traditional methods*

Traditional techniques, such as oil bath, hydrothermal and solvothermal procedures, will still represent major sources of nanomaterials in the future and for this reason solutions tailored to improve their environmental friendliness have been proposed. The substitution of hazardous chemicals with greener alternatives has been of great interest for chemists and engineers. Ionic liquids (ILs) are one example, organic salts with melting points under 100 °C, with good solvent properties, very low vapour pressure and flammability. Elemental metals of various nature, at the nanoscale and mondisperse, were prepared with ILs including Au [406], Ag [407], Fe [408], Pt [409] by reduction with metal salts or decomposition of organometallic compounds.

ILs have a double advantage as they allow maintaining the catalytic properties of the particles by means of weak bounds on the surface, but at the same time they stabilize the particles, preventing aggregation [390, 408].

#### 6.1.1.5 *Bio-inspired methods*

A wide variety of “alternative” raw materials have been employed to produce nanomaterials so far, including bacteria, fungi, plants, plants extracts, yeasts and algae [375, 376, 410], receiving the label of bio-inspired reduction approaches. They have the potentials of implementing several principles of green chemistry, including renewable materials use, synthesis at ambient temperature and pressure as well as safe processing conditions [375, 378, 411]. An overview is presented below.

**Fungi**

Fungi produce nanomaterials through reduction processes that take place in the cell wall, in the cytoplasmic membrane and also on the inner surface of their cells. They perform both reducing and capping agent functions. A wide spectrum of nanomaterials have been produced via this synthesis route, including metal oxides of $Fe_3O_2$ [412], $SiO_2$ [413], $Bi_2O_3$ [414] and barium titanate [415] as well as silver nanoparticles [416, 417], all processed at mild temperature without the need of additional chemicals.

**Bacteria**

Growth of nanomaterials has also been reported in bacteria cells, which actually preserve their viability after the particle formation. Ag, Au nanocrystals, CdS quantum dots, Pt nanoparticles, were produced successfully even though the processes required long reaction times in the order of days [418-421].

### Algae

Algae, such as diatoms, can produce nanomaterials as well through their biosilicate cells that are composed of nanosized slits and pores between 10 nm and 1,000 nm [376]. These nanosized bio-minerals are produced inside deposition vesicles starting from silicic acid solution. As an example Ag (7-16 nm), Au (6-10 nm) and bimetallic (17-25 nm) nanoparticles were obtained from *Spirulina platensis* in 120 h at 37 °C [422].

### Plants

Scalable synthesis processes for nanomaterials need to satisfy the requirements of quick reactions completion, simplicity of operation and cost efficiency in order to be competitive with traditional methods [378]. The bio-inspired processes listed above (i.e. fungi, algae and bacteria) do not satisfy these prerequisites whereas the production via plants and plants extracts do [374]. This is the reason why over the last decade a lot of research has been focused on expanding this synthesis technique and understanding the optimal reaction conditions [378].

Depending on the renewable material source and the operating conditions, nanomaterials of different shape and size can be obtained including spherical, rod-shaped, flat sheets and triangular [391, 423]. What is more, the combined use of alternative energy sources as microwave technology and also waste material (e.g. grape pomace) can further enhance the attractiveness of these processes since reaction times can be reduced to the order of minutes and by-products can became high value raw materials [424, 425].

Critical factors that affect nanoparticles properties are the size, shape and monodispersity [426]. Consequently, the development of synthesis protocols that enable controlling these parameters is of vital importance [410]. This applies to bio-inspired reduction protocols, and it is one of the reasons why researchers have examined different synthesis routes aimed to optimize the synthesis process including choice of feedstock, pH, reaction time, temperature and pressure, precursor concentrations and MW irradiation/agitation [374, 378, 426].

One of the drawbacks of the use of microorganisms to synthesize nanoparticles is the longer time period required in comparison with conventional techniques [426]. Different considerations emerge from the studies using plants and plants extracts, where it has been shown that the reactions can be as low as a few minutes and be optimized more easily than the other bio-inspired routes. Hence these processes can be considered as more cost effective, environmentally friendly and best candidates for scale-up and industrial synthesis of nanomaterials [375, 378, 411].

A research gap that emerged from the review of this literature and which has also been highlighted by experts in the area as Prof Hutchinson [24, 33, 62] and Ms Bergeson [29] as well as professional organizations (e.g. American Chemical Society [30]) and governmental agencies (e.g. US Environmental Protection Agency [50], German Federal Ministry for the Environment, Nature Conservation, building and Nuclear Safety [22, 23]), is that there are currently no design guidelines that can be used as reference handbook to aid decision-making for the greener production of nanomaterials and assign a performance label based on green chemistry principles to nanosynthesis processes.

Being the aim of this thesis the advancement of sustainable nanotechnology via structured decision-making, the above mentioned research gap was tackled throughout this Ph.D. and this chapter and Chapter 7 describe how this was achieved.

The bio-inspired synthesis route, employing plants and plants extracts, showed the most promising potentials when compared to conventional processes due to the use of benign and renewable reagents as well as favourable processing conditions, namely low temperature and pressure [16, 25, 28, 30, 32, 144, 359, 373, 375, 390, 391, 396, 411, 427-429]. This background justified the selection of such processes for the development of a classification model for the synthesis of nanoparticles based on green chemistry principles.

### 6.1.2 Sustainability assessment of nanosynthesis processes

Even though various strategies for the synthesis of nanoparticles have emerged, the assessment of the environmental implications of such processes is limited. The routes that are more established are those that have also been assessed more in detail and quantitatively, among which arc discharge, laser ablation, chemical vapour deposition and chemical reduction [34, 63, 145, 149, 331, 342, 430-433]. This is not the case for the emerging bio-inspired processes. During the last decade a lot of literature was published, as summarized above, in terms of individual studies proposing the implementation of GCP at different extents, from the substitution of synthetic harmful materials with renewable and benign ones, to the use of low temperatures and equipment defined as alternative, including microwave and sonication.

As far as metal nanoparticles are concerned, one study has been published recently on the LCA of synthesis protocols for metal nanoparticles (gold) that adopt renewable sources [144]; the main limitation has been the lack of information about the reducing agents, which lead to their exclusion in most of the LCA calculations. Regarding silver nanoparticles, six conventional and one bio-based production processes were compared through LCA, demonstrating how the use of particle size/function as an alternative functional unit than the mass provides more insightful results in the assessment. In fact, the rescaling of the LCA impacts from a mass-based to a particle size/function-based comparison leads to significantly different considerations regarding the implications of the processes [145]. A major impediment for the quantification of impacts of the bio-based synthesis protocols is the lack of understanding of the reduction mechanism of gold and silver salt to respective nanoparticles. Several proposals of such mechanism have been suggested [434-436] but there is still a level of uncertainty about the crucial role of phenolic compounds in the reaction, which limits the modelling and consequent quantitative assessment of such processes. Another limitation in this regard is the allocation of upstream input to waste material, due to the bio-renewable nature of the feedstocks.

The evaluation of the environmental implications of NPs can be performed via different tools as described in more detail in Chapter 3. Some operate with quantitative information and are data intensive, such as LCA, while others are more flexible and less demanding in terms of data requirement as well as from a modelling viewpoint. Specific attention for the sustainable development of nanosynthesis processes is currently placed on bio-inspired approaches, though quantitative assessment of their sustainability is severely hampered due to the limited data availability. Although scientific research will lead to the generation of experimental data to be used in quantitative tools, the available information and expertise can be used and integrated to provide a qualitative evaluation of these synthesis protocols.

As Chapter 3 depicted, a lot of various synthesis routes have been put forward, however most of the studies focus on the individual proposition of a synthesis protocol and not on comparing them to:

i. Identify the specific reasons and the extent for which some perform better than others from a green chemistry perspective (i.e. design rules/guidelines);
ii. Assess the implementation of GCP in new nanosynthesis processes in the form of a performance class (e.g. “green” nano).

The provision of these solutions characterized the fourth objective of this Ph.D. thesis. From a decision-making viewpoint they represent a specific classification problem. Considering that MCDA has been specifically developed to handle comparisons and provide classifications (among other types of decision recommendation) of competing alternatives, it was selected here to provide the solutions mentioned above. The case study material selected for the development of the classification model was “silver nanoparticles”. Nanosilver is widely used in many applications [2, 26, 49], which advances concerns about its implications during the life cycle stages. Synthesis is one of those and its impacts, however small when compared to other stages, can be reduced by practitioners in this area, who are green chemists. This stage in the life cycle of Ag nanoparticle synthesis was chosen to test the effectiveness of MCDA [70] for comparing synthetic approaches and thus quantifying how “green” they are, using as a case study an example that would be understood by most green chemistry practitioners.

### 6.1.3 Decision support through Multiple Criteria Decision Aiding

The assessment of how “green” the synthesis methods of nanoparticles truly are requires the consideration of a variety of protocol attributes/criteria for a certain number of alternatives, and this problem can be effectively tackled with MCDA [101, 103]. Chapter 4 treated MCDA in detail, highlighting that it is a process to support DMs in structuring their decision problems and to offer them tools and methods leading to recommendations about the decisions at stake [101, 437]. The recommendations are usually based on the comprehensive evaluation of the considered alternatives, by performing some kind of aggregation of evaluations of the alternatives on the criteria used to characterize the protocols. Detailed explanation of the MCDA process is provided in Chapter 4.

MCDA has several advantages in supporting decision-making [55, 191, 438]:

i. It does not necessarily require a pre-defined set of data as input;
ii. It works with very limited and uncertain information;
iii. It can include experts' and other stakeholders' knowledge;
iv. It provides an adaptable structure that is adequate for the process of identification of criteria and management thereof.

The definition of MCDA shows the potential to support the assessment of the performance of synthesis protocols that lack quantitative information allowing one to conduct screening-level environmental sustainability evaluations.

There is a wide availability of MCDA methods that can be used to integrate information and either classify alternatives into preference-ordered classes or rank them from the best to the worst [103, 180]. Chapter 4 explains them in detail and shows how they are excellent tools to support decision-making processes oriented towards sustainability. This chapter proposes a model based on the MCDA method Dominance-based Rough Set Approach (DSRA), for the green chemistry-based classification of synthesis protocols used for nanoparticles into preference-ordered performance classes, by combining the information available in the peer-reviewed literature with the knowledge of experts in the field. Furthermore, the model presented in terms of "*if … , then …*" decision rules provides the methodological basis for the development of a set of design guidelines for the synthesis of greener silver nanoparticles, representing one of the current research gaps in the area. An important consideration that underlines this reasoning is that a successful assessment tool should use the same language of the DM and it must be perceived as a "glass box" rather than as a "black box" that provides the DM with some "right" answer that is guaranteed by the analyst's authority [185, 211, 439, 440].

This chapter shows that the MCDA process can have a substantial contribution in supporting decision-making for the governance of silver nanoparticles synthesis. An important remark is that the scope of this part of the research is to introduce a decision support procedure for assessment of synthesis protocols for nanomaterials that can be improved on a regular basis. The MCDA model described in this chapter is a tool for the assessment of synthesis protocols in view of preferences a DM could have in favor of green aspects of the protocols. The synthesis of silver nanoparticles was selected as the case study to develop the model for three main reasons: (i) it was possible to create a database of comparable synthesis protocols using green chemistry-based criteria for this nanomaterial; (ii) experts with knowledge in the area agreed to take part in the decision aiding process; and (iii) a wide range of successful applications are enabled and envisioned by silver nanoparticles, such as electronic products, composite fibers, biosensor materials, cosmetics and antimicrobial products [374, 393, 411].

## 6.2 Methodology

Assessing the implementation of GCP in silver nanoparticles synthesis is a complex decision-making problem that requires measurement and integration of several evaluation criteria. What is more, information about the processing conditions is scarce, unstructured and not always quantitative. These limitations represent major impediments for the application of established assessment techniques such as LCA and RA. Nonetheless, a lot of literature has been published on production processes for nanosilver, which posed the basis for the development of a model capable of integrating such information and expert knowledge in a decision support system.

Case study was the research method selected to develop the model for the classification in preference-ordered classes of synthesis processes for nanoparticles based on the implementation of the GCP. The research objective was achieved through knowledge elicitation techniques based on MCDA, grounded on the direct interaction between the analyst and the DMs.

Knowledge elicitation can be performed with a variety of methods, grouped in three sets by [288]: (i) “analysis of familiar tasks”; (ii) interviews and; (iii) contrived techniques. This case study uses the first and third methods.

Documentation analysis belongs to the first family of methods and in this case it was conducted to build the database from the available literature on nanosilver synthesis protocols. The use of these realistic scenarios is in line with the need to limit artificiality when a knowledge engineer wants to extract a reasoning model from an expert [290].

Interviews were considered as a complementary tool to shape the case study and also to discuss the results with the DMs. However, the methodology changed during the practical phase of the work as such interviews resulted unnecessary, considering the satisfactory outcome of the project scoping performed at the beginning of the MCDA process and the model explanation and validation, both built on informal discussions via email, phone, video calls and face-to-face meetings.

Contrived techniques are based on the modification of the familiar task the expert works with and can provide very useful information about how he/she reasons and insights on his/her sub-domains of knowledge [285, 290]. The use of limited information is one of these methods and it can be tailored to obtain information from the experts in the case of situations where decisions need to be made under uncertainty [288, 290]. In this case study, the nature of the dataset implies the use of limited-information tasks, as the production processes are characterized by scarce data, being it qualitative in most (6 out of 8) of the cases and covering a constrained spectrum of GCP (see section 6.2.3 and Table 6-2 for details).

Contrived techniques, where MCDA methods belong, are the best in terms of knowledge elicitation efficiency expressed as "informative propositions" produced per "total task minute" [285, 288, 289]. Furthermore these approaches are appropriate to derive tacit or unconscious knowledge and strategies.

The research methodology was complemented by the adoption of concept mapping to define the relationships among the different factors that affect the decision-making procedures [441]. These maps are excellent tools to represent the knowledge model in a structured and condensed manner, representing also "living repertoires of expert knowledge to support knowledge sharing as well as knowledge preservation" [441]. MindMaps[5] was used as a graphical representation technique for the extracted knowledge.

The overall structure of the knowledge elicitation and MCDA model construction process can be summed in these steps (Figure 6-1):

i. MCDA process phase 1 -> Problem situation representation
    - Acquisition of research domain familiarity: broad literature review of production processes for nanoparticles, with identification of potential research gaps reported in the literature;

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[5] http://www.mindjet.com

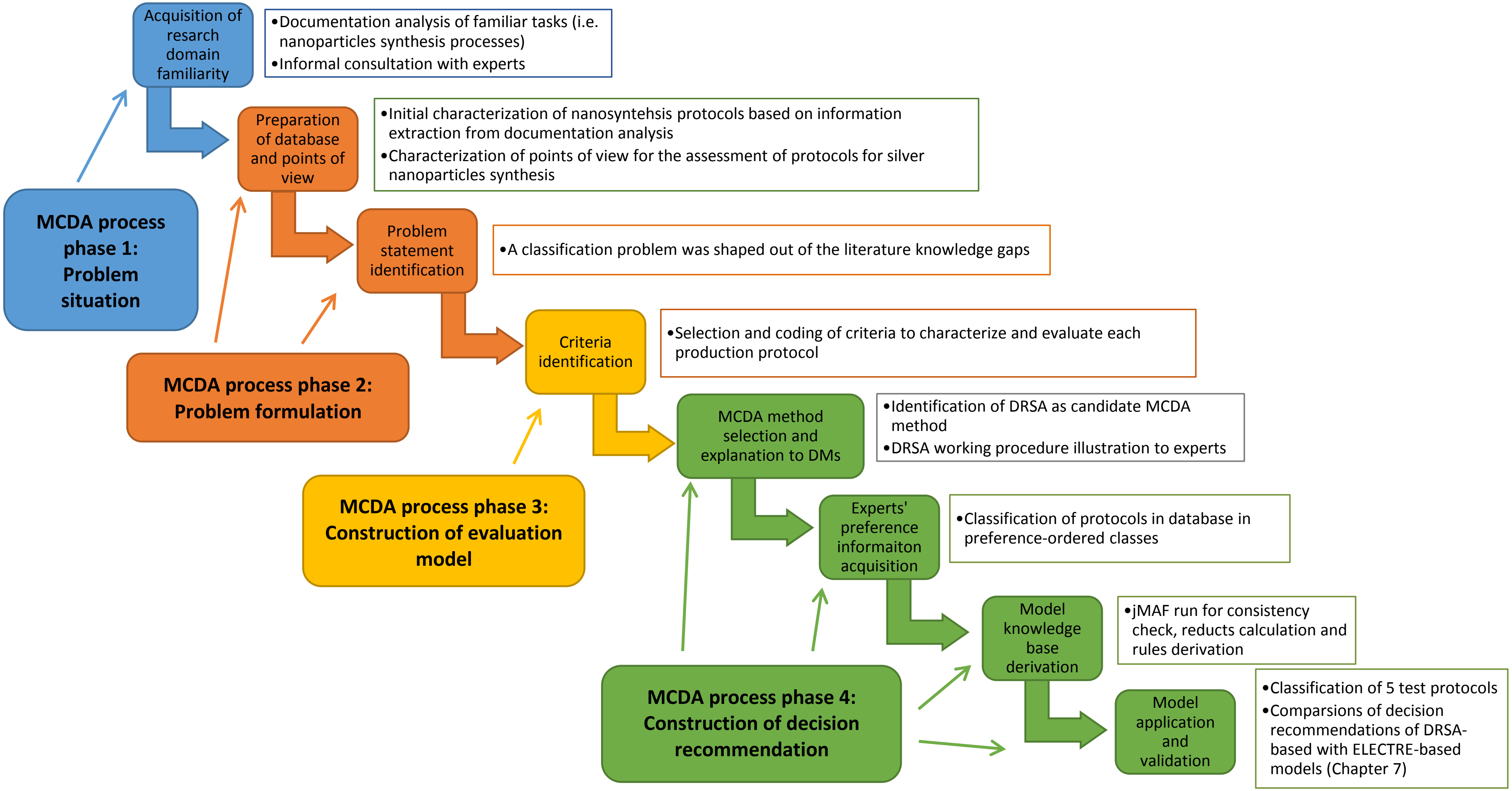

**Figure 6-1: MCDA process phases for classification model construction (adapted from [175, 288])**

ii. MCDA process phase 2 -> Problem formulation
   - Database preparation: an initial set of assessment protocols was prepared and discussed with the experts, with a specific focus on a relevant set of potential criteria;
   - Problem statement identification: the literature reports a lack of design guidelines for green-chemistry oriented synthesis of nanomaterials, which from an MCDA perspective can be seen as a classification problem;

iii. MCDA process phase 3 -> Construction of evaluation model
   - Construction of assessment criteria to be used for characterization of production processes;

iv. MCDA process phase 4 -> Construction of decision recommendation
   - MCDA method selection and explanation: the selected MCDA method (DRSA) was explained to the experts, in terms of preference information requirements, operational procedure and results typology;
   - Experts' preference information acquisition: the experts classified each of the 48 production processes in a preference-oriented classes;
   - Knowledge base derivation of classification model and discussion: jMAF software[6] was employed to check experts' consistency, derive minimum set of relevant criteria (reduct) and identification of decision rules. The decision rules derived from the expertise of researchers are in the form of "*if* condition *x, then* decision *y*" allowing the DMs to trace and discuss them in a simple and direct manner;
   - Model application and validation: the model was tested on five non-reference production protocols and in order to check its robustness a correspondence assessment between the decision recommendation of this model and the same recommendation but derived from another MCDA method based on Monte-Carlo simulations was conducted (Chapter 7).

As indicated above MCDA is both a process and a set of methods and it can be implemented through a four-step process. Such process fits with the challenge described in section 6.1, namely the development of guidelines for the sustainability-oriented

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[6] http://idss.cs.put.poznan.pl/site/139.html

production of nanomaterials, and for this reason it was selected as the research approach.

Expert input is pivotal in a field that is characterized by uncertainty and lack of quantitative data, as it is the case for “green”-labelled nanomaterials synthesis. At this time there is a lack of available knowledge regarding the synthesis of nanomaterials because of either proprietary issues or due to the lack of research findings [34, 42, 144, 433]. The use of expert judgment is considered as a reliable solution when limited data is available and quantitative or historical information is not in place [285, 288, 293].

Consequently, the inclusion of expert opinions in the context of nanomaterials synthesis assessment is a solution to overcome the existing data gaps. The inclusion of the experts in this problem did fit perfectly with the MCDA process as it is actually a success factor for decision aiding procedures. Every step of the MCDA process is discussed in detail in the following sections.

### 6.2.1 Problem situation representation

The synthesis of silver nanoparticles and the evaluation of their performance in terms of application of GCP represent the *problem situation* that was addressed with MCDA. The silver nanoparticles that have been selected are different in a fundamental sense, but they would be expected to be used for the same purpose (i.e. antimicrobial activity). This allows for a fair comparison in terms of the implementation of GCP in the overall production of silver nanoparticles and assessment of their performance (based on the range of particle sizes produced). Two experts (the DMs) in this area of nanotechnology agreed to take part in the decision aiding process. The selection of these researchers followed the definitions of experts reported in the literature, namely those individuals who are “highly regarded by peers, […], whose performance shows consummate skill and economy of effort, and who can deal effectively with rare and “tough” cases” [288]. Additionally, the experts were are also “qualified to teach those at a lower level” and are part of “an elite group of experts whose judgments set the regulations, standards, or ideals”, fitting for the highest level of expertise as defined by Hoffman and colleagues [288].

Expert judgement has already been applied in the nanomanufacturing area for the identification of appropriate risk management measures. The developed model demonstrated how the use of expertise with domains that lack quantitative data and tools can advance the safety of nanomanufacturing [442].

### 6.2.2 Problem formulation

The first sub-step of the MCDA *problem formulation* process consisted in the construction of the database composed of the synthesis processes of silver nanoparticles, which represented the alternatives to be used as input for the model development (see Appendix B.1 for full dataset). These alternatives were defined as “silver nanoparticle synthesis protocols based on bottom-up approaches that use reducing and capping agents to convert a silver salt to silver nanoparticles”. The main reason for the selection of this type of alternative is that the chemical and biological reduction route for the synthesis of noble metals nanoparticles has been frequently labeled as green and more sustainable [16, 25, 28, 30, 32, 144, 359, 373, 375, 390, 391, 396, 411, 427-429]. This provided a suitable training set to develop and test the implementation of green and environmentally oriented criteria. Next, was the definition of the points of view (POVs) used to characterize and assess the synthesis protocols which are essentially the GCP [388]. Lastly, the problem statement was formulated, namely the definition of what decision(s) need to be made with the set of alternatives. Based on the specified need indicated in the literature for the development of standards to define products as “green” [16, 29, 30, 373] and design rules that comply with quality requirements [24, 30, 32], a classification problem where each alternative has to be assigned to a preference-ordered class (e.g. low, medium, or high performance) was identified. The reason behind the use of a classes system instead of a simple label one is that there are several possibilities for implementing the principles of green chemistry in the nanosynthesis, which necessarily lead to different extents of environmental friendliness of the processes so that it would be too reductionist using “green” and “no-green” labels only.

### 6.2.3 Construction of evaluation model

The development of an *evaluation model* was the third stage of the MCDA process and it consisted of the identification of the criteria to characterize and evaluate each alternative. The selection of the criteria used to assess the synthesis protocols was based on the framework for SA of NPs presented in Chapter 5. Two major considerations applied here: (i) the expertise of the DMs was primarily in green chemistry; (ii) secondary information from published literature on nanosynthesis processes for silver nanoparticles should have been used due to the lack of equipment, infrastructure and funding to generate own data. These operational conditions lead to the selection of a sub-set of criteria from the framework of Chapter 5, which were aligned with the expertise of the DMs and tailored to the assessment of synthesis processes of nanoparticles based on the synthesis route described above.

Table 6-1 summarizes the links and correspondence between the criteria identified in the survey and those used in the development of the MCDA model. The criteria selected for the latter include (i) type of reducing agent, (ii) type of capping agent, (iii) solvent typology, (iv) use of local resources, (v) reaction time, (vi) reaction temperature, (vii) equipment type, and (viii) size range of ensuing nanoparticles.

**Table 6-1: Correspondence between criteria used in survey and those employed in the MCDA model development**

| Criteria in survey (Chapter 5) | Criteria in the MCDA model |
|---|---|
| Use of renewable resources / Use of raw materials / Hazardous materials used or produced | Reducing agent |
| | Capping agent |
| | Solvent |
| Local resources use | Local resources use |
| Processing conditions | Reaction time |
| | Reaction temperature |
| Energy efficiency | Equipment type |
| Energy consumption | |
| Functionality | Particle size range |

The criteria for the survey are more general (i.e. refer to a concept rather than a specific measure) in the case of (i) use of renewable resources / use of raw materials / hazardous materials used or produced and (ii) processing conditions. The first include reducing agent, capping agent and solvent used in the synthesis route. The second includes the reaction time and temperature. On the other hand, energy consumption and energy efficiency in the survey refer to the single criterion “Equipment type” used (which is representative of energy consumption and efficiency) in the selected synthesis strategies.

Table 6-2 shows the coding of the MCDA model criteria together with their preference order as well as the rational for such choice.

**Table 6-2: Criteria selected for the MCDA assessment of synthesis protocols**

| Criterion | Criterion values | Preference order of the values | Rationale for the preference order |
|---|---|---|---|
| Reducing agent | Renewable – waste | ↑ | Reducing, capping and solvent are three main areas of opportunity for the implementation of green chemistry in the reduction of metal ion salts in metal nanoparticles [434, 443-445]. It is possible to choose among waste from renewable sources (RW), primary renewable materials (RP), biodegradable polymers (BP) and synthetic chemicals (SC). Preference was defined as: RW > RP > BP > SC.<br>Renewable materials are preferred options not only for their non-exhaustible nature, but also because they are sources acknowledged as being benign, recurrently used for medicinal or even for feeding purposes. The biodegradable polymer category includes polymers that have to be synthesized but are biodegradable and not hazardous.<br>On the other hand the synthetic category includes chemicals that are usually hazardous and require dedicated synthesis processes.<br>Furthermore, some materials can perform both the role of reducing and capping agent [443]. In this case they allow implementing multifunctionality that is a key requirement from a green chemistry perspective.<br>*Implementable GCP:* P 1, 3, 4, 5, 7, 8, 10, 12 |
| | Renewable – primary | | |
| | Biodegradable polymer | | |
| | Synthetic | | |
| Capping agent | Not needed | ↑ | |
| | Renewable – waste | | |
| | Renewable – primary | | |
| | Biodegradable polymer | | |
| | Synthetic | | |
| Solvent | Renewable – waste | ↑ | |
| | Renewable – primary | | |
| | Biodegradable polymer | | |
| | Synthetic | | |
| Local resources use | Yes | ↑ | This parameter relates to the protocols that employ renewable materials. When local resources are used, this can be considered a benefit in terms of reduction of transportation impacts and costs.<br>*Implementable GCP:* P 7 |
| | No | | |
| Reaction time | In seconds | ↓ | Reaction speed is important in materials synthesis as the longer the process the higher the amount of energy needed to run the equipment. As a result this criterion has to be minimized.<br>*Implementable GCP:* P 6, 12 |

**Table 6-2: Criteria selected for the MCDA assessment of synthesis protocols (cont.)**

| | | | |
|---|---|---|---|
| Reaction temperature | In Celsius | ↓ | Synthesis processes can be performed at different temperatures depending on the reaction, type of equipment and its setup. From a green chemistry perspective the lower the temperature the better as less energy is required and safer operating conditions are in place. Consequently the criterion has to be minimized.<br>*Implementable GCP:* P 6, 12 |
| Equipment type | Static | ↑ | Several bottom-up approaches are available starting from very simple equipment such as a stirring plate, up to a laboratory microwave oven and oil baths.<br>Static conditions do not imply any use of energy which are ideal from a green chemistry perspective.<br>Stirring systems are placed as the next best choice as they are the processes that require the lowest amounts of energy to sustain the reaction (in the range of watts fractions depending on the rpm rate) [446]. Furthermore they are very simple pieces of equipment with higher degree of control over the process and safer reactions conditions.<br>Microwave (MW) was introduced as a specific class as it is a widely recognized alternative source of energy for the rapid synthesis of well-defined nanosized particles. The main advantages of MW heating compared to conventional heating techniques are [395-397, 401, 403-405]:<br>• Reactions kinetics increase by 1-2 orders of magnitude;<br>• Possibility of producing better defined (uniform) and smaller particles;<br>• Enhanced kinetics of crystallization;<br>• Reduction in waste production (as wall effects can cause crusting and degradation in conventionally-heated reactors that increases impurities and consequently byproducts).<br>The reduction in reactions time and faster crystallization kinetics can lead to energy savings compared to conventional techniques. This consideration coupled with the fact that MW-assisted process allows reduction in unwanted byproducts from the reactions justifies the location in a preferred position for this method compared to the conventional ones (oil baths).<br>The energy consumption of microwaves has been studied in the literature and it has |
| | Stirring for at most 5 minutes | | |
| | Stirring | | |
| | Microwave – sealed vessel ($\leq 300$ W) | | |
| | Microwave – sealed vessel ($> 300$ W) | | |
| | Microwave – open vessel | | |
| | Conventional (oil bath, steam bath) | | |
| | Not reported | | |

**Table 6-2: Criteria selected for the MCDA assessment of synthesis protocols (cont.)**

| | | | |
|---|---|---|---|
| | | | been shown that the systems that employ MW heating in sealed vessels at small scales (up to 50 mL) use less energy than conventional techniques under comparable conditions. This consideration derives from the fact that they allow obtaining the same amount of product in a much shorter period of time and consequently with less energy consumption [405, 447-449]. However, their actual energy efficiency is under debate and so it was not assumed higher energy efficiency for MW compared to conventional techniques (see for details [405]). Nonetheless, the use of MW technique with open vessels at laboratory scales does not imply a better energetic performance compared to conventional heating and so this option is placed in a lower preferred class [447], though still accounting for the reduction in byproducts, simplicity of the process and inherent safety [390] compared to conventional approaches.<br>There can also be cases with missing information about the type of equipment used, which is considered as a worst case due to the uncertainty of the information.<br>*Implementable GCP:* P 1, 6, 11, 12 |
| Size range | $0 \le particle\ size \le 30$ nm | ↑ | Synthesis protocols lead to the silver nanoparticles that are normally within a certain size range rather than of a unique and particular size. The preference introduced for this criterion is that the smaller the particles the better. This is in accordance with what has been reported for the antimicrobial activity of silver, which has shown size-dependency; the smaller the size the higher the antimicrobial potential [450-453]. However, there are no agreed cut-offs values for the sizes of the particles that can induce higher antimicrobial effects and hence five size range classes where introduced. |
| | $0 \le particle\ size \le 60$ nm | | |
| | $30 < particle\ size \le 60$ nm | | |
| | $0 < particle\ size \le 100$ nm | | |
| | $60 < particle\ size \le 100$ nm | | |

Specifically, the arrow up says that the greater the value, or the higher its rank on the list of possible values, the better it is, and the arrow down says the opposite. While criteria (v) and (vi) have cardinal (i.e. quantitative) evaluation scales, all the others have ordinal (i.e. qualitative) evaluation scales.

Web of Science[7], which includes more than 12,000 journals and 30,000 books worldwide, was used as the database for the identification of potential studies reporting synthesis of silver nanoparticles through chemical or biological reduction. The studies selected to be part of the dataset (48 in total) were those reporting information for the criteria selected for the evaluation model (see Table 6-2 for details on rationale for protocols comparability).

### 6.2.4 Construction of decision recommendation: Dominance-based Rough Set Approach for performance classification of silver nanoparticles synthesis protocols

Selection of MCDA method is an important and fundamental step in any MCDA process as it affects the type of preference information required from the DMs, the typology of data that can be used and most importantly the type of results and decision recommendation. As discussed in Chapter 4 and section 6.1.3 of this chapter, MCDA methods satisfy requirements for conducting SA. The challenge is thus to select the correct method for the correct problem or to develop an approach ad hoc in the case there is not a suitable one. In this case study, the selection of the MCDA method to be used was focused on these desired features for the approach:

i. Be simple to understand by the experts in the area (i.e. DMs), without being perceived as a black box;
ii. Avoid highly demanding cognitive efforts that can discourage the DMs from responding or reasoning;
iii. Define sustainability design practices/guidelines to improve how “green” a production protocols for nanoparticles can be;
iv. Provide a classification system recommending preference-oriented classes (e.g. low, medium, high) based on implementation of GCP in production protocols for nanoparticles;

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[7]: http://thomsonreuters.com/thomson-reuters-web-of-science/

v. Produce easily understandable and communicable results.

These requirements were used to re-evaluate the different MCDA approaches and some drawbacks emerged when considering the potential use of direct preference elicitation techniques [185, 209, 210, 454]:

i. They can be demanding in terms of approach structuring, such as in the identification of the utility functions and transformation of all criteria on a quantitative scale (e.g. MAUT);
ii. The definition of reliable and realistic thresholds in the outranking approaches (e.g. ELECTRE and PROMETHEE) can be very challenging and time consuming;
iii. The elicitation of weights can be a laborious and difficult process for the DMs.

On the other hand, the possible use of indirect preference elicitation methods with utility and outranking approaches could have been less tiresome and thus preferable for the DMs. However, other methodological considerations were introduced in the methods assessment: (i) utility approaches would have provided utility functions for each criterion, the comprehensive performance for each of the processes and the trade-offs between the criteria; (ii) outranking approaches would have provided insights into the discriminatory thresholds for the criteria, the relative importance of the criteria and the preference-oriented class recommendation. Both families of methods would have been able to satisfy the classification requirement of this MCDA problem, however they would not have provided decision recommendations in the form of design guidelines and produced easily intelligible and traceable results.

These were notable downsides of utility and outranking based methods for this case study, considering that there are calls in the literature for easily understandable design rules/practices/guidelines for “green” nanomaterials [24, 30, 32]. On the contrary the DRSA approach, an MCDA method introduced and characterized in [185, 207, 208], satisfies all the requirements listed above for this type of problem and thus it was selected to tackle it (see Chapter 4 for generic description of DRSA).

DRSA handles knowledge about alternatives in the form of an information table (Table 6-3), whose rows are defined as objects to be evaluated, while the columns are divided in condition attributes (*C*), namely the evaluation criteria that are needed to assess the objects, and the decision attribute (*D*) which represents an overall evaluation of each object in the table.

**Table 6-3: Exemplary information table for DRSA application**

| Silver nanoparticle synthesis protocol | Condition attributes (criteria) | | | Decision attribute (Performance class) |
|---|---|---|---|---|
| | Reducing agent | Temperature (°C) | Reaction time (s) | |
| I | Renewable-waste | 35 | 120 | high |
| II | Biodegradable polymer | 40 | 2400 | low |
| … | … | … | … | … |

More formally, an information table can be characterized as *S* = < *U,Q,V,f* >, where *U* = set of objects; *Q* = set of attributes; *V* = $\bigcup_{q \in Q} V_q$, $V_q$ = domain of attribute q; and *f: U* × *Q* → *V* is a total function so that *f (x,q)* ∈ $V_q$ for every *q* ∈ *Q*, *x* ∈ *U*, defined as information function.

In this case study, the objects under assessment are the considered nanoparticle synthesis protocols (I, II, etc.), while the criteria are those reported in Table 6-2, and the decision attribute represents the level of "performance" of each synthesis protocol from set *U*. This performance can take one of five possible preference-ordered classes, which can be assigned by the DM on the basis of the implementation of GCP and satisfaction of quality requirements that the criteria of each protocol convey. The preference-ordered classes (i.e. 5 > 4 > 3 > 2 > 1) are:

- 5 (very high) = a comprehensive set of GCP is adopted and the process can be seen as a reference for future research aimed to improve the performance of synthesis protocols for silver nanoparticles;
- 4 (high) = quality requirements are satisfied, a considerable set of GCP is applied;
- 3 (medium) = principles of green chemistry are partially implemented and there can be quality improvements possibilities;
- 2 (low) = the synthesis protocol shows limited implementation of principles of green chemistry and/or satisfaction of quality requirements;
- 1 (very low) = complete lack of green chemistry perspective and disregard for environmental implications of the synthesis protocol.

The class for each synthesis protocol was assigned by two experts who participated in the decision aiding process, after a series of sessions that lead to a classification agreement. The complete information table with silver nanoparticles synthesis protocols and experts classification is reported in Appendix B.1. DRSA, implemented with jMAF software[8], was used to analyze the information table in this appendix and derive a set of logical statements in the form of *"if … , then …"* rules, which explain the classifications made by the DMs.

For comparisons of objects performance in DRSA, it is necessary to use the notion of weak preference relation $\geq_q$ on *U* with respect to criterion *q*, so that $x \geq_q y$ stands for "object *x* is at least as good as object *y* with respect to criterion *q*".

The decision attribute is used to define a set of classes (**Cl**) for the classification of the nanoparticle production protocols, so that **Cl** = $\{Cl_t, t \in \{1, \dots, n\}\}$ and *n* is the total number of classes, and each object *x* ∈ *U* can belong to one $Cl_t$. Furthermore, considering two classes *r* and *s*, with *r* > *s*, objects from $Cl_r$ are better than those from $Cl_s$, which is in relation to the previous notation $x \geq y$ , so that $[x \in Cl_r, y \in Cl_s, r > s] \implies [x \geq y \text{ and not } y \geq x]$.

In the context of evaluation of the nanoparticle production protocols, this can be seen as a decision-making process in terms of classification into different classes based on the GCP implementation: $Cl_1, Cl_2$, $Cl_3$, $Cl_4$ and $Cl_5$ which represent a very low, low, medium, high and very high performance of each protocol, respectively.

The classes are ordered in increasing level of desirability, so that, e.g., $x > y$ if $x \in Cl_3$ and $y \in Cl_2$, nanosynthesis protocol *x* performs at a medium level, whereas nanosynthesis protocol *y* is only implementing GCP at a low level.

DRSA performs approximations of two types of unions of classes - the upward one $Cl_t^{\geq}$ = $\bigcup_{s \geq t} Cl_s$, and the downward one $Cl_t^{\leq}$ = $\bigcup_{s \leq t} Cl_s$, with *t* = 1, …, *n*.

In this decision problem, we have that the upward union of classes are:

- $Cl_1^{\geq}$, nanoparticle production protocols with GCP implementation at least very low, i.e. very low or low or medium or high or very high;

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[8] : http://www.cs.put.poznan.pl/jblaszczynski/Site/jRS.html

- $Cl_2^{\geq}$, nanoparticle production protocols with GCP implementation at least low, i.e. low or medium or high or very high;
- $Cl_3^{\geq}$, nanoparticle production protocols with GCP implementation at least medium, i.e. medium or high or very high;
- $Cl_4^{\geq}$, nanoparticle production protocols with GCP implementation at least high, i.e. high or very high;
- $Cl_5^{\geq}$, nanoparticle production protocols with GCP implementation at least very high, i.e. very high.

On the contrary, the downward union of classes are:

- $Cl_1^{\leq}$, nanoparticle production protocols with GCP implementation at most very low, i.e. very low;
- $Cl_2^{\leq}$, nanoparticle production protocols with GCP implementation at most low, i.e. low or very low;
- $Cl_3^{\leq}$, nanoparticle production protocols with GCP implementation at most medium, i.e. medium or low or very low;
- $Cl_4^{\leq}$, nanoparticle production protocols with GCP implementation at most high, i.e. high or medium or low or very low;
- $Cl_5^{\leq}$, nanoparticle production protocols with GCP implementation at most very high, i.e. very high or high or medium or low or very low.

The notion $x \in Cl_3^{\geq}$ signifies that “protocol *x* belongs at least to class $Cl_3$”, while $x \in Cl_3^{\leq}$ means that “protocol *x* belongs at most to class $Cl_3$”.

One property that has to be noted here is that

$$Cl_{t-1}^{\leq} = U - Cl_t^{\geq} \quad \text{and} \quad Cl_t^{\geq} = U - Cl_{t-1}^{\leq}$$

In this case study, the nanoparticle production protocols that do not have at least medium environmental sustainability, i.e. $-\ Cl_3^{\geq}$, are those with environmental sustainability at most low, i.e. $Cl_2^{\leq}$.

The decision rule approach approximates the information reported with the decision attributes by considering the knowledge reported in the condition attributes (criteria). In order to extract information from these attributes, the DRSA defines:

- Nanoparticle production protocols dominating *x,* i.e. nanoparticle production protocols that perform at least as good as *x* in terms of the set of condition attributes;
- Nanoparticle production protocols dominated by *x*, i.e. nanoparticle production protocols which perform worse than *x* in relation to the set of condition attributes.

*x* dominates *y* is denoted as $x\, D_P y$ (with $P \subseteq C$), if $x \geq_q y$ for every $q \in P$ (set of *q*). Pieces of information can be then obtained and are defined as granules of knowledge:

- Objects dominating *x*, named *P*-dominating set: $D_P^+(x) = \{y \in U: yD_P x\}$
- Objects dominated by *x*, named P-dominated set: $D_P^-(x) = \{y \in U: xD_P y\}$ .

For example, if the criterion is the use of reducing agent, assessed with preference-ordered values (renewable > synthetic), and reducing agent for nanosynthesis protocol *x* is assessed as renewable, then:

- $D_P^+(x)$ includes all the nanoparticle production protocols with 'renewable' score for type of reducing agent; whereas
- $D_P^-(x)$ includes all the nanoparticle production protocols with 'synthetic' score for type of reducing agent.

DRSA can also handle ambiguous information, which for an object *x* and criteria from *P* arises when there is at least one object which is not worse than *x* with respect to the condition attributes but it was assigned to a lower class. For instance, in the previous example protocol *x* was assessed as renewable for the type of reducing agent. In the case that synthesis protocol *x* is assigned to medium performance ($Cl_3$) and another protocol *y* is assessed as renewable for the type of reducing agent but assigned to low performance ($Cl_2$), then an ambiguity is in place between *x* and *y* in relation to the criterion "type of reducing agent". Information management including ambiguity handling is performed with DRSA by means of approximation sets. With respect to $P \subseteq C$, the objects belonging to $Cl_t^{\geq}$ with no ambiguity represent the *P*-lower approximation of $Cl_t^{\geq}$ ($\text{i.e.}\, \underline{P}(Cl_t^{\geq})$), while the group of objects that could belong to $Cl_t^{\geq}$ are the *P*-upper approximation of $Cl_t^{\geq}$ (i.e. $\overline{P}(Cl_t^{\geq})$):

$$\underline{P}(Cl_t^{\geq}) = \{x \in \cup : D_P^+(x) \subseteq Cl_t^{\geq}\},$$

$$\overline{P}(Cl_t^{\geq}) = \cup_{x \in Cl_t^{\geq}} D_P^{+}(x), \text{ for } t = 1, \ldots, n.$$

For example, if there is no ambiguity between nanoparticle production protocols *x* and *y*, then *x* and *y* are part of the lower approximations of the nanoparticle production protocols that are at least medium in performance, $\underline{P}(Cl_3^{\geq})$. If there is an ambiguity in place, the two nanoparticle production protocols belong only to the upper approximations of the class medium, $\overline{P}(Cl_3^{\geq})$, but none to its lower approximation $\underline{P}(Cl_3^{\geq})$.

The reasoning is the same for the dominated sets:

$$\underline{P}(Cl_t^{\leq}) = \{x \in \cup : D_P^{-}(x) \subseteq Cl_t^{\leq}\},$$

$$\overline{P}(Cl_t^{\leq}) = \cup_{x \in Cl_t^{\geq}} D_P^{-}(x), \text{ for } t = 1, \ldots, n.$$

The areas of ambiguity in relation to criteria from *P* are defined as *P*-doubtful regions and are expressed as:

$$Bn_P(Cl_t^{\geq}) = \overline{P}(Cl_t^{\geq}) - \underline{P}(Cl_t^{\geq}),$$

$$Bn_P(Cl_t^{\leq}) = \overline{P}(Cl_t^{\leq}) - \underline{P}(Cl_t^{\leq}), \text{ for } t = 1, \ldots, n.$$

In the illustrative example, *x* and *y* are part of the boundary regions of nanoparticle production protocols at least in the medium performance class, $Bn_P(Cl_3^{\geq})$.

For every $t = 1, \ldots, n$, and $P \subseteq C$, the quality of the approximation is defined as:

$$\gamma_P(Cl) = \frac{card\,[U - (\cup_{t \in T} Bn_P(Cl_t^{\geq})]}{card\,(U)} = \frac{card\,[U - (\cup_{t \in T} Bn_P(Cl_t^{\leq})]}{card\,(U)}$$

This important ratio indicates the number of objects correctly classified with respect to the whole set. In general, the higher the number of criteria, the higher the quality of classification, as additional criteria can render non-ambiguous objects that were ambiguous with fewer criteria. Lastly, the minimal (with respect to inclusion) subset of criteria $P \subseteq C$ so that $\gamma_P(Cl)$ = $\gamma_C(Cl)$ is named reduct of **Cl**, indicated as $RED_{\mathbf{Cl}}$. The reduct *P* represents the minimal group of criteria from *C* so that no ambiguous object can become non-ambiguous when new criteria are added.

#### *6.2.4.1 Decision rules*

DRSA provides useful contribution to the decision-making process, as from the upward and downward union of classes it is possible to induce structured information in the form of *"if … , then …"* decision rules [212]. For unions of classes $Cl_t^{\geq}$ or $Cl_s^{\leq}$, the certain or possible decision rules are supported by objects ∈ $\underline{P}(Cl_t^{\geq})$ or $\underline{P}(Cl_s^{\leq})$ , or by objects ∈ $\overline{P}(Cl_s^{\leq})$ or $\overline{P}(Cl_t^{\geq})$, respectively; they advance the classification to "at least class $Cl_t$" or "at most class $Cl_s$", either certainly or possibly. In the other cases, the decision rules supported by objects ∈ $Bn_P(Cl_t^{\geq})$ or $Bn_P(Cl_t^{\leq})$ advance the approximate classification to classes between $Cl_s$ and $Cl_t$ (s<t).

Five types of decision rules can be obtained:

- Certain $D_{\geq}$- decision rules: they present the conditions to assign object to $Cl_t^{\geq}$ without ambiguity: if $x_{q1} \geq_{q1} r_{q1}$ and $x_{q2} \geq_{q2} r_{q2}$ … and $x_{qn} \geq_{qn} r_{qn}$, then $x \in Cl_t^{\geq}$;
- Possible $D_{\geq}$- decision rules: they present the conditions to assign object to $Cl_t^{\geq}$ with or without ambiguity: if $x_{q1} \geq_{q1} r_{q1}$ and $x_{q2} \geq_{q2} r_{q2}$… and $x_{qn} \geq_{qn} r_{qn}$, then $x\ possibly \in Cl_t^{\geq}$;
- Certain $D_{\leq}$- decision rules: they present the conditions to assign object to $Cl_t^{\leq}$ without ambiguity: if $x_{q1} \leq_{q1} r_{q1}$ and $x_{q2} \leq_{q2} r_{q2}$ … and $x_{qn} \leq_{qn} r_{qn}$, then $x \in Cl_t^{\leq}$;
- Possible $D_{\leq}$- decision rules: they present the conditions to assign object to $Cl_t^{\leq}$ with or without ambiguity: if $x_{q1} \leq_{q1} r_{q1}$ and $x_{q2} \leq_{q2} r_{q2}$… and $x_{qn} \leq_{qn} r_{qn}$, then $x\ possibly \in Cl_t^{\leq}$;
- Approximate $D_{\geq\leq}$- decision rules: they present the conditions to assign object to $Cl_s \cup Cl_{s+1} \cup \ldots \cup Ct_t$: if $x_{q1} \geq_{q1} r_{q1}$ … and $x_{qn} \geq_{qn} r_{qn}$ and $x_{qn+1} \leq_{qn+1} r_{qn+1}$ … and $x_{qp} \leq_{qp} r_{qp}$, then $x \in Cl_s \cup Cl_{s+1} \cup \ldots \cup Cl_t$.

The rules derived from DRSA represent robust knowledge of the DM that participated in classification of protocols. Once these rules are discussed and accepted by the DM they become a decision model that can be used to assess new (unseen) alternatives [209, 211, 212]. In this case study, they could be adopted for the classification of new synthesis protocols for silver nanoparticles with reference to GCP. More specifically, the model that derives from the comprehensive use of the decision rules could be employed as a decision support tool for the assignment to performance classes of new or existing synthesis protocols for silver nanoparticles. Two classification schemes, named standard and new [455], were selected and contextualized to this multiple criteria problem.

#### 6.2.4.2 Standard classification scheme

In the standard scheme, as a first step, the rule(s) that match the new protocol under assessment is/are identified. In cases where only the same types of rule match the protocol (either “at most” $D_{\leq}$-decision rules or “at least” $D_{\geq}$-decision rules), the standard method assigns the process to the highest class of the intersection of “at most” $D_{\leq}$-decision rules or to the lowest class of the intersection of “at least” $D_{\geq}$-decision rules. When rules of different types are matching the protocol, the intersection between the highest class from the “at most” $D_{\leq}$-decision rules (e.g. $Cl_s$) is matched with the lowest class of the “at least” $D_{\geq}$-decision rules ($\text{e.g.}\, Cl_t$). If $Cl_s$ and $Cl_t$ coincide, the assignment is univocal, otherwise an interval of classes is proposed, without possibility of refinement.

#### 6.2.4.3 New classification scheme

The new classification scheme has the advantage of providing a univocal recommendation for the class of a new or existing protocol, by means of a score (i.e. $Score_R^{net}(Cl_t, m)$) that indicates the strength of confidence for the assignment of the protocol to each class.

This value is based on the credibility ($CR_{\rho_i}$) and coverage factor ($CF_{\rho_i}$) of every decision rule ($\text{e.g.}\, \rho_i$) with respect to any individual class ($\text{e.g.}\, Cl_t$):

$$CR_{\rho_i}(Cl_t) = \frac{\left|Cond_{\rho_i} \cap Cl_t\right|}{\left|Cond_{\rho_i}\right|}$$

$$CF_{\rho_i}(Cl_t) = \frac{\left|Cond_{\rho_i} \cap Cl_t\right|}{\left|Cl_t\right|}$$

where $Cond_{\rho_i}$ is the set of protocols that satisfy the conditions of rule $\rho_i$, and $\left|Cond_{\rho_i}\right|$, $|Cl_t|$, and $\left|Cond_{\rho_i} \cap Cl_t\right|$ are the cardinalities of the group of protocols verifying $Cond_{\rho_i}$, the protocols belonging to class $Cl_t$ , and the protocols satisfying $Cond_{\rho_i}$ and belonging to class $Cl_t$, respectively. In order to identify the recommended class, two additional scores need to be calculated. The first one, $Score_R^{+}(Cl_t, m)$, accounts for the credibility and coverage factors of all the rules (i.e. $R$) that suggests the assignment of the protocol to class $Cl_t$. $Score_R^{+}(Cl_t, m)$ is calculated as follows:

$$Score_R^{+}(Cl_t, m) = \frac{\left|\left(Cond_{\rho_1} \cap Cl_t\right) \cup \ldots \cup \left(Cond_{\rho_k} \cap Cl_t\right)\right|^2}{\left|Cond_{\rho_1} \cup \ldots \cup Cond_{\rho_k}\right| \, |Cl_t|}$$

where $Cond_{\rho_1}$, …, $Cond_{\rho_k}$ are the conditions parts of the rules supporting the assignment to class of interest $Cl_t$.

The other score, $Score_R^-(Cl_t, m)$, embraces the credibility and coverage factors of all the rules that suggest an assignment of the protocol to a class other than $Cl_t$. This score has the following formula:

$$Score_R^-(Cl_t, m) = \frac{\left|\left(Cond_{\rho_{k+1}} \cap Cl_{\rho_{k+1}}^{\geq}\right) \cup \ldots \cup \left(Cond_{\rho_l} \cap Cl_{\rho_l}^{\geq}\right) \cup \left(Cond_{\rho_{l+1}} \cap Cl_{\rho_{l+1}}^{\leq}\right) \cup \ldots \cup \left(Cond_{\rho_h} \cap Cl_{\rho_h}^{\leq}\right)\right|^2}{\left|Cond_{\rho_{k+1}} \cup \ldots \cup Cond_{\rho_l} \cup Cond_{\rho_{l+1}} \cup \ldots \cup Cond_{\rho_h}\right| \left|Cl_{\rho_{k+1}}^{\geq} \cup \ldots \cup Cl_{\rho_l}^{\geq} \cup Cl_{\rho_{l+1}}^{\leq} \cup \ldots \cup Cl_{\rho_h}^{\leq}\right|}$$

where $Cl_{\rho_{k+1}}^{\geq}, \ldots, Cl_{\rho_l}^{\geq}$ and $Cl_{\rho_{l+1}}^{\leq}, \ldots, Cl_{\rho_h}^{\leq}$ are the upward and downward unions of classes other than $Cl_t$ recommended by the decision rules. The net value, $Score_R^{net}(Cl_t, m)$, resulting from $Score_R^+(Cl_t, m) - Score_R^-(Cl_t, m)$, is an indication of the strength of the assignment to class $Cl_t$ and the final recommendation of a class depends on the highest net score.

## 6.3 Results and discussion

The MCDA process was applied with the collaboration of the DMs and it allowed exploiting unstructured information about nanosynthesis processes in a very efficient manner. Once the problem had been accurately formulated, the assessment criteria were identified and the explanation of the operating principles of DRSA were clear to the DMs, their expert judgment (i.e. global preference) on the 48 synthesis protocols in the database was input in jMAF software [255], which implements DRSA (Figure 6-1). Such software was used to answer five questions that characterized the decision-making challenge posed by this research:

i. Have the DMs been consistent with their judgments?
ii. Are there any subsets of criteria (reducts) that allow achieving the same quality of approximation as the whole group of criteria?
iii. What is the classification model based on decision rules derived from the experts judgments?
iv. What are the most relevant criteria for the classification?
v. How can the decision model be used to classify existing or new synthesis protocols for silver nanoparticles?

### 6.3.1 Consistency evaluation

Firstly, DRSA shows that the assignment of classes to the synthesis protocols by the experts was completely consistent, resulting in a quality of approximation equal to 1. This indicates that there are no ambiguous objects in the information table and the criteria finely discriminate the choice of the classes (Table 6-4). The DRSA analysis shows full consistency in the assessment, which is a significant prerequisite for acceptance of the results and their credibility. Unitary quality of approximation is an indication of proper problem formulation and model set-up, including criteria choices and database construction. However, full consistency and agreement among experts is not a necessary prerequisite for DRSA, as inconsistent input information and multiple DMs with different judgments can be handled as well [456, 457]. Initial runs of knowledge elicitation actually led to emergence of a few inconsistencies, however discussions with the DMs allowed further reasoning and voluntary adjustment of judgment in line with consistency principle. This step of the MCDA process proved the pivotal importance that direct interaction between decision analysts and DMs has to lead a successful MCDA model development.

**Table 6-4: Number of protocols in union of classes and resulting accuracy of approximation ([a]: Difference between lower and upper approximation; [b]: Ratio of the number of protocols in the lower approximation to the number of protocols in the upper approximation)**

| | At most 1 | At most 2 | At least 2 | At most 3 | At least 3 | At most 4 | At least 4 | At least 5 |
|---|---|---|---|---|---|---|---|---|
| **Lower approximation** | 2 | 14 | 46 | 21 | 34 | 33 | 27 | 15 |
| **Upper approximation** | 2 | 14 | 46 | 21 | 34 | 33 | 27 | 15 |
| **Boundary[a]** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Accuracy[b]** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

### 6.3.2 Reducts

As far as the reducts are concerned, only one was found composed of all the criteria with the exclusion of parameter “local resources use”. This means that all criteria but one were used to distinguish the assignment of the protocols among the classes. The irrelevance of “local resources use” is an indication that this parameter is not needed to obtain the same quality of classification as with the whole set of criteria. The reason for this is that the DMs did not perceive sufficient the information about materials origin to be able to judge how the source location could change the environmental impacts. As a consequence they discarded the information expressed by this criterion. What is more, this was seen as a “boundary” criterion from the green chemistry perspective as it embraces environmentally implications but not necessarily detachable at the synthesis step.

### 6.3.3 Classification model based on decision rules (DRSA-based model)

The application of DRSA to the database lead to a decision model (DRSA-based model) composed of 26 decision rules (Figure 6-2, Figure 6-3, Table 6-5): four for class at least 5 (very high); three for class at least 4 (high); three for class at least 3 (medium); three for class at least 2 (low); two for class at most 1 (very low); three for class at most 2 (low); four for class at most 3 (medium); and four for class at most 4 (high).

Each rule is composed of a conditional part (i.e. *if* part) that includes the value(s) of the criterion/criteria and a decisional part (i.e. *then* part), which is the assigned class to every process. These decision rules represent the partial fulfillment of the research goals reported in section 6.1.2, i.e. identify the specific reasons and the extent for which some nanosynthesis processes perform better than others from a green chemistry perspective.

The rules were shown to the experts using maps obtained with Mindjet software [458] in order to aid graphical representation and intelligibility (Figure 6-2 and Figure 6-3). Each rule is represented with the conditions that characterize it, the resulting decision/performance class assignment, its support and coverage factor in percentage (see also Table 6-5 for details). The DMs easily understood the rules and agreed on all of them, which became the decision model for this classification problem. The rules obtained with DRSA highlight the assumptions that the experts made in their choices, which pose the basis for directing future quantitative assessment of green synthesis of silver nanoparticles.

The decision model can be used to support the development of new and emergent synthesis protocols for silver nanoparticles or for the assessment of current ones. The synthesis protocols that satisfy the conditions of the class 5 (very high) are covered by rule 1 to 4. Rule 1 includes very simple systems that operate with renewable solvents in static conditions or with limited stirring.

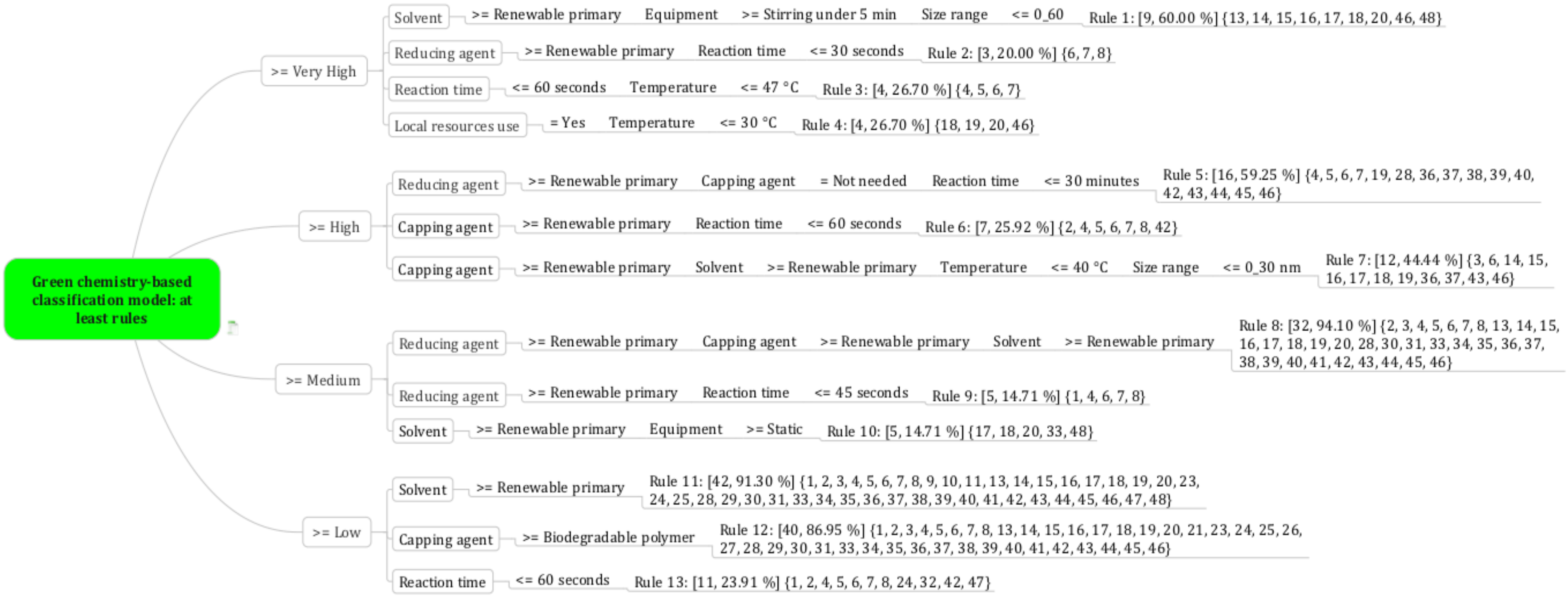

**Figure 6-2: Green chemistry-based classification model - At least rules. Each rule is reported as follows: Rule x: [y, z] $\{p, q, t\}$ with: x = rule number; y = number of protocols that support the rule; z = coverage factor of the rule (i.e. percentage of number of protocols that satisfy the conditions and are assigned to the class or union of classes); p, q, t = identification numbers of the protocols in the dataset**

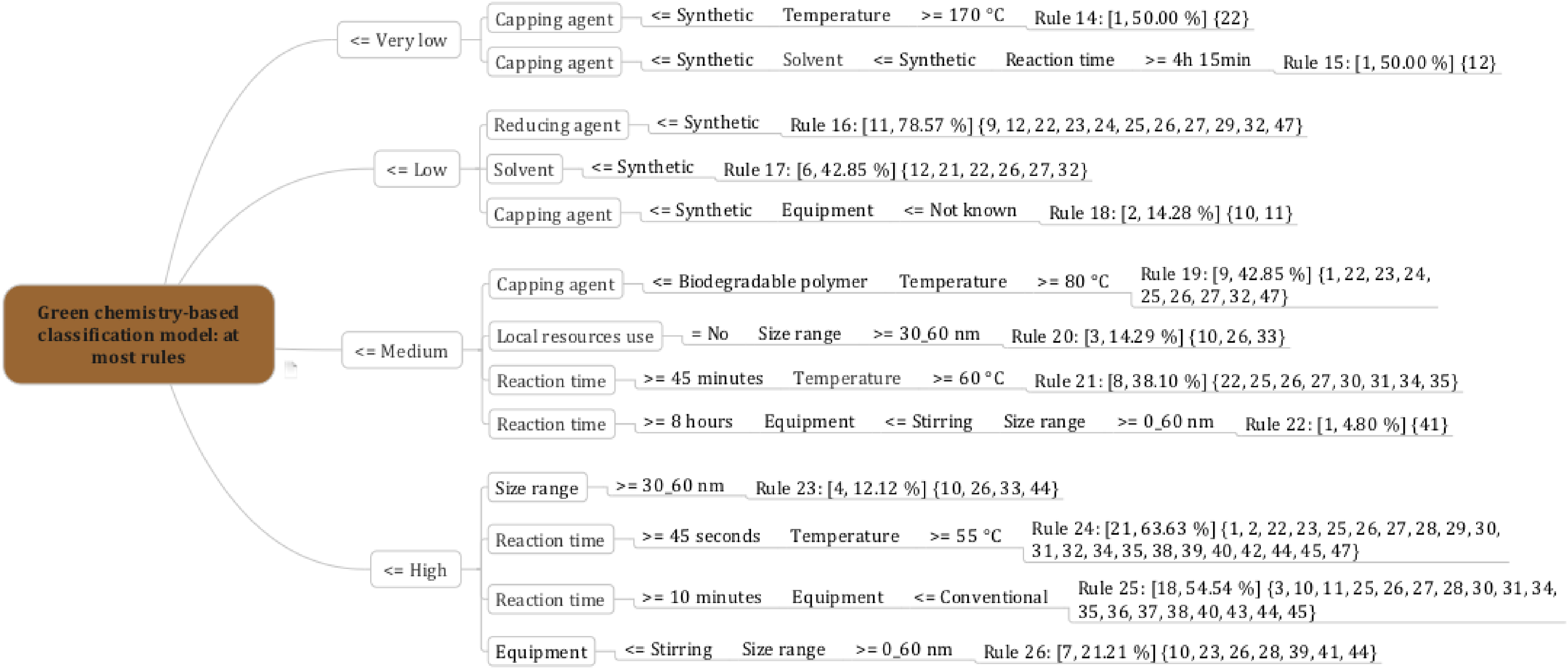

**Figure 6-3: Green chemistry-based classification model - At most rules. Each rule is reported as follows: Rule x: [y, z] $\{p, q, t\}$ with: x = rule number; y = number of protocols that support the rule; z = coverage factor of the rule (i.e. percentage of number of protocols that satisfy the conditions and are assigned to the class or union of classes); p, q, t = identification numbers of the protocols in the dataset**

**Table 6-5: Decision rules obtained for the case study ([a] = Rule Identification Number (IN); [b] = number of protocols that support the rule; [c] = percentage of number of protocols that satisfy the conditions of the rule and are assigned to the class or union of classes)**

| Rule type | Rule IN[a] | Conditions | Decision / Performance class | Supporting protocols[b] | Rule coverage factor[c] |
|---|---|---|---|---|---|
| At least | 1 | (Solvent >= Renewable primary) & (Equipment >= Stirring under 5 min) & (Size range <= 0_60 nm) | >= 5 | 9 | 60.00 % |
| | 2 | (Reducing agent >= Renewable primary) & (Reaction time <= 30 s) | >= 5 | 3 | 20.00 % |
| | 3 | (Reaction time <= 60 s) & (Temperature <= 47 °C) | >= 5 | 4 | 26.70 % |
| | 4 | (Local resources use >= Yes) & (Temperature <= 30 °C) | >= 5 | 4 | 26.70 % |
| | 5 | (Reducing agent >= Renewable primary) & (Capping agent >= Not needed) & (Reaction time <= 30 min) | >= 4 | 16 | 59.25 % |
| | 6 | (Capping agent >= Renewable primary) & (Reaction time <= 60 s) | >= 4 | 7 | 25.92 % |
| | 7 | (Capping agent >= Renewable primary) & (Solvent >= Renewable primary) & (Temperature <= 40 °C) & (Size range <= 0_30 nm) | >= 4 | 12 | 44.44 % |
| | 8 | (Reducing agent >= Renewable primary) & (Capping agent >= Renewable primary) & (Solvent >= Renewable primary) | >= 3 | 32 | 94.10 % |
| | 9 | (Reducing agent >= Renewable primary) & (Reaction time <= 45 s) | >= 3 | 5 | 14.71 % |
| | 10 | (Solvent >= Renewable primary) & (Equipment >= Static) | >= 3 | 5 | 14.71 % |
| | 11 | (Solvent >= Renewable primary) | >= 2 | 42 | 91.30 % |
| | 12 | (Capping agent >= Biodegradable polymer) | >= 2 | 40 | 86.95 % |
| | 13 | (Reaction time <= 60 s) | >= 2 | 11 | 23.91 % |
| At most | 14 | (Capping agent <= Synthetic) & (Temperature >= 170 °C) | <= 1 | 1 | 50.00 % |
| | 15 | (Capping agent <= Synthetic) & (Solvent <= Synthetic) & (Reaction time >= 4 h 15 min) | <= 1 | 1 | 50.00 % |
| | 16 | (Reducing agent <= Synthetic) | <= 2 | 11 | 78.57 % |
| | 17 | (Solvent <= Synthetic) | <= 2 | 6 | 42.85 % |
| | 18 | (Capping agent <= Synthetic) & (Equipment <= Not known) | <= 2 | 2 | 14.28 % |
| | 19 | (Capping agent <= Biodegradable polymer) & (Temperature >= 80 °C) | <= 3 | 9 | 42.85 % |
| | 20 | (Local resources use <= No) & (Size range >= 30_60 nm) | <= 3 | 3 | 14.28 % |
| | 21 | (Reaction time >= 45 min) & (Temperature >= 60 °C) | <= 3 | 8 | 38.10 % |
| | 22 | (Reaction time >= 8 h) & (Equipment <= Stirring) & (Size range >= 0_60 nm) | <= 3 | 1 | 4.80 % |
| | 23 | (Size range >= 30_60 nm) | <= 4 | 4 | 12.12 % |
| | 24 | (Reaction time >= 45 s) & (Temperature >= 55 °C) | <= 4 | 21 | 63.63 % |
| | 25 | (Reaction time >= 10 min) & (Equipment <= Conventional) | <= 4 | 18 | 54.54 % |
| | 26 | (Equipment <= Stirring) & (Size range >= 0_60 nm) | <= 4 | 7 | 21.21 % |

All the protocols qualifying for class 5 use renewable reducing agents, which were indicated by the experts as another driving consideration for this choice (i.e. PIN[9] 4, 5, 6, 7, 8, 13, 14, 15, 16, 17, 18, 19, 20, 46, 48). Based on experts' judgments, such protocols can implement several GCP concurrently, including waste prevention, reduction in use of hazardous chemicals and derivatives, adoption of safer solvents and renewable feedstocks, and inherently safer chemistry.

A major consideration that emerges from rule 1 is the need for further research on the role that different compounds of renewable materials have in the formation, kinetics and stabilization of the nanomaterials. Such understanding can lead to a more informed selection of those materials that can have the widest potentials for increasing reaction speed and yield, thus posing strong basis for large scale synthesis. Nowadays, a preliminary understanding of the compounds that are responsible for the reduction of metal salts for the production of nanoparticles is available, with phenolic compounds indicated as primary responsible for nanomaterials formation [434-436, 459].

Notwithstanding, the individual compounds accountable for the reaction have not been investigated thoroughly, and studies with various findings emerged in recent years. Gallic acid was put forward as the responsible reducing agent for the synthesis of nano-Ag with *Anacardium occidentale* leaf extract, while proteins constituents (i.e. leucine, glutamic acid) acted as the capping agents [460]. Caffeic acid was proposed as the major reducing agent in the formation of nano-Ag starting from *Macrotyloma uniflorum*, due to its higher antioxidant activity compared to the other phenolic acids present in the extract [435]. In a study published in 2014, it was reported that the synthesis of Ag NPs with *Eucalyptus globulus Labill* bark extract was driven mainly by galloyl derivatives, which are considered to be the main electron donors in the redox reaction [436]. On the contrary, the proteins and sugars (i.e. glucose and fructose) present in the extract had a negligible role in the salt reduction, but possibly contributed to the stabilization of the nanoparticles. Nevertheless, other studies that employed sugars as glucose, sucrose and maltose under MW irradiation and conventional heating lead to nano-Ag of various sizes and shapes, which shows the potential role of sugars as reducing agents in NPs synthesis [387, 402, 461, 462].

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[9] Protocol Identification Number (PIN): Identification number for silver nanoparticles synthesis protocols as reported in Appendix B.1

Other protocols satisfying the assignment to class 5 are those employing MW technology with reaction times and temperature equal to or lower than 1 min and 47 °C, respectively, together with the use of renewable materials (rule 2 and 3). Microwave (MW)-enhanced protocols have received great attention in the green chemistry literature as they allow remarkable increment of reaction speed, leading to complete salt reductions with very low irradiation power (e.g. 50 W), even in less than one minute [444]. MW irradiation has the advantages, when compared to conventional techniques, of providing uniform heating, increase kinetics of the reactions by one or two orders of magnitude, improve the kinetics of crystallization and reduce the production of waste [395-397, 401, 403-405]. Several protocols that adopt MW heating technique (i.e. PIN 2, 4, 5, 6, 7, 8, 39, 42), couple it with the use of renewable resources as substitutes for harsh chemicals (e.g. sodium borohydride), which leads to fulfillment of many GCP, namely reduction in hazardousness of chemical synthesis together with the resulting waste, use of safer solvents (e.g. water) and inherently safer chemistry (e.g. closed vessels and low power). Although these protocols under consideration are for small and medium scales reactions, the scale-up of MW technology has been investigated, showing that these systems perform even better at higher scales (i.e. liters) from an energy efficiency perspective [405], which additionally improves the appeal of this equipment.

As far as class 4 (high) synthesis protocols are concerned, rule 5 focuses on protocols that adopt multifunctional materials, in other words those having both a reducing and capping agent function, which can be an environmental sustainability upside as it allows decreasing materials usage and waste production, together with elimination of synthesis steps. Phenolic compounds can both reduce silver salts to nanoparticles and prevent their aggregation by providing excellent capping function, as reported for example in the case of silver nanoparticles synthesis with basil plant [434], red pomace [425] and *Lippia citriodora* [459]. Furthermore, proteins present in the extract can have a premier role in the capping of NPs [434, 436, 463]. The rule indicates that multifunctionality has to be coupled with the use of renewable reducing agent(s) and reaction times as long as 30 minutes. Almost 60% of the protocols in at least the class 4 satisfy these conditions, showing a strong pattern in the dataset. Plants extracts are the primary candidates for this multifunctional advantage, as has been widely reported in the literature [375, 396, 397, 411, 436, 443, 445]. However, the specific reducing and capping mechanisms of these multifunctional materials are not yet well understood [436], and this represents a major area of investigation that could lead to more rational and motivated investments on certain plants types.

Nonetheless, conventional techniques for synthesis protocols are still a major option for producing silver nanoparticles and they can achieve high performance too in cases where renewable materials are used for reactions operating at temperatures up to 40°C (rule 7). More specifically, these mild reaction temperatures can be coupled with reaction times as low as 10 minutes, which are relatively short for this type of equipment (i.e. PIN 36, 37, 43). Such protocols show the potential high performance even for conventional heating techniques when combined with multifunctional renewable reducing agents (i.e. basil plant [434] and Xerophytes – *Bryophyllum* sp. [464]).

94.1 % of the protocols that were assigned to classes 5, 4 and 3 utilize at a minimum a renewable-primary reducing and capping agent together with a renewable-primary solvent (rule 8). This is a strong pattern, which shows how the GCP are widely implementable, even when varying the renewable raw materials choice (e.g. sugars [402, 461], amino acids [444, 465], plants extracts of various sources [443, 460], vitamins [445] and renewable polymers [462]). These choices lead to prevention of harmful waste, less hazardous chemical synthesis and reduction of derivatives. Some of them even perform both reducing and capping actions using waste materials (i.e. red grape pomace and orange peels extract) [391, 425]. Further consideration is needed to better understand the viability of waste materials as candidate sources for high value green products [144, 396, 425].

Opposite considerations are obtained with the "at most" rules. Rule 14 includes worst performing protocols, whose conditions are the use of a capping agent that is of synthetic origin and a temperature above or equal to 170 °C. Processes covered by this rule violate several GCP, including the reduction of waste production, the elimination of synthesis steps and the use of renewable and benign reagents, leading to assignment in the lowest class. Similar considerations emerge from rule 15, which states that the use of synthetic capping agent and solvent for reactions lasting over 4 hours and 15 minutes heavily compromises the GCP, resulting in a very low class due to reduced energy efficiency and process safety.

Analysis of rules 16 and 17 (Figure 6-3 and Table 6-5) shows over 75 % and 40 % of the protocols assigned to *at most class 2* used a synthetic reducing agent and solvent, respectively. More specifically, the DMs underlined the fact that most of the chemicals used in these protocols are hazardous (e.g. sodium borohydride, 1-nonanethiol, chloroformic solution, dodecylthiol, toluene, polypropyleneimine, naphthalene, hydrazine), which is in conflict with the need of using renewable feedstocks, reducing waste production and adopting safer chemistry.

Almost 43 % of the protocols assigned to *at most class 3* operate at a temperature of at least 80 °C with either a biodegradable polymer or a synthetic capping agent (rule 19). This is an interesting feature of the decision model, which reaffirms how use of a redundant component as the capping agent and a relatively high temperature can relegate protocols to class 3 at maximum.

Reaction time and temperature have an important role in the assignment to *at most class 3* (rule 21). A reaction period of at least 45 minutes in conjunction with temperature of at least 60 °C is trigger for assignment up to medium performance. This kind of information can be seen as indirect extraction through DRSA of combined discriminatory thresholds for reaction length and temperature. The experts stressed how the combination of relatively long reaction times and high temperatures are indicative of the need to develop energy efficient protocols to minimize energy use. With the exclusion of one protocol that employs MW (i.e. PIN 22), all the remaining ones are based on conventional heating. Relatively long times for complete reaction are actually one of the major drawbacks of this equipment when compared to MW technology [395, 401, 466, 467].

### 6.3.4 Relevancy of criteria

The different relevance that the criteria have in the assessment can be measured by means of their frequency in the rules [193, 468], which is shown in Figure 6-4. Reaction time and capping agent type are the most recurrent criteria in the decision rules (present 11 times and 9 times respectively), which is confirmed by the unquestionable link that they have with the potentials of reducing environmental impact and improving design for waste prevention and energy efficiency. The remaining parameters are rather equal in terms of appearance in the rules, with the exclusion of the use of local resources, which scores very low (in two rules only), possibly due to the limited discriminatory potentials of its two-categories domain as discussed above, as well as the limited account that the experts placed on it during their classes assignments.

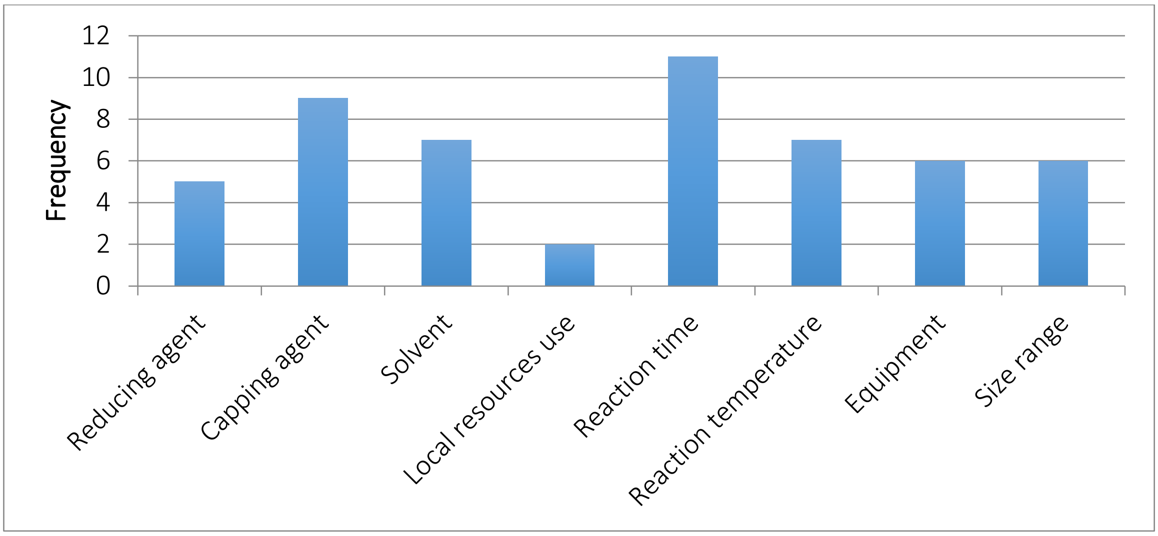


**Figure 6-4: Frequency of criteria in decision rules**

### 6.3.5 Use of DRSA-based model to support decision-making

The results presented so far provide a deep understanding of the reasoning of the DMs, the thinking behind their expertise when judging the implementation of the principles of green chemistry in the synthesis of nanomaterials, in this specific case nanosilver. The DRSA method lead to a decision model composed of decision rules that are easily intelligible and grounded on literature findings and rational explanations (that need quantitative verification in some cases). In order to contribute fulfilling the goals of this chapter, i.e. assess the implementation of GCP in new nanosynthesis processes in the form of a performance class, the decision model has been employed following the methodology proposed in [455], adapted to this decision-making problem (see Section 6.2.4 for details).

As an example, five hypothetical test synthesis protocols (Table 6-6) were prepared and the recommended classes for standard and new classification scheme of DRSA are presented in Table 6-7. Both classification strategies allocate process $t_1$ to $C_5$, whereas they assign $t_2$ and $t_5$ to $C_2$. Protocol $t_3$ and $t_4$ are appointed to more than one class with standard classification method, $C_2$ or $C_3$ for $t_3$ and $C_3$ or $C_4$ for $t_4$, respectively.

**Table 6-6: Test protocols for classification example**

| Test protocol | Reducing agent class | Capping agent class | Solvent class | Local resource use class | Reaction time | Temperature (Celsius) | Equipment class | Size class |
|---|---|---|---|---|---|---|---|---|
| $t_1$ | Renewable primary | Not needed | Renewable primary | No | 55 seconds | 42 | Microwave – sealed vessel (≤ 300 W) | 0-30 nm |
| $t_2$ | Renewable primary | Biodegradable polymer | Synthetic | Yes | 43 minutes | 85 | Conventional | 0-60 nm |
| $t_3$ | Biodegradable polymer | Biodegradable polymer | Renewable primary | No | 10 minutes | 90 | Conventional | 30-60 nm |
| $t_4$ | Renewable primary | Renewable primary | Renewable primary | No | 70 seconds | 65 | Microwave – sealed vessel (≤ 300 W) | 0-30 nm |
| $t_5$ | Synthetic | Synthetic | Synthetic | No | 8 minutes | 100 | Microwave – open vessel | 0-30 nm |

Such outcome is due to the interval of classes that result from the intersection of the covering rules. However, a univocal assignment can be obtained with the new classification scheme, which suggests $C_2$ for $t_3$ and $C_4$ for $t_4$.

Figure 6-5 illustrates the rationale behind the assignment of class with the standard classification scheme for test protocol $t_1$. Seven decision rules (i.e. 3, 5, 6, 8, 11, 12, 13), all of the type “at least”, match the conditions of the test protocol. Rules 3 recommends at least $C_5$ (green colour), rules 5 and 6 suggest class at $C_4$ (yellow colour), rule 8 advances class at $C_3$ (orange colour) and rules 11, 12 and 13 suggest at least $C_2$ (purple colour). The recommended class derives from the intersection of the lowest class covered by all the rules, which in this case is $C_5$.

**Table 6-7: Performance classes assigned by DRSA-based decision support model (* = identification number of rules whose conditions match the test protocol)**

| Test protocol | Recommended class by standard scheme | Recommended class by new scheme | *Maximum score for new scheme* | IN of matching rules* |
|---|---|---|---|---|
| $t_1$ | 5 | 5 | 0.33 | 3, 5, 6, 8, 11, 12, 13 |
| $t_2$ | 2 | 2 | 0.22 | 12, 17, 19, 24, 25, 26 |
| $t_3$ | 2 or 3 | 2 | 0.26 | 11, 12, 19, 20, 23, 24, 25, 26 |
| $t_4$ | 3 or 4 | 4 | 0.26 | 8, 11, 12, 24 |
| $t_5$ | 2 | 2 | 0.33 | 16, 17, 19, 24 |

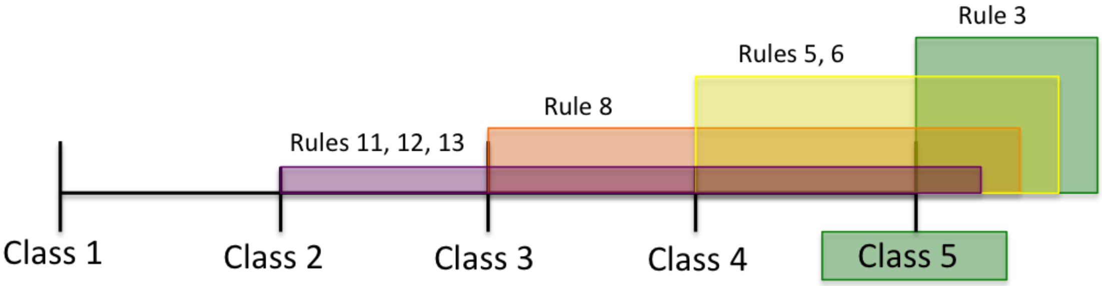


**Figure 6-5: Recommendation of class for test protocol $t_1$ based on standard classification scheme**

This result is reinforced by the new classification scheme, whose highest score (0.33) is also for $C_5$, indicating that the strongest concordance of the decision rules is on such class (Table 6-8). Its value is calculated as follows:

$$Score_R^{+}\left(Cl_{5\,=\,very\ high}, t_1\right) =$$

$$\frac{|\text{Protocols satisfying conditions of rules 3,5,6,8,11,12,13 and belonging to class 5}|^2}{|\text{Protocols satisfying conditions of rules 3,5,6,8,11,12,13}|\ |\text{Protocols belonging to class 5}|} =$$

$$\frac{|4,5,6,7,8,13,14,15,16,17,18,19,20,46,48|^2}{|1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17,18,19,20,21,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48|*15}$$

$$= \frac{15^2}{(46*15)} = 0.33$$

$Score_R^{-}\left(Cl_{5\,=\,very\ high}, t_1\right)$ is 0 as there are no rules that do not cover $C_5$ as a possible recommendation and consequently $Score_R^{net}\left(Cl_{5\,=\,very\ high}, t_1\right)$ is equal to 0.33. Table 6-8 reports all the scores for each class based on the new classification scheme (see Appendix B.2 for detailed scores calculations for each class). The *Score⁺* values indicate the strength of the support that the covering rules provide in the assignment to each class. More specifically, for $C_5$, all the covering rules (i.e. 3, 5, 6, 8, 11, 12, 13) include it and they all concur to the calculation of the value. For $C_4$ all the covering rules but rule 3 embrace it, which results in a slightly lower value than that for the best class. Conversely, *Score⁻* values account for the strength of assignment to a different class from the one under consideration. In the case of $C_5$, there are no rules that do not cover it and consequently *Score⁻* is 0, whereas it increases as the classes become worse. $C_4$ has rule 3 that does not include it and consequently it works against its assignment to such class. For $C_3$ and $C_2$, rules 3, 5, 6 and 3, 5, 6 and 8 exert this role, respectively.

**Table 6-8: Scores of each class for test protocol $t_1$ based on new classification scheme**

| Class | *Score⁺* | *Score⁻* | *Score^net^* |
|---|---|---|---|
| **5** | 0.33 | 0.00 | 0.33 |
| **4** | 0.27 | 0.05 | 0.22 |
| **3** | 0.15 | 0.44 | – 0.29 |
| **2** | 0.22 | 0.89 | – 0.67 |

A different case is test protocol $t_3$, where the standard classification method suggests the assignment to $C_2$ or $C_3$ without possibility of refinement (Figure 6-6). This is the interval between the recommended class from “at least” rules (i.e. 2, rules 11 and 12) and the worst one from “at most” rules (i.e. 3, lowest intersection of classes for rules 19, 20, 23, 24, 25, 26). Nonetheless, the new scheme indicates that the strongest support of the rules is for $C_2$, which results in the assignment to a specific class in this ambiguous case too (Table 6-7 and Table 6-9). More specifically, the scores for $C_2$ are the following:

$$Score_R^{+}(Cl_{2\,=\,low}, t_3) =$$

$$\frac{|\text{Protocols satisfying conditions of rules }11,12,19,20,23,24,25,26\text{ and belonging to class }2|^2}{|\text{Protocols satisfying conditions of rules }11,12,19,20,23,24,25,26|\ |\text{Protocols belonging to class }2|} =$$

$$\frac{|9,10,11,21,23,24,25,26,27,29,32,47|^2}{|1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48|*12}$$

$$= \frac{12^2}{(47*12)} = 0.26$$

$$Score_R^{-}(Cl_{2\,=\,low}, t_3) = 0$$

$$Score_R^{net}(Cl_{2\,=\,low}, t_3) = 0.26 - 0 = 0.26$$

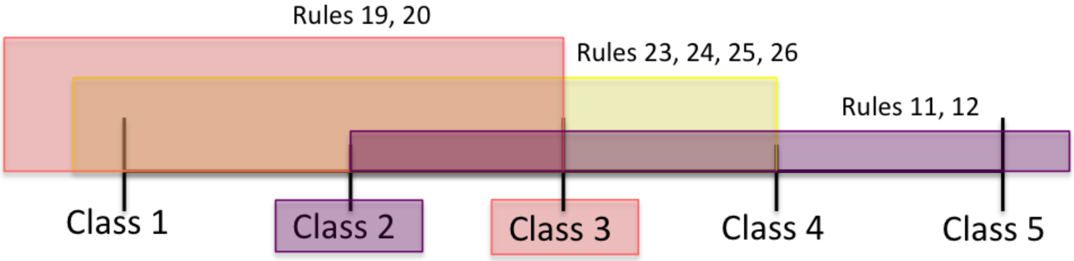


**Figure 6-6: Recommendation of class for test protocol $t_3$ based on standard classification scheme**

**Table 6-9: Scores of each class for test protocol $t_3$ based on new classification scheme**

| Class | *Score⁺* | *Score–* | *Score^net* |
|---|---|---|---|
| **5** | 0.33 | 0.91 | – 0.58 |
| **4** | 0.27 | 0.31 | – 0.04 |
| **3** | 0.15 | 0.00 | 0.15 |
| **2** | 0.26 | 0.00 | 0.26 |
| **1** | 0.02 | 0.98 | – 0.96 |

Table 6-9 indicates that although the strength of the recommendation for $C_3$ is much higher than that for $C_1$, $C_4$ or $C_5$, the value for $C_2$ is the highest, which triggers the assignment to such class (see Appendix B.2 for detailed scores calculations for each class). $C_5$ has a relatively high *Score*$^+$ (i.e. 0.33) due to the strong support of rules 11 and 12, however rules 19, 20, 23, 24, 25, 26 advance the assignment to a class other than 5, resulting in a high *Score*$^-$ (0.91). The difference between these scores is – 0.58, which conveys a strong discouragement for the assignment of the protocol to $C_5$. On the other hand, $C_3$ and $C_2$ are supported by all the covering rules and consequently their *Score*$^-$ is 0.

*Score⁺* for $C_3$ is lower than that for $C_2$ as their value depends on the number of protocols in each class, which is higher for $C_2$ compared to $C_3$.

This example demonstrates the potential use of the rules as decision-making support for the green chemistry-oriented synthesis of silver nanoparticles. More generally, the exploitation of the decision rules through the DRSA classification schemes demonstrated that it is possible forging a classification model assigning performance classes for new nanomaterials following the implementation of GCP during its synthesis, which was actually the research objective listed in the introduction. In fact, the DM can define the synthesis protocol that needs to be assessed, obtain the recommended performance class with both classification schemes based on DRSA and trace the decision recommendation to the trigger decision rules.

### 6.3.6 Practical benefits of the DRSA-based model

This model shows as a proof of concept that integrating available information on synthesis processes for nanoparticles and expert knowledge can result in a qualitative model for the classification of new or existing processes in preference-ordered classes. The practical benefits that the DRSA-based model can provide include:

i. Reduce the direct training required for new or novice researchers as they can learn from the decision rules;
ii. Allow less experienced researchers to have more responsibility since they can use the decision rules as screening evaluation tools for new processes development;
iii. Reduce the effort for practitioners in the field in terms of evaluation of green alternatives to pursue (i.e. quick screening of production processes by means of the classification recommendation);
iv. Allow the experts to focus on more challenging tasks as they do not need to spend so much time on training others;
v. Use the available unstructured information in an efficient and effective manner.

It must be stressed that the result of the model is a decision recommendation and not an absolute answer, as it is based on limited and mostly qualitative information as well as on experts' judgment. However, it can be used as a first-stage screening tool that can support practitioners in the area to reason about the synthesis process they are developing, the decision rules that fit with it and the agreement or not with the type of class that was recommended.

### 6.3.7 MCDA as a support for sustainability assessment

The potentials of MCDA to aid SA have emerged in the last decade. DRSA was confirmed as a good candidate for such goal (see Chapter 4) and it was adopted in this case study since it satisfied the main research requirements: (i) provision of design guidelines and (ii) development of a classification model. This last part of the chapter analyses how MCDA and more specifically DRSA can address complex systems management and sustainability-related research. It is based on the question-answer approach described in [227] and structured in three sets: (i) systems characteristics; (ii) principles of sustainable development and (iii) procedure of decision-making.

#### *6.3.7.1 MCDA and systems characteristics*

- *Are relevant dimensions and resulting objectives and criteria addressed?*

  The case study was focused on the assessment of implementation of GCP in the synthesis processes for nanosilver. The dataset of processes was based on the available published information, which resulted in the consistent set of 8 assessment criteria for each of the 48 production protocols. Even though this is not a comprehensive set of criteria to assess the quantitative implementation of green chemistry criteria, it can be regarded as the best available use of the fragmented literature available so far. The relevancy of the criteria is justified by their selection from a comprehensive and reliable framework of criteria described in Chapter 5.

- *Was incommensurability of criteria allowed for?*

  DRSA satisfied excellently the capacity of handling incommensurable (i.e. no need for a common measure) scales for the criteria, without the necessity of converting all the evaluation scales to a unified one.

- *Were trade-offs between objectives addressed and compromised found?*

  DRSA expresses trade-offs through the decision rules, by combining the conditions of the criteria with the resulting classification recommendation. Once discussed and accepted by the DMs they become the decision model. As a consequence, DRSA highlights clearly the trade-offs and DMs can accept or reject them by going back to their expert judgment (preference information provision) step.

- *Were mechanisms applied to address uncertainty/risk/ignorance and indeterminacy?*

  Detailed assessment of the DRSA-based model robustness is discussed in Chapter 7, which confirms its stability to variable input data as well as DMs' preferences.

- *Could the decision aid cope with different forms of data (quantitative, qualitative, linguistic, fuzzy, ...)?*

  DRSA can handle various types of data and more importantly it does not require any data pre-treatment.

#### *6.3.7.2 MCDA and principles of sustainable development*

- *Was strong sustainability supported by the decision aid?*

  DRSA does not accept compensation between the criteria and thus allows enforcing a strong concept of sustainability.

- *Did decision-making allow for or require participation of all affected people? Did it enhance empowerment? Was the information and knowledge gathered from the stakeholders integrated into the decision? In other words, was democracy supported?*

  The collaboration with experts was performed at the U.S. Environmental Protection Agency, a centre of excellence for research on sustainability science. The original aim was to include various experts into the assessment as well as criteria from different sustainability domains. However, the current information does not allow for a quantitative characterization of the impacts, which phased out the possible use of any LCA or similar quantitative assessment tools. The socio-economic sphere was also not tackled because of the lack of accessible information on the various production processes, as well as competent experts in such domains. It is important to note that this is not a deficiency of the MCDA method selected here, but it is rather due to the lack of available information on these processes and the consequent availability of experts in such areas.

#### *6.3.7.3 MCDA and the decision-making procedure*

- *Was the focus of the decision-making put on the process and the result?*

The case study was built upon the MCDA process (which lasted around 12 months), which is inherently based on the co-construction of the decision support model together with the DMs. As a consequence, MCDA satisfies completely the need for comprehensive support to the whole decisional process.

- *Did the decision-making process allow for and support the learning of individuals and groups?*

  Yes, the learning is supported by DRSA through the verification of consistency in judgments, the minimum set(s) of criteria that constitute the reduct and the decision rules that cluster knowledge in an easy-to-grasp information format.

- *Was there room for non-agreement between DMs/actors? Were different scenarios applied?*

  Yes, DRSA has been specifically developed to handle inconsistencies and disagreement among DMs. However, in this case study the experts involved in the MCDA process provided the same preference input for the classification of the alternatives.

- *Was the process transparent and understandable?*

  The MCDA procedure was perceived as very useful and understandable by the experts/DMs. The structuring of the problem performed in cooperation between the analysts and DMs was important to allow the development and use of a “common language”. The preference input in terms of global judgment was perceived as reasonable and simple to exert by the experts. Furthermore, the decision rules where very easy to understand and their straightforward traceability was a strong advantage of DRSA.

- *Did the decision-making lead to a result which could be expressed in the form of implementable action?*

  Yes, the resulting decision model proves conceptually that even in the realm of limited information it is possible developing tools that can provide classification of existing or new production processes for nanomaterials in preference-ordered classes for which information on the 8 assessment criteria is made available.

- *Was the result acceptable for the stakeholders?*

The model is the result of direct interaction and involvement of the stakeholders, in this case the two green chemistry experts, which lead to a very high acceptance of the model.

- *Was there an evaluation of the process and the result carried out (interim and ex-post)?*

  The resulting classification model was tested in terms of robustness of its recommendations. This step is described in Chapter 7.

- *Was the language used understood by all people involved?*

  A few meetings were necessary to find a "common language" to support communication between the analysts and the DMs. This is an important aspect to be satisfied in any MCDA applications, otherwise there can be loss of motivation and efficacy and potentially also of successful and consistent model construction.

- *Was the applied decision aid flexible and adaptive, including feedback loops and the possibility of redesigning options, criteria, and impacts?*

  Yes, the MCDA process and the DRSA are easily adaptable to the decisional problem. Further criteria can be added as well as preference information. The software (i.e. JMAF) for decision rules calculation is rather straightforward to use, even though a competent decision analyst is a highly recommended figure to ease and guarantee a smooth aiding procedure.

### 6.3.8 Discussion

MCDA has been shown to be very useful in engaging the DMs in selecting the evaluation criteria and the development of the dataset. Additionally, the explanation of experts' choices through the use of *"if … , then …"* decision rules is easily intelligible and the model is seen as supportive for future screening of new silver nanoparticles production protocols. The structured process that MCDA follows provides stakeholders with the possibility of tracking all the evaluation stages and its conclusions, thus supporting more transparent decision-making.

Regarding the criteria selection, main constraints to their number and possible values have been the limited information reported in many protocols that are part of the dataset. In this regard, the categories for the types of reducing agent, capping agent and solvent were limited to renewable (waste or primary), biodegradable polymers and synthetic. No considerations about the effective toxicity of most of the renewable materials were taken into account due to the lack of this type of information. Another constrain was the lack of data about the availability of some of the materials that were used, which did not allow accounting for the potential large scale implementation of the synthesis protocols.

Furthermore, the applicability of the rules for the practical synthesis of silver nanoparticles might depend on the location the synthesis is planned for. The quantitative assessment of the impacts of these choices are out of the scope of this research and they could become a focus of future studies if more detailed information about the implications of materials selection becomes available.

Due to the limitations reported above the model that was developed in this case study is not to be seen as a comprehensive tool for evaluating how green silver nanoparticles synthesis protocols are, but rather it is a demonstration that the MCDA process can be of help to better define the complex task of developing synthesis protocols for silver nanoparticles, including the identification of the main parameters and stakeholders that drive this decision-making problem. DRSA has shown how a wide variety of information type and quality can be aggregated through experts' elicitation, posing the basis for the development of easily intelligible decision support tools for green chemistry-based synthesis of nanomaterials.

This research advances recommendations that can be used to conceive tools for more detailed assessment of synthesis protocols for silver nanoparticles. Firstly, comparability of processes can be greatly increased if information about how the surface chemistry, samples purity, and particles coating affect their function (which should be a measurable target in each study). Secondly, a thorough investigation of the toxicity of the materials used and produced is needed so that toxicity-based categories for the types of materials can be added, strengthening the approach from a regulatory perspective. Thirdly, investigations about the availability of the raw materials should be conducted in order to consider the potentials for actual exploitation of raw materials for large-scale synthesis. In addition, quantification of the synthesis processes in terms of reactions yield, waste production and energy consumption of the considered (and additional) equipment (e.g.

sonication) would greatly benefit quantitative assessments of the implications of each protocol.

The model that was developed is not limited to the use of GCP, and it can be expanded to include other sustainability-related criteria (available from the framework described in Chapter 5), provided that this additional information is made available and domain-specific experts are involved in the MCDA process. The latter consideration is of paramount importance as each problem is characterized by DMs who have the role of making decisions. The DMs in MCDA are the individuals who are involved in defining the problem, collaborating in the selection the evaluation criteria and construction of the decision model. If these persons are not involved in the MCDA procedure there is not real decision aiding, which also will not lead to implementation of assessment criteria in the real value chain of the alternatives (e.g. nanomaterials synthesis protocols, nanomaterials recycling, nanomaterials distribution, etc.) under assessment.

The ensuing model is based on current information of synthesis processes for nanoparticles and the experts' knowledge. It can be expected that new information will become available, uncertainties will be reduced and the preferences might change, which calls for a regular update of the decision model to keep it up-to-date [469].

## 6.4 Summary

This chapter provides an overview of the types of sustainability-oriented synthesis techniques that were developed to produce nanomaterials during more than one decade. As a result of the increasing concerns about the implications of nanotechnology, several attempts were made to integrate green chemistry and engineering principles in this life cycle stage. This led to the emergence of "non-conventional" approaches such as template method, ultrasound and microwave-based procedures and also the adoption of "greener" solvents such as ionic liquids. However, the synthesis route that experienced the broadest interest was the bio-inspired one due to the use of benign and renewable reagents that also allowed very favourable processing conditions, namely mild temperature and ambient pressure. Several biogenic sources, also combined to the "non-conventional" routes mentioned above, were studied including fungi, bacteria, algae and plants, among which the latter showed the most promising potentials when compared to conventional processes. Such advantage is due to the relatively quick reaction processes that can be faster than the conventional ones, cost efficiency, as well as easier scale-up in respect to other biogenic options.

Overall, the analysis of the various production routes has confirmed that several attempts have been tried to integrate sustainability principles in the synthesis step of nanomaterials, however most of the studies focus on the individual proposition of a synthesis protocol, especially in the case of bio-inspired route. Furthermore, design guidelines to aid greener nanomaterials development and production have been advocated by researchers as well as professional organizations and governmental agencies, but they were missing so far.

The integration of sustainability practices into the life cycle of NPs is a necessity to be satisfied in order to guarantee a prosperous development of nanotechnology. Chapter 5 provided an initial robust ground for the achievement of this goal by proposing a comprehensive cluster of SA criteria for NPs. What is more, assessment tools that can convey comprehensible and reliable indication about the extent of the sustainability performance of NPs are an impelling necessity and are also in accordance with the aim of this Ph.D., i.e. supporting responsible development of nanotechnology. This chapter presented the research that tackled such challenge and partially satisfied the fourth objective of the thesis by developing a classification model based on GCP for silver nanoparticles synthesis processes, where the fulfilment of certain synthesis conditions (i.e. design rules) trigger assignment of a “green” label (i.e. performance class) for the nanomaterial synthesis.

The focus on the synthesis stage was due to the wide interest that has been placed on it since it is the phase where the functionality of the NPs is determined and the characteristics of the manufacturing can be influential from the sustainability impacts perspective, considering the type of materials employed, the equipment and the processing conditions. Silver nanoparticles were used as the case study because of (i) the ample literature information that allowed creating a workable database, (ii) the availability of knowledgeable experts in the area who agreed to take part in the decision aiding process and (iii) the business potential of these materials, considering the wide range of applications that are enabled and envisioned by silver nanoparticles.

Developing synthesis processes for NPs that follow the vision of sustainability principles and shaping guidelines for their responsible and sustainable production need multidisciplinary networks of people from various expert backgrounds. From a holistic perspective all the stakeholders and the life cycle implications should be included and accounted for. In order to achieve this objective it is necessary to have sound methodological approaches as support. MCDA provides a process and tools that are excellent for such challenge (as Chapter 2-4 confirmed) and thus it was employed here. Although this research covers only one step of the life cycle of a NP due to the limited accessible information and experts as well as the time and effort available, it is an important proof of concept that shows how moving sustainable nanotechnology forward is possible if the relevant people collaborate within the proper research approach.

The MCDA process was used as a knowledge elicitation and decision aid tool to include DMs in the development and assessment of protocols for the synthesis of silver nanoparticles. The approach was used to structure the decision problem, identify the alternatives and the criteria to be used for comparing them, elicit the preferences of DMs and derive a classification model for existing or new silver nanoparticles synthesis protocols. Such classification model provides two major contributions:

i. Identification of the specific reasons and the extent for which some nanosyntehsis processes perform better than others from a green chemistry perspective (i.e. design rules);
ii. Assessment of the implementation of GCP in new nanosynthesis processes in the form of a performance class.

DRSA was selected as a MCDA method due to its flexibility in handling heterogeneous information, the lack of compensation among the criteria, the intelligibility of its results in the form of *"if* condition*, then* decision*"* rules, and the simplicity of their application. All these factors were well received from the two DMs involved in the decision aiding process, confirming that this methodology can be considered as a ”glass box” when compared to conventional MCDA approaches. DMs also provided their expert classification for each synthesis process among a five-class set from very high to very low on the basis of their interpretation of implementation of the principles of green chemistry.

DRSA results show that DMs’ judgments were all consistent, leading to a unitary quality of classification, an indication of relevant problem structuring. The presence of a reduct with all but one of the criteria suggests that almost the whole set plays a discriminatory role in the protocols evaluations.

26 decision rules, that explain DMs' expertise and knowledge for the classification of silver nanoparticles synthesis in preference-ordered classes, were derived; 13 for the *at least classes* and 13 for the *at most classes*. The best performance (class 5) was assigned to the protocols that adopt very simple equipment, renewable resources and low temperatures (≤ 30°C).

Use of multifunctional renewable materials is a main driver for high performance classification. Nonetheless, more research should be devoted to the understanding of the reducing and capping mechanisms of such materials, in order to pose strong basis for the selection and exploitation on a large scale of the optimum resources types. This would require further investigation in the formation, kinetics and stabilization processes for the synthesis of silver nanoparticles mediated by renewable sources. On the other hand, the use of a synthetic material as a capping agent relegates the synthesis process to a low performance class because such a choice results in an increase of waste production, harmful processing and no implementation of raw materials multifunctionality. Use of hazardous synthetic materials is against the need of employing benign feedstocks and reducing solvent-intensive purification steps. As a result, protocols with these features are normally relegated to a low to very low category. Furthermore, thresholds for combinations of reaction times and temperatures were derived for classification of some medium to very low performance protocols, showing the potentials of the MCDA approach as an aid to identify preference values that would be otherwise difficult to elicit from DMs.

The decision rules represent a decision model that can be utilized as a tool supporting the assignment of new or existing synthesis protocols for silver nanoparticles to performance classes, based on GCP, showing that as a proof of concept a classification model in this area of research can be devised. Nonetheless, there are still limitations in terms of data availability for the development of an assessment tool inclusive of important parameters that can render the model applicable in experimental settings, such as materials toxicity and availability.

Several advantages emerged from the use of DRSA in this case study:

i. It does not require direct elicitation of cognitively demanding information (such as criteria weights, assessment of virtual lotteries, pairwise comparisons of criteria and alternatives on an intensity scale, and comparison thresholds) from the DMs, as it is for other MCDA methods when employed with direct preference elicitation techniques (e.g. Multi Attribute Utility Theory, Analytical Hierarchy Process, outranking methods);
ii. The preference information is obtained by means of comprehensive judgments on exemplary protocols, which can be provided in an easy and comfortable manner from the DMs;
iii. No transformation of criteria domains from ordinal to cardinal scales is required;
iv. The approach provides information about the classification ability of the selected criteria and the minimal set of criteria indispensable for the consistent assessment;
v. The decision model is composed of decision rules expressed as *"if* condition, *then* decision*"*, which are transparent and easily understandable by the DMs. The rules are related to specific alternatives (e.g. nanoparticle synthesis protocols), which allows tracing and improving the decision process;
vi. It can deal with the inconsistencies in judgments and handle heterogeneous information;
vii. DRSA does not need any preliminary or additional information about the data, such as probability distributions in statistics, or grade of membership or the value of possibility in fuzzy set theory;
viii. DRSA employs a strong concept of sustainability, which does not accept performance compensation on the criteria.

The whole DRSA-based procedure has been shown to be a good solution to support decision-making for the governance of silver nanoparticles synthesis, introducing several benefits that might not be achievable with traditional approaches. The process is transparent and structured, qualifying for a management tool that can be updated regularly. Stakeholders can be directly involved in the decisional process, additional perspectives and relevant criteria can be included on the problem at hand. An important remark is that in order to effectively tackle decision-making problems, inclusion of DMs in the whole MCDA process is mandatory, since there cannot be real decision aiding without actually supporting the persons who make the decisions. DRSA fully satisfies this requirement and it can be used as an indirect preference elicitation tool that can support DMs in better understanding their choices, knowledge and expectations. A model based on DRSA can be proved useful not only to academics and researchers trying to derive robust and transparent recommendations about their choices but also to businesses whose interest is to find justifiable and understandable explanations to the decisions that they made.

The research that was described in this chapter partially fulfills the fourth objective of this Ph.D. thesis, considering that a model (DRSA-based) for the classification of nanoparticles based on the GCP, coupled with the provision of design rules for greener nanosynthesis, was achieved. Nonetheless the decision recommendation from decision support tools needs to be tested in terms of robustness before being justifiable and credible. This last step was conducted through the development of another classification model, independent from the one described here, which provided uncertainty-characterized robust classifications for the same test protocols of the DRSA-based model. This allowed comparing the decision recommendations of the two models, assessing their agreement and testing the robustness of the DRSA-based one. The next chapter explains this research stage in detail.

# Chapter 7. Robustness Analysis of DRSA-based Classification Model for the Synthesis of Silver Nanoparticles

## 7.1 Introduction

The DRSA-based model described in Chapter 6 is a notable achievement from a decision aiding perspective [226]. In fact it shows how the MCDA process and one of its methods can be used through the disaggregation approach for preferences elicitation by posing limited burden on the DMs and obtaining condensed and intelligible representation of their knowledge in the form of decision rules.

More importantly, the DRSA-based model represents a partial fulfilment of the fourth objective of this Ph.D., which is the development of a model for the assignment of a performance class to nanosynthesis processes depending on the observance of GCP. The adjective “partial” is due to the fact that another condition must be satisfied in order to achieve this objective and that consists in the model to be robust, providing in such a way a well-grounded decision support tool [57, 218, 470]. The research presented in this chapter describes the procedure that was adopted to assess its complete fulfilment. This was attained through a robustness analysis of the DRSA-based model, which allowed comparing the decision recommendations of this model with those of another one (named ELECTRE-based model) built on Stochastic Multi-criteria Acceptability Analysis (SMAA-TRI), providing uncertainty-characterized robust findings.

## 7.2 Methodology

Robustness analysis and uncertainty management in MCDA have been subject to growing interest from the scientific community. This is due to the impelling necessity of accounting for limited data availability and quality as well as the subjectivity inherent in decision support model settings and construction [57, 471, 472].

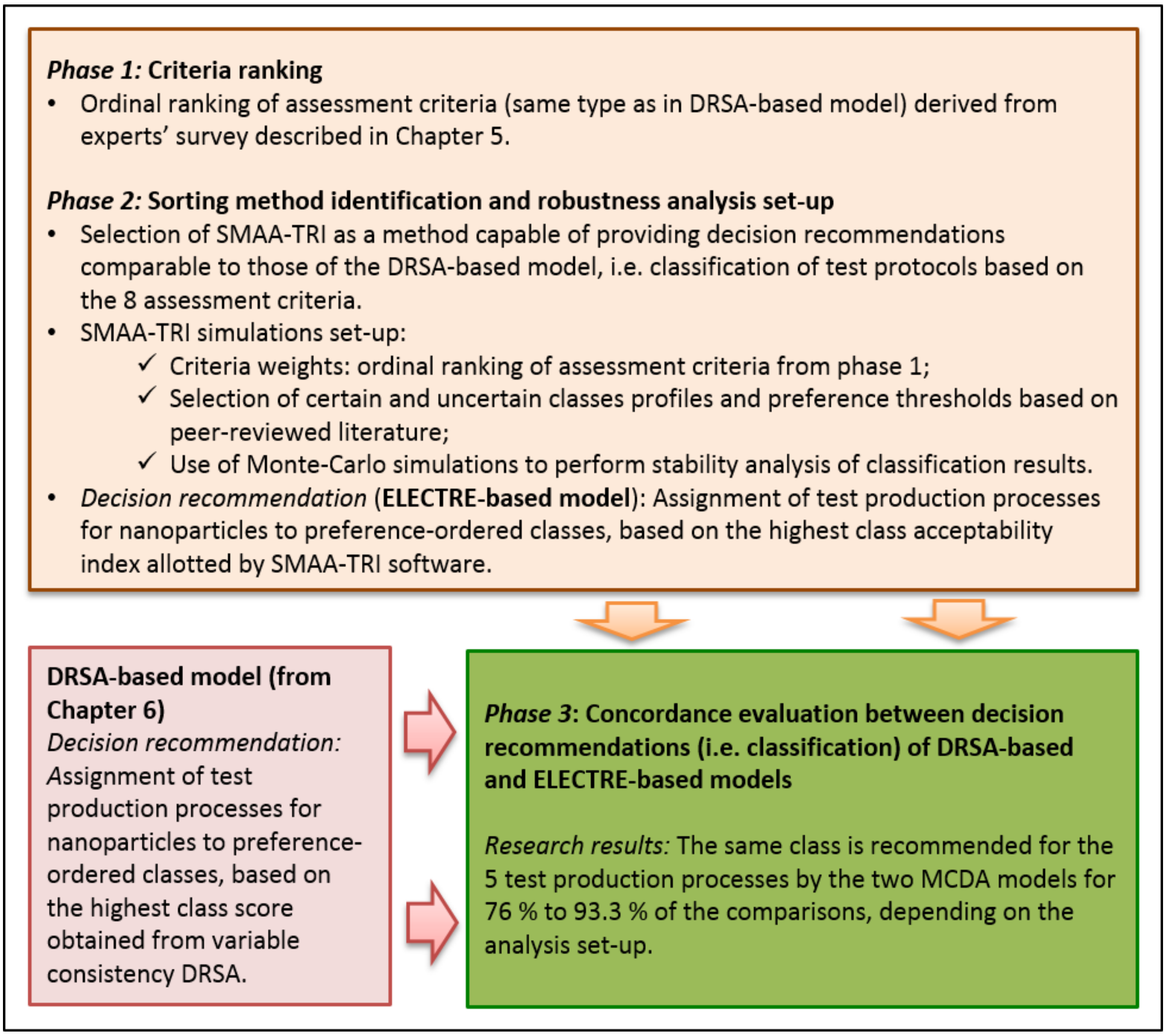
Robustness analysis in decision aiding can take three different forms [471]:

- Ex-ante: this is common of optimization problems, where the model is constructed and the respective algorithm is used to identify a solution that is robust with respect to one or more target criteria (e.g. cost minimization, efficiency maximization);

- Ex-post: this form is concerned with the validity of the recommendation and the potential change from one model version to the other. Robust conclusions can be seen as results that are compatible with different model versions deemed compatible with modelling settings.
- Interactive: RA is iteratively repeated throughout the decision process to aid the DMs reaching an agreed recommendation that complies with their modelling requirements. Starting from a relatively wide set of model versions, the RA will help the DMs reducing them to a smaller set in compliance with compatible preferences elicited during the process.

In the context of this research, which is grounded on the decision aiding paradigm, the uncertainty is related to model performance (i.e. technical data) and DMs' preference. The RA adopted in this case is ex-post, because the research objective consists in assessing the stability of the recommendations according to a pre-defined set of compatible models.

This part of the research builds upon the decision-making problem tackled in Chapter 6 (and published as a journal paper [226]). Consequently, only a limited description of the decision-making challenge is provided here, whereas the focus in placed on the approach adopted to perform the robustness analysis of the DRSA-based model, which was structured in three phases as summarized in Figure 7-1. This included the elaboration of the relative ranking of SA criteria from Chapter 5 (phase 1), the selection process for the suitable sorting method, as well as the modelling used to obtain comparable classifications for the test alternatives (phase 2), and the strategy used to assess the robustness of the DRSA-based model recommendations (phase 3).



***Phase 1:* Criteria ranking**

- Ordinal ranking of assessment criteria (same type as in DRSA-based model) derived from experts' survey described in Chapter 5.

***Phase 2:* Sorting method identification and robustness analysis set-up**

- Selection of SMAA-TRI as a method capable of providing decision recommendations comparable to those of the DRSA-based model, i.e. classification of test protocols based on the 8 assessment criteria.
- SMAA-TRI simulations set-up:
  - ✓ Criteria weights: ordinal ranking of assessment criteria from phase 1;
  - ✓ Selection of certain and uncertain classes profiles and preference thresholds based on peer-reviewed literature;
  - ✓ Use of Monte-Carlo simulations to perform stability analysis of classification results.
- *Decision recommendation* (**ELECTRE-based model**): Assignment of test production processes for nanoparticles to preference-ordered classes, based on the highest class acceptability index allotted by SMAA-TRI software.

**DRSA-based model (from Chapter 6)**
*Decision recommendation:* Assignment of test production processes for nanoparticles to preference-ordered classes, based on the highest class score obtained from variable consistency DRSA.

***Phase 3*: Concordance evaluation between decision recommendations (i.e. classification) of DRSA-based and ELECTRE-based models**

*Research results:* The same class is recommended for the 5 test production processes by the two MCDA models for 76 % to 93.3 % of the comparisons, depending on the analysis set-up.

**Figure 7-1: DRSA-based model validation procedure and outcomes summary**

### 7.2.1 Identification of alternatives and assessment criteria

The alternatives used in this MCDA problem are "silver nanoparticle synthesis protocols based on bottom-up approaches that use reducing and capping agents to convert a silver salt to silver nanoparticles". The points of view used to assess these processes were essentially the GCP [388] and technical performance of the ensuing nanoparticles. Since the objective of this research phase was to test the robustness of the DRSA-based model recommendations, the same test (i.e. non-reference) protocols used to show its decision support as in Chapter 6 and [226], characterized by the same criteria measurements, were employed in this case as well.

The criteria selected for the assessment are 8 and are shown in Table 7-1, together with their coding and preference direction. Criteria $g_5$ and $g_6$ have cardinal (i.e. quantitative) evaluation scales while all the others have ordinal (i.e. qualitative) evaluation.

**Table 7-1: Criteria selected for assessment of synthesis protocols, including coding and rationale for preference order (the arrow 'up' means that the higher its rank on the list of possible values, the better it is, and the arrow 'down' says the opposite)**

| Criterion | Criterion values | Code | Preference order of the values |
|---|---|---|---|
| $g_1$ = Reducing agent | Renewable – waste | 4 | ↑ |
| | Renewable – primary | 3 | |
| | Biodegradable polymer | 2 | |
| | Synthetic | 1 | |
| $g_2$ = Capping agent | Not needed | 5 | ↑ |
| | Renewable – waste | 4 | |
| | Renewable – primary | 3 | |
| | Biodegradable polymer | 2 | |
| | Synthetic | 1 | |
| $g_3$ = Solvent | Renewable – waste | 4 | ↑ |
| | Renewable – primary | 3 | |
| | Biodegradable polymer | 2 | |
| | Synthetic | 1 | |
| $g_4$ = Local resources use | Yes | 1 | ↑ |
| | No | 0 | |
| $g_5$ = Reaction time | In seconds | integer | ↓ |
| $g_6$ = Reaction temperature | In Celsius | integer | ↓ |
| $g_7$ = Equipment type | Static | 8 | ↑ |
| | Stirring for at most 5 minutes | 7 | |
| | Stirring | 6 | |
| | Microwave – sealed vessel (≤ 300 W) | 5 | |
| | Microwave – sealed vessel (> 300 W) | 4 | |
| | Microwave – open vessel | 3 | |
| | Conventional (oil bath, steam bath) | 2 | |
| | Not reported | 1 | |
| $g_8$ = Particles size range | 0 ≤ particle size ≤ 30 nm | 1 | ↑ |
| | 0 ≤ particle size ≤ 60 nm | 2 | |
| | 30 < particle size ≤ 60 nm | 3 | |
| | 0 < particle size ≤ 100 nm | 4 | |
| | 60 < particle size ≤ 100 nm | 5 | |

Table 7-2 shows the five synthesis protocols that were used as test dataset.

**Table 7-2: Non-reference protocols used to show DRSA-based model applicability and to perform its robustness analysis (from [226])**

| Test protocol | $g_1$ | $g_2$ | $g_3$ | $g_4$ | $g_5$ | $g_6$ | $g_7$ | $g_8$ |
|---|---|---|---|---|---|---|---|---|
| | Reducing agent code | Capping agent code | Solvent code | Local resource use code | Reaction time (seconds) | Tempera-ture (Celsius) | Equipment type code | Size range code |
| $t_1$ | 3 | 5 | 3 | 0 | 55 | 42 | 5 | 1 |
| $t_2$ | 3 | 2 | 1 | 1 | 2500 | 85 | 2 | 2 |
| $t_3$ | 2 | 2 | 3 | 0 | 600 | 90 | 2 | 3 |
| $t_4$ | 3 | 3 | 3 | 0 | 70 | 65 | 5 | 1 |
| $t_5$ | 1 | 1 | 1 | 0 | 480 | 100 | 3 | 1 |

### 7.2.2 Assessment criteria priorities

The first phase of the DRSA-based model validation procedure (see Figure 7-1) was shaped around the consideration that relevant information about the relative importance of the assessment criteria mentioned above could be extrapolated from the results of the survey questionnaire described in Chapter 5 (Table 7-3).

**Table 7-3: Relative ranking of criteria from survey described in Chapter 5 and correspondence between those employed in DSRA-based model and its robustness analysis (ELECTRE-based model)**

| Criteria in survey (Chapter 5) and relative ranking | | Correspondent criteria in DRSA-based model and its robustness analysis (ELECTRE-based model) |
|---|---|---|
| 1 | Functionality | Particle size range |
| 2 | Hazardous materials used or produced | Reducing agent / Capping agent / Solvent |
| 3 | Use of renewable resources | Reducing agent / Capping agent / Solvent |
| 4 | Energy efficiency | Equipment type |
| 5 | Energy consumption | Equipment type |
| 6 | Use of raw materials | Reducing agent / Capping agent / Solvent |
| 7 | Local resources use | Local resources use |
| 8 | Processing conditions | Reaction time |
| | | Reaction temperature |

The criteria in the survey were ranked according to their relative importance, which provides an ordinal ranking of such parameters, as reported in Table 7-3 a type of preference information that was considered as potentially useful in the robustness analysis procedure (more details in section 7.2.3). Similar approaches emerged in alike research contexts, where rankings of criteria based on experts' survey were used as preference information to develop MCDA models [283, 473].

### 7.2.3 Sorting method selection and robustness analysis set-up

The decision recommendation provided by the DRSA-based model is in the form of a classification that results from the comprehensive assessment of the test protocols. This implies that the evaluation of the robustness of its recommendation requires a tool capable of providing a suitable result it can be compared with (second phase of the DRSA-based model validation procedure, see Figure 7-1). As this doctoral research has shown and as it also emerged in the literature, MCDA is ideal for aggregating information and providing a classification or ranking of the alternatives under evaluation [47, 49, 58, 85, 105, 110, 158, 225, 438, 474]. Consequently, the development of the tool to test the robustness of the DRSA-based model was also grounded on an MCDA method, with these requirements driving its selection:

i. Need for enforcement of strong sustainability, so that limited compensation between criteria is guaranteed. Non-substitution of different forms of capital is a modelling capability that DRSA enforces (as discussed in Chapter 4) and thus the MCDA method must be able to support such preference construct;
ii. Independence of criteria weights from their measurements scales. This is due to the nature of the importance of the criteria extracted from the survey in Chapter 5, i.e. “intrinsic” (details about weights typology is available in Chapter 4, section 4.7.2.1);
iii. Decision recommendations (i.e. classes assignment) must be robust. The MCDA approach needs to investigate the possible changes in results by accounting for the uncertainty of input parameters, in this case weights and classes profiles (details in section 7.2.3.4);

iv. Most of the assessment criteria (six out of the eight) are expressed on an ordinal scale, with two on a cardinal one (see Table 7-1). MCDA method has thus to be tailored for this data typology.

An assessment of the MCDA methods available in the literature (drawing from the findings presented in Chapter 4 too) in relation to the requirements listed above led to the identification of SMAA method [470] as a relevant candidate to tackle the research challenge. In this case, SMAA-TRI was selected as it is an MCDA classification method based on ELECTRE-TRI, with the added capability of using imprecise measurements values, thresholds, weights and classes profiles, so that robust decision recommendations can be achieved through parameter stability analysis [475]. SMAA-TRI uses a finite space of parameters values to define the stability of the classification recommendation, by providing the probability of the membership to each category/class [470]. Applications of SMAA have already emerged in the nanotechnology area [158, 171], as well as in risk assessment of land subsistence [470], drug development [476, 477], LCA of detergents [261], energy policies [260] and fuel transportation options [478], confirming the advantage of incorporating uncertainty of input parameters in the model to provide robustness analysis that can strengthen the decision recommendations, limiting the compensation between criteria and handling efficiently information of different typology.

The main differences that this research introduces with the previous studies dealing with nanotechnology synthesis processes assessment based on sustainability metrics [51, 171] are that in this case:

i. The aim of the assessment is to classify the processes rather to rank them;
ii. Real preference information is employed as data input: ordinal ranking of criteria is used from the questionnaire described in Chapter 5;
iii. The focus of the approach is on the synthesis of nanomaterials based on techniques which have been frequently labelled as green and more sustainable [16, 25, 28, 30, 32, 144, 359, 373, 375, 390, 391, 396, 411, 427-429].

For the sake of simplicity the model that was developed for the robustness analysis based on SMAA-TRI will be called “ELECTRE-based model”.

#### 7.2.3.1 Classes profiles and thresholds

The aim of the decision-aiding model is to classify synthesis protocols in preference-ordered classes, on the basis of the implementation of the GCP and the technical performance, represented by the size range of the nanoparticles.

Five classes ($C_1 < C_2 < C_3 < C_4 < C_5$), which are the same as those presented in Chapter 6, were devised by accounting for the nature of the data, as well as the arbitrariness that is inherent in the coding of the criteria values (Table 7-1):

- $C_1$ = GCP are completely overlooked;
- $C_2$ = limited implementation of GCP and/or satisfaction of quality requirements;
- $C_3$ = partial fulfilment of GCP and potentials for quality improvements;
- $C_4$ = performance standards are satisfied and many GCP are implemented;
- $C_5$ = the process is very good both from a green chemistry and technical perspective.

This set of classes was used to screen synthesis processes in terms of how “green” they are, by integrating the information conveyed by the 8 assessment criteria through the outranking method SMAA-TRI (details in section 7.2.3.2). $C_4$ and $C_5$ represent the processes with high potentials, where various GCP are implemented. On the other hand, processes assigned to $C_1$ and $C_2$ are those that require thorough considerations about the worthiness of such approaches and need improvement work to lower their environmental implications.

Every performance class $C$ ($C \in \{1,2,3,4,5\}$) in SMAA-TRI is delimited by a threshold profile $\mathrm{Pr}_h$ (see Figure 7-2), so that each of them has a certain discriminatory value for every criterion $g_j$. Being $C_1$ the worst class, profile $\mathrm{Pr}_1$ indicates a performance at least as bad as $\mathrm{Pr}_2$ for every criterion.

The selection of the values of the profiles for the criteria was based on an analysis of the production strategies reported in the literature, which did also benefit from the MCDA process conducted for the DRSA-based model development (see Chapter 6 for details). Table 7-4 shows a summary of the selected profiles values and Appendix C.1 provides the scientific rationale on selection of such figures.

**Table 7-4: Classes profiles, thresholds and preferences directions for criteria used in SMAA-TRI**

| **Classes profiles** | | **$g_1$** | **$g_2$** | **$g_3$** | **$g_4$** | **$g_5$** | **$g_6$** | **$g_7$** | **$g_8$** |
|---|---|---|---|---|---|---|---|---|---|
| | | **Reducing agent code** | **Capping agent code** | **Solvent code** | **Local resource use code** | **Reaction time (seconds)** | **Tempera-ture (Celsius)** | **Equipment type code** | **Size range code** |
| **Case A: Certain** | $Pr_4$ = Very high - High | Renewable – primary (3*) | Renewable – waste (4) | Renewable – primary (3) | Yes (1) | 50 | 30 | Stirring ≤ 5 minutes (7) | 0 ≤ particle size ≤ 30 nm (1) |
| | $Pr_3$ = High - Medium | Renewable – primary (3) | Renewable – primary (3) | Renewable – primary (3) | Yes (1) | 100 | 40 | Stirring (6) | 0 ≤ particle size ≤ 60 nm (2) |
| | $Pr_2$ = Medium - Low | Biodegradable polymer (2) | Renewable – primary (3) | Biodegradable polymer (2) | No (0) | 400 | 60 | Microwave – sealed vessel (> 300 W) (4) | 30 < particle size ≤ 60 nm (3) |
| | $Pr_1$ = Low - Very low | Synthetic (1) | Biodegradable polymer (2) | Synthetic (1) | No (0) | 1500 | 95 | Conventional (2) | 0 < particle size ≤ 100 nm (4) |
| | | | | | | | | | |
| **Case B: Uncertain** | $Pr_4$ = Very high – High | 3.0 - 3.5 | 4.0 - 4.5 | 3.0 - 3.5 | 1 | 35 - 75 | 25 - 35 | 5 - 7 | 1 |
| | $Pr_3$ = High - Medium | 2.5 - 3.0 | 3.5 - 4.0 | 2.5 - 3.0 | 1 | 75 - 125 | 35 - 50 | 4 - 5 | 2 |
| | $Pr_2$ = Medium - Low | 2.0 - 2.5 | 3.0 - 3.5 | 2.0 - 2.5 | 0 | 125 - 675 | 50 - 80 | 3 - 4 | 3 |
| | $Pr_1$ = Low - Very low | 1.0 - 2.0 | 1.0 - 3.0 | 1.0 - 2.0 | 0 | 675 - 2250 | 80 - 115 | 2 - 3 | 4 |
| | | | | | | | | | |
| **Indifference threshold** | | 0 | 0 | 0 | 0 | 10 | 5 | 0 | 0 |
| **Preference threshold** | | 1 | 1 | 1 | 0 | 30 | 10 | 1 | 1 |
| **Criterion preference** | | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↑ | ↓ |
| (*: the numbers within brackets indicate the code used for the value of each criterion) | | | | | | | | | |

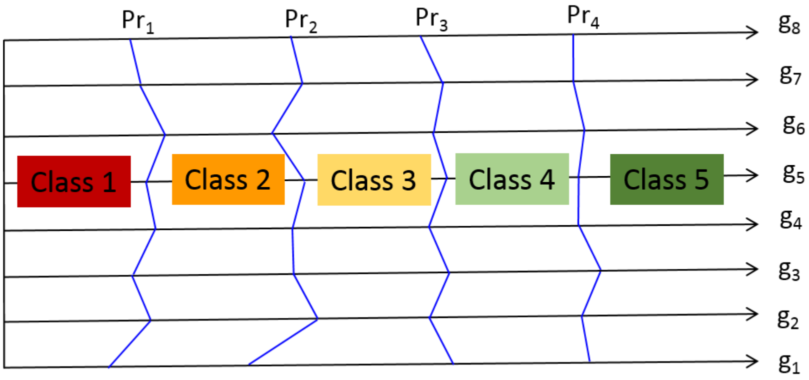


**Figure 7-2: Examples of classes profiles ($Pr_h$) for each criterion $g_j$ (Adapted from *[479]*)**

Elaborate preferences can be accounted for by this MCDA method through the use of two types of thresholds: indifference threshold $q_j$ and preference threshold $p_j$. The first one refers to the difference in performance between each criterion $g_j$ and the class profile $Pr_h$ that can be considered insignificant, while the latter is the smallest value of such difference that can be considered significant. The range between $q_j$ and $p_j$ is defined as ambiguity zone and it indicates a situation of weak preference. The use of preference thresholds allows accounting for the weak preference, inherent in the hesitation that the DM can have, in favour of one alternative over the other when their performances are rather close. There are currently no guidelines to define such thresholds, however an elaboration of the research considerations reported by relevant authors in the published literature allowed extracting them (Table 7-4). Appendix C.1 provides the scientific details for such values selection.

It must be noted that an additional threshold (i.e. veto) can be used in SMAA-TRI to account for the cases where the alternative under evaluation performs extremely poorly on a certain criterion so that it will never receive a relatively good assessment in comparison with the other alternatives. Even though such parameter could have enriched the refinement of the modelling quality it could not be introduced in this model due to the lack of this type of information in the relevant literature.

### *7.2.3.2 Classification of synthesis processes*

SMAA-TRI operates with an outranking relation approach based on pairwise comparisons of alternatives, which means that the performance on each criterion $g_j$ of each production process $t_m$ is compared to the profile $Pr_h$ to verify whether the synthesis protocol $t_m$ is “at least as good as” $Pr_h$, in other words whether $t_m$ S $b_h$[10] [58, 475]. The same process is performed for the classes profiles in comparison with the production process, to verify if $b_h$ S $t_m$. This leads to the calculation of a credibility index ρ for the outranking relations $t_m$ S $b_h$ and $b_h$ S $t_m$, by means of a concordance index $C_j(t_m, b_h)$ and a discordance index $D_j(t_m, b_h)$.

More formally, the concordance index to measure if $t_m$ S $b_h$ for every criterion $g_j$ (assuming increasing performance with higher criterion value), is given by the following formula [480]:

$$C_j(t_m, b_h) = \begin{cases} 1 & if\ g_j(t_m) \geq g_j(b_h) - q_j\left(g_j(b_h)\right) \\ 0 & if\ g_j(t_m) < g_j(b_h) - p_j\left(g_j(b_h)\right) \\ \dfrac{g_j(t_m) - g_j(b_h) + p_j\left(g_j(b_h)\right)}{p_j\left(g_j(b_h)\right) - q_j\left(g_j(b_h)\right)} & otherwise \end{cases}$$

with $q_j\left(g_j(b_h)\right)$ and $p_j\left(g_j(b_h)\right)$ the indifference and preference thresholds, respectively.

Once concordance indexes for all the criteria have been calculated, it is possible deriving the final concordance index, as follows [101]:

$$C(t_m, b_h) = \frac{\sum_{j=1}^{n} w_j\ C_j(t_m, b_h)}{\sum_{j=1}^{n} w_j}$$

with $w_j$ the weight of each criterion.

On the other hand, the discordance of every criterion $g_j$ for the assertion $t_m$ S $b_h$ is based on the introduction of the veto threshold $v_j\left(g_j(b_h)\right)$, which is the worst performance of protocol $t_m$ on criterion $g_j$ that invalidates the credibility index ρ ($t_m$ S $b_h$). The discordance index is defined formally as [101]:

$$D_j(t_m, b_h) = \begin{cases} 1 & if\ g_j(t_m) < g_j(b_h) - v_j\left(g_j(b_h)\right) \\ 0 & if\ g_j(t_m) \geq g_j(b_h) - p_j\left(g_j(b_h)\right) \\ \dfrac{g_j(b_h) - g_j(t_m) - p_j\left(g_j(b_h)\right)}{v_j\left(g_j(b_h)\right) - p_j\left(g_j(b_h)\right)} & otherwise \end{cases}$$

---

[10] “S” is the MCDA outranking notation, that literally means “at least as good as”

The concordance and discordance indexes are used to obtain an outranking relation so that $t_m$ is said to outrank $b_h$ with credibility ρ, which is comprised between 0 and 1 and it is obtained from the following equation [101]:

$$\rho\ (t_m, b_h) = \begin{cases} C_j(t_m, b_h) & if\ D_j(t_m, b_h) \leq C_j(t_m, b_h)\ \forall j \\ C_j(t_m, b_h) \displaystyle\prod_{j\ \in J(t_m, b_h)} \frac{1 - D_j(t_m, b_h)}{1 - C_j(t_m, b_h)} & otherwise \end{cases}$$

with $J(t_m, b_h)$ being the criteria where $D_j(t_m, b_h) > C_j(t_m, b_h)$. In the cases where no veto thresholds are used, the credibility index ρ is dependent solely on the first part of the formula above, which is actually the approach adopted in this robustness analysis.

Such index (ρ) represents the performance of each production protocol in relation to the category profile that affects the recommendation of its assignment to a certain class or another. The credibility index is calculated for all the process-class profile under consideration.

In order to transform the fuzzy outranking relation in a crisp one, the *λ-cutting level* is introduced to verify whether the credibility index ρ recommending the assignment of a protocol to a certain class is strong enough. λ (normally between 0.5 and 1) thus represents the necessary majority of assessment criteria to discriminate between the recommendation of assignment to Class $C_h$ or not [475]. λ is the smallest value for the credibility index that validates the assertion $t_m$ S $b_h$, so that $\rho(t_m, b_h) \geq \lambda$, then $t_m$ S $b_h$. More specifically:

$$\rho(t_m, b_h) \geq \lambda \longrightarrow t_m \text{ S } b_h$$

$$\rho(t_m, b_h) < \lambda \longrightarrow \neg t_m \text{ S } b_h$$

$$\rho(b_h, t_m) \geq \lambda \longrightarrow b_h \text{ S } t_m$$

$$\rho(b_h, t_m) < \lambda \longrightarrow \neg b_h \text{ S } t_m$$

The relations that are built through the pairwise comparisons can be exploited to evaluate whether a production process is preferred (≻), it is indifferent (*I*) or it is incomparable (*R*) to a class profile or vice-versa. The resulting crisp relations are:

$$t_m \succ b_h \leftrightarrow t_m \text{ S } b_h \wedge \neg b_h \text{ S } t_m$$

$$b_h \succ t_m \leftrightarrow \neg t_m \text{ S } b_h \wedge b_h \text{ S } t_m$$

$$t_m \boldsymbol{I}\ b_h \leftrightarrow t_m S\, b_h \wedge b_h S\, t_m$$

$$t_m \boldsymbol{R}\ b_h \leftrightarrow \neg t_m S\, b_h \wedge \neg b_h S\, t_m$$

The visual representation of preference (≻), indifference (*I*) and incomparability (*R*) relations is reported in Figure 7-3.

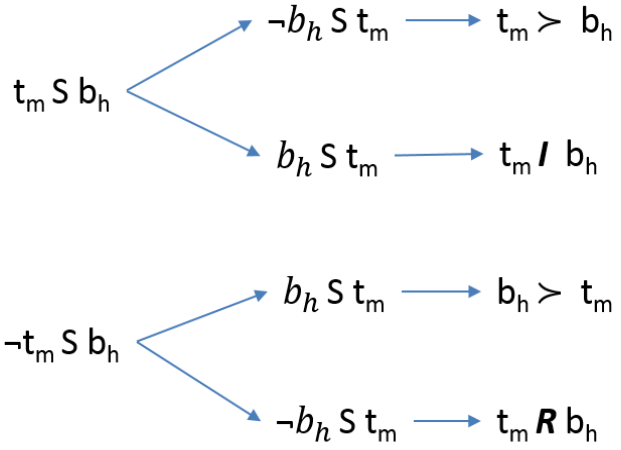


**Figure 7-3: Possible performance relations of production processes and classes profiles**

The assignment of a performance class to each production protocol is based on an iterative procedure that can be of two types:

i. Risk-averse/conservative: $t_m$ is successively compared with classes profile from the best to the worst until $t_m S\, b_{h-1}$. The process $t_m$ is then assigned to the best class $C_h$ such that $t_m S\, b_{h-1}$.
ii. Risk-prone/optimistic: $t_m$ is successively compared with classes profile from the worst to the best until $b_h \succ t_m$. The process $t_m$ is then assigned to the worst class $C_h$ such that $b_h \succ t_m$.

SMAA-TRI operates with the conservative procedure by performing a high number of simulations (i.e. 10,000), sampling at each run a set of weights (see below case A) as well as classes profiles (see below case B) for the criteria for each synthesis process from a uniform probability distribution [475]. Four weights typologies can be used with an increasing level of certainty: (i) no information at all; (ii) ordinal ranking; (iii) interval weights; and (iv) exact weights.

The alternatives performance and criteria weight information is then integrated through the procedure described above and the class for the synthesis protocol for that set of input data is recommended. The procedure is repeated 10,000 times and the final results are classes acceptability indices (CAI), which indicate the share of possible parameters (expressed as a percentage) that lead a protocol to be assigned to each class $C_{h.}$ These computations have $\pm 1\%$ accuracy (with 95% confidence) for the resulting classes acceptability index [475]. The CAI are thus an instrument to measure the sensitivity and robustness of the results, accounting for the uncertainty of the input data and preferences modelling. Class acceptability index is an intelligible tool that conveys the stability of the input information, communicating whether the data is of acceptable quality to make an informed decision. The higher the score for a class, the higher the confidence for such class. The range of this index is between 0 and 1, with 0 indicating that the process will never be assigned to the specific class whereas 1 denoting that the process will be assigned to the target class with every combination of uncertain input values.

#### *7.2.3.3 Criteria weights*

SMAA-TRI uses weights as intrinsic measures of importance of each criterion [203]. This means that the value of the weight is independent from the measurement scale as well as from the coding of the criterion [203, 438]. There are various strategies that can be used to assign the weights values to the criteria in outranking methods [203, 481]. The approach selected in this case benefits from part of the results of Chapter 5 on the survey of experts in the area of sustainable nanotechnology, which resulted in a comprehensive and reliable set of sustainability criteria for NPs. As discussed in section 7.2.2 the criteria priorities obtained from the survey questionnaire allow defining an ordinal ranking of such criteria, which can actually be used in SMAA-TRI.

Table 7-3 summarizes the correspondence between the criteria from the survey of Chapter 5 and those used in the development of the DRSA-based as well as ELECTRE-based model. All the criteria refer to the environmental impacts area with the exclusion on the functionality one. The latter criterion belongs to a different area (i.e. technical performance) and it was placed at the top of the priorities as it is represents the main reason for the interest in NPs, i.e. their improved performance when compared to competitive non-nano enhanced products [10, 63, 342]. This suggests that whether such technical advantage would not be a characteristic of the NPs, there would not even be interest in them from a production/business perspective and consequently there would be no need to perform a SA [5, 62]. Furthermore Chapter 5 shows that the relative index obtained by this criterion in comparison with all the others is relatively higher, providing reinforcement to the choice of placing it at the top of the list in the ELECTRE-based model priorities.

A trend of criteria rankings emerges from the survey, however multiple correspondences between the criteria in the survey and the ELECTRE-based model indicate that various combinations of criteria priorities are possible (Table 7-3). In fact, reducing agent can be in the second, third or sixth position and the same applies to capping agent and solvent type. Similarly, reaction time can be the second-to-last or the last in the ranking, as it can be for reaction temperature. As a result, these differences in placement had to be accounted for and combinations of possible ranking were tested in SMAA-TRI (see section below).

#### *7.2.3.4 Accounting for uncertainty in the analysis*

Two types of uncertainty had to be treated in the construction of the ELECTRE-based model: (i) selection of criteria weights; and (ii) definition of discriminatory profiles between the performance classes. Consequently, two modelling layouts were defined in this model to take such uncertainties into account.

**Case A: certain classes profiles**

The first modelling set-up with SMAA-TRI considered only the uncertainty in the weighing procedure. As described in section 7.2.2 and 7.2.3.3 the weights of the criteria are based on an ordinal ranking, which does not impose a specific value for each of the weights. Furthermore, priorities of the criteria must be varied as well, due to the multiple correspondences between them and those from the survey (see Table 7-3).

**Case B: uncertain classes profiles**

The second set-up of the SMAA-TRI model included the previous type of uncertainty and also the one related to the values for the classes profiles. This was performed in order to account for the fact that the profiles of the classes adopted for the discrimination of synthesis processes performance were selected from a range of possible values. Even though their appointment was based on the published literature as discussed above and in Appendix C.1, expert judgment was adopted to choose the individual discriminatory values. This represents a second type of uncertainty that was considered in the model, together with the variability of the criteria weights as in the previous case.

SMAA-TRI confirmed its suitability to handle these modelling requirements as it has been specifically developed to take input data and preferences modelling uncertainties into account [158, 259, 475, 480]. Table 7-4 summarizes the SMAA-TRI set-up for both case A and B.

## 7.3 Results

SMAA-TRI allowed testing the robustness of the DRSA-based model through several simulations set-up settings, which included certain (i.e. case A) and uncertain (i.e. case B) classes profiles with criteria in different importance ranks according to the combinations explained in section 7.2.3.3.

The same five test protocols used to show the decision support of DRSA-based model were employed to test its robustness through the ELECTRE-based model (Table 7-2), by assessing the decision recommendation agreement (i.e. classification) of the two models (third phase of DRSA-based model validation procedure). In addition, no veto threshold for any criteria was applied considering the lack of such type of information in the relevant literature, which means that only concordance indexes contributed to the calculation of the credibility indexes. Such an approach is in line with a comparable case study application in the area of risk assessment of nanomaterials [158]. Lastly, the $\lambda$-*cutting level* range was $[0.65; 0.85]$, the recommended and sensible interval to be used for the ELECTRE-TRI method [105, 158, 470, 474].

Table 7-5 and Table 7-6 show the results of the robustness analysis (case A and case B layouts, respectively) by accounting for the change in preference positions of the materials types criteria (i.e. reducing agent, capping agent and solvent types). In each case six different combinations of the materials type criteria were tested with SMAA-TRI, which leads to a total of 30 agreement comparisons between the two models. Regarding the processing conditions criteria, reaction time was kept as the second-to-last (7th rank) and reaction temperature was the last one (8th rank). The results that account for the change in the preference ranking for the latter criteria (7th rank for reaction temperature and 8th rank for reaction time) are reported in the Appendices C.2 and C.3, as the outcomes are similar to the cases above.

Each summary sub-table in Table 7-5 and Table 7-6 includes the ordinal criteria ranking that was used for those SMAA-TRI simulations, the recommended class from DRSA-based model, namely the standard and variable consistency DRSA, the CAI (i.e. the fraction of SMAA-TRI Monte Carlo simulations for which a protocol is assigned to each class) and the concordance assessment between DRSA-based and ELECTRE-based models recommendations.

### 7.3.1 Case A: Certain classes profiles

The outcomes obtained with SMAA-TRI using different ordinal rankings of assessment criteria and certain classes profiles are shown in Table 7-5. A trend of assignment emerges from the 30 classification cases that result from varying the criteria priorities for the types of materials used. Test protocol $t_1$ always receives the highest CAI (i.e. 81%) for $C_5$, confirming the recommendation from DRSA-based model and indicating that it is a process that makes ample use of GCP. Similarly, $t_4$ is consistently assigned for the majority of the simulations to $C_4$, still an indication of careful process design to accommodate a green chemistry perspective. What is more, the other class that receives second-highest acceptability score for this protocol is the medium one (i.e. $C_3$), in agreement with the standard DRSA scheme that also provided $C_3$ as a possible allotment.

On the other hand $t_2$, $t_3$ and $t_5$ do not receive a positive evaluation from both MCDA models. More specifically, $t_2$ is classified between 92% and 99% of the SMAA-TRI simulations to $C_2$, showing high agreement with DRSA-based model. Slight better performance can be seen for $t_3$, in which case $C_2$ receives still the majority of support, but a relatively high share of simulations (up to 55 %) assigns $t_3$ to $C_3$. The ambiguity that emerges with SMAA-TRI is confirmed by the standard scheme of DRSA, where classes 2 or 3 are indicated as possible recommendations for $t_3$.

Lastly, both MCDA models indicate $t_5$ as the worst performing protocol from the green chemistry perspective, receiving high support for $C_2$ by DRSA and the highest percentage of CAI for $C_2$ by SMAA-TRI and a minor share between 7% and 33% for the worst class ($C_1$).

**Table 7-5: Ordinal criteria ranking used in SMAA-TRI, recommended classes from DRSA-based model, CAI obtained with SMAA-TRI using certain classes profiles and concordance assessment between models recommendations (*: +/-1 = higher or lower SMAA-TRI class compared to new DRSA scheme)**

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_1$ |
| 3 | $g_2$ |
| 4 | $g_7$ |
| 5 | $g_3$ |
| 6 | $g_4$ |
| 7 | $g_5$ |
| 8 | $g_6$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm.* |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 13% | 6% | **81%** | **Yes** |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 0% | **92%** | 0% | 8% | 0% | **Yes** |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 0% | **77%** | 23% | 0% | 0% | **Yes** |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 19% | **67%** | 14% | **Yes** |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 7% | **93%** | 0% | 0% | 0% | **Yes** |

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_2$ |
| 3 | $g_1$ |
| 4 | $g_7$ |
| 5 | $g_3$ |
| 6 | $g_4$ |
| 7 | $g_5$ |
| 8 | $g_6$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 13% | 6% | **81%** | **Yes** |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 0% | **98%** | 0% | 2% | 0% | **Yes** |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 0% | **94%** | 6% | 0% | 0% | **Yes** |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 19% | **78%** | 3% | **Yes** |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 33% | **67%** | 0% | 0% | 0% | **Yes** |

**Table 7-5: Ordinal criteria ranking used in SMAA-TRI, recommended classes from DRSA-based model, CAI obtained with SMAA-TRI using certain classes profiles and concordance assessment between models recommendations (cont.)**

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_3$ |
| 3 | $g_2$ |
| 4 | $g_7$ |
| 5 | $g_1$ |
| 6 | $g_4$ |
| 7 | $g_5$ |
| 8 | $g_6$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 13% | 6% | **81%** | **Yes** |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 0% | **99%** | 0% | 1% | 0% | **Yes** |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 0% | **77%** | 23% | 0% | 0% | **Yes** |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 19% | **67%** | 14% | **Yes** |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 7% | **93%** | 0% | 0% | 0% | **Yes** |

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_3$ |
| 3 | $g_1$ |
| 4 | $g_7$ |
| 5 | $g_2$ |
| 6 | $g_4$ |
| 7 | $g_5$ |
| 8 | $g_6$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 13% | 6% | **81%** | **Yes** |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 0% | **98%** | 0% | 2% | 0% | **Yes** |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 0% | 45% | **55%** | 0% | 0% | **No (+1)** |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 19% | **41%** | 40% | **Yes** |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 0% | **100%** | 0% | 0% | 0% | **Yes** |

**Table 7-5: Ordinal criteria ranking used in SMAA-TRI, recommended classes from DRSA-based model, CAI obtained with SMAA-TRI using certain classes profiles and concordance assessment between models recommendations (cont.)**

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_1$ |
| 3 | $g_3$ |
| 4 | $g_7$ |
| 5 | $g_2$ |
| 6 | $g_4$ |
| 7 | $g_5$ |
| 8 | $g_6$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 13% | 6% | **81%** | **Yes** |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 0% | **92%** | 0% | 8% | 0% | **Yes** |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 0% | 45% | **55%** | 0% | 0% | **No (+1)** |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 19% | **41%** | 40% | **Yes** |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 0% | **100%** | 0% | 0% | 0% | **Yes** |

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_2$ |
| 3 | $g_3$ |
| 4 | $g_7$ |
| 5 | $g_1$ |
| 6 | $g_4$ |
| 7 | $g_5$ |
| 8 | $g_6$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 13% | 6% | **81%** | **Yes** |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 0% | **99%** | 0% | 1% | 0% | **Yes** |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 0% | **94%** | 6% | 0% | 0% | **Yes** |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 19% | **78%** | 3% | **Yes** |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 33% | **67%** | 0% | 0% | 0% | **Yes** |

**Table 7-6: Ordinal criteria ranking used in SMAA-TRI, recommended classes from DRSA-based model, CAI obtained with SMAA-TRI using uncertain classes profiles and concordance assessment between models recommendations (*: +/-1 = higher or lower SMAA-TRI class compared to new DRSA scheme)**

| Rank | Criterion | Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm.* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | | | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| 1 | $g_8$ | | | | | | | | | |
| 2 | $g_1$ | | | | | | | | | |
| 3 | $g_2$ | | | | | | | | | |
| 4 | $g_7$ | $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 0% | 40% | **60%** | **Yes** |
| 5 | $g_3$ | $t_2$ | $C_2$ | $C_2$ (0.22) | 18% | **73%** | 0% | 9% | 0% | **Yes** |
| 6 | $g_4$ | $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 5% | **83%** | 12% | 0% | 0% | **Yes** |
| 7 | $g_5$ | $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 20% | **72%** | 8% | **Yes** |
| 8 | $g_6$ | $t_5$ | $C_2$ | $C_2$ (0.33) | **55%** | 45% | 0% | 0% | 0% | **No (-1)** |

| Rank | Criterion | Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | | | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| 1 | $g_8$ | | | | | | | | | |
| 2 | $g_2$ | | | | | | | | | |
| 3 | $g_1$ | | | | | | | | | |
| 4 | $g_7$ | $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 0% | 33% | **67%** | **Yes** |
| 5 | $g_3$ | $t_2$ | $C_2$ | $C_2$ (0.22) | 25% | **74%** | 0% | 1% | 0% | **Yes** |
| 6 | $g_4$ | $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 10% | **86%** | 4% | 0% | 0% | **Yes** |
| 7 | $g_5$ | $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 40% | **57%** | 3% | **Yes** |
| 8 | $g_6$ | $t_5$ | $C_2$ | $C_2$ (0.33) | **61%** | 39% | 0% | 0% | 0% | **No (-1)** |

**Table 7-6: Ordinal criteria ranking used in SMAA-TRI, recommended classes from DRSA-based model, CAI obtained with SMAA-TRI using uncertain classes profiles and concordance assessment between models recommendations (cont.)**

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_3$ |
| 3 | $g_2$ |
| 4 | $g_7$ |
| 5 | $g_1$ |
| 6 | $g_4$ |
| 7 | $g_5$ |
| 8 | $g_6$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 0% | 40% | **60%** | **Yes** |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 42% | **57%** | 0% | 1% | 0% | **Yes** |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 5% | **75%** | 20% | 0% | 0% | **Yes** |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 20% | **71%** | 9% | **Yes** |
| $t_5$ | $C_2$ | $C_2$ (0.33) | **55%** | 45% | 0% | 0% | 0% | **No (-1)** |

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_3$ |
| 3 | $g_1$ |
| 4 | $g_7$ |
| 5 | $g_2$ |
| 6 | $g_4$ |
| 7 | $g_5$ |
| 8 | $g_6$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 0% | 47% | **53%** | **Yes** |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 36% | **63%** | 0% | 2% | 0% | **Yes** |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 1% | **56%** | 43% | 0% | 0% | **Yes** |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 5% | **74%** | 21% | **Yes** |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 48% | **52%** | 0% | 0% | 0% | **Yes** |

**Table 7-6: Ordinal criteria ranking used in SMAA-TRI, recommended classes from DRSA-based model, CAI obtained with SMAA-TRI using uncertain classes profiles and concordance assessment between models recommendations (cont.)**

| Rank | Criterion | Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $g_8$ | | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| 2 | $g_1$ | | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| 3 | $g_3$ | | | | | | | | | |
| 4 | $g_7$ | $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 0% | 48% | **52%** | **Yes** |
| 5 | $g_2$ | $t_2$ | $C_2$ | $C_2$ (0.22) | 24% | **67%** | 0% | 9% | 0% | **Yes** |
| 6 | $g_4$ | $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 1% | **63%** | 36% | 0% | 0% | **Yes** |
| 7 | $g_5$ | $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 5% | **74%** | 21% | **Yes** |
| 8 | $g_6$ | $t_5$ | $C_2$ | $C_2$ (0.33) | **49%** | **51%** | 0% | 0% | 0% | **Yes** |

| Rank | Criterion | Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $g_8$ | | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| 2 | $g_2$ | | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| 3 | $g_3$ | | | | | | | | | |
| 4 | $g_7$ | $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 0% | 33% | **67%** | **Yes** |
| 5 | $g_1$ | $t_2$ | $C_2$ | $C_2$ (0.22) | 36% | **63%** | 0% | 1% | 0% | **Yes** |
| 6 | $g_4$ | $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 10% | **85%** | 5% | 0% | 0% | **Yes** |
| 7 | $g_5$ | $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 40% | **57%** | 3% | **Yes** |
| 8 | $g_6$ | $t_5$ | $C_2$ | $C_2$ (0.33) | **62%** | 38% | 0% | 0% | 0% | **No (-1)** |

### 7.3.2 Case B: Uncertain classes profiles case

Because of the subjectivity of the classes' profiles selection, the second simulation set-up added to the various criteria ordinal rankings also the variability of classes profiles, with ranges shown in Table 7-4. The outcomes for this analysis are reported in Table 7-6. It emerges that the same trend described in the previous section and shown in Table 7-5 appears in this case as well. $t_1$ is mostly allotted to the best class and $t_4$ receives the highest share of recommendations for $C_4$.

Conversely, $t_3$ is mostly assigned to $C_2$, with a considerable share for $C_3$ as well. $t_2$ is the second-to-last protocol in terms of green chemistry performance, with the highest share of classes acceptability index for $C_2$. The worst protocol is still $t_5$, with a rather even share of assignment index for $C_1$ and $C_2$.

## 7.4 Discussion

Considering that a total of six different ordinal rankings for the criteria was performed for the five test protocols, an overall number of 30 comparisons are possible to assess the agreement between the assignment of performance class to the synthesis protocols based on the new DRSA scheme (i.e. variable consistency) and the highest class acceptability index assigned by SMAA-TRI.

Out of 120 classifications comparisons, the overall correspondence was just under 86%, a satisfactory value for such a novel application of MCDA [482, 483]. The summary of the recommendation agreement between the MCDA models is shown in Table 7-7, distinguishing between the simulations set-ups with criterion "reaction time" in 7th position and "reaction temperature" in 8th position, and vice-versa. In all the comparisons it can be seen that there is a high to very high correspondence between decision recommendations of the two MCDA models, with values up to 93.3 % (i.e. same class recommended for 28 out of 30 protocols assignments). The lowest agreement (76 %) is reached in the case of uncertain classes profiles and "reaction temperature" in 7th rank and "reaction time" in 8th rank, still an acceptable concordance level in this case as well [483, 484].

Most of the discordance between the models (14 out of 17 discordance cases) is centered around protocols $t_3$ and $t_5$. As far as $t_3$ is concerned, the reason is that the protocol employs a renewable primary material as a solvent (that is very good from a green chemistry perspective) and a bio-polymer as a capping agent (not a favourable option). When the solvent is placed at a high position in the ordinal ranking, its relative weight increases while when the capping agent is assigned a lower position its weight decreases, which overall determines a higher assignment to class 3 (medium) rather than 2 (low) as VC-DRSA does. In the case of $t_5$, the reason is that the process uses a synthetic capping agent, the worst condition from the green chemistry perspective considering that a synthetic material should be avoided and the capping agent can be eliminated if a multifunctional reducing agent is used. For this reason, the class very low receives a lot of support for this process from SMAA-TRI, especially when the capping agent is high in the ordinal rankings and thus has a higher weight.

**Table 7-7: Class recommendation agreement between new DRSA scheme and SMAA-TRI, based on class with highest acceptability index (+/- = higher or lower SMAA-TRI classes compared to new DRSA scheme)**

| Criteria ranking | Case A: Certain classes profiles | Case B: Uncertain classes profiles case |
|---|---|---|
| 7th rank for reaction time ($g_5$) and 8th rank for reaction temperature ($g_6$) | 93.3 % (28/30 protocols) | 86.0 % (26/30 protocols) |
| | + 1 class in 2 cases: protocol $t_3$ | - 1 class in 4 cases: protocol $t_5$ |
| 7th rank for reaction temperature ($g_6$) and 8th rank for reaction time ($g_5$) | 86.0 % (26/30 protocols) | 76.0 % (23/30 protocols) |
| | + 1 class in 2 cases: protocol $t_3$<br>+ 1 class in 2 cases: protocol $t_4$ | - 1 class in 4 cases: protocol $t_5$<br>2 cases of same index for two classes: protocol $t_5$<br>1 case of same index for two classes: protocol $t_4$ |

The analysis conducted on the DRSA-based model confirms that it is robust in terms of decision recommendations, based on the set-up of the simulations conducted with SMAA-TRI. This allows furthering the discussion with some considerations on the decision aiding support provided by the two models.

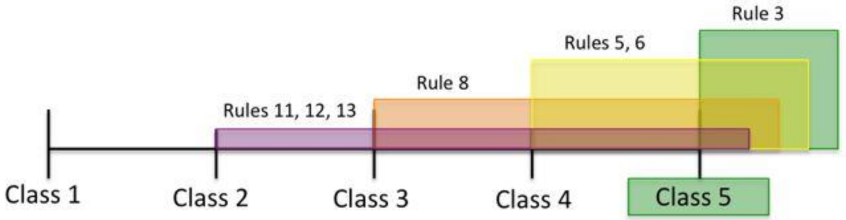
In the case of $t_1$, the DRSA-based model provides a recommendation that is supported by the decision rules 3, 5, 6, 8, 11, 12, 13 (see Scheme 1). These rules point out very important characteristics of green chemistry protocols, including the possibility of producing nanoparticles within very short timeframes and mild temperatures (rule 3, 13) in combination with the use of a renewable capping agent or the adoption of multifunctional renewable materials that eliminate the need for a capping agent in the process (rule 5, 6). This is coupled with the possibility of using benign solvents such as water (rule 8, 11). These set-ups lead to fulfilment of several GCP, including reduction in hazardousness of chemical synthesis, prevention of waste and reduction of derivatives, use of safer solvents and inherently safer chemistry (e.g. closed vessels and low power). The decision recommendations provided by the DRSA-based model can be easily traced back to the protocols that applied these principles and that are at the base of the decision rules (see Chapter 6 for details on the processes).

The example for $t_3$ leads to other considerations as the matching rules are 11, 12, 19, 20, 23, 24, 25, 26 (see Scheme 2). The learning process in this case is more elaborate as there are both types of rules involved, “at least” and also “at most”. As far as the “at least” rules are concerned (i.e. 11, 12), the DRSA-based model indicates a potentially at least low performance based on the use of a renewable primary material as a solvent and a bio-polymer as a capping agent instead of synthetic chemicals. On the other hand, the other types of rules (i.e. at most) are indicative of several concerns. Firstly, the use of a rather high temperature (80 $^0$C) and the selection of a capping agent at most bio-polymer (rule 19) in addition to the use of non-local resources as well as producing lower quality particles (between 30 and 60 nm) (rule 20) suggest a maximum assignment to medium class. This is complemented by the use of a conventional heating technique that requires rather long reaction times (10 minutes in this case) (rule 25), not desirable when looking at the process from the green chemistry perspective [62]. The intersection of the rules following the standard DRSA procedure would suggest a low or medium class as a decision recommendation, whereas the variable consistency approach provides the low class as an assignment.

These assessment examples show that, from a decision aiding perspective, the recommendation provided by the DRSA-based model is traceable and supported by previous knowledge that in this case was extracted from the two experts that collaborated during the case study as discussed in Chapter 6. These rules are a summary of the characteristics of synthesis processes that have already been developed in reality and can thus be used as comparative measures when developing own new processes or when assessing existing ones.

| Test protocol | Reducing agent class | Capping agent class | Solvent class | Local resource use class | Reaction time | Temperature | Equipment class | Size class |
|---|---|---|---|---|---|---|---|---|
| $t_1$ | Renewable primary | Not needed | Renewable primary | No | 55 s | 42 Celsius | Microwave – sealed vessel (≤ 300 W) | 0 ≤ particle size ≤ 30 nm |

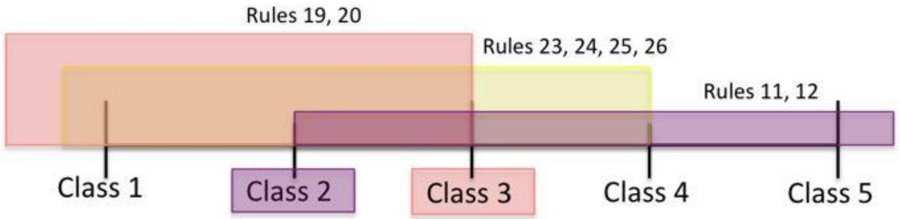
| Rule type | Rule n. | Conditions | Recommended class | Support protocols[a] | Coverage factor[b] |
|---|---|---|---|---|---|
| At least | 3 | (Reaction time <= 60 s) & (Temperature <= 47 °C) | >= 5 (Very high) | 4 | 26.70 % |
| | 5 | (Reducing agent >= Renewable primary) & (Capping agent >= Not needed) & (Reaction time <= 30 min) | >= 4 (High) | 16 | 59.25 % |
| | 6 | (Capping agent >= Renewable primary) & (Reaction time <= 60 s) | >= 4 (High) | 7 | 25.92 % |
| | 8 | (Reducing agent >= Renewable primary) & (Capping agent >= Renewable primary) & (Solvent >= Renewable primary) | >= 3 (Medium) | 32 | 94.10 % |
| | 11 | (Solvent >= Renewable primary) | >= 2 (Low) | 42 | 91.30 % |
| | 12 | (Capping agent >= Biodegradable polymer) | >= 2 (Low) | 40 | 86.95 % |
| | 13 | (Reaction time <= 60 s) | >= 2 (Low) | 11 | 23.91 % |



**Scheme 1: Performance of test protocol $t_1$, matching rules from DRSA-based model and recommendation of performance class based on standard classification scheme ([a] = number of protocols that support the rule; [b] = percentage of number of protocols that satisfy the conditions of the rule and are assigned to the class or union of classes)**

| Test protocol | Reducing agent class | Capping agent class | Solvent class | Local resource use class | Reaction time | Temperature | Equipment class | Size class |
|---|---|---|---|---|---|---|---|---|
| $t_3$ | Biodegradable polymer | Biodegradable polymer | Renewable primary | No | 10 min | 90 | Conventional | 30 ≤ particle size ≤ 60 nm |

| Rule type | Rule n. | Conditions | Recommended class | Support protocols[a] | Coverage factor[b] |
|---|---|---|---|---|---|
| At least | 11 | (Solvent >= Renewable primary) | >= 2 (Low) | 42 | 91.30 % |
|  | 12 | (Capping agent >= Biodegradable polymer) | >= 2 (Low) | 40 | 86.95 % |
| At most | 19 | (Capping agent <= Biodegradable polymer) & (Temperature >= 80 °C) | <= 3 (Medium) | 9 | 42.85 % |
|  | 20 | (Local resources use <= No) & (Size range >= 30_60 nm) | <= 3 (Medium) | 3 | 14.29 % |
|  | 23 | (Size range >= 30_60 nm) | <= 4 (High) | 4 | 12.12 % |
|  | 24 | (Reaction time >= 45 s) & (Temperature >= 55 °C) | <= 4 (High) | 21 | 63.63 % |
|  | 25 | (Reaction time >= 10 min) & (Equipment <= Conventional) | <= 4 (High) | 18 | 54.54 % |
|  | 26 | (Equipment <= Stirring) & (Size range >= 0_60 nm) | <= 4 (High) | 7 | 21.21 % |



**Scheme 2: Performance of test protocol $t_3$, matching rules from DRSA-based model and recommendation of performance class based on standard classification scheme ([a] = number of protocols that support the rule; [b] = percentage of number of protocols that satisfy the conditions of the rule and are assigned to the class or union of classes)**

**Table 7-8: Performance of $t_1$ with respect to the classes profiles of ELECTRE-based model and resulting share of classes acceptability index (case for reducing agent > capping agent > solvent)**

| Classes profiles | | $g_1$ | $g_2$ | $g_3$ | $g_4$ | $g_5$ | $g_6$ | $g_7$ | $g_8$ | Class acceptability index |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Reducing agent** | **Capping agent** | **Solvent** | **Local resource use** | **Reaction time (seconds)** | **Tempera-ture (Celsius)** | **Equipment type** | **Size range** | |
| **Case A: Certain** | Class very high (5) | $t_1$ | $t_1$ | $t_1$ | | $t_1$ | | | $t_1$ | **81%** |
| | $Pr_4$ = Very high - high | Renewable – primary | Renewable – waste | Renewable – primary | Yes | 50 | 30 | Stirring ≤ 5 minutes | 0 ≤ particle size ≤ 30 nm | |
| | Class high (4) | | | | | | $t_1$ | | | 6% |
| | $Pr_3$ = High - medium | Renewable – primary | Renewable – primary | Renewable – primary | Yes | 100 | 40 | Stirring | 0 ≤ particle size ≤ 60 nm | |
| | Class medium (3) | | | | $t_1$ | | | $t_1$ | | 13% |
| | $Pr_2$ = Medium - low | Biodegradable polymer | Renewable – primary | Biodegradable polymer | No | 400 | 60 | Microwave – sealed vessel (> 300 W) | 30 < particle size ≤ 60 nm | |
| | Class low (2) | | | | | | | | | |
| | $Pr_1$ = Low - very low | Synthetic | Biodegradable polymer | Synthetic | No | 1500 | 95 | Conventional | 0 < particle size ≤ 100 nm | |
| | Class very low (1) | | | | | | | | | |

**Table 7-9: Performance of $t_3$ with respect to the classes profiles of ELECTRE-based model and resulting share of classes acceptability index (case for reducing agent > capping agent > solvent)**

| Classes profiles | | $g_1$ | $g_2$ | $g_3$ | $g_4$ | $g_5$ | $g_6$ | $g_7$ | $g_8$ | Class acceptability index |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Reducing agent | Capping agent | Solvent | Local resource use | Reaction time (seconds) | Tempera-ture (Celsius) | Equipment type | Size range | |
| **Case A: Certain** | Class very high (5) | | | **$t_3$** | | | | | | |
| | $Pr_4$ = Very high - high | Renewable – primary | Renewable – waste | Renewable – primary | Yes | 50 | 30 | Stirring ≤ 5 minutes | 0 ≤ particle size ≤ 30 nm | |
| | Class high (4) | | | | | | | | | |
| | $Pr_3$ = High - medium | Renewable – primary | Renewable – primary | Renewable – primary | Yes | 100 | 40 | Stirring | 0 ≤ particle size ≤ 60 nm | |
| | Class medium (3) | **$t_3$** | | | **$t_3$** | | | | **$t_3$** | 23% |
| | $Pr_2$ = Medium - low | Biodegradable polymer | Renewable – primary | Biodegradable polymer | No | 400 | 60 | Microwave – sealed vessel (> 300 W) | 30 < particle size ≤ 60 nm | |
| | Class low (2) | | **$t_3$** | | | **$t_3$** | **$t_3$** | **$t_3$** | | **77%** |
| | $Pr_1$ = Low - very low | Synthetic | Biodegradable polymer | Synthetic | No | 1500 | 95 | Conventional | 0 < particle size ≤ 100 nm | |
| | Class very low (1) | | | | | | | | | |

ELECTRE-based model provides a different perspective on each process by accounting for the performance on each criterion and aggregating the information following the procedure discussed in section 7.2.3. This means that the decision aiding support is focused on the identification of the performance of each protocol in respect to a performance profile for each class. For example, when $t_1$ is considered in the ELECTRE-based assessment it can be seen from Table 7-8 that the performance of the protocol on every criterion is compared individually to every criterion. The synthesis process performs well in relation to the classes profiles which explains the high percentage for the very high class acceptability index (i.e. 81%), though there is not a specific indication/explanation about the combined effect of the criteria on the decision recommendation. Similarly, when considering process $t_3$ it is evident that the process does not perform well on the green chemistry criteria, which discloses the reason behind the recommendation mostly for a low performance class (Table 7-9). In this case, the developer of a new process could consider the improvement on the worst criteria (e.g. capping agent, PC and equipment), however he/she would not be provided with a recommendation on how the process could be improved by taking exemplary real case processes as indicative guidelines, which is what the DRSA-based model does through the supporting protocols for the rules.

## 7.5 Summary

Models to support decision-making processes in the area of sustainable nanotechnology are needed to improve the understanding of the different implications that NPs can have on the environment, the economy and society too. Throughout this Ph.D. thesis, the contribution that MCDA methods can have in this area has been widely discussed (Chapter 3) and also brought further through primary research. This allowed filling a major research gap that the literature review highlighted and which was selected as the fourth and last objective of this research project, namely the development of a robust model providing design guidelines for greener nanomaterials synthesis processes. The model itself was presented and discussed in detail in Chapter 6 (DRSA-based model), whereas the validation of its decision recommendations has been advanced in this chapter. Such validation, achieved through a three-step procedure, represents a legitimate requirement for the justification of the decision suggestion provided by the DRSA-based model and it was accomplished through the development of another model

(ELECTRE-based model) via the use of Stochastic Multicriteria Acceptability Analysis (SMAA-TRI).

The first part of this validation did benefit from the research presented in Chapter 5 about the comprehensive framework of SA criteria for NPs. Considering that there was a correspondence between the criteria framework and those in the DRSA-based model, it was also possible deriving an ordinal ranking of these parameters and consequently determining their relative priorities.

The second part of this research consisted in identifying a suitable method capable of providing a result comparable with the one of the DRSA-based model, i.e. a classification of the performance of silver nanoparticles synthesis processes in preference-ordered classes based on GCP implementation. Considering that MCDA is an excellent set of methods that can be used to aggregate the information on target alternatives conveyed by sustainability criteria of different types in the form of preference-ordered classes, rankings and choices recommendations, the robustness analysis of the DRSA-based model was also based on an MCDA method. SMAA-TRI emerged as a suitable approach for this challenge since it satisfies several requirements that characterized this decision-making problem, including the provision of robust results, the acceptance of criteria priorities in the form of ordinal rankings, the implementation of a strong concept of sustainability and the tailored suitability for criteria mainly with ordinal scales. SMAA-TRI was used to develop an ELECTRE-based model to obtain probabilistically characterized quality classes for the same test protocols the DRSA-based model was tested with. SMAA-TRI was an excellent tool to provide stability analysis of the classification recommendations and robust conclusions, as it adopts Monte-Carlo simulations (10,000 in number and $\pm 1\%$ accuracy) to yield class acceptability indices, the share in percentage of the possible parameters that lead an alternative to a certain category assignment.

The last part of the DRSA-based model validation procedure consisted in the comparison of the classifications recommended by such model and those of the ELECTRE-based one. Several simulation set-up settings where adopted with SMAA-TRI in order to account for the different weights of the criteria as well as the discriminatory classes profiles used to run the method. It was found that, in the majority of the cases, the two models agree in terms of decision recommendations, both in terms of relative ranking of the synthesis protocols as well as for the preference-ordered classes the protocols are assigned to. In fact, the overall classification correspondence is just under 86%, varying between 76% and 93.3% depending on the settings of the analysis, which allows affirming that the decision support from DRSA-based model can be considered as robust, valid and legitimate.

# Chapter 8. Conclusions and Recommendations for Future Research

The doctoral research described in this Ph.D. thesis proposed solutions to aid responsible development of nanotechnology, which has been achieved by (i) improving the capacity of assessing the sustainability implications of NPs, as well as (ii) providing DMs with support when they are faced with such complex problems.

This chapter discusses the main contributions of the thesis that allowed the presented research objectives to be achieved and provides some recommendations for future research.

## 8.1 Objective 1: Review the state-of-the-art for SA of NPs

It was found that all the studies investigating the sustainability implications of NPs fit within one of the main categories of SA tools (Chapter 3):

i. Biophysical indicators;
ii. Monetary indicators;
iii. Social indicators;
iv. Indicators sets and sustainability dashboards;
v. MCDA.

The review highlighted that a major obstacle for the responsible governance of nanotechnology was the lack of a comprehensive, reliable and validated framework of criteria that can be used to perform holistic SAs of a NP. As a result, work to fill this knowledge gap was conducted and was presented in Chapter 5; the highlights are provided below in section 8.3.

Another significant finding was that the use of MCDA to conduct SA of NPs is widespread and its process is emerging as a premier candidate to lead decision-making for nanotechnology based on sustainability principles. This justified the review of capabilities of MCDA methods for SA of NPs, whose results are presented in Chapter 4 and summarized in the next section.

## 8.2 Objective 2: Evaluate the potentials of MCDA methods to support SAs of NPs

Among the SA tools used to evaluate the implications of NPs, MCDA methods have been employed increasingly, as a result of their capacities of handling unstructured information of different type and quality, as well as offering traceable decision support to the assessors. Such studies showed that the reasons for the selection of the MCDA methods are not always very transparent and their actual strengths and weaknesses in the context of the typologies of the decision-making problems are not motivated and explained with rigour and detail. This justified the in-depth analysis (Chapter 4) of the potentials and limitations of MCDA methods mostly used or promising in relation to their capabilities of performing sustainability evaluations (i.e. MAUT, AHP, ELECTRE, PROMETHEE, DRSA) of NPs. A literature review of these methods was performed with respect to ten performance indicators, clustered in three areas; scientific soundness, applicability and utility of the methods [438].

The review confirmed that these MCDA methods are excellent instruments for conducting SAs and they can all manage quantitative and qualitative information, as well as support a life cycle perspective. Weak sustainability modeling paradigms can be enforced with MAUT and AHP, whereas a strong sustainability concept is supported by ELECTRE, PROMETHEE and DRSA. All the methods but DRSA are usually applied with a direct preference elicitation strategy, which is perceived as cognitively demanding by the DMs. DRSA strengths are that it is easy to understand and provides a straightforward set of decision rules expressed in the form of elementary “if … then …” conditions, which proved as a promising candidate for the achievement of the fourth objective of the thesis (section 8.4).

Interestingly, the review highlighted that there is currently an emerging consensus that the development of SAs should be performed with the “co-constructive modeling” paradigm. This implies that the collaboration of the decision analysts, domain experts and other stakeholders affected by the decisions at stake co-construct the problem, the alternatives, the assessment criteria and the evaluation model, implying a legitimate dependency of the model decision recommendations on the decision-making context.

## 8.3 Objective 3: Develop a comprehensive set of SA criteria for NPs

NPs have entered the market or are expected to do so in the near future, thus robust and science-based criteria are required to appraise and manage their sustainability. A comprehensive and agreed group of criteria for the evaluation of sustainability of NPs was missing and this thesis described the research that filled such knowledge gap (Chapter 5). This was achieved by adopting the co-constructive MCDA philosophy in the form of a three-phase research procedure, structured on literature review and experts' knowledge elicitation through a survey. This allowed developing a holistic and reliable framework of 68 criteria for NPs, integrating literature review findings with more than 1,500 years of cumulative experience from 119 experts and practitioners in sustainable nanotechnology [485]. Six main areas characterize the framework, distinguishing along established research themes that draw from the triple-bottom-line pillars of sustainable development: economy, environment and society.

Economic performance was identified as an area by itself for the "economy" pillar, with the key priority being the improvement of collaboration embedment among various stakeholders along the value chain of NPs to improve control over raw materials price volatility. The "environment" pillar was split into two areas, one referring to the environmental impacts caused by the NP during its lifecycle. In this regard, the reduction of materials and energy inefficiencies in the production processes, as well as the typologies and implications of selected resources need to receive chief attention by environmentally-oriented process developers. The other focus area has been the assessment and management of environmental risks, where the necessity of identifying the complex mechanisms regulating NP's behaviour received a high rank in the priorities list. In a similar fashion, one of the two components of the "society" pillar has been also concerned with the risks caused by NPs, though in this case those affecting humans. Exposure characterization and mitigation was a prerogative for these experts too, followed by the necessity of comparable toxicity results, which first of all depends on consensus on the exposure metrics, alternative testing strategies, capability to link NP-specific properties to ADME profiles and physicochemical properties for toxicity testing. The other domain of the "society" pillar is the evaluation of the broader ethical, legal and governance implications of NPs, providing a representation of the complex management of this emerging technology. As an example, the criteria span from regulatory compliance to contribution to environmental management and up to development of military equipment and personal data management. The last area of the framework accounts for the technical performance of NPs, with a major focus on the quality assurance, including functionality and reliability of NP together with reproducibility of characterization techniques. These are core aspects at the basis of NPs' success, since products that do not meet (or exceed) technical standards would not even be considered for production, which would render any effort to assess their sustainability worthless.

A key learning from this study is that sustainability-related research on nanotechnology is complex because of the varied background of the stakeholders involved in such decision-making processes. This suggests the need for the development of more cohesive networks of experts from different domains in the area of nanotechnology, which could empower more efficient knowledge gathering and sharing.

## 8.4 Objective 4: Develop and validate a model for the classification of synthesis processes for nanomaterials on the basis of green chemistry principles implementation

The synthesis step is pivotal in determining the performance of the ensuing nanomaterial and the resulting sustainability impacts are highly dependent on the equipment, type and origin of the employed materials and processing conditions. This led, during the last decade, to the emergence of an extensive set of production protocols highlighting their contribution in terms of implementation of green chemistry principles. The line of research that showed very promising in the area of green and sustainable nanosynthesis has been the one labelled as “bio-inspired approaches”, employing alternative raw materials to produce nanomaterials, including bacteria, fungi, plants, plants extracts, yeasts and algae. They have potentials of implementing several principles of green chemistry, including renewable materials use, synthesis at ambient temperature and pressure as well as safe processing conditions. Protocols employing plants and plants extracts showed the most promising as the reactions can be as low as a few minutes and be optimized more easily than the other bio-inspired routes.

Even though several attempts have been tried to integrate sustainability principles in this life cycle stage, most of the studies focused on the individual proposition of synthesis protocols. However, none of the research studies proposed in the literature satisfied the requests by prominent experts and organizations in the area to:

i. Identify design guidelines for the development of green nanomaterials;
ii. Assess the implementation of green chemistry principles in new nanosynthesis processes in the form of a performance class.

These two challenges were tackled in this thesis through MCDA by developing a model for the green chemistry-based classification of silver nanoparticles synthesis protocols into preference-ordered performance classes (Chapter 6). The focus was placed on this type of nanomaterial because of:

i. The availability of published information to create a relevant dataset;
ii. The successful applications that are enabled and envisioned by such material;
iii. The availability of experts in this area to take part in the decision aiding process.

DRSA was selected as the MCDA method due to its flexibility in handling heterogeneous information that was a primary characteristic of the working dataset, the lack of compensation among the criteria and because its results in the form of *"if* condition*, then* decision*"* rules provide a practical example of the design guidelines mentioned above as a research gap. The DRSA-based model is composed of 26 decision rules that represent the knowledge of the two DMs who classified silver nanoparticles synthesis processes in preference-ordered classes based on the application of green chemistry principles [226]. What is more, the decision rules can also be employed for the classification of new or existing production processes for silver nanoparticles depending on how many and what type (i.e. at least, at most) of rules they satisfy. This provides an easily understandable, traceable and transparent decision support platform that confirms how DRSA can be used as a "glass box" in MCDA applications focused on sustainability evaluations.

Even though the DRSA-based model was developed with the collaboration of two knowledgeable practitioners in the area, its robustness required testing in order to consider its decision recommendation as valid. The validation of the DRSA-based model was achieved through a three-step procedure that integrated the results from the experts' survey presented in the previous section with another MCDA method [486] (Chapter 7). Firstly, an ordinal ranking of the assessment criteria used in the DRSA-based model was derived from the relative priorities of the criteria from the comprehensive set described previously. Secondly, a suitable and robust method capable of providing a decision recommendation comparable with the one of the DRSA-based model was identified. This was the Stochastic Multiple Criteria Acceptability Analysis (SMAA-TRI), an MCDA method specifically tailored to supply uncertainty-characterized robust classifications. The integration of criteria rankings and SMAA-TRI method led to another model, called ELECTRE-based model to derive probabilistically characterized quality classes for the same test protocols the DRSA-based model was tested with. The last validation stage consisted in comparing the decision recommendations from the two models to assess the robustness of the DRSA-based one. This was achieved by comparing the classification for five test protocols from the model based on DRSA with those derived by the one based on ELECTRE, adopting different criteria weights and discriminatory classes profiles to account for input data variability. Out of 120 classifications comparisons, the overall correspondence reached a satisfactory level of just under 86%, whereas it varied between 76% and 93.3% depending on the settings of the analysis.

Overall, the results of the three-step validation approach confirm that the DRSA method can be used as a flexible technique to derive an easily intelligible and robust decision support tool for classification of synthesis processes of silver nanoparticles on the basis of green chemistry perspective. Furthermore, the traceability of the recommended class in the form of design rules adds transparency to the decision aiding and it provides comparative measures (i.e. already existing protocols) when developing own new processes or when evaluating existing ones. More generally, this research confirms MCDA as an excellent framework and set of methods to be used to integrate relevant criteria in the form of performance rankings and preference-ordered classes, so that the decision-making process is enhanced and robust recommendations can be advanced.

## 8.5 Recommendations for future research

i. There is a wide and growing variety of MCDA methods which can be (or are already) used to conduct SAs. This thesis presented the analysis of five of them in relation to their potentials to support such evaluations. The review could be expanded to include additional MCDA methods in order to extend the support for researchers who want to make an informed and justifiable choice of these approaches depending on the typology of SA challenge.

ii. One potential solution to aid the identification of the appropriate MCDA techniques depending on the problem at hand and not vice-versa is to expand the concept of stakeholders’ involvement during the SA process, by directly including the computer scientists, mathematicians and informatics that are “behind" the MCDA algorithms and constructing in cooperation with them the most relevant decision support model.

iii. The development of multidisciplinary teams is a necessary requirement for the advancement of sustainability research (in general and) in the area of nanotechnology. In fact analysts aiming at performing SAs of nanotechnology need to face rather unstructured problems at first, which is due to the lack of clarity on what the alternatives under assessment are, the objectives of the foreseen evaluation and also the features that characterize such alternatives. In order to tackle this challenge in a successful manner one solution is including, from the start of the assessment process, the affected stakeholders in each area of interest, being it environment-, economy-, society- or technology-related. They can provide invaluable insights into the problem under consideration and help formulating it in a rigorous manner.

iv. The framework of sustainability assessment criteria for NPs can be used to increase the knowledge about their implications. One possibility is the application of the criteria from one or more areas to a single or more NPs. In the first case it is possible to identify a benchmark evaluation for the NP and understand the criteria where it performs poorly and the reasons for that. In the case when multiple NPs are compared (with the same criteria), a relative assessment of sustainability level can be obtained. An important consideration in the implementation of the framework is the lack of complete information on each criterion. A potential solution to this problem is to decrease the quality of the measurement scale for the criteria. For example, it would be possible to switch from a quantitative to a qualitative scale, which requires much less information on the parameters while still providing an indication of the performance of the NP.

v. The sustainability assessment criteria for NPs can also be used to develop integrative assessments based on MCDA methods. In this regard, Chapter 7 describes how this was conducted with a limited set. Further work in this direction would consist in the integration of larger sets of criteria with MCDA methods to develop comparative sustainability evaluations for a grouo of NPs, by evaluating their performance on more than one area and identifying where they excel or perform poorly and recognise improvement strategies.

vi. The decision recommendations of the classification models for synthesis processes of silver nanoparticles could be analysed in terms of life cycle perspective implications, to assess whether the use of green chemistry principles at the synthesis stage implies lower environmental impacts across the whole life cycle when compared to conventional synthesis processes. In order to increase the validity of the model, it would be possible to involve more experts from the green chemistry domain and elicit their preferences on the production processes as it was done with the two chemists at the US EPA.

vii. The development of a model similar to the DRSA-based one in other high-interest areas, such as manufacturing of graphene, would be very useful both from a decision aiding as well as from a green nanomanufacturing perspective. In order to render the model more flexible as far as equipment type is concerned, the use of a quantitative measurement scale (e.g. energy consumption) could be considered;

viii. The classification models described in the thesis could be implemented in two stand-alone software packages (or one single package implementing both) so that researchers and other interested stakeholders could use them to:

- Reduce the direct training required for new or novice researchers as they can learn from the decision rules of the DRSA-based model and the assessment of the alternatives in relation to the classes profiles of the ELECTRE-based model;
- Focus on more challenging tasks as they do not need to spend so much time on training others;
- Reduce the time needed for evaluation of green alternatives through quick screening of production routes by means of the recommended performance class;
- Use the available unstructured information in an efficient and effective manner.

ix. The stakeholders that contributed to the development of the criteria framework were experts who operated in one or more of its areas and the input they provided was focused on the individual criteria in each one. The potential advancement of the framework could consist in including policy makers, who can provide preference judgements on the importance of the different areas of the framework. This would lead to a complete weighted framework both for the main areas of analysis (e.g. economic performance, environmental impacts, social implications) and for the individual criteria in each of them. Consequently, this whole set of preferences could be used to develop an MCDA model providing a class, score or rank of a NP (or a set) from a comprehensive sustainability perspective accounting for all the criteria in the framework simultaneously.

# *Appendix A - Appendix of Chapter 5*

## Appendix A.1 - Sustainability assessment criteria selected from the literature review

| Area | Criteria | | Criteria explanation | Reference |
|---|---|---|---|---|
| **Economic performance criteria** | Economic viability of manipulation processes | | Economic viability of NP manipulation processes (e.g. extraction, processing, recycling, incineration) | 3,11 |
| | External social costs | Health and welfare | Health and welfare social costs caused by a NP during its life cycle phases | 2 |
| | | Remediation-conservation of ecosystems | Ecosystems remediation-conservation social costs caused by a NP during its life cycle phases | 2 |
| | Funding trend | | Governmental funding for research, development and application of a NP | 1 |
| | Manufacturing costs | | Costs incurred during production phase of a NP | 3,11,15,19,22,34,40,44,70-73 |
| | Raw materials | | Raw materials costs in the life cycle stages of a NP (e.g. extraction, processing, recycling, incineration) | 19,34,40,44,70-73 |
| | Waste treatment and disposal | | Costs for waste treatment and disposal incurred during the life cycle phases of a NP | 19 |

**Appendix A.1 - Sustainability assessment criteria selected from the literature review (cont.)**

| | | | | |
|---|---|---|---|---|
| **Environmental impacts criteria** | Energy | Energy consumption | Energy consumed at the life cycle stages of a NP (e.g. extraction, production, waste management, recycling) | 1,2,4,6,7,10,11,15,16,17,20,21,23,26,27 |
| | | Energy efficiency | Energy efficiency of the processes involving manipulation of NP (e.g. extraction, processing, recycling, incineration) | 3,5,7,10,11,19,20,22,34,40-47 |
| | Materials efficiency | | Materials efficiency of the processes involving manipulation of a NP (e.g. extraction, processing, recycling, incineration) | 5,6,7,9,11,15,16,17,19,21,27,28 |
| | Hazardous materials used or produced | | The use or production of hazardous materials during the life cycle phases of a NP | 4,19,21,22,24 |
| | Processing conditions | | Processing conditions during the life cycle phases of a NP (e.g. temperature, pressure, enthalpy) | 5,7,16,17,24 |
| | | Local resource use | Use of local resources in the life cycle phases of a NP | 1 |
| | | Rare materials use | Use of rare materials in the life cycle phases of a NP | 1,11,28 |
| | | Raw materials use | Amount of raw materials used in the life cycle phases of a NP | 2,4,6,7,11,16,17,19,20,21,2 |

**Appendix A.1 - Sustainability assessment criteria selected from the literature review (cont.)**

| | | | | |
|---|---|---|---|---|
| 🟩 | Resources management and use | | | 8 |
| | | Renewable resources use | Use of renewable resources in the life cycle phases of a NP | 3,5,7,9,10,15 |
| | | Resources demand trend | Trend of total resources demand during the life cycle phases of a NP | 5,7,17 |
| | | Supply risks | Possible risks related to availability of resources needed for NP manufacturing (e.g. regional concentration of mining, physical shortage) | 1 |
| | | Water use | Use of water in the life cycle phases of a NP | 2,6,7,16,17,21 |
| | Waste production | | Generation of waste due to NP manipulation during the life cycle phases | 2,3,4,6,9,16,19,20,21,28 |
| 🟨 | Adaptation of exposure modelling tools | | Adaptation of current exposure models that include NP-specific information (e.g. aerodynamic size distribution) | 26,74,75,78 |
| | Applicability of exposure modelling tools | | Applicability of current environmental exposure models for a NP | 74,75,78 |
| | Applicability of testing methods | | Applicability of current ecotoxicity tests for a NP (e.g. OECD guidelines) | 34,35,64-67,76,77,78 |
| | Bioaccumulation | | Scientific knowledge about bioaccumulation mechanisms | 11,34,77,78 |

## Appendix A.1 - Sustainability assessment criteria selected from the literature review (cont.)

| | | | |
|---|---|---|---|
| **Environmental risk assessment and management** | Biodegradability | Biodegradation of the NP in environmental media | 36-39,77,78 |
| | Ecological hazard assessment based on available knowledge | Ecological hazard assessment of a NP based on current scientific knowledge | 4,9,18,34,35,62-67,69,78 |
| | Environmental exposure | Knowledge about environmental exposure to a NP | 1,4,7,9,22,34,35,62-65,67 |
| | NP definition | An agreed-upon definition for a NP | 74,78 |
| | Physicochemical properties agreement for ecotoxicity testing | Agreed-upon physicochemical properties for NP-specific ecotoxicological testing | 6,18,34,35,67,74,78 |
| | Risk quantification based on current scientific knowledge | Risk quantification of a NP based on current scientific knowledge | 1,4,11,13,15,18,34,35,64,65,70,74,78 |
| | Non-nanomaterial to nanomaterial properties extrapolation | Appropriateness of available extrapolation processes for properties to identify relationships between nanoscale and non-nanoscale materials | 74,78 |
| | Assessment endpoints for ecotoxicity testing | Agreed-upon NP-specific assessment endpoints | 11,34,35,55,58,64-67,69 |
| | Transformation, degradation and persistence tests | Agreed-upon NP-specific transformation, degradation and persistence tests | 74,78 |
| | Use of ecotoxicity data on close analogues | Using ecotoxicity data for a NP from analogous NPs ("read-across approach") | 74,78 |
| | Toxicity tests applicability to NP | Applicability of current toxicity tests for a NP (e.g. OECD | 34,35,51- |

## Appendix A.1 - Sustainability assessment criteria selected from the literature review (cont.)

| | | | |
|---|---|---|---|
| **Human health risk assessment and management** | | guidelines) | 55,59,60,61,67,74,76,78 |
| | Dose metrics for hazard characterization | Scientific agreement on NP-specific dose metric for hazard characterization | 35,51,52,55,58,64,65,67,68,74,78,80 |
| | Effective dose for adverse effects | Scientific agreement on NP-specific effective concentration | 35,51,61,67,68,74,78,80 |
| | Human hazard assessment based on available knowledge | Human health hazard assessment of a NP based on current scientific knowledge | 1,4,9,18,34,35,67,78 |
| | Human exposure | Knowledge about human exposure to a NP | 1,4,7,8,9,18,34,35,56,57,60,62,63,67 |
| | Links of NP's properties with ADME profiles | Capability to link NP-specific properties to absorption, distribution, metabolism, excretion and toxic effects | 9,78 |
| | NP definition | An agreed-upon definition for a NP | 74,78 |
| | Non-nanomaterial to nanomaterial properties extrapolation | Properties extrapolation from non-nanoscale to nanoscale materials | 74,78 |
| | Nanomaterial to nanomaterial properties extrapolation | Properties extrapolation between different nanoscale materials | 74,78,79 |
| | Physicochemical properties | Agreed-upon physicochemical properties for NP-specific | 6,18,34,35,74 |

**Appendix A.1 - Sustainability assessment criteria selected from the literature review (cont.)**

| | | | | |
|---|---|---|---|---|
| 🟪 | agreement for toxicity testing | | toxicological testing | ,78 |
| | Risk quantification based on current scientific knowledge | | Risk quantification of a NP based on current scientific knowledge | 4,11,13,15,34,35,57 |
| | Assessment endpoints for toxicity testing | | Agreed-upon NP-specific assessment endpoints | 11,34,35,67 |
| | Risk management and communication | | Development and adoption of risk management and communication measures (e.g. technical measures, precautionary programmes) tailored for NPs | 1,8,16,18,34,35,67 |
| | Use of toxicity data on close analogues | | Using toxicity data for a NP from analogous NPs ("read-across approach") | 74,78 |
| 🟩 | Employment effects from NP production | | Employment effects deriving from a NP production | 1,2,7,14,15,34 |
| | Regulatory compliance | | Regulatory compliance of a NP with current and possible regulations | 4,12,13 |
| | Social benefits | Tackling environmental issues | A NP contribution to solving environmental problems (e.g. pollution, clean energy production, climate change) | 1 |
| | | Promotion of health | Promoting health through NPs (e.g. reduction of child mortality, improvement of maternal health) | 4 |
| | | Promotion of education and | Promoting education and information management through NPs (e.g. more efficient and reliable information | 1 |

## Appendix A.1 - Sustainability assessment criteria selected from the literature review (cont.)

| | | | | |
|---|---|---|---|---|
| **Social implications criteria** | | information | technology) | |
| | | Reduction of the "nano-divide" | Reducing the "nano-divide" (i.e. nano-related technological imbalance between developed and developing countries) through NPs | 1, 4,12,14 |
| | Social issues | Collection of personal data or trace individual behaviour | Possible use of NP-enabled applications to collect personal data or trace individual behaviour | 4,12 |
| | | Military purposes use | Possible use of NP-enabled applications for military purposes | 2,7,12 |
| | User benefits | Added value for user | Improvement of user experience (e.g. functionality improvement compared to reference product, convenience) | 1 |
| | | Symbolic benefits for user | Symbolic benefits of a NP (e.g. prestige, identity creation) | 1,2,7 |
| | Durability | | Targeted durability of the NP | 1,3,4,22 |
| | Functionality | | Targeted functionality of the NP | 2,3,4,7,11,27, |

## Appendix A.1 - Sustainability assessment criteria selected from the literature review (cont.)

| | | | |
|---|---|---|---|
| **Technical performance criteria** | | | 29-33 |
| | Maintainability | Targeted maintainability of the NP | 1 |
| | Recyclability | Recyclability of the NP | 1,3,4,5,6,7,10,11,19,28,30,34,48 |
| | Reliability | Reliability of the NP | 1,3 |
| | Reusability | Reusability of the NP | 4,28,49,50 |
| | Technology maturity | Technological maturity of the NP manufacturing process | 3,9 |

**References: 1**: [5]; **2**: [43]; **3**: [44]; **4**: [20]; **5**: [23]; **6**: [117]; **7**: [22]; **8**: [157]; **9**: [24]; **10**: [25]; **11**: [59]; **12**: [19]; **13**: [487]; **14**: [367]; **15**: [2]; **16**: [61]; **17**: [28]; **18**: [488]; **19**: [51]; **20**: [392]; **21**: [18]; **22**: [317]; **23**: [489]; **24**: [330]; **25**: [432]; **26**: [433]; **27**: [490]; **28**: [331]; **29**: [491]; **30**: [492]; **31**: [493]; **32**: [369]; **33**: [494]; **34**: [318]; **35**: [495]; **36**: [496]; **37**: [497]; **38**: [498]; **39**: [499]; **40**: [319]; **41**: [500]; **42**: [501]; **43**: [502]; **44**: [320]; **45**: [503]; **46**: [504]; **47**: [505]; **48**: [506]; **49**: [507]; **50**: [508]; **51**: [509]; **52**: [510]; **53**: [511]; **54**: [512]; **55**: [513]; **56**: [514]; **57**: [515]; **58**: [37]; **59**: [516]; **60**: [517]; **61**: [518]; **62**: [519]; **63**: [520]; **64**: [521]; **65**: [522]; **66**: [523]; **67**: [524]; **68**: [525]; **69**: [526]; **70**: [324]; **71**: [321]; **72**: [322]; **73**: [323]; **74:** [129]; **75:** [34]; **76:** [344]; **77:** [343]; **78:** [126]; **79:** [527]; **80:** [528]

# Appendix A.2 - Pilot Survey

The first page of the questionnaire is the cover letter that each expert received in the e-mails that invited him/her to take part to the survey. The second page is the actual initial page of the online questionnaire the expert was redirected to.

THE UNIVERSITY OF WARWICK EPSRC Engineering and Physical Sciences Research Council WMG Innovative Solutions

## Questionnaire for the Assessment of Sustainability Criteria for NPs

Dear …..

The Warwick Manufacturing Group (WMG) department at the University of Warwick has undertaken *a research project to support the sustainable development of NPs, including nanomaterials and products containing such materials*.

The following *questionnaire* has been developed to allow nanotechnology experts as you are to *evaluate the importance of the criteria currently used to assess the impacts and implications of NPs.* Furthermore *you can suggest those criteria that you consider relevant and that were left out of this list*.

We are aware that the questionnaire will take some of your valuable time but without your kind and expert input the improvement of sustainability of NPs this project aims at cannot be realised.

Full information about the research project and the conduct of the study are reported in the attached “Participant Information Leaflet”.

We thank you very much for your invaluable input and consideration.

***Please click this link to fill in the questionnaire:***
https://perception.warwick.ac.uk/perception5/perception.php

**Please note:** If you do not want to be part of the study and receive follow-up e-mails you can reply to this first invitation e-mail indicating that you are not interested.

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This questionnaire is structured as follows:

**Specification of professional expertise and evaluation of importance of sustainability criteria for NPs**

- You can choose your professional expertise among six main areas of NPs sustainability implications.
- For each area, you can indicate your years of experience, your scale of operation and *score the criteria for evaluating sustainability of NPs in terms of their importance (on a 5-point scale from very low to very high).*
- You can also *add any criteria* that were not reported here and you consider relevant, indicating their importance accordingly, *and comment* on the criteria set and evaluation procedure.

**Important:** In this questionnaire the term **NP** is considered as follows[a]:

- A nanomaterial defined as:

  An engineered material with *"at least one dimension in the order between 0.5 nm and 200 nm (primary nanoparticles), and agglomerates and aggregates derived from such materials."*

- A mixture or solution containing nanomaterials (as defined above);
- A semi-finished or finished product containing nanomaterials (as defined above).

[a] = Moller, M. *et al.* Analysis and Strategic Management of NPs with Regard to their Sustainability Potential. Nano-Sustainability Check (Oko-Institut e.V., 2012)

For some criteria different life cycle phases are accounted for. Please consider that phases are intended as follows:

- *Production phase* includes: research and development, resource extraction, manufacturing, logistics and distribution up to the final application use;
- *Use phase* includes: business and private (end) use;
- *End-of-life phase* includes: recycling, treatment for reuse, and disposal (e.g. landfill).

**Please note:** At the end of the questionnaire you will be asked whether you would like to contribute to develop and test a model for NPs sustainability assessment that will be structured on the basis of your replies and those from other respondents.

- Please indicate your main expertise in the area of NPs so that you will be redirected to the appropriate section (if you have more than one you will be able to complete that/those one at a time):
  - ***Economic performance***: this part covers the economic implications of a NP during its life cycle;

- ***Environmental implications (excluding risks)***: this part covers the environmental loadings (e.g. energy consumption, waste production, resource consumption) of a NP during its life cycle excluding risks aspects;
- ***Environmental risk assessment and management***: this part covers aspects and issues related to the environmental risks of a NP during its life cycle;
- ***Human health risk assessment and management***: this part covers aspects and issues related to the human health (consumers and workers) risks of a NP during its life cycle;
- ***Social implications***: this part covers ethical, legal and social implications of a NP during its life cycle;
- ***Technical performance***: this part covers the technical aspects and properties of a NP during its life cycle.

## ECONOMIC PERFORMANCE CRITERIA

Welcome to the **economic performance section** (11 questions overall) which covers the economic implications of a NP during its life cycle.

1. How many **years of work experience** have you got in the *area of economic performance of NPs* (please indicate in number)?

2. What is **your scale of operation** in the *area of economic performance of NPs*?

   Local National Supranational Global

3. What is the importance of the **economic viability of processes involving manipulation of a NP** (e.g. production furnace, recycling, incinerator) in affecting its *economic performance*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

4. What is the importance of the **social costs caused by a NP production and end-of-life phases to be bear by society for health and welfare implications** in affecting its *economic performance*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

5. What is the importance of the **social costs caused by a NP production and end-of-life phases to be bear by society for remediation-conservation of ecosystems** in affecting its *economic performance*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

6. What is the importance of the **governmental or international funding for research, development and application of a NP** in affecting its *economic performance*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

7. What is the importance of the **manufacturing costs of a NP** in affecting its *economic performance*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

8. What is the importance of the **raw materials costs for a NP production and end-of-life phases** in affecting its *economic performance*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

9. What is the importance of the **costs for waste treatment and disposal incurred in the production and end-of-life phases of a NP** in affecting its *economic performance*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

10. Please **add any criteria** that were not reported here and you consider relevant, indicating their importance accordingly

11. Please provide **any opinions and comments** that you may have about the criteria set and evaluation procedure, including:

    - ambiguous questions
    - irrelevant questions
    - general comments

### ENVIRONMENTAL IMPLICATIONS (EXCLUDING RISKS) CRITERIA

Welcome to the **environmental implications (excluding risks) section** (17 questions overall) which covers the environmental loadings of a NP during its life cycle excluding risks aspects.

*1.* How many **years of work experience** have you got in the *area of environmental implications of NPs* (please indicate in number)?

2. What is **your scale of operation** in the *area of environmental implications of NPs*?

Local National Supranational Global

3. What is the importance of the **energy consumed during the life cycle of a NP** (e.g. production, waste management, recycling) in affecting its *environmental impacts*?

Do not know Very low Low
Medium High Very high

4. What is the importance of the **energy efficiency of the processes involving manipulation of a NP** (i.e. production furnace, recycling, incinerator) in affecting its *environmental impacts*?

Do not know Very low Low
Medium High Very high

5. What is the importance of the **materials efficiency of the processes involving manipulation of a NP** (e.g. production furnace, recycling, incinerator) in affecting its *environmental impacts*?

Do not know Very low Low
Medium High Very high

6. What is the importance of the **hazardous materials used or produced during the life cycle of a NP** (evaluated on e.g. toxicity, flammability, persistence, mobility) in affecting its *environmental impacts*?

Do not know Very low Low
Medium High Very high

7. What is the importance of the **processing conditions during production and end-of-life phases of a NP** (e.g. temperature, pressure, enthalpy) in affecting its *environmental impacts*?

Do not know Very low Low
Medium High Very high

8. What is the importance of the **trend of demand for resources needed in production and end-of-life phases of a NP** in affecting its *environmental implications*?

Do not know Very low Low
Medium High Very high

9. What is the importance of the **use of local resources in production and end-of-life phases of a NP** in affecting its *environmental implications*?

Do not Very low Low

| | | |
|---|---|---|
| know | | |
| Medium | High | Very high |

10. What is the importance of the **use of rare materials in production and end-of-life phases of a NP** in affecting its *environmental implications*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

11. What is the importance of the **amount of raw materials used in production and end-of-life phases of a NP** (e.g. production, maintenance, disposal) in affecting its *environmental implications*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

12. What is the importance of the **use of renewable resources in production and end-of-life phases of a NP** in affecting its *environmental implications*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

13. What is the importance of the **possible risks related to availability of resources needed to NP manufacturing** (e.g. regional concentration of mining, physical shortage) in affecting its *environmental implications*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

14. What is the importance of the **use of water in production and end-of-life during NP manipulation** in affecting its *environmental impacts*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

15. What is the importance of the **generation of waste due to NP manipulation during the life cycle** in affecting its *environmental impacts*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

16. Please **add any criteria** that were not reported here and you consider relevant, indicating their importance accordingly

17. Please provide **any opinions and comments** that you may have about the criteria set and evaluation procedure, including:

- ambiguous questions

- irrelevant questions
- general comments

**ENVIRONMENTAL RISK ASSESSMENT AND MANAGEMENT CRITERIA**

Welcome to the **environmental risk assessment and management section** (18 questions overall) which covers aspects and issues related to the environmental risks of a NP during its life cycle.

1. How many **years of work experience** have you got in the *area of environmental risk assessment and management of NPs* (please indicate in number)?

2. What is **your scale of operation** in the *area of environmental risk assessment and management of NPs*?

   Local National Supranational Global

3. What is the importance of the **adaptation of available tools to model NP exposure by including nano-specific information** (e.g. distribution, aerodynamic size distribution) in supporting its *environmental risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

4. What is the importance of the **applicability of available tests to perform ecotoxicity studies of a NP** (e.g. OECD guidelines) in supporting its *environmental risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

5. What is the importance of the **applicability of available environmental exposure models for a NP** in supporting its *environmental risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

6. What is the importance of **bioaccumulation mechanisms of a NP** in affecting its *environmental risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

7. What is the importance of **biodegradation of a NP in environmental media** in affecting its *environmental risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |

| | | |
|---|---|---|
| Medium | High | Very high |

8. What is the importance of **ecological hazard assessment for classification and labelling of a NP based on current scientific knowledge** in supporting its *environmental risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

9. What is the importance of the **likelihood of exposing the environment to unbound NPs** in affecting their *environmental risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

10. What is the importance **a proper definition for a NP intended as a nanomaterial**, including properties to characterize it (e.g. composition, crystallinity, size, morphology), in supporting its *environmental risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

11. What is the importance of the **properties extrapolation from non-nanoscale to nanoscale materials** in supporting *NP environmental risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

12. What is the importance of **an internationally agreed set of physico-chemical properties necessary for eco-toxicological testing of a NP** in supporting its *environmental risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

13. What is the importance the of the **risk quantification of a NP based on available scientific knowledge** in supporting its *environmental risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

14. What is the importance of **internationally agreed assessment endpoints to be considered in ecotoxicity tests of a NP** in supporting its *environmental risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

15. What is the importance of **transformation, degradation and persistence tests of a NP** in supporting its *environmental risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

16. What is the importance of the possibility to **use ecotoxicity data for a NP from analogous NPs ("read-across approach")** in supporting its *environmental risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

17. Please **add any criteria** that were not reported here and you consider relevant, indicating their importance accordingly

18. Please provide **any opinions and comments** that you may have about the criteria set and evaluation procedure, including:

- ambiguous questions
- irrelevant questions
- general comments

## HUMAN HEALTH RISK ASSESSMENT AND MANAGEMENT CRITERIA

Welcome to the **human health risk assessment and management section** (18 questions overall) which covers aspects and issues related to the human health (consumers and workers) risks of a NP during its life cycle.

1. How many **years of work experience** have you got in the *area of human health risk assessment and management of NPs* (please indicate in number)?

2. What is **your scale of operation** in the *area of human health risk assessment and management of NPs*?

| | | | |
|---|---|---|---|
| Local | National | Supranational | Global |

3. What is the importance of the **applicability of available tests to perform toxicity studies of a NP** (e.g. OECD guidelines) in supporting its *human health risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

4. What is the importance of the **scientific agreement on dose metric for NP hazard characterization** in supporting its *human health risk assessment*?

| | | |
|---|---|---|
| Do not | Very low | Low |

| | | |
|---|---|---|
| know | | |
| Medium | High | Very high |

5. What is the importance of **scientific agreement on effective concentration of a NP causing an adverse biological effect** in supporting its *human health risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

6. What is the importance of the **human health hazard assessment for classification and labelling of a NP based on current scientific knowledge** in supporting its *human health risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

7. What is the importance of the **likelihood of exposing humans to unbound NPs** in affecting their *human health risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

8. What is the importance of the **capability to link NP properties to absorption, distribution, metabolism and excretion and toxic effects** in affecting its *human health risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

9. What is the importance **a proper definition for a NP intended as a nanomaterial**, including properties to characterize them (e.g. composition, crystallinity, size, morphology), in supporting its *human health risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

10. What is the importance of the **properties extrapolation from non-nanoscale to nanoscale materials** in supporting *NP human health risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

11. What is the importance of the **properties extrapolation from nanoscale to nanoscale materials** in supporting *NP human health risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

12. What is the importance of **an internationally agreed set of physico-chemical properties necessary for toxicological testing of a NP** in supporting its *human health risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

13. What is the importance the of the **risk quantification of a NP based on available scientific knowledge** in supporting its *human health risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

14. What is the importance of **internationally agreed assessment endpoints to be considered in toxicity tests of a NP** in supporting its *human health risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

15. What is the importance of **adoption of risk management and communication measures** (e.g. technical measures, precautionary programmes) in supporting *NP human health risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

16. What is the importance of the possibility to **use toxicity data for a NP from analogous NPs ("read-across approach")** in supporting its *human health risk assessment*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

17. Please **add any criteria** that were not reported here and you consider relevant, indicating their importance accordingly

18. Please provide **any opinions and comments** that you may have about the criteria set and evaluation procedure, including:

- ambiguous questions
- irrelevant questions
- general comments

## SOCIAL IMPLICATIONS CRITERIA

Welcome to the **social implications section** (14 questions overall) which covers ethical, legal and social implications of a NP during its life cycle.

1. How many **years of work experience** have you got in the *area of social implications of NPs* (please indicate in number)?

2. What is **your scale of operation** in the *area of social implications of NPs*?

   Local National Supranational Global

3. What is the importance of the **employment effects deriving from a NP production** in affecting its *social implications*?

   Do not know Very low Low

   Medium High Very high

4. What is the importance of the **regulatory compliance of a NP with current and upcoming regulations** in affecting its *social implications*?

   Do not know Very low Low

   Medium High Very high

5. What is the importance of **a NP contribution to fighting environmental issues** (e.g. pollution, clean energy production) in affecting its *social implications*?

   Do not know Very low Low

   Medium High Very high

6. What is the importance of **a NP promotion of health** (e.g. reduction of child mortality, maternal health) in affecting its *social implications*?

   Do not know Very low Low

   Medium High Very high

7. What is the importance of **a NP promotion of education and information** (e.g. more efficient and reliable information technology products) in affecting its *social implications*?

   Do not know Very low Low

   Medium High Very high

8. What is the importance of **a NP reduction of the "nano-divide" (i.e. nano-related technological imbalance between develop and developing countries)** in affecting its *social implications*?

   Do not Very low Low

| | | |
|---|---|---|
| know | | |
| Medium | High | Very high |

9. What is the importance of the **possible use of NP enabled applications to collect personal data or trace individual behaviour** in affecting *NPs social implications*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

10. What is the importance of the **possible use of NP enabled applications for military purposes** in affecting its *social implications*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

11. What is the importance of the **added value of a NP** (e.g. functionality improvement compared to reference product, coveniency) in affecting *user benefits*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

12. What is the importance of the **symbolic benefits of a NP** (e.g. prestige, identity creation) in affecting *user benefits*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

13. Please **add any criteria** that were not reported here and you consider relevant, indicating their importance accordingly

14. Please provide **any opinions and comments** that you may have about the criteria set and evaluation procedure, including:

- ambiguous questions
- irrelevant questions
- general comments

## TECHNICAL CRITERIA

Welcome to the **technical performance section** (11 questions overall) which part covers the technical aspects and properties of a NP during its life cycle.

1. How many **years of work experience** have you got in the *area of technical performance of NPs* (please indicate in number)?

2. What is **your scale of operation** in the *area of technical performance of NPs*?

Local National Supranational Global

3. What is the importance of **targeted durability of a NP** in affecting *its technical performance*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

4. What is the importance of the **functionality of a NP** in affecting *its technical performance*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

5. What is the importance of the **maintainability of a NP** in affecting *its technical performance*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

6. What is the importance of the **recyclability of a NP** in affecting *its technical performance*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

7. What is the importance of the **reliability of a NP** in affecting *its technical performance*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

8. What is the importance of the **reusability of a NP** in affecting *its technical implications*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

9. What is the importance of the **technology maturity of a NP manufacturing process** in affecting *its technical implications*?

| | | |
|---|---|---|
| Do not know | Very low | Low |
| Medium | High | Very high |

10. Please **add any criteria** that were not reported here and you consider relevant, indicating their importance accordingly

11. Please provide **any opinions and comments** that you may have about the criteria set and evaluation procedure, including:

    - ambiguous questions
    - irrelevant questions
    - general comments

Would like to **contribute to develop and test a model for NPs sustainability assessment** that will be structured on the basis of your replies and those from other respondents?

This will consist in **another questionnaire** and **a phone interview** to be conducted *within the next 12 months*.

Yes No

Please indicate **your first name and surname** in the field below *(**required** for data tracking and follow-up e-mails only; this data will not be shared with any third party for any purpose)*

Thank you very much for your time.

If you have any questions please contact:

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## Appendix A.3 – Approach adopted for selection of key informants for survey administration

Potential respondents for the survey were selected following the guidelines developed by [285, 289, 290, 293]:

- Participants to experts workshops and symposium on green and sustainable NPs;
- Members of advisory bodies (e.g. OECD party on safety of nanotechnology);
- Leaders of research centres and groups oriented towards sustainability of NPs (e.g. Centre for the Environmental Implications of Nanotechnology);
- Governmental organization leaders in nanotechnolgoy (e.g. U.S. EPA nanotechnology division);
- Relevant journal editors;
- Researchers who publish extensively on the topic of sustainability and green nanotechnology.

## Appendix A.4 – Demographics and reliability results of pilot survey

**Table A.4.1: Years of experience and scale of operation of the respondents clustered in sustainability area (pilot survey)**

| Area of expertise | N | Years of experience | Frequency | % | N | Scale of operation | Frequency | % |
|---|---|---|---|---|---|---|---|---|
| Economic performance | 8 | ≤3 | 1 | 12.5 | 9 | Local | 1 | 11.1 |
| | | 4-6 | 3 | 37.5 | | National | 5 | 55.6 |
| | | 7-9 | 2 | 25.0 | | Supranational | 1 | 11.1 |
| | | ≥10 | 2 | 25.0 | | Global | 2 | 22.2 |
| Environmental impacts | 16 | ≤3 | 4 | 25.0 | 16 | Local | 2 | 12.5 |
| | | 4-6 | 5 | 31.3 | | National | 3 | 18.8 |
| | | 7-9 | 3 | 18.8 | | Supranational | 4 | 25.0 |
| | | ≥10 | 4 | 25.0 | | Global | 7 | 43.8 |
| Environmental risk assessment and management | 14 | ≤3 | 1 | 7.1 | 17 | Local | 1 | 5.9 |
| | | 4-6 | 3 | 21.4 | | National | 1 | 5.9 |
| | | 7-9 | 6 | 42.9 | | Supranational | 5 | 29.4 |
| | | ≥10 | 4 | 28.6 | | Global | 10 | 58.8 |
| Human health risk assessment and management | 15 | ≤3 | 1 | 6.7 | 17 | Local | 3 | 17.6 |
| | | 4-6 | 4 | 26.7 | | National | 0 | 0.0 |
| | | 7-9 | 4 | 26.7 | | Supranational | 0 | 0.0 |
| | | ≥10 | 6 | 40.0 | | Global | 14 | 82.4 |
| Social implications | 13 | ≤3 | 1 | 7.7 | 14 | Local | 1 | 7.1 |
| | | 4-6 | 4 | 30.8 | | National | 2 | 14.3 |
| | | 7-9 | 5 | 38.5 | | Supranational | 3 | 21.4 |
| | | ≥10 | 3 | 23.1 | | Global | 8 | 57.1 |
| Technical performance | 14 | ≤3 | 0 | 0.0 | 14 | Local | 4 | 28.6 |
| | | 4-6 | 2 | 14.3 | | National | 4 | 28.6 |
| | | 7-9 | 2 | 14.3 | | Supranational | 1 | 7.1 |
| | | ≥10 | 10 | 71.4 | | Global | 5 | 35.7 |

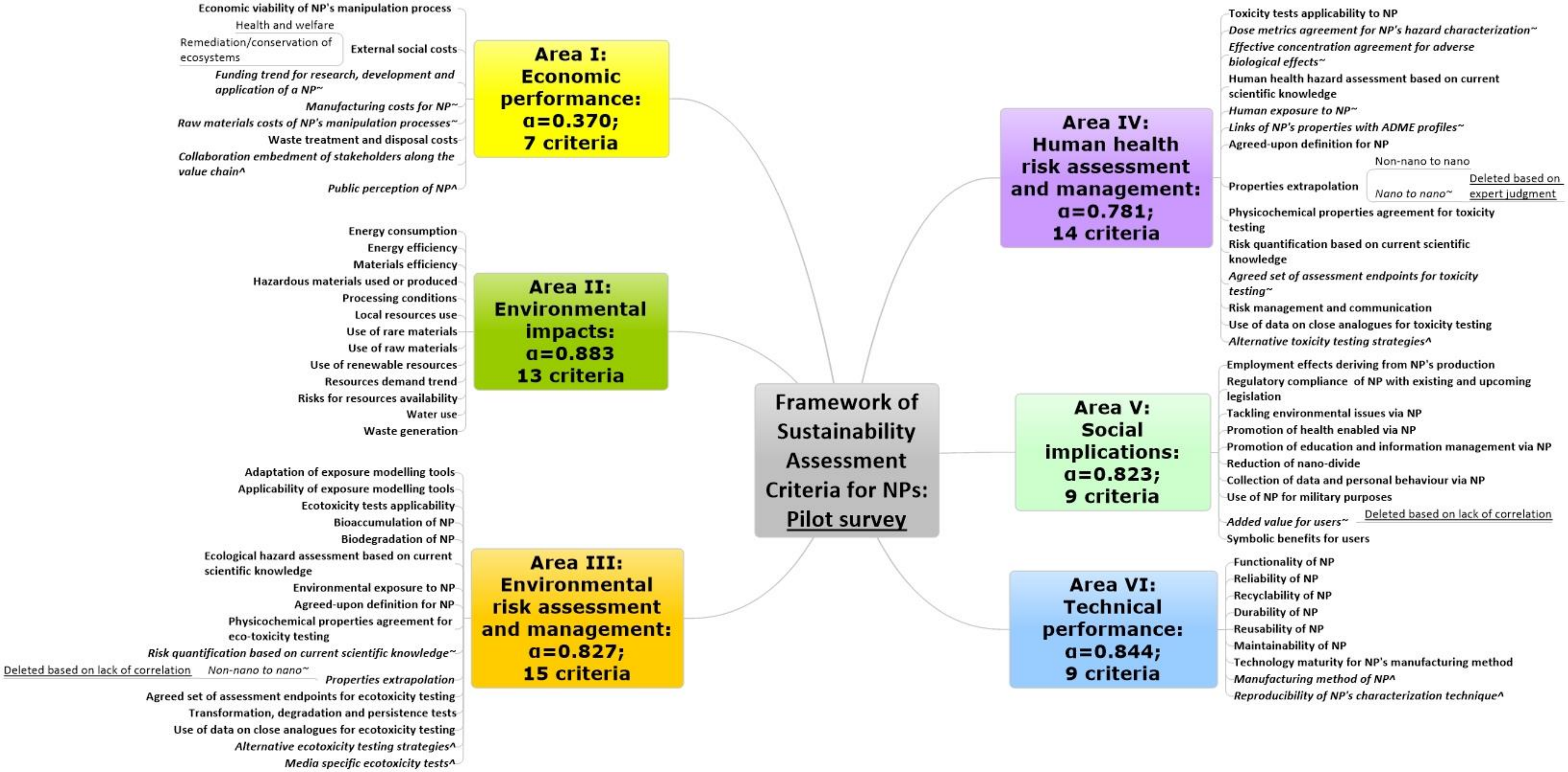

**Figure A.4.1: Results of pilot survey (α = reliability of scale; ~ = unreliable criterion based on internal consistency check; ^ = criterion added based on respondents' recommendation)**

## Economic performance

The demographics of the experts' responses (Table A.4.2) shows that they had a rather even distribution of years of expertise, whereas the operational scale was mainly national (i.e. 55.6 %).

**Table A.4.2: Years of experience and scale of operation of the respondents for economic implications criteria, pilot survey**

| N | Years of experience | % | N | Scale of operation | % |
|---|---|---|---|---|---|
| 8 | ≤3 | 12.5 | 9 | Local | 11.1 |
|  | 4-6 | 37.5 |  | National | 55.6 |
|  | 7-9 | 25.0 |  | Supranational | 11.1 |
|  | ≥10 | 25.0 |  | Global | 22.2 |

The reliability test for the economic implications criteria indicate that ordinal alpha is low (i.e. 0.370) and this finding would suggest the deletion or questions re-wording of three parameters, (i) "funding trend for research, development and application of a NP", (ii) "manufacturing costs" and (iii) "raw material costs" (Table A.4.3).

**Table A.4.3: Ordinal alpha for economic implications criteria and relevant correlation with scale, pilot survey (* = unreliable criterion based on internal consistency check)**

| Ordinal alpha | |
|---|---|
| 0.370 | |
| **Criterion** | **Correlation of criterion with scale** |
| Economic viability of NP manipulation processes | .719 |
| External social costs for health and welfare | .772 |
| External social costs for remediation-conservation of ecosystems | .833 |
| *Funding trend for research, development and application of a NP** | *-.261* |
| *Manufacturing costs for NP** | *.185* |
| *Raw materials costs of NP manipulation processes** | *-.054* |
| Waste treatment and disposal costs | .732 |

The deletion of these indicators would not be in agreement with the wide information reported in the literature [5, 44, 51, 59, 317-320, 322] and in the comments from some respondents (see Appendix A.5 below), which actually put these three parameters forward as crucial in nano-economics. As one of the experts stated, "These questions are not always about implications, but rather about conditions for NPs to emerge". This can be one of the reasons for this mismatch and as a result the questions have been re-worded by including this aspect in the main survey.

Furthermore, respondents suggested that this area lacked relevant performance evaluation features, which were thus structured in two additional criteria, (i) “the embedment of collaboration among various actors in the value chain”, and (ii) the business capital investment for “public perception of NPs” (see Appendix A.5 below).

## Environmental impacts

The 16 respondents for the environmental impacts area had a rather even distribution in terms of years of expertise, while their operational areas were mostly widespread, with 25% at supranational and 43.8% at global levels (Table A.4.4).

**Table A.4.4: Years of experience and scale of operation of the respondents for environmental impacts criteria, pilot survey**

| N | Years of experience | % | N | Scale of operation | % |
|---|---|---|---|---|---|
| 16 | ≤3 | 25.0 | 16 | Local | 12.5 |
| | 4-6 | 31.3 | | National | 18.8 |
| | 7-9 | 18.8 | | Supranational | 25.0 |
| | ≥10 | 25.0 | | Global | 43.8 |

Ordinal alpha for environmental implications is 0.883 indicating a very good internal consistency. When looking at the individual correlations of the criteria with the scale (Table A.4.5) they all result to fit although there are two which are close to the 0.300

**Table A.4.5: Ordinal alpha for environmental impacts criteria and relevant correlation with scale, pilot survey. All criteria refer to the manipulation processes of NP over the entire life-cycle**

| Ordinal alpha | |
|---|---|
| 0.883 | |
| **Criterion** | **Correlation of criterion with scale** |
| Energy consumption | .478 |
| Energy efficiency | .717 |
| Materials efficiency | .512 |
| Hazardous materials used and produced | .312 |
| Processing conditions | .552 |
| Resources demand trend | .739 |
| Local resources use | .431 |
| Use of rare materials | .305 |
| Use of raw materials | .744 |
| Use of renewable resources | .633 |
| Risks for resources availability | .850 |
| Water use | .729 |
| Waste generation | .489 |

acceptance threshold. They are “hazardous materials used or produced” and “use of rare materials”. These parameters are kept in the framework for the main survey as they are reported as crucial factors in the green (nano)-chemistry literature [16, 24, 25, 59, 390].

## Environmental risk assessment and management

The area of environmental risk assessment and management has the majority of respondents between seven and nine or at least ten years of expertise. These two categories sum up to 71.5 % of the cumulative years of practice. What is more, their activities are widespread, with more than 80 % of the responses falling in the supranational and global scales (Table A.4.6).

**Table A.4.6: Years of experience and scale of operation of the respondents for environmental risk assessment criteria, pilot survey**

| N | Years of experience | % | N | Scale of operation | % |
|---|---|---|---|---|---|
| 14 | ≤3 | 7.1 | 17 | Local | 5.9 |
| | 4-6 | 21.4 | | National | 5.9 |
| | 7-9 | 42.9 | | Supranational | 29.4 |
| | ≥10 | 28.6 | | Global | 58.8 |

The overall internal consistency for environmental risk assessment indicates good results with an ordinal alpha of 0.827 (Table A.4.7). The parameter “properties extrapolation from non-nanoscale to nanoscale materials” does not result to be part of the scale and this can be related to the very scare information about the link between non-nanoscale and nanoscale materials that cannot support current environmental risk assessment [126, 529]. Due to this scarcity of information, the parameter was deleted from the scale (and the main survey), resulting in a higher alpha coefficient (i.e. 0.860).

Furthermore, although risk quantification criterion is slightly below 0.300 it was decided to keep it in the scale because it received importance scores equal or above medium with the exception of one reply. What is more, the need to use the available scarse information for performing risk assessment is indicated as a priority in the area of NPs [41, 121, 126, 157]. This is actually the assessment target of this parameter and consequently it was maintained in the framework.

Lastly, two additional parameters were introduced based on experts’ suggestions, being the “use of alternative ecotoxicity testing strategies” and the “development of media specific ecotoxicity tests for NPs” (see Appendix A.5 below).

**Table A.4.7: Ordinal alpha for environmental risk assessment criteria and relevant correlation with scale, pilot survey (* = unreliable criterion based on internal consistency check)**

| Ordinal alpha | |
|---|---|
| 0.827 | |
| **Criterion** | **Correlation of criterion with scale** |
| Adaptation of exposure modeling tools | .732 |
| Applicability of environmental exposure models | .449 |
| Ecotoxicity tests applicability to NP | .666 |
| Bioaccumulation of NP | .387 |
| Biodegradation of NP | .433 |
| Ecological hazard assessment based on current scientific knowledge | .501 |
| Environmental exposure | .611 |
| Agreed-upon definition for a NP | .569 |
| *Properties extrapolation from non-nanoscale to nanoscale materials** | *-.024* |
| Physicochemical properties agreement for ecotoxicity testing | .434 |
| *Risk quantification based on current scientific knowledge** | *.258* |
| Agreed set of assessment endpoints for ecotoxicity testing | .675 |
| Transformation, degradation and persistence tests | .615 |
| Use of ecotoxicity data of close analogues for target NP | .614 |

## Human health risk assessment and management

Experts in the human health risk assessment and management domain operated mostly globally (82.4%) and had a considerable amount of long lasting expertise, with 40% indicating at least 10 years of work in this field, as Table A.4.8 conveys.

**Table A.4.8: Years of experience and scale of operation of the respondents for human health risk assessment and management criteria, pilot survey**

| N | Years of experience | % | N | Scale of operation | % |
|---|---|---|---|---|---|
| 15 | ≤3 | 6.7 | 17 | Local | 17.6 |
| | 4-6 | 26.7 | | National | 0.0 |
| | 7-9 | 26.7 | | Supranational | 0.0 |
| | ≥10 | 40.0 | | Global | 82.4 |

Ordinal alpha for human health risk assessment and management is satisfactory, with a score of 0.781. However, some criteria correlations suggest that these need to be rephrased in the questions or deleted (Table A.4.9).

The ordinal alpha test and the comments reported from experts (see Appendix A.5 below) indicate that the criteria (i) “dose metric agreement for NP hazard characterization”, (ii) “effective concentration agreement for adverse biological effect”, (iii) “properties link with absorption, distribution, metabolism, excretion profiles” and (iv) “agreed set of assessment endpoints for toxicity testing” would not be part of the scale.

This can adduced to the erroneous consideration, made during the pilot design, that a case-by-case (i.e. NP-specific) assessment would not be needed. In fact the questions asked in the pilot questionnaire referred to a NP in general. This emerged as a wrong approach that the piloting results and the literature [126, 129, 529] made emerge, which means that several properties and tests are dependent and have to be tailored to the NP under consideration rather than a NP in general. Consequently the questions have been modified to account for this aspect in the main survey.

**Table A.4.9: Ordinal alpha for human health risk assessment and management criteria and relevant correlation with scale, pilot survey (* = unreliable criterion based on internal consistency check)**

| **Ordinal alpha** | |
|---|---|
| 0.781 | |
| **Criterion** | **Correlation of criterion with scale** |
| Toxicity tests applicability to NP | .740 |
| *Dose metric agreement for NP hazard characterization** | *-.089* |
| *Effective concentration agreement for adverse biological effect** | *-.022* |
| Human health hazard assessment based on current scientific knowledge | .730 |
| *Human exposure** | *.206* |
| *Links of NP’s properties with ADME profiles** | *.134* |
| Agreed-upon definition for a NP | .686 |
| Properties extrapolation from from non-nanoscale to nanoscale materials | .563 |
| Properties extrapolation from nanoscale to nanoscale materials | .499 |
| Physicochemical properties agreement for toxicity testing | .735 |
| Risk quantification based on current scientific knowledge | .576 |
| *Agreed set of assessment endpoints for toxicity testing** | *.262* |
| Risk management and communication | .452 |
| Use of toxicity data of close analogues for target NP | .763 |

As far as the humans' exposure criterion is concerned, a low correlation is reported too. This was unexpected since the assessment of the exposure is a fundamental pillar of the risk assessment [126, 129, 529, 530]. The cause of this mismatch was related to the wording of the question (as it referred to the likelihood of exposure), which has been modified for the main survey to clearly refer to the importance of knowing the exposure of humans to perform risk assessment.

Similarly to the environmental RA, "use of alternative toxicity testing strategies" was introduced as an additional criterion to complete the human health RA scale.

The last change applied to the framework was the deletion, based on expert input, of the parameter considering properties extrapolation from different NPs, as it was considered not being at a still reliable scientific stage to be of relevant use for RA.

## Social implications

In the area of social implications the respondents operate primarily on a global scale (i.e. 57.1 %) with 30.8 % having between four and six years of expertise and 38.5 % between seven and nine years (Table A.4.10).

**Table A.4.10: Years of experience and scale of operation of the respondents for social implications criteria, pilot survey**

| N | Years of experience | % | N | Scale of operation | % |
|---|---|---|---|---|---|
| 13 | ≤3 | 7.7 | 14 | Local | 7.1 |
| | 4-6 | 30.8 | | National | 14.3 |
| | 7-9 | 38.5 | | Supranational | 21.4 |
| | ≥10 | 23.1 | | Global | 57.1 |

Very good internal consistency (i.e. 0.823 ordinal alpha) was achieved for the social implications criteria, although the criterion "added value for users" did not fit with the scale (Table A.4.11). This can be explained by the fact that it is the only criterion that is focused on the social implications for the individual rather than the society as a whole and consequently it does not reflect the same construct. As a consequence, it was deleted and ordinal alpha rose to 0.836.

**Table A.4.11: Ordinal alpha for social implications criteria and relevant correlation with scale, pilot survey (* = unreliable criterion based on internal consistency check)**

| Ordinal alpha | |
|---|---|
| 0.823 | |
| **Criterion** | **Correlation of criterion with scale** |
| Employment effects deriving from a NP production | .743 |
| Regulatory compliance of NP with current and upcoming legislation | .488 |
| Tackling environmental issues via NP | .558 |
| Promotion of health enabled via NP | .737 |
| Promotion of education and information management via NP | .720 |
| Reduction of nano-divide | .353 |
| Collection of personal data or trace individual behavior via NP | .713 |
| Use of nano-enabled products for military purposes | .746 |
| _Added value for users*_ | _.222_ |
| Symbolic benefits for users | .363 |

## Technical performance

The technical performance group shows an impressively high number of years of experience, with 71.4 % indicating more than 10 years, as summarized in Table A.4.12. Their operational scale is spread on local (i.e. 28.6 %), national (i.e. 28.6 %) and global scale (i.e. 35.7 %).

**Table A.4.12: Years of experience and scale of operation of the respondents for technical performance criteria, pilot survey**

| N | Years of experience | % | N | Scale of operation | % |
|---|---|---|---|---|---|
| 14 | ≤3 | 0.0 | 14 | Local | 28.6 |
| | 4-6 | 14.3 | | National | 28.6 |
| | 7-9 | 14.3 | | Supranational | 7.1 |
| | ≥10 | 71.4 | | Global | 35.7 |

All the criteria fit with the scale (Table A.4.13) and ordinal coefficient alpha is very good (0.844), which does not require changes to the starting criteria. However, the scale was modified by adding two criteria suggested by the respondents, increasing the whole set from 7 to 9. The new parameters are the “method of manufacturing for the NP” and the “reproducibility of NP characterization technique”.

**Table A.4.13: Ordinal alpha for technical performance criteria and relevant correlation with scale, pilot survey**

| Ordinal alpha | |
|---|---|
| 0.844 | |
| **Criterion** | **Correlation of criterion with scale** |
| Functionality of NP | .357 |
| Reliability of NP | .526 |
| Recyclability of NP | .780 |
| Durability of NP | .446 |
| Maintainability of NP | .906 |
| Reusability of NP | .804 |
| Technology maturity for manufacturing method | .386 |

## Appendix A.5 - Experts' comments on pilot survey and relevant measure adopted

| Economic performance criteria | | | |
|---|---|---|---|
| **Criteria to add suggested by participant** | **Adopted measure for main survey** | **Opinions and comments of participant** | **Adopted measure for main survey** |
| 1) Collaboration, cooperation between different actors across and beyond the value chain is very important;<br>2) Multidisciplinary cooperation is very important;<br>3) Clarification of future performance of envisioned products is very important;<br>4) Clarification of requirements by users and their willingness to pay for NPs is very important;<br>5) Role of investors, venture capitalists, is important;<br>6) Role of university spin-offs, start-ups and SMEs is important;<br>7) Researchers and firms anticipation on the future introduction and embedding of products in value chains, business practices, regulatory regimes and societal acceptance is essential. | Added question: Criteria 1,2,5,6 and 7 were combined to provide a criterion assessing the role that the envisioning and embedding of collaboration among different actors can have in the emergence of nanoprodcucts.<br>Concerning criteria 3 and 4, the performance of the product is already considered as a technical parameter in the relevant section and the users requirement is addressed in the social aspects with the added value and symbolic benefits that the NP can provide. | These questions are not always about implications, but rather about conditions for NPs to emerge. | This consideration was added in the description of the area of expertise referring to the economics of NPs and in questions themselves. |

## Appendix A.5 - Experts' comments on pilot survey and relevant measure adopted (cont.)

| | | | |
|---|---|---|---|
| Public perception plays a very high role in the economic success of a NP, and most businesses exert a lot of money and effort in controlling public perceptions. | Added question. | --- | --- |
| --- | --- | The methodology was appropriate.<br>Companies that produce nanomaterials are controlled by the demand for these nanomaterial products. No company that has produced nanomaterials has ever failed due to EHS. Companies that succeed produce quality nanomaterials. | Comment acknowledged in the discussion part. |
| Fundamentally, the performance of a nanomaterial in an application must be a non-linear improvement over the performance of standard materials and the cost of that nanomaterial must provide a viable price/performance ratio to make the use of the material worthwhile. The days of nanomaterials adding marketing cache and commanding a premium price are over. | Comment acknowledged in the discussion part. | --- | --- |

## Appendix A.5 - Experts' comments on pilot survey and relevant measure adopted (cont.)

| Environmental impacts criteria | | | |
|---|---|---|---|
| **Criteria to add suggested by participant** | **Adopted measure for main survey** | **Opinions and comments of participant** | **Adopted measure for main survey** |
| --- | --- | The survey questions are not very clear and may be difficult to analyze. | Questions were simplified where possible. |
| --- | --- | It's hard to answer these questions generally since they can be so different depending on the particular product or process in question. This is the whole point of LCA which is to quantify the environmental impacts of different products. I'm not sure how you will compile this info, but some aspects which your survey may show as low may not be low in all cases. It also seems difficult to separate environmental from other risks. Some environmental risks turn into human health risks. | In the case of this questionnaire the aim is to assess the role that the criteria can have in relation to a reference product or a comparable material. This is a point that has been emphasized in the main survey. |
| --- | --- | "Importance" is not necessarily best judge. Sometimes it's important if it is too high (or too low), but otherwise unimportant. | Comment acknowledged in the discussion part. |
| None. | --- | They are all relevant. | Comment acknowledged in the discussion part. |
| 1) The functional use of the NP and its useful life for this application - very high. | These criteria are already considered in the technical performance section. | The survey does not capture the importance of the functional use, functional life, and product fraction of | This consideration was added in the description of the area of expertise referring to the environmental |

## Appendix A.5 - Experts' comments on pilot survey and relevant measure adopted (cont.)

| | | | |
|---|---|---|---|
| 2) The ability to recover nanomaterials from NPs - very high. | | the nanomaterial as well as the benefits the nanomaterial provides to the product application. For example, assume the production of nanosilver for an antimicrobial fabric used to prevent foot infections for diabetics requires 100 MJ/kg of nanosilver produced. The textile material requires 10 MJ to produce. Further assume the amount of silver required is only 0.01 kg/product unit. The amount of energy in the product life cycle attributed to the nanosilver is only 1 MJ/product unit and the total manufacturing energy consumption is 11 MJ for the product unit. Now assume the silver maintains its antimicrobial properties for 1 year and the alternative product is a foot powder that requires 10 MJ/kg powder during manufacturing and must be applied weekly in the amount of 0.1 kg. Over a 1 year product life, the nanosilver textile will actually save 41 MJ/year in manufacturing energy even though the nanosilver requires 10 times the energy of the other materials to produce. The point of this example is to illustrate that your criteria can each be of high importance to the environmental implications of NPs | implications of NPs. |

## Appendix A.5 - Experts’ comments on pilot survey and relevant measure adopted (cont.)

| | | | |
|---|---|---|---|
| | | when considered in isolation, but may be irrelevant when considered within the context of a product life cycle. Your questions and criteria will be more meaningful if you factor this into the decision process. | |
| What about energy/material efficiency of the products containing nanomaterials? This should be one of the prime reasons to use the technology! | This aspect refers to the performance of the NP and it is considered in the technical performance section. | I'm not too much into LCA, but I found some of the questions hard to grasp. | Clarity improved in the main survey. |
| Recycling processes are missing. Are they sufficient for nanomaterials? Are materials released when using conventional recycling methods etc. | This criterion is considered in the technical performance section. | --- | --- |
| --- | --- | The questions asked are too general. There is not the simple interaction NP and environmental impacts. This is in the various application areas but very different. | Comment acknowledged in the discussion part. |
| Formation of toxic byproducts or greenhouse gases (e.g., from vapor deposition processes that rely on carbon feedstocks). | These criteria are considered in the questions related to energy consumption and hazardous materials use and production. | --- | --- |

## Appendix A.5 - Experts' comments on pilot survey and relevant measure adopted (cont.)

| Environmental risk assessment and management criteria | | | |
|---|---|---|---|
| **Criteria to add suggested by participant** | **Adopted measure for main survey** | **Opinions and comments of participant** | **Adopted measure for main survey** |
| --- | --- | 1) "Importance in supporting" is vague.<br>2) Also, what is "current" models & data may be perceived very different by different people depending on how much they are keeping up with the literature. | 1) Supporting changed in performing where relevant.<br>2) The issue was clarified by indicating that the current knowledge is based on the moment when the risk assessment is to be performed. |
| --- | --- | Q2. researchers will work at more than one level.<br>Q3. The tests are required, the importance is not in question. The applicability of the results is the problem.<br>Q4 & 11. Loaded questions, respondents will choose high. Better to reword and make them choose characteristics in order of importance.<br>Q6. The bioaccumulation test is not fit for purpose, and the commission is writing new guidelines for nano hopefully this year.<br>Q11. This is a trigger for the risk assessment - prove the nano form is different from the existing non-nano product. | Q3. The applicability is what the question asks about.<br>Q4&11. These questions actually assess the agreement at the date of the survey about the applicability of ecotoxicity tests and properties extrapolation procedures.<br>Q6. The bioaccumulation criterion is indicated as a relevant parameter in the literature and the statistical tests confirm its appropriateness with the scale. As a result it was not deleted.<br>Q11. Question about properties extrapolation deleted.<br>Q12. This question investigates whether an agreement in terms of properties is crucial or not.<br>Q13&14. These questions were modified to render them material- |

## Appendix A.5 - Experts’ comments on pilot survey and relevant measure adopted (cont.)

| | | | |
|---|---|---|---|
| | | Q12. Is more about identifying the properties for exposure modelling, and health & safety in the work place (dust, explosion risk).<br>Q13 & 14. Loaded question, of course the answer is high.<br>Q15. This question needs to be related to types of materials. For example, a metal NP may not be metabolised, but a carbon one might be. Also risk assessement concerns are persistent, bioaccumulative, toxic (PBT) for all chemicals, including nano.<br>Q16. Depends on agency and use. In the US EPA, the intended application determines what can be done in terms of read across. The assessment might be application specific, e.g., under biocides regulations. | specific.<br>Q15. The material specificity was added to the question. |
| --- | --- | The questions are framed very much within traditional risk assessment and maybe other approaches could and should be explored as well. | The survey tries to assess the agreement on criteria that are needed to perform the risk assessment in its traditional form. Another scale could anyhow be developed for alternative approaches. |
| 1) Physico-chemical attributes of the receiving environment.<br>2) Ability to measure chronic, long- | 1) Already included in the applicability and adaptation of exposure modelling tools which | These issues are all of generally high importance to performing a proper environmental risk assessment of | The survey measures the relative importance of the criteria from the respondents’ replies. However, the |

## Appendix A.5 - Experts' comments on pilot survey and relevant measure adopted (cont.)

| | | | |
|---|---|---|---|
| term impacts (sub-lethal assays). | requires the knowledge of mentioned parameters<br>2) This is already considered in the question on applicability of available tests to perform ecotoxicity studies. | NPs. Perhaps requiring respondents to rank the criteria in order of most to least important would be of more benefit to your survey. | approach proposed here could be used as an alternative. |
| --- | --- | The term "current scientific knowledge" is a bit ambiguous. Do you mean at the time of filling out the questionnaire or the current knowledge at the time you are performing an ERA? | The issue was clarified by indicating that the current knowledge is based on the available information when filling out the questionnaire. |
| 1) Reaction kinetics in different media;<br>2) Sorption behaviour in different media;<br>3) Redox activity;<br>4) International agreement on product labeling. | Criteria 1,2,3, are already included in the applicability and adaptation of exposure modelling tools which requires the knowledge of these parameters.<br>Criterion 4 can be considered linked to the proper definition of nanomaterial criterion already available. | Why don't you ask about my background (e.g. research vs. business!), or is this restricted to academics? | This comment was not considered as relevant because expertise is not measured on the basis of the background. |
| Defining product characteristics that influence nanomaterial release. | These characteristics are already included in the applicability and adaptation of exposure modelling tools, which require the knowledge of these characteristics. | Q6. Is unclear to me: In very limited instances there can be bioaccumulation of NPs. I think bioaccumulation would occur after nanomaterials are released from NPs.<br>Q9. Do you mean unbound nanomaterials released from NPs? Maybe your definition of a NP is a little bit different from mine. I think of NPs as industrialized products | Q6. The term NP includes nanomaterial and product containing such material.<br>Q9. The term NP includes nanomaterial and product containing such material. |

## Appendix A.5 - Experts' comments on pilot survey and relevant measure adopted (cont.)

| | | | |
|---|---|---|---|
| | | enhanced with nanomaterials. | |
| Dynamical Energy Budget (DEB) modeling can provide risk ranking of potential ecological impacts of NPs based data generated from ecotoxicity tests/assays/experiments conducted on different taxa. DEB precludes the need to identify and use standardized sentinel organisms for nano-ecotoxicity testing or screening. See work by Nisbet and Muller. | This consideration is linked to the criterion about the adaptation of models of exposure. | --- | --- |
| 1) The development of alternative testing strategies that can rapidly screen nanomaterials/products in diverse media;<br>2) The assessment of the appropriateness of current testing methods for chemical substances for nanomaterials. | 1) Added question.<br>2) This is already considered in the question on applicability of available tests to perform ecotoxicity studies. | None of the questions raised seem unimportant to me. | Comment acknowledged in the discussion part. |
| The ecotoxicity impacts will be very environmentally media specific. So a set of media specific toxicity tests would be useful in nano risk assessment. | Added question. | --- | --- |

## Appendix A.5 - Experts' comments on pilot survey and relevant measure adopted (cont.)

| Human health risk assessment and management criteria | | | |
|---|---|---|---|
| **Criteria to add suggested by participant** | **Adopted measure for main survey** | **Opinions and comments of participant** | **Adopted measure for main survey** |
| 1) The mode of action of any hazard induced | This was considered in the question about the link between nanomaterial properties and its absorption, distribution, metabolism, excretion and toxic effects. | Some questions are rather 'wordy' and difficult to interpret | Clarity improved whenever possible. |
| --- | --- | Q11. was ambiguous. In answering questions, I generally assumed by human health risk assessment you meant conventional quantitative risk assessment. | The focus is on the parameters to support the actual performance of conventional risk assessment, but also on the aspects that contribute to an understanding of NPs health and safety-related issues. |
| --- | --- | Some of these questions are irrelevant. All solid and liquid matter has nanostructure and many products can be classified as "NPs" by your definition. Some may and others will not be amenable to rational hazard assessment. It is important that we do not use a definition around intentionally engineered products as only those of concern as there are many NPs which are accidently created. With really few exceptions (e.g. carbon nanotubes) NPs exhibit a gradation of properties from the nanoscale to the bulk - biological endpoints for toxicity will often show | This is adduced to erroneous consideration that a case-by-case (i.e. nanomaterial specific) assessment would not be needed and the questions asked referred to a NP (which includes nanomaterial) in general. This was a wrong approach that the expert underlined. Consequently, the questions have been modified accordingly to account for this aspect in the main survey. |

## Appendix A.5 - Experts’ comments on pilot survey and relevant measure adopted (cont.)

| | | | |
|---|---|---|---|
| | | a gradation - a 200nm particle or larger agglomerate of such particles generally show toxicity profiles as the "bulk".<br>Q4 & 5 are very disturbing - it sounds like you are trying to come up with a single metric & concentration for NP toxicity. Different NPs - different properties - different metrics.<br>How can Qs 7 & 12 also encompass such a position? Toxicity of a product will depend upon its various states as it travels through its lifecycle. The trend in the EC, in particular, to try to define such parameters is misguided. Specifically, regulations imposed upon the manufacturer or the first user of a NP ignores subsequent stages in the product lifecycle. | |
| Need to split this up: Occupational health and safety in the work place. Safety of public and consumers from NPs/processes. Clinical safety – nanomedicines. | This criterion actually assesses the importance of the knowledge about the exposure rather than the scenario where the exposure takes place. | --- | --- |
| Beneficial aspects of nanotechnology should be considered as well. | Aspects considered in the social implications section. | Multimodal approach and a combination of assays should be implemented. | Comment acknowledged in the discussion part. |
| In addition to adoption of risk management and communication measures, there should be efforts to | This consideration was added in the relevant question. | All of these are important. Having respondents rank criteria might be helpful. | The survey measures the relative importance of the criteria from the respondents replies. However, the |

## Appendix A.5 - Experts' comments on pilot survey and relevant measure adopted (cont.)

| | | | |
|---|---|---|---|
| focus on the identification and/or development of these measures. Adoption assumes that those measures already exist, and that might not necessarily be the case. | | | approach proposed here could be used as an alternative. |
| --- | --- | "Current scientific knowledge" is vague. My answer will change if you mean the knowledge at the time of feeling out this questionnaire or the knowledge at the time of performing an HHRA. | The issue was clarified by indicating that the current knowledge is based on the moment when the risk assessment is to be performed. |
| --- | --- | Q11. Wasn't very clear to me. What's the difference between "nanoscale" and "nanoscale materials"? | This question was misunderstood as the question asks about the extrapolation from two different nanoscale materials. |
| Development of alternative testing strategies for ENM to allow rapid screening (high) validation of chemical testing methods for nanomaterials. | Added question. | Again, could not find any low priorities. Consider all of these to be very important. | Comment acknowledged in the discussion part. |
| The problem in doing risk assessments now, is that we I do not know which physicochemical properties of nanomaterials actually correlate to biological effects, especially after chronic exposure. My fear of establishing "internationally agreed upon metrics" before the correlative data are even available is that we most likely will be wrong. A | This is adduced to erroneous consideration that a case-by-case (i.e. nanomaterial specific) assessment would not be needed and the questions asked referred to a NP (which includes nanomaterial) in general. This was a wrong approach that the expert underlined. Consequently, the questions have been modified accordingly to account | --- | --- |

## Appendix A.5 - Experts’ comments on pilot survey and relevant measure adopted (cont.)

| | | | |
|---|---|---|---|
| lot of older in vitro assessments are now known to be wrong. We need much more data to make these decisions. | for this aspect in the main survey. | | |

| **Social implications criteria** | | | |
|---|---|---|---|
| **Criteria to add suggested by participant** | **Adopted measure for main survey** | **Opinions and comments of participant** | **Adopted measure for main survey** |
| --- | --- | "product" sometimes rendered as "prodcut" "I do not know" means "I I do not know" or "it is not known" in a more cosmic sense"...if the former than "no opinion/don't know might be better but the overall structure strikes me as odd | The term was rephrased in “I do not know”. |
| These questions are about implications of nano products. As there are not many products yet, the questions should be rephrased as 'expected implications'. It may actually be useful to differentiate between implications of products already on the market, and expected implications. | The term expected was added in brackets in the relevant section. | Questions about implications are slightly more complex than as they are presented here. E.g. compliance with regulatory guidelines will co-shape technology developments, which in turn may enable or constrain the possibility of technologies to enter the market and have effects at all. I puzzled a bit with the phrasing of the questions. I assumed that they referred to what the implications of NPs are on this and that area. | Comment acknowledged in the discussion part. |
| The vast majority of Americans (95%) | Comment acknowledged in the | The criteria and methodology was | Comment acknowledged in the |

## Appendix A.5 - Experts' comments on pilot survey and relevant measure adopted (cont.)

| | | | |
|---|---|---|---|
| have little or no knowledge in regard to the science of nanotechnology. Since Americans have no fundamental understanding in the science of nanotechnology, their opinions in regard to the societal implications are irrelevant. | discussion part. | appropriate. | discussion part. |

| **Technical performance criteria** | | | |
|---|---|---|---|
| **Criteria to add suggested by participant** | **Adopted measure by authors** | **Opinions and comments of participant** | **Adopted measure by authors** |
| None. | --- | All questions are relevant. | Comment acknowledged in the discussion part. |
| There needs to be some criterion around "fit for purpose". | The functionality criterion has this role. | Several questions are not capable of a single answer. Issues such as maintainability and reliability are quite application specific. Some products are designed to be ephemeral whereas others need to last for decades. It is most concerning if you are attempting to "lump" different types of NP into single categories. It will inevitably lead to incorrect conclusions. | This consideration was added in the description of the area of expertise referring to the technical performance of NPs. |
| Cost and EH&S. These are co-#1. Without low enough cost, nobody will want it and if it cannot gain | Aspects covered in the social and economic sections. | Scale is odd. For technical people, we are both local and global as we are not production facilities. | The question about the scale of operation investigates the range of operation of the respondent in terms |

## Appendix A.5 - Experts’ comments on pilot survey and relevant measure adopted (cont.)

| | | | |
|---|---|---|---|
| regulatory approval, then it doesn't matter. | | | of professional activities, rather than what happens once the NP is on the market. |
| Method of manufacturing: high. | Added question. | --- | --- |
| Reproducibility of a NP reference/standard techniques of characterization. | Added question. | --- | --- |
| I recommend that you engage the participants in sustainability and technical performance, as these are not orthogonal metrics. They should be considered concurrently, as new nanotechnology products are being developed. | The collaboration with the participants from more domains is part of the model development, the second part of this PhD work. | This survey will achieve the exact results that it was tuned to achieve, i.e. a set of siloed responses, which miss the interdependent nature of product development. | This survey identifies a set of criteria to be considered when developing a nanomaterial or a NP. The collaboration with the participants from more domains is part of the model development, the second part of this PhD work. |
| --- | --- | The mindset of NPs is not apparent. It seems leaning toward industrial products such as machine parts, tools, or durable products. There are vast arrays of "soft" product possibilities such as drugs and bio-nanomaterial based products are not captured well in this survey. What is the explanation of it? | This set of questions refers to the technical properties of NPs in terms of their function to be performed. The application sector in terms of product possibilities is considered in the social section. |
| Quality assessment related to nanomanufacturing is a challenge (and could limit the technology maturity of a NP manufacturing process). | Comment acknowledged in the discussion part. | The importance of the durability or longevity of a nanomaterial-enabled product will depend on its ultimate application. For example, most electronics are designed to have limited longevity, whereas | This consideration was added in the description of the area of expertise referring to the technical performance of NPs. |

## Appendix A.5 - Experts' comments on pilot survey and relevant measure adopted (cont.)

| | | | |
|---|---|---|---|
| | | mechanical applications (such as aerospace skins) should last much longer. | |

## Appendix A.6 - Main Survey

### Questionnaire for the Assessment of Sustainability Criteria for NPs

Dear … Member,

Please take part in a questionnaire designed to support the development of sustainable NPs, by prioritizing criteria to assess their sustainability in these categories:

- ***Economic performance***: includes the economic implications of a NP and the conditions for its emergence in the market (it covers expertise in application and development of NPs)*;*
- ***Environmental impacts (excluding risks)***: includes the environmental impacts (e.g. energy consumption, waste production, resource consumption) of a NP during its life cycle;
- ***Environmental risk assessment and management***: includes aspects and issues related to the environmental risks of a NP during its life cycle;
- ***Human health risk assessment and management***: includes aspects and issues related to the human health (consumers and workers) risks of a NP during its life cycle;
- ***Social implications***: includes ethical, legal and social implications of a NP during its life cycle (it covers expertise in application and development of NPs);
- ***Technical performance***: includes the technical performance of a NP during its life cycle, compared to the same product without nanomaterial(s) (it covers expertise in application and development of NPs).

You will choose one category initially and have the opportunity to choose others if you wish.

***Please click the link below to fill in the questionnaire:***

https://perception.warwick.ac.uk/perception5/perception.php

The username is: **…** The password is: **…**

This study is part of a research project on sustainable nanotechnology undertaken by the Warwick Manufacturing Group at the University of Warwick. Full information about the research project and the conduct of the study are reported in the attached "Participant Information Leaflet".

Your contact information for participating is optional, unless you wish to receive the results of the survey.

We thank you very much for your invaluable input and consideration.

Please note that if you have already participated in the piloting of this questionnaire you can discard this email.

**Omowunmi Sadik**

SNO President / Co-Founder

SUNY-Binghamton University

**Barbara Karn**

SNO Executive Director / Co-Founder

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**Important:** This questionnaire addresses the term NP as a nanomaterial or a product containing nanomaterial(s).

Please select **your main area of expertise** (you will have the opportunity to choose others if you wish):

- ***Economic performance***: includes the economic implications of a NP and the conditions for its emergence in the market (it covers expertise in application and development of NPs)*;*
- ***Environmental impacts (excluding risks)***: includes the environmental impacts (e.g. energy consumption, waste production, resource consumption) of a NP during its life cycle;
- ***Environmental risk assessment and management***: includes aspects and issues related to the environmental risks of a NP during its life cycle;
- ***Human health risk assessment and management***: includes aspects and issues related to the human health (consumers and workers) risks of a NP during its life cycle;
- ***Social implications***: includes ethical, legal and social implications of a NP during its life cycle (it covers expertise in application and development of NPs);
- ***Technical performance***: includes the technical performance of a NP during its life cycle, compared to the same product without nanomaterial(s) (it covers expertise in application and development of NPs).

## ECONOMIC PERFORMANCE CRITERIA

Welcome to the **economic performance section** (13 questions overall) which includes the economic implications of a NP and the conditions for its emergence in the market.

A **NP** is a nanomaterial per se or a product containing such material.

1. **Years of work experience** in the *area of economic performance of NPs*

2. **Scale of operation** in the *area of economic performance of NPs*

Local National Supranational Global

**Compared to a non-NP with the same functionality, select the importance of**

**:**

3. **Economic viability of processes involving manipulation of a NP** (e.g. extraction, processing, recycling, incineration)

I do not know Very low Low

Medium High Very high

4. **Health and welfare social costs caused by a NP during its life cycle phases**

I do not know Very low Low
Medium High Very high

5. **Ecosystems remediation-conservation social costs caused by a NP during its life cycle phases**

I do not know Very low Low
Medium High Very high

6. **Government funding for research, development and application of a NP**

I do not know Very low Low
Medium High Very high

7. **Manufacturing costs of a NP**

I do not know Very low Low
Medium High Very high

8. **Raw materials costs in the life cycle stages of a NP** (e.g. extraction, processing, recycling, incineration)

I do not know Very low Low
Medium High Very high

9. **Costs for waste treatment and disposal incurred during the life cycle phases of a NP**

I do not know Very low Low
Medium High Very high

10. **Collaboration among different actors (e.g. investors, university spin-offs, start-ups) along the value chain** to launch the NP

I do not know Very low Low
Medium High Very high

11. **Public perception of new NPs**

I do not know Very low Low
Medium High Very high

12. Please **add any relevant criteria** and indicate their importance

13. Other **opinions and comments**

## ENVIRONMENTAL IMPACTS (EXCLUDING RISKS) CRITERIA

Welcome to the **environmental impacts (excluding risks) section** (17 questions overall) which includes the environmental impacts (e.g. energy consumption, waste production, resource consumption) of a NP during its life cycle.

A **NP** is a nanomaterial per se or a product containing such material.

1. **Years of work experience** in the *area of environmental implications of NPs*

2. **Scale of operation** in the *area of environmental implications of NPs*

   Local National Supranational Global

**Compared to a non-NP with the same functionality, select the importance of :**

3. **Energy consumed at the life cycle stages of a NP** (e.g. extraction, production, waste management, recycling)

   I do not know Very low Low
   Medium High Very high

4. **Energy efficiency of the processes involving manipulation of a NP** (e.g. extraction, processing, recycling, incineration)

   I do not know Very low Low
   Medium High Very high

5. **Materials efficiency of the processes involving manipulation of a NP** (e.g. extraction, processing, recycling, incineration)

   I do not know Very low Low
   Medium High Very high

6. **The use or production of hazardous materials during the life cycle phases of a NP**

   I do not know Very low Low
   Medium High Very high

7. **Processing conditions during the life cycle phases of a NP** (e.g. temperature, pressure, enthalpy)

   I do not know Very low Low
   Medium High Very high

8. **Use of local resources in the life cycle phases of a NP**

   I do not know Very low Low
   Medium High Very high

9. **Use of rare materials in the life cycle phases of a NP**

I do not know    Very low    Low
Medium    High    Very high

10. **Amount of raw materials used in the life cycle phases of a NP**

I do not know    Very low    Low
Medium    High    Very high

11. **Use of renewable resources in the life cycle phases of a NP**

I do not know    Very low    Low
Medium    High    Very high

12. **Trend of total resources demand during the life cycle phases of a NP**

I do not know    Very low    Low
Medium    High    Very high

13. **Possible risks related to availability of resources needed for NP manufacturing** (e.g. regional concentration of mining, physical shortage)

I do not know    Very low    Low
Medium    High    Very high

14. **Use of water in the life cycle phases of a NP**

I do not know    Very low    Low
Medium    High    Very high

15. **Waste generation due to NP manipulation during the life cycle phases**

I do not know    Very low    Low
Medium    High    Very high

16 Please **add any relevant criteria** and indicate their importance:

17 Other **opinions and comments**:

**ENVIRONMENTAL RISK ASSESSMENT AND MANAGEMENT CRITERIA**

Welcome to the **environmental risk assessment and management section** (19 questions overall) which includes aspects and issues related to the environmental risks of a NP during its life cycle.

A **NP** is a nanomaterial per se or a product containing such material.

1. **Years of work experience** in the *area of environmental risk assessment and management of NPs*

2. **Scale of operation** in the *area of environmental risk assessment and management of NPs*

    Local National Supranational Global

**In support of the environmental risk assessment of NPs, select the importance of:**

3. **Adaptation of current exposure models that include NP-specific information** (e.g. aerodynamic size distribution)

    I do not know Very low Low
    Medium High Very high

4. **Applicability of current environmental exposure models for a NP**

    I do not know Very low Low
    Medium High Very high

5. **Applicability of current ecotoxicity tests for a NP** (e.g. OECD guidelines)

    I do not know Very low Low
    Medium High Very high

6. **Bioaccumulation of a NP**

    I do not know Very low Low
    Medium High Very high

7. **Biodegradation of a NP**

    I do not know Very low Low
    Medium High Very high

8. **Ecological hazard assessment of a NP based on current scientific knowledge**

    I do not know Very low Low
    Medium High Very high

9. **Knowledge about environmental exposure to a NP**

    I do not know Very low Low
    Medium High Very high

10. **An agreed-upon definition for a NP**

    I do not know Very low Low
    Medium High Very high

11. **Agreed-upon physicochemical properties for NP-specific ecotoxicological testing**

    I do not know Very low Low
    Medium High Very high

12. **Risk quantification of a NP based on current scientific knowledge**

I do not know    Very low    Low
Medium    High    Very high

13. **Agreed-upon NP-specific assessment endpoints**

I do not know    Very low    Low
Medium    High    Very high

14. **Agreed-upon NP-specific transformation, degradation and persistence tests**

I do not know    Very low    Low
Medium    High    Very high

15. **Using ecotoxicity data for a NP from analogous NPs ("read-across approach")**

I do not know    Very low    Low
Medium    High    Very high

16. **Developing alternative testing strategies for rapid screening of NPs**

I do not know    Very low    Low
Medium    High    Very high

17. **Developing a set of media-specific ecotoxicity tests for NPs**

I do not know    Very low    Low
Medium    High    Very high

18. Please **add any relevant criteria** and indicate their importance

19 Other **opinions and comments**

## HUMAN HEALTH RISK ASSESSMENT AND MANAGEMENT CRITERIA

Welcome to the **human health risk assessment and management section** (18 questions overall) which includes aspects and issues related to the human health (consumers and workers) risks of a NP during its life cycle.

A **NP** is a nanomaterial per se or a product containing such material.

1. **Years of work experience** in the *area of human health risk assessment and management of NPs*

2. **Scale of operation** in the *area of human health risk assessment and management of NPs*

Local National Supranational Global

**In support of the human health risk assessment of NPs, select the importance of:**

3. **Applicability of current toxicity tests for a NP** (e.g. OECD guidelines)

I do not know Very low Low
Medium High Very high

4. **Scientific agreement on NP-specific dose metric for hazard characterization**

I do not know Very low Low
Medium High Very high

5. **Scientific agreement on NP-specific effective concentration**

I do not know Very low Low
Medium High Very high

6. **Human health hazard assessment of a NP based on current scientific knowledge**

I do not know Very low Low
Medium High Very high

7. **Knowledge about human exposure to a NP**

I do not know Very low Low
Medium High Very high

8. **Capability to link NP-specific properties to absorption, distribution, metabolism, excretion and toxic effects**

I do not know Very low Low
Medium High Very high

9. **An agreed-upon definition for a NP**

I do not know Very low Low
Medium High Very high

10. **Properties extrapolation from non-nanoscale to nanoscale materials**

I do not know Very low Low
Medium High Very high

11. **Agreed-upon physicochemical properties for NP-specific toxicological testing**

I do not know Very low Low
Medium High Very high

12. **Risk quantification of a NP based on current scientific knowledge**

I do not know Very low Low
Medium High Very high

13. **Agreed-upon NP-specific assessment endpoints**

    I do not know    Very low    Low

    Medium    High    Very high

14. **Development and adoption of risk management and communication measures** (e.g. technical measures, precautionary programmes) tailored for NPs

    I do not know    Very low    Low

    Medium    High    Very high

15. **Using toxicity data for a NP from analogous NPs ("read-across approach")**

    I do not know    Very low    Low

    Medium    High    Very high

16. **Developing alternative testing strategies for rapid screening of NPs**

    I do not know    Very low    Low

    Medium    High    Very high

17. Please **add any relevant criteria** and indicate their importance

18. Other **opinions and comments**

## SOCIAL IMPLICATIONS CRITERIA

Welcome to the **social implications section** (13 questions overall) which includes ethical, legal and social implications of a NP during its life cycle.

A **NP** is a nanomaterial per se or a product containing such material.

1. **Years of work experience** in the *area of social implications of NPs*

2. **Scale of operation** in the *area of social implications of NPs*

    Local    National    Supranational    Global

**In support of the assessment of ethical, legal and social implications of NPs, select the importance of:**

3. **Employment effects deriving from a NP production**

I do not know Very low Low
Medium High Very high

4. **Regulatory compliance of a NP with current and possible regulations**

I do not know Very low Low
Medium High Very high

5. **A NP contribution to solving environmental problems** (e.g. pollution, clean energy production, climate change)

I do not know Very low Low
Medium High Very high

6. **Promoting health through NPs** (e.g. reduction of child mortality, improvement of maternal health)

I do not know Very low Low
Medium High Very high

**7.** **Promoting education and information management through NPs** (e.g. more efficient and reliable information technology)

I do not know Very low Low
Medium High Very high

8. **Reducing the "nano-divide" (i.e. nano-related technological imbalance between developed and developing countries) through NPs**

I do not know Very low Low
Medium High Very high

9. **Possible use of NP-enabled applications to collect personal data or trace individual behaviour**

I do not know Very low Low
Medium High Very high

10. **Possible use of NP-enabled applications for military purposes**

I do not know Very low Low
Medium High Very high

11. **Symbolic benefits of a NP** (e.g. prestige, identity creation)

I do not know Very low Low
Medium High Very high

12. Please **add any relevant criteria** and indicate their importance

13. Other **opinions and comments**

**TECHNICAL PERFORMANCE CRITERIA**

Welcome to the **technical performance section** (13 questions overall) which includes the technical performance of a NP during its life cycle.

A **NP** is a nanomaterial per se or a product containing such material.

1. **Years of work experience** in the *area of technical performance of NPs*

2. **Scale of operation**

Local National Supranational Global

**Compared to a non-NP with the same functionality, select the importance of :**

3. **Targeted durability of the NP**

| | | |
|---|---|---|
| I do not know | Very low | Low |
| Medium | High | Very high |

4. **Targeted functionality of the NP**

| | | |
|---|---|---|
| I do not know | Very low | Low |
| Medium | High | Very high |

5. **Targeted maintainability of the NP**

| | | |
|---|---|---|
| I do not know | Very low | Low |
| Medium | High | Very high |

6. **Recyclability of the NP**

| | | |
|---|---|---|
| I do not know | Very low | Low |
| Medium | High | Very high |

7. **Reliability of the NP**

| | | |
|---|---|---|
| I do not know | Very low | Low |
| Medium | High | Very high |

8. **Reusability of the NP**

| | | |
|---|---|---|
| I do not know | Very low | Low |
| Medium | High | Very high |

9. **Technological maturity of the NP manufacturing process**

| | | |
|---|---|---|
| I do not know | Very low | Low |
| Medium | High | Very high |

10. **Method of manufacturing of the NP**

I do not know Very low Low
Medium High Very high

11. **Reproducibility of the NP characterization**

I do not know Very low Low
Medium High Very high

12. Please **add any relevant criteria** and indicate their importance

13. Other **opinions and comments**

Please indicate **your first name, surname and email address** if you wish to receive results (optional)

Thank you very much for your time.
If you have any questions please contact:
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## Appendix A.7 - Experts’ comments on main survey

| Economic performance criteria | | | |
|---|---|---|---|
| **Criteria to add suggested by participant** | **Researcher’s comment** | **Opinions of participant** | **Researcher’s comment** |
| Thin films for solar cell applications | The survey is meant to be general in scope, without targeting a specific NP application. | Ecofriendly, non-hazardous thin film synthesis | Broad applicability of criteria is a requirement. No specific sector can be a target. |
| Environment effect should be minimum as disposal and handling of nanoparticles should be tightly regulated; nanoparticles can be digested and cycle back | These aspects are dealt with in the environmental implications area. | --- | --- |
| --- | --- | Public perception is a problem - it's low in Europe but high in Asia | This comment highlights a situation of disparity between two major markets. |
| --- | --- | The public perception issue is re-emerging, because of lobby groups such as Friends of the Earth, Soil Association spreading inaccurate and misleading information. This has to be dealt with. | The respondent confirms the relevance and importance that the public perception issue is receiving. |

## Appendix A.7 - Experts' comments on main survey (cont.)

| | | | |
|---|---|---|---|
| Ease of use for the manufacturing partner and/or end-user | This aspect depends on the application of interest. | Not sure of the rationale for this question. If the functionality is the same for a non-NP then the decision will simply come down to cost and based on the current early stage of nano-enabled products coming to the market and the corresponding limited economies of scale, customers will choose the non NP every time. | There might have been a misunderstanding of the use of functionality. The term refers to a product that aims to satisfy the same function, but the performance level is not considered. |

| **Environmental impacts criteria** | | | |
|---|---|---|---|
| **Criteria to add suggested by participant** | **Researcher's comment** | **Opinions of participant** | **Researcher's comment** |
| Development of mixed metal chalcogenide thin film for solar cell applications | The criterion is not relevant to this survey, because the survey has not a specific application of reference and the criterion does not refer to any specific environmental implications. | --- | --- |
| --- | --- | The questions are too generic. The answer is: it depends!! It is not possible to treat all nano products in the same way, therefore I'm not able to answer. And I think nobody else can (or he/she just has one product in mind - for a special case an answer is of course possible) | This consideration is tackled in the discussion of the results. |

## Appendix A.7 - Experts’ comments on main survey (cont.)

| | | | |
|---|---|---|---|
| Impact of releases on environmental receptors! Very high! | This aspect is handled in the environmental risk assessment section. | Your focus appears to be resources and energy but the primary issues concerning environmental impact are releases. What is the effect on aquatic organisms of releases of silver from washed textiles? What is the impact on microorganisms of releases of buckyballs that don't degrade the same way as what they usually experience? | These aspects are all handled in the environmental risk assessment section. |
| Improving the properties of a cost-effective, renewable, or bioavailable material through incorporation of nanoparticles that would otherwise not be practical in many applications | The functionality of the NP is covered in the technical performance section. | --- | --- |
| Stability of NP containing the nanomaterial because this will determine the potential for environmental releases and what type of end-of-life processes are needed. Reusability/Recyclability of NPs because this will determine how much nanomaterial must be produced from primary (virgin) materials and the potential that recycling can have for reducing the impacts. If the material is not highly recyclable, trying to recover the material during EOL may lead to worse impacts than primary production. Functional efficiency of | These criteria are all handled in the technical performance section. | The survey questions as written are a bit hard to rate because the answers can change from life cycle stage to life cycle stage. I could have potentially answered medium for all questions because I can think of examples when each factor may or may not be highly important. It's very situation-specific. For example, the answers should depend on other information like the intended use and functional life of the NP. Regarding question 11, there seems to be an implied thought that renewable always means better. This isn't necessarily the case and is the | These considerations are tackled in the discussion of the results. |

## Appendix A.7 - Experts’ comments on main survey (cont.)

| | | | |
|---|---|---|---|
| nanomaterial because this determines if a "little bit of nanomaterial" can go a long way providing the same function. For example, a smaller quantity of CNTs can be used as a strengthener/filler in polymer blends than traditional materials. This means less material needs to be produced to meet the same market demand. | | reason people should perform environmental impact assessments of alternatives. | |
| Use of sustainable biological/agricultural as primary resource for NP (example: graphene, nanocellulose etc.) Very High | This consideration is highlighted in the discussion of the results. The main issue in this case is that the sustainability of the resources must be evaluated through relevant tools. | With current advancements in technology and research and development of Agricultural Solutions in nano production example: http://www.acs.org/content/acs/en/pressroom/newsreleases/2014/august/could-hemp-nanosheets-topple-graphene-for-making-the-ideal-supercapacitor.html#.VKjEzE8RX8I.google_plusone_share Sustainable development of these NPs with proven agricultural methods is essential. National Agroforestry Center http://nac.unl.edu/#about | This consideration is tackled in the discussion of the results. |
| --- | --- | The structure of the questions might mask significant information as different life cycles may have very different material requirements and emissions and we need to lump the answer. Uncertainty further | This consideration is tackled in the discussion of the results. |

## Appendix A.7 - Experts’ comments on main survey (cont.)

| | | | |
|---|---|---|---|
| | | increases when you think about different types of product (fullerene, vs. nano-metal particles vs. CNT) | |
| Appropriate tests: Very High<br>Hierarchical Assessment Methods: Very High | These comments are difficult to interpret. However it seems like the respondent seems to focus on the development of reliable evaluation tools that can provide reliable results, by adopting a tiered assessment approach. | --- | --- |
| --- | --- | Not sure how you are interpreting these results - my answers relate to the importance of considering these factors in assessing the impact of a given nanomaterial, not the likelihood that I think a given factor is to be an important contributor to environmental impact. I'm also not sure how you are determining the comparative functionality of the nano vs non-nano product and whether in that you mean the functionality of the nanomaterial within the product or the impact of the nanotechnology on the functionality of the end product. In many cases I don't think the latter has been considered adequately and that there are assumptions about both questions (e.g. as long as the | There might have been a misunderstanding of the use of functionality as well as in the economic performance area. The term refers to a product that aims at satisfying the same function, but the performance level is not considered. |

## Appendix A.7 - Experts' comments on main survey (cont.)

| | | | |
|---|---|---|---|
| | | nanoscale material generates the same conditions as the non-nano material within a product, then functionality is the same, but this may not be the case). | |
| End of life disposal and risks of nanoparticles entering the environment is a big issue | The end of life is covered in the technical performance area, while the risks issue is treated in the dedicated section. | Much of the above is rather meaningless at present because apart from car tyres and a few nanocomposites, and niche medical applications the industry is not well enough developed. | The stage of development does not mean that the life cycle of NPs is not having an impact on the environment. |
| recovery of high value materials for re-use is very important. | This aspect is covered in the technical performance area. | Most of the questions from 8-15 depend very strongly on the type of material and process, so many of the responses are probably at best "average" or erroneous. For example one process I used for making nanophosphors resulted in large quantities of waste urea. This process was replaced by a much more difficult process but since then there is a market for waste urea, which would render the original process viable. There are many other examples to illustrate these questions and give completely different answers to the ones above. | This consideration is tackled in the discussion of the results. |

## Appendix A.7 - Experts' comments on main survey (cont.)

| Environmental risk assessment and management criteria | | | |
|---|---|---|---|
| **Criteria to add suggested by participant** | **Researcher's comment** | **Opinions of participant** | **Researcher's comment** |
| --- | --- | I don't know understand some of the pro phrases, it is not helping me answering the questions. | The comment is rather too generic to be able to contextualize it. |
| --- | --- | "I don't know" in some cases mean "nobody can know" - there is ignorance not in the sense of "knowledge gaps" but in the sense of Frank Knight (1921) and Brian Wynne (1992), please consult the scholarly work on nano hazards by e.g. Fern Wickson. | This consideration has been acknowledged in the discussion of the results |

| Human health risk assessment and management criteria | | | |
|---|---|---|---|
| **Criteria to add suggested by participant** | **Researcher's comment** | **Opinions of participant** | **Researcher's comment** |
| Agreed upon urgency of the matter - low!<br>Enforcement of general requirements, action to avoid liabilities, prevent harm, | These comments might be driven by the primary attention that health and safety issues in regard to NPs received at the expenses of all other aspects of sustainability of such goods. | --- | --- |

# Appendix A.7 - Experts' comments on main survey (cont.)

| | | | |
|---|---|---|---|
| precautionary approach - very low! | This consideration is included in the discussion of the results. | | |
| --- | --- | Preclinical animal models for safety and efficacy must be scrutinized as they may not be reliable or predictive of human use.<br>Claims for "targeting" of therapeutic are never proven: less than 5% of dosing of most NP formulations ever reaches target site. | This issue has to be related with the applicability of toxicity tests and endpoints agreement.<br>The "targeting"-related comment is a demonstration of the need for improved functionality of the NP. |
| Solution stability of the NP must be conducted before cell viability studies | The comment confirms the need for a sample preparation guidance that guarantees reproducibility of results. | Properties of NPs might vary with synthesis method, precursors, reactants etc | This consideration is included in the discussion of the results. |
| Acute and chronic impact: Very High<br>Objective database on beneficial, safe, and unsafe levels of exposure; e.g. trace metal metabolites: Very High! | These needs can only be solved if the following activities represented by these criteria are implemented: (i) toxicity tests applicability; (ii) dose metric agreement for nanoproducct hazard characterization; (iii) effective concentration agreement for adverse biological effect; and (iv) physicochemical properties agreement for toxicity testing. | --- | --- |

## Appendix A.7 - Experts’ comments on main survey (cont.)

| | | | |
|---|---|---|---|
| Using relevant tests and doses. Understanding the relationship between physicochemical properties and bioactivity. | These characteristics are covered by the criteria: (i) toxicity tests applicability; (ii) dose metric agreement for nanoproducct hazard characterization; (iii) effective concentration agreement for adverse biological effect; and (iv) physicochemical properties agreement for toxicity testing. | --- | --- |
| Determine the relationship between physicochemical properties and bioactivity - High | Issue covered by the criterion “physicochemical properties agreement for toxicity testing”. | --- | --- |
| Grouping nanoparticles by properties and/or mechanisms of action – High<br>Validation of more rapid in vivo tests (bolus dosing of=r short tern inhalation) as a replacement of 90 inhalation exposure - High | These recommendations can be covered by the further development of alternative testing strategies approaches. | --- | --- |
| Very high priority needed to assess indirect impacts of nanomaterials on safety of materials and systems in contact with nanomaterials. For example, the ability of | These considerations are included in the discussion of the results. | --- | --- |

## Appendix A.7 - Experts' comments on main survey (cont.)

| | | | |
|---|---|---|---|
| nanomaterials to act as a carrier by which other toxins gain entry into other parts of the body or undergo biochemical transformations that affect their toxicity and bioavailability.<br>Equally important is the assessment of impact of impurities and transformation productions of nanomaterials in production, distribution and use phases of the life cycle, vis a vis the specificity of the toxicity assessment. We know that small changes in nanostructures can translate to huge differences in toxicity, but we don't have information on the specificity of the production process once they are scaled up from the lab to large scale manufacturing and how that affects the purity, durability and stability of the end products or byproducts at the nanoscale. | | | |
| Interaction of science and politics, better integration between risk assessment and risk management: high importance | This comment is handled by the criterion on the importance of collaboration embedment of actors along the value chain. | Opening up scientific risk assessment for other stakeholders, importance of inclusion and responsiveness<br>Development of adaptive and | The role of collaboration is also extended to the practitioners from different areas. This is considered in the collaboration embedment criterion. |

# Appendix A.7 - Experts' comments on main survey (cont.)

| | | | |
|---|---|---|---|
| | | iterative processes | |
| Precautionary principle use | This consideration is included in the discussion of the results. | --- | --- |

| Social implications criteria | | | |
|---|---|---|---|
| **Criteria to add suggested by participant** | **Researcher's comment** | **Opinions of participant** | **Researcher's comment** |
| Consumers' right to know is not respected! Communities having to deal with impacts from waste products without knowing there are nano releases from them! Increased illness and health costs that everyone pays for from exposures they don't even know about. These are the huge social issues that need to be addressed. Right to know! Very high! | The respondent refers to two issues that the questions actually address. The first one is the regulatory compliance of a NP with existing or upcoming legislation. It would be the responsibility of such legislation to impose stringent requirements on identification and characterization of nano-releases, which would results in customers' information.<br>As far as the illness and health costs, this is tackled by the question on the external costs caused by a NP on health and welfare system. | The questions above lean too heavily on the potential benefits and do not explore the costs to society of imposed risks that they cannot even detect. | The survey considers risks to society at two levels. The first one is the question on the externality costs for health and welfare implications and the second one is the whole category dedicated to the health risk assessment and management criteria. |

## Appendix A.7 - Experts' comments on main survey (cont.)

| | | | |
|---|---|---|---|
| --- | --- | Good set of criteria. It is unfortunate that to most the primary issue is environmental and human toxicology. These issues have become clearly secondary. | Confirmation of appropriateness of the criteria. |
| Actual toxic/environmental performance of nanomanufcaturing and/or nanoenabled products: Very High | These aspects are covered in the environmental implications and environmental risk assessment areas. | --- | --- |
| General public knowledge and awareness of nanotech, its products and possible social, environmental implications. Very important | This consideration is included in the discussion of the results. | I did not understand well the questions; example "Promoting health through NPs" you want to know our perception of how important is to know the ELS implications of it, or the chances this technology has to promote health? I have the same confusion with all the questions. | The aim of the question is to investigate the latter issue. This will be of use for improving clarity of future studies. |
| --- | --- | Main concern is that we not overlook the net impact of nanomaterials in using them to solve a specific health and environmental problem. For example, occupational risks go way up with attempts at justifying them based on the benefits they offer in terms of reducing carbon emissions - new and different risks, not necessarily lower risks overall. I fear this may be the case with "clean" | This consideration is included in the discussion of the results. |

## Appendix A.7 - Experts' comments on main survey (cont.)

| | | | |
|---|---|---|---|
| | | diesel vehicle emissions - fewer, smaller particles may be as bad, or worse for health than more larger diesel particulate emissions. | |
| Development of nano-specific regulations: very high | The question of regulatory compliance actually tackles this aspect. | Deliberations about concerns, benefits, uncertainties are needed | This consideration is included in the discussion of the results. |
| --- | --- | Strange framing of these criteria... why "promoting health" - why not "affecting health"? There seems to be a technological optimist bias in the framing of the questions | The concern of affecting health is handled with the dedicated section human health risk assessment and management. |
| Maybe I read #8 wrong... but an entry that looks at whether nanotechnology will exacerbate existing inequities would be useful. And I'd rate that as high. | Confirmation of appropriateness of the criterion. | --- | --- |

| **Technical performance criteria** | | | |
|---|---|---|---|
| **Criteria to add suggested by participant** | **Researcher's comment** | **Opinions of participant** | **Researcher's comment** |
| Dose-response (potency) human-human reproducibility in therapeutic use | This is actually what the concept of reliability and functionality refer to. | Most animal experiments used preclinical do not provide indicators for human use. Models must be scrutinized. | This consideration is included in the discussion of the results. |

## Appendix A.7 - Experts' comments on main survey (cont.)

| | | | |
|---|---|---|---|
| Functionality can be different than many types of characterization. However regular characterization is needed for reliability and reproducibility. | These considerations confirm the relevancy of functionality and reliability of NPs as well as reproducibility of characterization technique. | --- | --- |
| Any NP or nanotechnology must concurrently consider the interdependence and trade-offs between performance, sustainability, and cost over its life cycle(s), along with its social and ethical considerations. Extremely high! | This is the main consideration that underlies the objective of the survey: identification of a reliable set of criteria as well as their interdependencies. | FYI. A few years ago, the National Academy asked me to share a presentation on Green Chemical Substitution and Manufacturing. It addresses and augments some of this survey's objectives. | --- |
| --- | --- | The recyclability is the biggest issue because it is extremely difficult to extract nanoparticles from a matrix in the case of smart functional composites for example. | This consideration is included in the discussion of the results. |
| High specificity, high efficiency | These notions are inherent in the concept of functionality. | None | --- |

# *Appendix B - Appendix of Chapter 6*

## Appendix B.1 – Dataset of production protocols for silver nanoparticles used for DRSA analysis

| **PIN = Protocol Identification Number** | **Criteria** | | | | | | | | **Performance class by DMs** | **Reference for criteria values** |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Reducing agent class** | **Capping agent class** | **Solvent class** | **Local resource use class** | **Reaction time** | **Temperature (Celsius)** | **Equipment class** | **Size class** | **Very high, High, Medium, Low, Very low** | |
| 1 | Renewable - Primary | Biodegradable polymer | Renewable - Primary | No | 45 s | 80 | Microwave - 1000 W - Open vessel | 0-30 nm | Medium | [402] |
| 2 | Renewable - Primary | Renewable - Primary | Renewable - Primary | No | 60 s | 100* | Microwave - 1000 W - Open vessel | 0-30 nm | High | [387] |
| 3 | Renewable - Primary | Renewable - Primary | Renewable - Primary | No | 20 h | 40 | Conventional | 0-30 nm | High | [461] |
| 4 | Renewable - Primary | Not needed | Renewable - Primary | No | 45 s | 41 | Microwave - sealed vessel - < 300W | 0-30 nm | Very high | [444] |
| 5 | Renewable - Primary | Not needed | Renewable - Primary | No | 60 s | 47 | Microwave - sealed vessel - < 300W | 0-30 nm | Very high | [444] |

## Appendix B.1 – Dataset of production protocols for silver nanoparticles used for DRSA analysis (cont.)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 6 | Renewable - Primary | Not needed | Renewable - Primary | No | 30 s | 39 | Microwave - sealed vessel - < 300W | 0-30 nm | Very high | [444] |
| 7 | Renewable - Primary | Not needed | Renewable - Primary | No | 30 s | 42 | Microwave - sealed vessel - < 300W | 0-30 nm | Very high | [444] |
| 8 | Renewable - Primary | Renewable - Primary | Renewable - Primary | No | 10 s | 150 | Microwave - sealed vessel - > 300W | 0-30 nm | Very high | [465] |
| 9 | Synthetic | Synthetic | Renewable - Primary | No | 30 min | 25 | Stirring | 0-30 nm | Low | [531] |
| 10 | Renewable - Primary | Synthetic | Renewable - Primary | No | 15 min | 25 | Not known | 30 -60 nm | Low | [532] |
| 11 | Renewable - Primary | Synthetic | Renewable - Primary | No | 15 min | 25 | Not known | 0-30 nm | Low | [532] |
| 12 | Synthetic | Synthetic | Synthetic | No | 4 h 15 m | 25 | Stirring | 0-30 nm | Very low | [533] |
| 13 | Renewable - Primary | Not needed | Renewable - Primary | No | 8 h | 25 | Stirring – under 5 min | 0-30 & 30 -60 nm | Very high | [534] |
| 14 | Renewable - Primary | Not needed | Renewable - Primary | No | 8 h | 25 | Stirring – under 5 min | 0-30 nm | Very high | [534] |
| 15 | Renewable - Primary | Not needed | Renewable - Primary | No | 2 h | 25 | Stirring – under 5 min | 0-30 nm | Very high | [443] |
| 16 | Renewable - Waste | Not needed | Renewable - Primary | No | 2 h | 25 | Stirring – under 5 min | 0-30 nm | Very high | [443] |
| 17 | Renewable - Primary | Not needed | Renewable - Primary | Yes | 8 h | 37 | Static | 0-30 nm | Very high | [535] |

## Appendix B.1 – Dataset of production protocols for silver nanoparticles used for DRSA analysis (cont.)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 18 | Renewable - Primary | Not needed | Renewable - Primary | Yes | 2 h | 26.85 | Static | 0-30 nm | Very high | [460] |
| 19 | Renewable - Primary | Not needed | Renewable - Primary | Yes | 8 min | 30 | Not known | 0-30 nm | Very high | [463] |
| 20 | Renewable - Primary | Not needed | Renewable - Primary | Yes | 6 h | 30 | Static | 0-30 & 30 -60 nm | Very high | [536] |
| 21 | Renewable - Primary | Not needed | Synthetic | No | 24 h | 25 | Static | 0-30 nm | Low | [445] |
| 22 | Synthetic | Synthetic | Synthetic | No | 3 h | 170 | Microwave - sealed vessel - > 300W | 0-30 nm | Very low | [537] |
| 23 | Synthetic | Biodegradable polymer | Renewable - Primary | No | 3 min | 198 | Microwave - sealed vessel - > 300W | 0-30 & 30 -60 nm | Low | [538] |
| 24 | Synthetic | Biodegradable polymer | Renewable - Primary | No | 5 s | 100* | Microwave - sealed vessel - > 300W | 0-30 nm | Low | [467] |
| 25 | Synthetic | Biodegradable polymer | Renewable - Primary | No | 2 h | 90 | Conventional | 0-30 nm | Low | [539] |
| 26 | Synthetic | Biodegradable polymer | Synthetic | No | 4 h | 160 | Conventional | 30-60 nm | Low | [540] |
| 27 | Synthetic | Biodegradable polymer | Synthetic | No | 4 h | 160 | Conventional | 0-30 nm | Low | [540] |
| 28 | Renewable - Primary | Not needed | Renewable - Primary | No | 30 min | 80 | Conventional | 0-30 & 30 -60 nm | High | [541] |

## Appendix B.1 – Dataset of production protocols for silver nanoparticles used for DRSA analysis (cont.)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 29 | Synthetic | Not needed | Renewable - Primary | No | 8 min | 100 | Microwave - sealed vessel - > 300W | 0-30 nm | Low | [542] |
| 30 | Renewable - Primary | Renewable - Primary | Renewable - Primary | No | 2 h | 70 | Conventional | 0-30 nm | Medium | [462] |
| 31 | Renewable - Primary | Not needed | Renewable - Primary | No | 8 h | 70 | Conventional | 0-30 nm | Medium | [543] |
| 32 | Synthetic | Synthetic | Synthetic | No | 60 s | 100* | Microwave - 1000 W - Open vessel | 0-30 nm | Low | [544] |
| 33 | Renewable - Waste | Not needed | Renewable - Primary | No | 75 min | 25 | Static | 30-60 nm | Medium | [391] |
| 34 | Renewable - Waste | Not needed | Renewable - Primary | No | 45 min | 60 | Conventional | 0-30 nm | Medium | [391] |
| 35 | Renewable - Primary | Not needed | Renewable - Primary | No | 3 h | 160 | Conventional | 0-30 nm | Medium | [386] |
| 36 | Renewable - Waste | Not needed | Renewable - Primary | No | 10 min | 40 | Conventional | 0-30 nm | High | [434] |
| 37 | Renewable - Primary | Not needed | Renewable - Primary | No | 10 min | 40 | Conventional | 0-30 nm | High | [434] |
| 38 | Renewable - Primary | Not needed | Renewable - Primary | Yes | 15 min | 80 | Conventional | 0-30 nm | High | [545] |
| 39 | Renewable - Primary | Not needed | Renewable - Primary | No | 10 min | 100 | Microwave - sealed vessel - > 300W | 0-30 & 30 -60 nm | High | [546] |
| 40 | Renewable - Primary | Not needed | Renewable - Primary | Yes | 20 min | 100 | Stirring and heating | 0-30 nm | High | [435] |

## Appendix B.1 – Dataset of production protocols for silver nanoparticles used for DRSA analysis (cont.)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 41 | Renewable - Primary | Not needed | Renewable - Primary | No | 8 h | 25 | Stirring | 0-30 & 30 -60 nm | Medium | [370] |
| 42 | Renewable - Waste | Not needed | Renewable - Primary | No | 60 s | 55 | Microwave - sealed vessel - < 300W | 0-30 nm | High | [425] |
| 43 | Renewable - Primary | Not needed | Renewable - Primary | Yes | 10 min | 40 | Conventional | 0-30 nm | High | [464] |
| 44 | Renewable - Primary | Not needed | Renewable - Primary | Yes | 20 min | 80 | Conventional | 30_60 | High | [547] |
| 45 | Renewable - Primary | Not needed | Renewable - Primary | Yes | 15 min | 95 | Conventional | 0_30 | High | [459] |
| 46 | Renewable - Primary | Not needed | Renewable - Primary | Yes | 20 min | 25 | Stirring_5min | 0_30 | Very high | [548] |
| 47 | Synthetic | Synthetic | Renewable - Primary | No | 60 s | 100* | Micro_sealed _o300W | 0_30 | Low | [549] |
| 48 | Renewable - Primary | Synthetic | Renewable - Primary | No | 24 h | 25 | Static | 0_30 | Very high | [550] |

*=assumed data

## Appendix B.2 - Calculations of scores for test protocol t₁ and t₃ with new (i.e. variable consistency) DRSA classification scheme

$$Score_R^{+}\left(Cl_p, t_1\right) = \frac{\left|\text{Protocols satisfying conditions of covering rules and belonging to } Cl_p\right|^2}{\left|\text{Protocols satisfying conditions of covering rules that include } Cl_p \text{ as a recommendation}\right| \left|\text{Protocols belonging to } Cl_p\right|}$$

$$Score_R^{-}\left(Cl_p, t_1\right) = \frac{\left|\text{Protocols satisfying conditions of covering rules and not belonging to } Cl_p\right|^2}{\left|\text{Protocols satisfying conditions of covering rules that recommend a class different from } Cl_p\right| \left|\text{Protocols not belonging to } Cl_p\right|}$$

$$Score_R^{net}\left(Cl_p, t_1\right) = Score_R^{+}\left(Cl_p, t_1\right) - Score_R^{-}\left(Cl_p, t_1\right)$$

## Test protocol t₁

Covering rules: 3, 5, 6, 8, 11, 12, 13.

**Class very high**

$$Score_R^{+}\left(Cl_{very\ high}, t_1\right) = \frac{|4,5,6,7,8,13,14,15,16,17,18,19,20,46,48|^2}{|1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17,18,19,20,21,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48| * 15}$$

$$= \frac{15^2}{(46*15)} = 0.33$$

$Score_R^{-}\left(Cl_{very\ high}, t_1\right)$ = 0

$Score_R^{net}\left(Cl_{very\ high}, t_1\right)$ = 0.33 – 0 = 0.33

**Class high**

$$Score_R^{+}\left(Cl_{\ high}, t_1\right) = \frac{|2,3,28,36,37,38,39,40,42,43,44,45|^2}{|1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17,18,19,20,21,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48| * 12}$$

$$= \frac{12^2}{(46*12)} = 0.27$$

$$Score_R^{-}\left(Cl_{\ high}, t_1\right) = \frac{|4,5,6,7|^2}{|4,5,6,7| * 36} = \frac{4^2}{(4*36)} = 0.05$$

$Score_R^{net}\left(Cl_{high}, t_1\right)$ = 0.27 – 0.05 = 0.22

**Class medium**

$Score_R^{+}(Cl_{medium}, t_1) =$

$$\frac{|1,30,31,33,34,35,41|^2}{|1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17,18,19,20,21,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48|*7}$$

$$= \frac{7^2}{(46*7)} = 0.15$$

$$Score_R^{-}(Cl_{medium}, t_1) = \frac{|2,4,5,6,7,8,19,28,36,37,38,39,40,42,43,44,45,46|^2}{|2,4,5,6,7,8,19,28,36,37,38,39,40,42,43,44,45,46|*41} = \frac{18^2}{(18*41)} = 0.44$$

$Score_R^{net}(Cl_{medium}, t_1)$ = 0.15 – 0.44 = – 0.29

**Class low**

$Score_R^{+}(Cl_{low}, t_1) =$

$$\frac{|9,10,11,21,23,24,25,26,27,29,32|^2}{|1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17,18,19,20,21,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48|*12}$$

$$= \frac{11^2}{(46*12)} = 0.22$$

$Score_R^{-}(Cl_{low}, t_1) =$

$$\frac{|2,3,4,5,6,7,8,13,14,15,16,17,18,19,20,28,30,31,33,34,35,36,37,38,39,40,41,42,43,44,45,46|^2}{|2,3,4,5,6,7,8,13,14,15,16,17,18,19,20,28,30,31,33,34,35,36,37,38,39,40,41,42,43,44,45,46|*36} = \frac{32^2}{(32*36)} = 0.89$$

$Score_R^{net}(Cl_{low}, t_1)$ = 0.22 – 0.89 = – 0.67

## Test protocol $t_3$

Covering rules: 11, 12, 19, 20, 23, 24, 25, 26.

**Class very low**

$Score_R^{+}(Cl_{very\ low}, t_3) =$

$$\frac{|22|^2}{|1,2,3,10,11,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,47|*2} = \frac{1^2}{(30*2)} = 0.02$$

$Score_R^{-}(Cl_{very\ low}, t_3) =$

$$\frac{|1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17,18,19,20,21,23,24,25,26,27,28,29,30,31,,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48|^2}{|1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17,18,19,20,21,23,24,25,26,27,28,29,30,31,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48|*46}$$

$$= \frac{45^2}{(45*46)} = 0.98$$

$Score_R^{net}(Cl_{very\ low}, t_3)$ = 0.02 – 0.98 = – 0.96

**Class low**

$Score_R^+(Cl_{low}, t_3) =$

$$\frac{|9,10,11,21,23,24,25,26,27,29,32,47|^2}{|1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48|*12}$$

$= \frac{12^2}{(47*12)} = 0.26$

$Score_R^-(Cl_{low}, t_3) = 0$

$Score_R^{net}(Cl_{low}, t_3)$ = 0.26 – 0 = 0.26

**Class medium**

$Score_R^+(Cl_{medium}, t_3) =$

$$\frac{|1,30,31,33,34,35,41|^2}{|1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17,18,19,20,21,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48|*7}$$

$= \frac{7^2}{(47*7)} = 0.15$

$Score_R^-(Cl_{medium}, t_3) = 0$

$Score_R^{net}(Cl_{medium}, t_3)$ = 0.15 – 0 = 0.15

**Class high**

$Score_R^+\left(Cl_{high}, t_3\right) =$

$$\frac{|2,3,28,36,37,38,39,40,42,43,44,45|^2}{|1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17,18,19,20,21,23,24,25,26,27,28,29,30,31,,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48|*12}$$

$= \frac{12^2}{(45*12)} = 0.27$

$Score_R^-\left(Cl_{high}, t_3\right) = \frac{|1,10,22,23,24,25,26,27,32,33,47|^2}{|1,10,22,23,24,25,26,27,32,33,47|*36} = \frac{11^2}{(11*36)} = 0.31$

$Score_R^{net}\left(Cl_{high}, t_3\right)$ = 0.27 – 0.31 = – 0.04

**Class very high**

$Score_R^+\left(Cl_{very\ high}, t_3\right) =$

$$\frac{|4,5,6,7,8,13,14,15,16,17,18,19,20,46,48|^2}{|1,2,3,4,5,6,7,8,9,10,11,13,14,15,16,17,18,19,20,21,23,24,25,26,27,28,29,30,31,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48|*15}$$

$= \frac{15^2}{(45*15)} = 0.33$

$Score_R^-\left(Cl_{very\ high}, t_3\right) =$

$$\frac{|1,2,3,10,11,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,47|^2}{|1,10,22,23,24,25,26,27,32,33,47|*36} = \frac{30^2}{(30*33)} = 0.91$$

$Score_R^{net}\left(Cl_{very\ high}, t_3\right)$ = 0.33 – 0.91 = – 0.58

# *Appendix C - Appendix of Chapter 7*

## Appendix C.1 – Rationale for classes profiles and preference thresholds selection of SMAA-TRI

The selection of the classes profiles and preference thresholds for SMAA-TRI drew from the review of the extensive literature published on the synthesis processes for nanoparticles (see also Table C.1.1 below).

As far as the reducing agent and solvent are concerned, the lowest profile ($Pr_1$ = Low - Very low) was assigned to the synthetic typology as it has been widely reported that such type of material is the worst from a green chemistry perspective (e.g. it requires dedicated synthesis steps and most of the times is hazardous) leading the assignment of a low performance [32, 62, 389, 461, 551]. An improvement in the process takes place when a biodegradable polymer is used [552] (e.g. not hazardous and biodegradable in the environment) which warrants the allocation to the medium category in the ELECTRE-based model (i.e. $Pr_2$ = Medium - Low). Lastly, the use of renewable feedstocks is the target from the green chemistry perspective (e.g. naturally produced and benign), which justifies profiles for a high (i.e. $Pr_3$ = High - Medium) and very high class ($Pr_4$ = Very high - High) [378, 390, 393, 436, 534, 553, 554].

Different consideration applies for the capping agent, as in this case it is possible to avoid its use when a multifunctional material is adopted [411]. Consequently, the requirement for the assignment to a very high preference class was imposed as more demanding and lifted by a class, which means that for the assignment to a very high class the protocol needs to employ at least a renewable material from a waste source ($Pr_4$ = Very high - High), whereas the use of a synthetic material can justify the worst class to the process [391, 425, 553].

Even though not directly linked to green chemistry, the adoption of local resources were underlined as a “green” characteristic of the synthesis process [459, 545], which was used to select the preference profiles for this criterion too.

Regarding the reaction time, the selection of the profiles was based on the published papers which show that producing nanoparticles is feasible in reactions that take place in very short timeframes, in the order of tens of seconds [402, 444], an advantage from an energy efficiency viewpoint ($Pr_4$ = Very high - High). A “few minutes” is indicated as a relatively short reaction process, thus the assignment of the $Pr_2$ = Medium - Low (i.e. 400 seconds as a threshold) [390, 425, 466]. Lastly, slower processes of the range of half an hour are indicated as considerably long compared with those that lead to nanoparticles within a few minutes, which supports the selection of 25 minutes as the boundary for the allotment to a low category ($Pr_1$ = Low - Very Low) [390, 402, 411, 444, 554].

As far as the reaction temperature is concerned, it was found that reactions that are carried out at room temperature of even close to such values lead to nanomaterials [32, 387, 436, 444], thus qualifying the processes for a very high class ($Pr_4$ = Very high - High), considering that temperatures close or equal to "room values" are a major requirement from a green chemistry perspective [30, 32, 62]. Similar considerations apply to processes that perform at temperatures labelled as "mild" (from 40°C to 60°C), leading to the selection of the values for the other two profiles [32, 444, 551] (i.e. $Pr_3$ = High - Medium and $Pr_2$ = Medium - Low). Processes performing at around 100°C and above are considered as performing poorly for green chemistry [390, 402, 411, 444, 554], which determines the choice of 95°C as the discriminatory value for $Pr_1$ = Low - Very low.

The equipment typology also affects how "green" a reaction can be. It is rationally undeniable that no mechanical instrumentation is the favourite option from a sustainability perspective. Stirring systems operate at a very low energy intensity and are thus preferred when compared to more elaborate and energy demanding processes [446]. For this reason, very high class is selected as a profile for such systems operating under 5 minutes ($Pr_4$ = Very high - High) and a high class for such systems that operate at longer times ($Pr_3$ = High - Medium). Microwaves have been labelled as green and environmentally friendly instruments for a variety of reasons, including safer operating conditions, lower energy consumption and higher yields when compared to conventional processes [390, 401, 403-405, 555]. This lead to the allocation of a partition profile between the low and medium class (i.e. $Pr_2$ = Medium - Low). Conventional approaches, such as oil bath, are currently considered as a low performing option [411, 448, 449], which is the reason for its allocation to $Pr_1$ = Low - Very low.

Lastly the performance of the nanoparticles, assumed to be the antimicrobial activity of silver, is dependent on the size of such particles. There are no clear indications about the threshold efficacy of such particles, however a general trend has been reported in the literature: the smaller the size of the particles the higher the antimicrobial activity [450, 452, 453, 556]. The thresholds of 30 nm and 60 nm where defined following the results reported in [450, 453].

Preference thresholds regarding the choice of the materials type are extracted from [378, 390, 393, 436, 534, 553, 554], reporting that the difference of one material class is enough to trigger a full preference. A handful of seconds (e.g. 10) and half a minute are reasonable values for the indifference and preference thresholds for the reaction time, whereas 5°C and 10°C are sensible in the case of reaction temperature, respectively [402, 444, 557]. Lastly, a single value difference justifies the score for the preference threshold of equipment type [32, 390, 402] and particles size ranges [450, 453].

**Table C.1.1: Classes profiles, thresholds, and related references used to run SMAA-TRI**

| **Classes profiles** | | **$g_1$** | **$g_2$** | **$g_3$** | **$g_4$** | **$g_5$** | **$g_6$** | **$g_7$** | **$g_8$** |
|---|---|---|---|---|---|---|---|---|---|
| | | **Reducing agent code** | **Capping agent code** | **Solvent code** | **Local resource use code** | **Reaction time (seconds)** | **Tempera-ture (Celsius)** | **Equipment type code** | **Size range code** |
| **Case A: Certain** | $Pr_4$ = Very high - High | Renewable – primary | Renewable – waste | Renewable – primary | Yes | 50 | 30 | Stirring ≤ 5 minutes | 0 ≤ particle size ≤ 30 nm |
| | Reference for profile value | [378, 390, 393, 436, 534, 553, 554] | [391, 425, 553] | [378, 390, 393, 436, 534, 553, 554] | [23, 459, 545] | [387, 402, 444, 466] | [32, 387, 436, 444] | [446] | [24, 32, 33, 450, 453, 558] |
| | $Pr_3$ = High - Medium | Renewable – primary | Renewable – primary | Renewable – primary | Yes | 100 | 40 | Stirring | 0 ≤ particle size ≤ 60 nm |
| | Reference for profile value | [378, 390, 393, 436, 534, 553, 554] | [378, 390, 393, 436, 534, 553, 554] | [378, 390, 393, 436, 534, 553, 554] | [23, 459, 545] | [32, 390, 425, 466] | [32, 444, 551] | [446] | [24, 32, 33, 450, 453, 558] |
| | $Pr_2$ = Medium - Low | Biodegradable polymer | Renewable – primary | Biodegradable polymer | No | 400 | 60 | Microwave – sealed vessel (> 300 W) | 30 < particle size ≤ 60 nm |
| | Reference for profile value | [402, 543, 552, 553] | [378, 390, 393, 436, 534, 553] | [402, 543, 552, 553] | [23, 459, 545] | [390, 425, 466] | [390, 444] | [390, 401, 403-405, 555] | [24, 32, 33, 450, 453, 558] |
| | $Pr_1$ = Low - Very low | Synthetic | Biodegradable polymer | Synthetic | No | 1500 | 95 | Conventional | 0 < particle size ≤ 100 nm |
| | Reference for profile value | [23, 32, 62, 389, 461, 551] | [402, 543, 552, 553] | [23, 32, 62, 389, 461, 551] | [23, 459, 545] | [390, 402, 411, 444, 554] | [390, 402, 411, 444, 554] | [411, 448, 449] | [24, 32, 33, 450, 453, 558] |
| **Indifference threshold** | | 0 | 0 | 0 | 0 | 10 | 5 | 0 | 0 |
| **Reference for threshold value** | | / | / | / | / | [402, 444] | [402, 444] | / | / |
| **Preference threshold** | | 1 | 1 | 1 | 0 | 30 | 10 | 1 | 1 |
| **Reference for threshold value** | | [378, 390, 393, 436, 534, 553, 554] | [378, 390, 393, 436, 534, 553, 554] | [378, 390, 393, 436, 534, 553, 554] | / | [402, 444] | [402, 444, 557] | [32, 390, 402] | [450, 453] |
| **Criterion preference** | | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↑ | ↓ |

## Appendix C.2: Ordinal criteria ranking used in SMAA-TRI, recommended classes from DRSA-based model and classes acceptability indices obtained with SMAA-TRI using certain classes profiles. 7th rank = reaction temperature ($g_6$); 8th rank = reaction time ($g_5$)

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_1$ |
| 3 | $g_2$ |
| 4 | $g_7$ |
| 5 | $g_3$ |
| 6 | $g_4$ |
| 7 | $g_6$ |
| 8 | $g_5$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm.* |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 13% | 14% | 73% | Yes |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 0% | 92% | 0% | 8% | 0% | Yes |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 0% | 77% | 23% | 0% | 0% | Yes |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 27% | 60% | 13% | Yes |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 7% | 93% | 0% | 0% | 0% | Yes |

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_2$ |
| 3 | $g_1$ |
| 4 | $g_7$ |
| 5 | $g_3$ |
| 6 | $g_4$ |
| 7 | $g_6$ |
| 8 | $g_5$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 13% | 14% | 73% | Yes |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 0% | 98% | 0% | 2% | 0% | Yes |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 0% | 94% | 6% | 0% | 0% | Yes |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 27% | 70% | 3% | Yes |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 33% | 67% | 0% | 0% | 0% | Yes |

(*: +/-1 = higher or lower SMAA-TRI class compared to new DRSA scheme)

**Appendix C.2: Ordinal criteria ranking used in SMAA-TRI, recommended classes from DRSA-based model and classes acceptability indices obtained with SMAA-TRI using certain classes profiles. 7th rank = reaction temperature ($g_6$); 8th rank = reaction time ($g_5$) (cont.)**

---

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_3$ |
| 3 | $g_2$ |
| 4 | $g_7$ |
| 5 | $g_1$ |
| 6 | $g_4$ |
| 7 | $g_6$ |
| 8 | $g_5$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 13% | 14% | 73% | Yes |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 0% | 99% | 0% | 1% | 0% | Yes |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 0% | 77% | 23% | 0% | 0% | Yes |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 27% | 60% | 13% | Yes |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 7% | 93% | 0% | 0% | 0% | Yes |

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_3$ |
| 3 | $g_1$ |
| 4 | $g_7$ |
| 5 | $g_2$ |
| 6 | $g_4$ |
| 7 | $g_6$ |
| 8 | $g_5$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 13% | 14% | 73% | Yes |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 0% | 98% | 0% | 2% | 0% | Yes |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 0% | 45% | 55% | 0% | 0% | No (+1) |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 27% | 36% | 37% | No (+1) |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 0% | 100% | 0% | 0% | 0% | Yes |

(*: +/-1 = higher or lower SMAA-TRI class compared to new DRSA scheme)

## Appendix C.2: Ordinal criteria ranking used in SMAA-TRI, recommended classes from DRSA-based model and classes acceptability indices obtained with SMAA-TRI using certain classes profiles. 7th rank = reaction temperature ($g_6$); 8th rank = reaction time ($g_5$) (cont.)

---

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_1$ |
| 3 | $g_3$ |
| 4 | $g_7$ |
| 5 | $g_2$ |
| 6 | $g_4$ |
| 7 | $g_6$ |
| 8 | $g_5$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 13% | 14% | 73% | Yes |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 0% | 92% | 0% | 8% | 0% | Yes |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 0% | 45% | 55% | 0% | 0% | No (+1) |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 27% | 36% | 37% | No (+1) |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 0% | 100% | 0% | 0% | 0% | Yes |

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_2$ |
| 3 | $g_3$ |
| 4 | $g_7$ |
| 5 | $g_1$ |
| 6 | $g_4$ |
| 7 | $g_6$ |
| 8 | $g_5$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 13% | 14% | 73% | Yes |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 0% | 99% | 0% | 1% | 0% | Yes |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 0% | 94% | 6% | 0% | 0% | Yes |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 27% | 70% | 3% | Yes |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 33% | 67% | 0% | 0% | 0% | Yes |

(*: +/-1 = higher or lower SMAA-TRI class compared to new DRSA scheme)

## **Appendix C.3:** Ordinal criteria ranking used in SMAA-TRI, recommended classes from DRSA-based model and classes acceptability indices obtained with SMAA-TRI using uncertain classes profiles. 7th rank = reaction temperature ($g_6$); 8th rank = reaction time ($g_5$)

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_1$ |
| 3 | $g_2$ |
| 4 | $g_7$ |
| 5 | $g_3$ |
| 6 | $g_4$ |
| 7 | $g_6$ |
| 8 | $g_5$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm.* |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 0% | 46% | 54% | Yes |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 14% | 77% | 0% | 9% | 0% | Yes |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 5% | 84% | 11% | 0% | 0% | Yes |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 28% | 65% | 7% | Yes |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 57% | 43% | 0% | 0% | 0% | No (-1) |

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_2$ |
| 3 | $g_1$ |
| 4 | $g_7$ |
| 5 | $g_3$ |
| 6 | $g_4$ |
| 7 | $g_6$ |
| 8 | $g_5$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 0% | 40% | 60% | Yes |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 20% | 78% | 0% | 2% | 0% | Yes |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 10% | 86% | 4% | 0% | 0% | Yes |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 49% | 50% | 1% | Yes |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 63% | 37% | 0% | 0% | 0% | No (-1) |

(*: +/-1 = higher or lower SMAA-TRI class compared to new DRSA scheme)

**Appendix C.3: Ordinal criteria ranking used in SMAA-TRI, recommended classes from DRSA-based model and classes acceptability indices obtained with SMAA-TRI using uncertain classes profiles. 7th rank = reaction temperature ($g_6$); 8th rank = reaction time ($g_5$) (cont.)**

| Rank | Criterion | Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $g_8$ | | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| 2 | $g_3$ | | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| 3 | $g_2$ | | | | | | | | | |
| 4 | $g_7$ | $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 0% | 47% | 53% | Yes |
| 5 | $g_1$ | $t_2$ | $C_2$ | $C_2$ (0.22) | 36% | 63% | 0% | 1% | 0% | Yes |
| 6 | $g_4$ | $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 5% | 76% | 19% | 0% | 0% | Yes |
| 7 | $g_6$ | $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 27% | 65% | 8% | Yes |
| 8 | $g_5$ | $t_5$ | $C_2$ | $C_2$ (0.33) | 57% | 43% | 0% | 0% | 0% | No (-1) |

| Rank | Criterion | Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $g_8$ | | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| 2 | $g_3$ | | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| 3 | $g_1$ | | | | | | | | | |
| 4 | $g_7$ | $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 0% | 54% | 46% | Yes |
| 5 | $g_2$ | $t_2$ | $C_2$ | $C_2$ (0.22) | 30% | 68% | 0% | 2% | 0% | Yes |
| 6 | $g_4$ | $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 1% | 58% | 41% | 0% | 0% | Yes |
| 7 | $g_6$ | $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 10% | 71% | 19% | Yes |
| 8 | $g_5$ | $t_5$ | $C_2$ | $C_2$ (0.33) | 50% | 50% | 0% | 0% | 0% | pair |

(*: +/-1 = higher or lower SMAA-TRI class compared to new DRSA scheme)

**Appendix C.3: Ordinal criteria ranking used in SMAA-TRI, recommended classes from DRSA-based model and classes acceptability indices obtained with SMAA-TRI using uncertain classes profiles. 7th rank = reaction temperature ($g_6$); 8th rank = reaction time ($g_5$) (cont.)**

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_1$ |
| 3 | $g_3$ |
| 4 | $g_7$ |
| 5 | $g_2$ |
| 6 | $g_4$ |
| 7 | $g_6$ |
| 8 | $g_5$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 0% | 54% | 46% | Yes |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 18% | 73% | 0% | 9% | 0% | Yes |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 1% | 65% | 34% | 0% | 0% | Yes |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 10% | 71% | 19% | Yes |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 50% | 50% | 0% | 0% | 0% | pair |

| Rank | Criterion |
|---|---|
| 1 | $g_8$ |
| 2 | $g_2$ |
| 3 | $g_3$ |
| 4 | $g_7$ |
| 5 | $g_1$ |
| 6 | $g_4$ |
| 7 | $g_6$ |
| 8 | $g_5$ |

| Test protocol | DRSA-based model (jMAF & jRS) | | ELECTRE-based model (SMAA-TRI) | | | | | Concordance between models recomm. |
|---|---|---|---|---|---|---|---|---|
| | $C_1 < C_2 < C_3 < C_4 < C_5$ | | | | | | | |
| | Standard DRSA scheme | New DRSA scheme (Max score for class) | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | |
| $t_1$ | $C_5$ | $C_5$ (0.33) | 0% | 0% | 0% | 40% | 60% | Yes |
| $t_2$ | $C_2$ | $C_2$ (0.22) | 31% | 68% | 0% | 1% | 0% | Yes |
| $t_3$ | $C_2$ or $C_3$ | $C_2$ (0.26) | 10% | 86% | 4% | 0% | 0% | Yes |
| $t_4$ | $C_3$ or $C_4$ | $C_4$ (0.26) | 0% | 0% | 49% | 49% | 2% | pair |
| $t_5$ | $C_2$ | $C_2$ (0.33) | 64% | 36% | 0% | 0% | 0% | No (-1) |

(*: +/-1 = higher or lower SMAA-TRI class compared to new DRSA scheme)

# *References*

1. Shapira, P. and J. Youtie, *The Economic Contributions of Nanotechnology to Green and Sustainable Growth*, in *Green Processes for Nanotechnology*, V.A. Basiuk and E.V. Basiuk, Editors. 2015, Springer International Publishing. p. 409-434.
2. Shapira, P. and J. Youtie, *Background Paper 3: The Economic contributions of Nanotechnology to Green and Sustainable Growth*, in *OECD/NNI International Symposium on Assessing the Economic Impact of Nanotechnology, Washington DC*. 2012, OECD and the US National Nanotechnology Initiative.
3. Iavicoli, I., et al., *Opportunities and challenges of nanotechnology in the green economy.* Environmental Health, 2014. **13**(78): p. 1-11.
4. Roy, B., *Decision-aid and decision-making.* European Journal of Operational Research, 1990. **45**(2): p. 324-331.
5. Moller, M., et al., *Analysis and Strategic Management of Nanoproducts with Regard to their Sustainability Potential. Nano-Sustainability Check*. 2012, Oko-Institut. Accessed on 16/09/2016 at: http://www.oeko.de/en/research-consultancy/issues/chemicals-management-and-technology-assessment/identifying-and-grasping-opportunities/.
6. EPA, U.S., *Nanotechnology White Paper*. 2007, Science Policy Council. Accessed on 13/03/2016 at: http://www2.epa.gov/sites/production/files/2015-01/documents/nanotechnology_whitepaper.pdf.
7. Palmberg C., Dernis H., and Miguet C., *Nanotechnology: An Overview Based on Indicators and Statistics*. 2009: OECD, Science, Technology and Industry Working Papers. Accessed on 22/09/2016 at: https://www.oecd.org/sti/inno/43179651.pdf.
8. Ramsden, J.R., *Applied Nanotechnology*. Micro & Nano Technologies Series. 2009: Elsevier.
9. Chen, H., et al., *Global nanotechnology development from 1991 to 2012: patents, scientific publications, and effect of NSF funding.* Journal of Nanoparticle Research, 2013. **15**(9): p. 1-21.
10. Roco, M.C., C.A. Markin, and M.C. Hersam, *Nanotechnology Research Directions for Societal Needs in 2020: Retrospective and Outlook*. 2011: Springer.
11. Allianz, *Small size that matters: Opportunities and risks of nanotechnologies*. 2009: Report in co-operation with the OECD International Figures Programme. Accessed on 13/03/2016 at: http://www.oecd.org/science/nanosafety/37770473.pdf.
12. Martin Palma, R.J. and A. Lakhtakia, *Nanotechnology. A Crash Course*. 2010, Bellingham, Washington USA: SPIE Press.
13. Seeboth, A., R. Ruhmann, and O. Mühling, *Thermotropic and Thermochromic Polymer Based Materials for Adaptive Solar Control.* Materials, 2010. **3**(12): p. 5143-5168.
14. Chen, J., *Recent Progress in Advanced Materials for Lithium Ion Batteries.* Materials, 2013. **6**(1): p. 156-183.

15. O'Byrne, J.P., et al., *High CO2 and CO conversion to hydrocarbons using bridged Fe nanoparticles on carbon nanotubes.* Catalysis Science & Technology, 2013. **3**(5): p. 1202-1207.

16. Karn, B. and S.S. Wong, *Ten Years of Green Nanotechnology*, in *Sustainable Nanotechnology and the Environment: Advances and Achievements.* 2013, American Chemical Society. p. 1-10.

17. Kuempel, E.D., C.L. Geraci, and P.A. Schulte, *Risk assessment and risk management of nanomaterials in the workplace: translating research to practice.* The Annals of Occupational Hygiene, 2012. **56**(5): p. 491-505.

18. Şengül, H., T.L. Theis, and S. Ghosh, *Toward Sustainable Nanoproducts. An Overview of Nanomanufacturing Methods.* Journal of Industrial Ecology, 2008. **12**(3): p. 329-359.

19. Türk, V., C. Kaiser, and S. Schaller, *Invisible but tangible? Societal opportunities and risks of nanotechnologies.* Journal of Cleaner Production, 2008. **16**(8-9): p. 1006-1009.

20. Mantovani, E., et al., *Developments in Nanotechnologies Regulation and Standards*. 2011, Report of the Observatory Nano. Accessed on 22/09/2016 at: http://www.nanotec.it/public/wp-content/uploads/2014/04/ObservatoryNano_Nanotechnologies_RegulationAndStandards_2011.pdf.

21. Subramanian, V., et al., *Sustainable nanotechnology: Defining, measuring and teaching.* Nano Today, 2014. **9**(1): p. 6-9.

22. NanoKommission, *Responsible Use of Nanotechnologies. Report and recommendations of the German NanoKommission 2011*. 2011, German Federal Ministry for Environment, Nature Conservation, Building and Nuclear Safety. Accessed on 22/09/2016 at: http://www.bmub.bund.de/fileadmin/Daten_BMU/Download_PDF/Nanotechnologie/nano_schlussbericht_2011_bf_en.pdf.

23. NanoKommission, *Responsible Use of Nanotechnologies. Report and recommendations of the German NanoKommission 2008*. 2008, German Federal Ministry for Environment, Nature Conservation, Building and Nuclear Safety. Accessed on 22/09/2016 at: http://ec.europa.eu/health/ph_risk/documents/nanokommission.pdf.

24. Hutchison, J.E., *Greener nanoscience. A proactive approach to advancing applications and reducing implications of nanotechnology* . ACSNano, 2008. **2**(3): p. 395-402.

25. Karn, B., *The Road to Green Nanotechnology.* Journal of Industrial Ecology, 2008. **12**(3): p. 263-266.

26. Lu, Y. and S. Ozcan, *Green nanomaterials: On track for a sustainable future.* Nano Today, 2015. **10**(4): p. 417-420.

27. Sadik, O., B. Karn, and A. Keller, *Editorial: Sustainable Nanotechnology.* ACS Sustainable Chemistry & Engineering, 2014. **2**(7): p. 1543-1544.

28. Senjen, R., *Challenges and opportunities to green nanotechnologies*, in *Nanotechnologies in the 21st century*. 2009, European Environmental Bureau: Accessed on 13/03/2016 at: http://www.bef.lt/fileadmin/Publications/2009-NanoBrochureNo1-WEB_Eng.pdf

29. Bergeson, L.L., *Sustainable Nanomaterials: Emerging Governance Systems.* ACS Sustainable Chemistry & Engineering, 2013. **1**(7): p. 724-730.

30. Matus, K.J.M., et al., *Green Nanotechnology Challenges And Opportunities*. 2011, American Chemical Society.

31. Reihlen, A. and D. Jepsen, *Sustainable nanotechnologies*. 2012, ÖKOPOL GmbH. Accessed on 22/09/2016 at: http://www.bmub.bund.de/fileadmin/Daten_BMU/Download_PDF/Nanotechnologie/nanodialog_3_fd3_bericht_en_bf.pdf.

32. Dahl, J.A., B.L.S. Maddux, and J.E. Hutchison, *Toward Greener Nanosynthesis.* Chemical Reviews, 2007. **107**(6): p. 2228-2269.

33. McKenzie, L.C. and J.E. Hutchison, *Green nanoscience: An integrated approach to greener products, processes, and applications.* Chemistry Today, 2004(September issue): p. 30-33.

34. Hischier, R. and T. Walser, *Life cycle assessment of engineered nanomaterials: state of the art and strategies to overcome existing gaps.* Science of the Total Environment, 2012. **425**: p. 271-82.

35. Meyer, D.E., M.A. Curran, and M.A. Gonzalez, *An examination of silver nanoparticles in socks using screening-level life cycle assessment.* Journal of Nanoparticle Research, 2010. **13**: p. 147-156.

36. Meyer, D.E., M.A. Curran, and M.A. Gonzalez, *An examination of existing data for the industrial manufacture and use of nanocomponents and their role in the life cycle impact of nanoproducts.* Environmental Science & Technology, 2009. **43**: p. 1256-1263.

37. de Lima, R., et al., *Evaluation of the genotoxicity of cellulose nanofibers.* International Journal of Nanomedicine, 2012. **7**: p. 3555-3565.

38. Shatkin, J.A., *Nanotechnology: Health and Environmental Risks*. 2nd ed. Perspectives in Nanotechnology. 2012: CRC Press.

39. Grieger, K., A. Baun, and R. Owen, *Redefining risk research priorities for nanomaterials.* Journal of Nanoparticle Research, 2010. **12**: p. 383-392.

40. Hristozov, D. and I. Malsch, *Hazards and risks of engineered nanoparticles for the environment and human health.* Sustainability, 2009. **1**: p. 1161-1194.

41. Hansen, S., *Regulation and risk assessment of nanomaterials – Too Little, Too Late?* 2009, Ph.D. Thesis. Department of Environmental Engineering, Technical University of Denmark. Accessed on 22/09/2016 at: http://www2.er.dtu.dk/publications/fulltext/2009/ENV2009-069.pdf.

42. Hischier, R., *Framework for LCI modelling of releases of manufactured nanomaterials along their life cycle.* The International Journal of Life Cycle Assessment, 2014. **19**(4): p. 838-849.

43. NanoKommission, *Final Report of NanoKommission Issue Group 2. Guidelines for collecting data and comparing benefit and risk aspects of nanoproducts*. 2010, German Federal Ministry for Environment, Nature Conservation, Building and Nuclear Safety. Accessed on 22/09/2016 at: http://www.bmub.bund.de/fileadmin/Daten_BMU/Download_PDF/Nanotechnologie/nanodialog_2_Tg2_en_bf.pdf.

44. Tyang, Q.Z. and C.Y. Miao, *Integrating human factors into nanotech sustainability assessment and communication*, in *5th Conference on Industrial Electronics and Applications (ICIEA)*. 2010: Taichung, Taiwan. p. 1-5.

45. Som, C., et al., *LICARA Guidelines for the sustainable competitiveness of nanoproducts*. 2014: Dübendorf, St. Gallen, Zeist. Accessed on 22/09/2016 at: https://www.tno.nl/media/4385/licara-guidelines-for-the-sustainable-competitiveness-of-nanoproducts.pdf.

46. Wigger, H., T. Zimmermann, and C. Pade, *Broadening our view on nanomaterials: highlighting potentials to contribute to a sustainable materials management in preliminary assessments.* Environment Systems and Decisions, 2014. **35**(1): p. 1-19.

47. Linkov, I. and E. Moberg, *Multi-Criteria Decision Analysis. Environmental Applications and Case Studies*. 2012, United States: CRC Press.

48. Subramanian, V., et al., *Review of decision analytic tools for sustainable nanotechnology.* Environment Systems and Decisions, 2015. **35**(1): p. 29-41.

49. Bates, M.E., et al., *How decision analysis can further nanoinformatics.* Beilstein Journal of Nanotechnology, 2015. **6**: p. 1594-1600.

50. Eason, T., et al., *Guidance to Facilitate Decisions for Sustainable Nanotechnology*. 2011, EPA/600/R-11/107. U.S. Environmental Protection Agency. Accessed on 22/09/2016 at: https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=238589.

51. Naidu, S., R. Sawhney, and X. Li, *A Methodology for Evaluation and Selection of Nanoparticle Manufacturing Processes Based on Sustainability Metrics.* Environmental Science & Technology, 2008. **42**(17): p. 6697-6702.

52. Linkov, I., et al., *Nanotechnology: promoting innovation through analysis and governance.* Environment Systems and Decisions, 2015. **35**(1): p. 22-23.

53. Tolaymat, T., et al., *A system-of-systems approach as a broad and integrated paradigm for sustainable engineered nanomaterials.* Science of The Total Environment, 2015. **511**: p. 595-607.

54. Antunes, P., et al., *Approaches to integration in sustainability assessment of technologies. PROSUITE project*. 2012: Accessed on 13/03/2016 at: http://www.prosuite.org/c/document_library/get_file?uuid=c378cd69-f785-40f2-b23e-ae676b939212&groupId=12772.

55. Munda, G., *Multi criteria decision analysis and sustainable development* in *Multiple Criteria Decision Analysis: State of the Art Surveys*, J. Figueira, S. Greco, and M. Ehrgott, Editors. 2005, Springer: New York. p. 953-986.

56. Polatidis, H., et al., *Selecting an Appropriate Multi-Criteria Decision Analysis Technique for Renewable Energy Planning.* Energy Sources, Part B: Economics, Planning, and Policy, 2006. **1**(2): p. 181-193.

57. Dias, L.C., C.H. Antunes, and D.R. Insua, *Dealing with uncertainty in Decision Support Systems: Recent trends 2000--2011.* Intelligent Decision Technologies, 2012. **6**(4): p. 245-264.

58. Dias, L.C. and V. Mousseau, *IRIS: a DSS for multiple criteria sorting problems.* Journal of Multi-Criteria Decision Analysis, 2003. **12**(4-5): p. 285-298.

59. Karn, B., *Inside the radar: select elements in nanomaterials and sustainable nanotechnology.* Journal of Environmental Monitoring, 2011. **13**(5): p. 1184-1189.

60. Gupta, N., A.R.H. Fischer, and L.J. Frewer, *Ethics, Risk and Benefits Associated with Different Applications of Nanotechnology: a Comparison of Expert and Consumer Perceptions of Drivers of Societal Acceptance.* NanoEthics, 2015. **9**(2): p. 93-108.

61. Schmidt, K.F., *Green Nanotechnology: It's Easier Than You Think*. 2007, Woodrow Wilson International Center for Scholars. Project on Emerging Nanotechnolgies. Accessed on 22/09/2016 at: http://www.nanotechproject.org/file_download/files/GreenNano_PEN8.pdf.

62. Gilbertson, L.M., et al., *Designing nanomaterials to maximize performance and minimize undesirable implications guided by the Principles of Green Chemistry.* Chemical Society Reviews, 2015. **44**(16): p. 5758-5777.

63. Meyer, D.E. and V.K.K. Upadhyayula, *The use of life cycle tools to support decision making for sustainable nanotechnologies.* Clean Technologies and Environmental Policy, 2014. **16**(4): p. 757-772.

64. Upreti, G., et al., *Life Cycle Assessment of Nanomaterials*, in *Green Processes for Nanotechnology*, V.A. Basiuk and E.V. Basiuk, Editors. 2015, Springer International Publishing. p. 393-408.

65. Mebratu, D., *Sustainability and sustainable development. Historical and conceptual review.* Environmental Impact Assessment Review, 1998. **18**(6): p. 493-520.

66. UNEP. *Declaration of the United Nations Conference on the Human Environment*. 1972. Accessed on 13/03/2016 at: http://www.unep.org/Documents.Multilingual/Default.asp?documentid=97&articleid=1503].

67. WCED, *Our Common Future*. 1987, Oxford, UK: Oxford University Press.

68. Johnson, S.P., *The Earth Summit: The United Nations Conference on Environment and Development (UNCED)*. 1993, London: Graham & Trotman/Martinus Nijhoff.

69. Gibson, R.B., *Sustainability assessment: basic components of a practical approach.* Impact Assessment and Project Appraisal, 2006. **24**(3): p. 170-182.

70. Gibson, R.B., *Beyond the Pillars: Sustainability Assessment as a Framework for Effective Integration of Social, Economic and Ecological Considerations in Significant Decision-Making.* Journal of Environmental Assessment Policy and Management, 2006. **8**(03): p. 259-280.

71. Elkington, J., *Cannibals with Forks: Triple Bottom Line of 21st Century Business*. 1999: Capstone.

72. Bond, A., A. Morrison-Saunders, and J. Pope, *Sustainability assessment: the state of the art.* Impact Assessment and Project Appraisal, 2012. **30**(1): p. 53-62.

73. Singh, R.K., et al., *An overview of sustainability assessment methodologies.* Ecological Indicators, 2009. **9**(2): p. 189-212.

74. Singh, R.K., et al., *An overview of sustainability assessment methodologies.* Ecological Indicators, 2012. **15**(1): p. 281-299.

75. Pope, J., D. Annandale, and A. Morrison-Saunders, *Conceptualising sustainability assessment.* Environmental Impact Assessment Review, 2004. **24**(6): p. 595-616.

76. Cinelli, M., S.R. Coles, and K. Kirwan. *Use of Multi Criteria Decision Analysis to Support Life Cycle Sustainability Assessment: An Analysis of the Appropriateness of the Available Methods*. in *Proceedings of the 6th International Conference on Life Cycle Management, p. 677-680, 25-28 August, 2013*. 2013. Gothenburg, Sweden.

77. Sala, S., F. Farioli, and A. Zamagni, *Life cycle sustainability assessment in the context of sustainability science progress (part 2).* The International Journal of Life Cycle Assessment, 2013. **18**(9): p. 1686-1697.

78. Devuyst, D., *Sustainability assessment: the application of a methodological framework.* Journal of Environmental Assessment Policy and Management, 1999. **14**(1): p. 459-487.

79. Pope, J., *Editorial: What's so special about sustainability assessment?* Journal of Environmental Assessment Policy and Management, 2006. **8**(3): p. v-x.

80. Ness, B., et al., *Categorising tools for sustainability assessment.* Ecological Economics, 2007. **60**(3): p. 498-508.

81. Zamagni, A., et al., *D20 Blue Paper on Life Cycle Sustainability Analysis*. 2009, EU FP 6 CALCAS Project. Accessed on 22/09/2016 at: http://fr1.estis.net/sites/calcas/default.asp?site=calcas&page_id=E2669B0F-9DB7-4D1E-95B0-407BC7949030.

82. Cinelli, M., et al., *Workshop on life cycle sustainability assessment: the state of the art and research needs—November 26, 2012, Copenhagen, Denmark.* The International Journal of Life Cycle Assessment, 2013. **18**(7): p. 1421-1424.

83. Sala, S., F. Farioli, and A. Zamagni, *Progress in sustainability science: lessons learnt from current methodologies for sustainability assessment: Part 1.* The International Journal of Life Cycle Assessment, 2013. **18**(9): p. 1653-1672.

84. Tatham, E., D. Eisenberg, and I. Linkov, *Sustainable Urban Systems: A Review of How Sustainability Indicators Inform Decisions*, in *Sustainable Cities and Military Installations*, I. Linkov, Editor. 2014, Springer Netherlands. p. 3-20.

85. Convertino, M., et al., *Multi-criteria decision analysis to select metrics for design and monitoring of sustainable ecosystem restorations.* Ecological Indicators, 2013. **26**(0): p. 76-86.

86. Bockstaller, C., et al., *Agri-environmental indicators to assess cropping and farming systems. A review.* Agronomy for Sustainable Development, 2008. **28**(1): p. 139-149.

87. Gasparatos, A., M. El-Haram, and M. Horner, *A critical review of reductionist approaches for assessing the progress towards sustainability.* Environmental Impact Assessment Review, 2008. **28**(4-5): p. 286-311.

88. Victor, P., S. Hanna, and A. Kubursi, *How Strong is Weak Sustainability?*, in *Sustainable Development: Concepts, Rationalities and Strategies*, S. Faucheux, M. O'Connor, and J. Straaten, Editors. 1998, Springer Netherlands. p. 195-210.

89. O'Neill, J., J. Martinez-Alier, and G. Munda, *Commensurability and compensability in ecological economics*, in *Valuation and the environment : theory, method, and practice*, M.O.C.C.S. Cheltenham, Editor. 1999, Elgar.

90. Gasparatos, A. and A. Scolobig, *Choosing the most appropriate sustainability assessment tool.* Ecological Economics, 2012. **80**: p. 1-7.

91. Gasparatos, A., *Embedded value systems in sustainability assessment tools and their implications.* Journal of Environmental Management, 2010. **91**(8): p. 1613-1622.

92. Andrews, E.S., et al., *Guidelines for Social Life Cycle Assessment of Products*. 2009: UNEP/SETAC. Accessed on 22/09/2016 at: http://www.unep.fr/shared/publications/pdf/dtix1164xpa-guidelines_slca.pdf.

93. UN, *Indicators of Sustainable Development: Guidelines and Methodologies. Third Edition*. 2007, United Nations Department of Economic and Social Affairs, Division for Sustainable Development: New York.

94. De Ridder, W., et al., *A framework for tool selection and use in integrated assessment for sustainable development.* Journal of Environmental Assessment Policy and Management, 2007. **9**(4): p. 423-441.

95. Kloppfer, W., et al., *Nanotechnology and Life Cycle Assessment: A Systems Approach to Nanotechnology and the Environment*. 2007, Woodrow Wilson International Center for Scholars. Accessed on 22/09/2016 at: http://www.nanotechproject.org/file_download/files/NanoLCA_3.07.pdf.

96. Hanley, N. and C.L. Spash, *Irreversibility, ecosystem complexity, institutional capture and sustainability*, in *Cost-Benefit Analysis and the Environment*. 1994, Edward Elgar.

97. Poveda, C.A. and M. Lipsett, *A Review of Sustainability Assessment and Sustainability/Environmental Rating Systems and Credit Weighting Tools.* Journal of Sustainable Development, 2011. **4**(6): p. 36-55.

98. Jørgensen, A., et al., *Methodologies for social life cycle assessment.* The International Journal of Life Cycle Assessment, 2008. **13**(2): p. 96-103.

99. Sala, S., et al., *Social Life Cycle Assessment - State of the art and challenges for supporting product policies*. 2015: EUR 27624 EN; doi:10.2788/253715.

100. Guinée, J., *Life Cycle Sustainability Assessment: What Is It and What Are Its Challenges?*, in *Taking Stock of Industrial Ecology*, R. Clift and A. Druckman, Editors. 2016, Springer International Publishing: Cham. p. 45-68.

101. Belton, V. and T.J. Stewart, *The multiple criteria problem*, in *Multiple criteria decision analysis; an integrated approach*. 2002, Kluwer Academic Publisher. p. 13-34.

102. Roy, B., *Multicriteria Methodology for Decision Aiding*. 1996: Kluwer Academic Publishers.

103. Figueira, J., S. Greco, and M. Ehrgott, *Multi Criteria Decision Analysis: State of the Art Surveys*. 2005, New York: Springer.

104. Noshadravan, A., et al., *Stochastic comparative assessment of life-cycle greenhouse gas emissions from conventional and electric vehicles.* The International Journal of Life Cycle Assessment, 2015. **20**(6): p. 854-864.

105. Domingues, A.R., et al., *Applying Multi-Criteria Decision Analysis to the Life-Cycle Assessment of vehicles.* Journal of Cleaner Production, 2015. **107**: p. 749-759.

106. Rowley, H.V., et al., *Aggregating sustainability indicators: beyond the weighted sum.* Journal of Environmental Management, 2012. **111**: p. 24-33.

107. Munda, G., *"Measuring Sustainability": A Multi-Criterion Framework.* Environment, Development and Sustainability, 2005. **7**(1): p. 117-134.

108. Munda, G., P. Nijkamp, and P. Rietveld, *Monetary and Non-Monetary Evaluation Methods in Sustainable Development Planning.* Economie Appliquée 1995. **48**(2): p. 143-160.

109. Silva, S., L. Alçada-Almeida, and L.C. Dias, *Biogas plants site selection integrating Multicriteria Decision Aid methods and GIS techniques: A case study in a Portuguese region.* Biomass and Bioenergy, 2014. **71**: p. 58-68.

110. Neves, L.P., et al., *A multi-criteria decision approach to sorting actions for promoting energy efficiency.* Energy Policy, 2008. **36**(7): p. 2351-2363.

111. Kujawski, E., *Multi-criteria decision analysis: Limitations, pitfalls, and practical difficulties*, L.B.N. Laboratory, Editor. 2003: Accessed on 13/03/2016 at: http://escholarship.org/uc/item/0cp6j7sj.

112. Riabacke, M., M. Danielson, and L. Ekenberg, *State-of-the-Art Prescriptive Criteria Weight Elicitation.* Advances in Decision Sciences, 2012. **2012**: p. 24.

113. Keisler, J. and I. Linkov, *Environment models and decisions.* Environment Systems and Decisions, 2014. **34**(3): p. 369-372.

114. Bouyssou, D., et al., *Problem Formulation and Structuring: The Decision Aiding Process*, in *Evaluation and Decision Models with Multiple Criteria: Stepping stones for the analyst*. 2006, Springer US: Boston, MA. p. 19-65.

115. Lotze-Campen, H., et al., *Tool use in integrated assessments - Integration and synthesis report for the SustainabilityA-Test project*, in *EU FP 6 SustainabilityA-Test Project.* 2007, Netherlands Environmental Assessment Agency. Accessed on 22/09/2016 at: http://www.pbl.nl/sites/default/files/cms/publicaties/555030001.pdf.

116. Bond, A.J. and A. Morrison-Saunders, *Re-evaluating Sustainability Assessment: Aligning the vision and the practice.* Environmental Impact Assessment Review, 2011. **31**(1): p. 1-7.

117. Vaseashta, A., *Nanomaterials Nexus in Environmental, Human Health, and Sustainability*, in *Silicon Versus Carbon. NATO Science for Peace and Security Series B: Physics and Biophysics* 2009. p. 105-118.

118. Stone, V., et al., *Engineered Nanoparticles. Review of Health and Environmental Safety.* 2009, EU Joint Research Centre. Accessed on 22/09/2016 at: http://www.nanowerk.com/nanotechnology/reports/reportpdf/report133.pdf.

119. SCENIHR, *Risk Assessment of Products of Nanotechnologies*. 2009, Scientific Committee on Emerging and Newly Identified Health Risks. Accessed on 22/09/2016 at: http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_023.pdf.

120. FIOH, *Nanosafety in Europe 2015-2025. Towards Safe and Sustainable Nanomaterials and Nanotechnology Innovations*, K. Savolainen, et al., Editors. 2013, Finnish Institute of Occupational Health. Accessed on 22/09/2016 at: http://www.ttl.fi/en/publications/Electronic_publications/Nanosafety_in_europe_2015-2025/Documents/nanosafety_2015-2025.pdf.

121. Hristozov, D., et al., *Risk assessment of engineered nanomaterials: a review of available data and approaches from a regulatory perspective.* Nanotoxicology, 2012. **6**: p. 880-898.

122. Wittmaack, K., *In Search of the Most Relevant Parameter for Quantifying Lung Inflammatory Response to Nanoparticle Exposure: Particle Number, Surface Area, or What?* . Environmental Health Perspectives, 2007. **115**: p. 187–194.

123. Stoeger, T., et al., *Instillation of Six Different Ultrafine Carbon Particles Indicates Surface Area Threshold Dose for Acute Lung Inflammation in Mice.* Environmental Health Perspectives, 2006. **114**(3): p. 328-333.

124. Hunt, G., et al., *Towards a consensus view on understanding nanomaterials hazards and managing exposure: knowledge gaps and recommendations.* Materials, 2013. **6**(3): p. 1090-117.

125. Syberg, K. and S.F. Hansen, *Environmental risk assessment of chemicals and nanomaterials — The best foundation for regulatory decision-making?* Science of The Total Environment, 2016. **541**: p. 784-794.

126. OECD, *Important Issues on Risk Assessment of Manufactured Nanomaterials.* 2012: ENV/JM/MONO 8. Series on Safety of Manufactured Nanomaterials. Available at: http://www.oecd.org/science/nanosafety/publications-series-safety-manufactured-nanomaterials.htm.

127. Powers, C., et al., *Data dialogues: critical connections for designing and implementing future nanomaterial research.* Environment Systems and Decisions, 2014. **35**: p. 76-87.

128. Gottschalk, F., T. Sun, and B. Nowack, *Environmental concentrations of engineered nanomaterials: Review of modeling and analytical studies.* Environmental Pollution, 2013. **181**(0): p. 287-300.

129. OECD, *Co-Operation on Risk Assessment. Prioritisation of Important Issues on Risk Assessment of Manufactured Nanomaterials - Final Report*. 2013: ENV/JM/MONO 18. Series on Safety of Manufactured Nanomaterials. Available at: http://www.oecd.org/science/nanosafety/publications-series-safety-manufactured-nanomaterials.htm.

130. Nowack, B., et al., *The Flows of Engineered Nanomaterials from Production, Use, and Disposal to the Environment*. 2015, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 1-23.

131. Bergamaschi, E., *Occupational exposure to nanomaterials: present knowledge and future development.* Nanotoxicology 2009. **3**: p. 194-201.

132. Hansen, S., et al., *Categorization framework to aid exposure assessment of nanomaterials in consumer products.* Ecotoxicology, 2008. **17**: p. 438-447.

133. Powers, C.M., et al., *Applying comprehensive environmental assessment to research planning for multiwalled carbon nanotubes: Refinements to inform future stakeholder engagement.* Integrated Environmental Assessment and Management, 2015. **12**(1): p. 96-108.

134. Linkov, I., et al., *Risk-based standards: integrating top–down and bottom–up approaches.* Environment Systems and Decisions, 2014. **34**(1): p. 134-137.

135. Cornelissen, R., F. Jongeneelen, and F. Van Broekhuizen, *Guidance working safely with nanomaterials and products, the guide for employers and employees*. 2011: Accessed on 13/03/2016 at: http://www.industox.nl/Guidance on safe handling nanomats&products.pdf.

136. Höck, J., et al., *Guidelines on the Precautionary Matrix for Synthetic Nanomaterials*. 2013, Federal Office of Public Health and Federal Office for the Environment, Berne. Accessed on 22/09/2016 at: http://www.bag.admin.ch/nanotechnologie/12171/12174/index.html?lang=en.

137. Ostiguy, C., et al., *Development of a specific control banding tool for nanomaterials*. 2010, Expert committee (CES) on physical agents. French Agency for Food, Environmental, and Occupational Health and Safety. Accessed on 22/09/2016 at: https://www.etui.org/content/download/3554/40003/file/ANSES_2011_nano.pdf.

138. Zalk, D., S. Paik, and P. Swuste, *Evaluating the Control Banding Nanotool: a qualitative risk assessment method for controlling nanoparticle exposures.* Journal of Nanoparticle Research, 2009. **11**(7): p. 1685-1704.

139. Van Duuren-Stuurman, B., et al., *Stoffenmanager Nano Version 1.0: A Web-Based Tool for Risk Prioritization of Airborne Manufactured Nano Objects.* Annals of Occupational Hygiene, 2012. **56**(5): p. 525-541.

140. Bouillard, J. and A. Vignes, *Nano-Evaluris: an inhalation and explosion risk evaluation method for nanoparticle use. Part I: description of the methodology.* Journal of Nanoparticle Research, 2014. **16**(2): p. 1-29.

141. Arvidsson, R., et al., *Prospective Life Cycle Assessment of Graphene Production by Ultrasonication and Chemical Reduction.* Environmental Science & Technology, 2014. **48**(8): p. 4529-4536.

142. Chiueh, P.-T., et al., *Assessing the environmental impact of five Pd-based catalytic technologies in removing of nitrates.* Journal of Hazardous Materials, 2011. **192**(2): p. 837-845.

143. Bonton, A., et al., *Comparative life cycle assessment of water treatment plants.* Desalination, 2012. **284**(0): p. 42-54.

144. Pati, P., M. Sean, and P. Vikeseland, *Life Cycle Assessment of "Green" Nanoparticle Synthesis Methods.* Environmental Engineering Science, 2014. **31**(7): p. 410-420.

145. Pourzahedi, L. and M.J. Eckelman, *Comparative life cycle assessment of silver nanoparticle synthesis routes.* Environmental Science: Nano, 2015. **2**(4): p. 361-369.

146. Lloyd, S.M., L.B. Lave, and H.S. Matthews, *Life cycle benefits of using nanotechnology to stabilize platinum-group metal particles in automotive catalysts.* Environmental Science & Technology, 2005. **39**: p. 1384-1392.

147. Mergula, A.L., V. Khanna, and R.B. Bakshi. *Comparative life cycle assessment: Reinforcing wind turbines blades with carbon nanofibers.* in *Proceedings of the 2010 IEEE International Symposium on Sustainable Systems and Technology, ISSST, 17-19 May 2010*. 2010.

148. Moign, A., et al., *Life cycle assessment of using powder and liquid precursors in plasma spraying: The case of yttria-stabilized zirconia.* Surface and Coating Technology, 2010. **205**: p. 668-673.

149. Gavankar, S., S. Suh, and A.F. Keller, *Life cycle assessment at nanoscale: review and recommendations.* The International Journal of Life Cycle Assessment, 2012. **17**(3): p. 295-303.

150. OECD, *Guidance Manual towards the Integration of Risk Assessment into Life Cycle Assessment of Nano-Enabled Applications*. 2015: ENV/JM/MONO 30. Series on Safety of Manufactured Nanomaterials. Available at: http://www.oecd.org/science/nanosafety/publications-series-safety-manufactured-nanomaterials.htm.

151. Pourzahedi, L. and M.J. Eckelman, *Environmental Life Cycle Assessment of Nanosilver-Enabled Bandages.* Environmental Science & Technology, 2015. **49**(1): p. 361-368.

152. Seager, T. and I. Linkov, *Coupling Multicriteria Decision Analysis and Life Cycle Assessment for Nanomaterials.* Journal of Industrial Ecology 2008. **12**(3): p. 282-285.

153. Huang, I.B., J. Keisler, and I. Linkov, *Multi-criteria decision analysis in environmental sciences: ten years of applications and trends.* Science of the Total Environment, 2011. **409**(19): p. 3578-94.

154. Hristozov, D., et al., *A weight of evidence approach for hazard screening of engineered nanomaterials.* Nanotoxicology, 2014. **8**(1): p. 72-87.

155. Grieger, K., et al., *A relative ranking approach for nano-enabled applications to improve risk-based decision making: a case study of Army materiel.* Environment Systems and Decisions, 2015. **35**(1): p. 42-53.

156. Beaudrie, C.H., et al., *Nanomaterial risk screening: a structured approach to aid decision making under uncertainty.* Environment Systems and Decisions, 2015. **35**(1): p. 88-109.

157. Hristozov, D., et al., *Application of a quantitative weight of evidence approach for ranking and prioritization of occupational exposure scenarios for titanium dioxide and carbon nanomaterials.* Nanotoxicology, 2014. **8**(2): p. 117-131.

158. Tervonen, T., et al., *Risk-based classification system of nanomaterials.* Journal of Nanoparticle Research 2009. **11**: p. 757-766.

159. Hansen, S., K. Jensen, and A. Baun, *NanoRiskCat: a conceptual tool for categorization and communication of exposure potentials and hazards of nanomaterials in consumer products.* Journal of Nanoparticle Research, 2013. **16**(1): p. 1-25.

160. Linkov, I., et al., *Multi-criteria decision analysis and environmental risk assessment for nanomaterials. .* Journal of Nanoparticle Research 2007. **9**: p. 543-554.

161. Esawi, A.M.K. and M.M. Farag, *Carbon nanotube reinforced composites: Potential and current challenges.* Materials & Design, 2007. **28**(9): p. 2394-2401.

162. Yu, P. and J.H. Lee, *A hybrid approach using two-level SOM and combined AHP rating and AHP/DEA-AR method for selecting optimal promising emerging technology.* Expert Systems with Applications, 2013. **40**(1): p. 300-314.

163. Dabaghian, M.R., et al., *The best available technology for small electroplating plants applying analytical hierarchy process.* International Journal of Environmental Science & Technology, 2008. **5**(4): p. 479-484.

164. Velmurugan, R., S. Selvamuthukumar, and R. Manavalan, *Multi criteria decision making to select the suitable method for the preparation of nanoparticles using an analytical hierarchy process.* Pharmazie, 2011. **66**(11): p. 836-42.

165. Kunasekaran, V. and K. Krishnamoorthy, *Multi criteria decision making to select the best method for the preparation of solid lipid nanoparticles of rasagiline mesylate using analytic hierarchy process.* Journal of Advanced Pharmaceutical Technology & Research, 2014. **5**(3): p. 115-121.

166. Çalışkan, H., *Selection of boron based tribological hard coatings using multi-criteria decision making methods.* Materials & Design, 2013. **50**(0): p. 742-749.

167. Chen, Y.-W. and M. Larbani, *Two-person zero-sum game approach for fuzzy multiple attribute decision making problems.* Fuzzy Sets and Systems, 2006. **157**(1): p. 34-51.

168. Sudhakaran, S., S. Lattemann, and G.L. Amy, *Appropriate drinking water treatment processes for organic micropollutants removal based on experimental and model studies — A multi-criteria analysis study.* Science of The Total Environment, 2013. **442**(0): p. 478-488.

169. Tsang, M.P., et al., *Benefits and Risks of Emerging Technologies: Integrating Life Cycle Assessment and Decision Analysis To Assess Lumber Treatment Alternatives.* Environmental Science & Technology, 2014. **48**(19): p. 11543-11550.

170. Mohan, M., et al., *Integrating Legal Liabilities in Nanomanufacturing Risk Management.* Environmental Science & Technology, 2012. **46**(15): p. 7955-7962.

171. Canis, L., I. Linkov, and T.P. Seager, *Application of Stochastic Multiattribute Analysis to Assessment of Single Walled Carbon Nanotube Synthesis Processes.* Environmental Science & Technology, 2010. **44**(22): p. 8704-8711.

172. Ghazinoory, S., M. Daneshmand-Mehr, and A. Azadegan, *Technology selection: application of the PROMETHEE in determining preferences[mdash]a real case of nanotechnology in Iran.* Journal of Operational Research Society, 2013. **64**(6): p. 884-897.

173. Roy, B., *Decision Aiding: Major Actors and the Role of Models*, in *Multicriteria Methodology for Decision Aiding*. 1996, Kluwer Academic Publishers. p. 7-18.

174. Jacquet-Lagrèze, E. and Y. Siskos, *Preference disaggregation: 20 years of MCDA experience.* European Journal of Operational Research, 2001. **130**(2): p. 233-245.

175. Tsoukiàs, A., *On the concept of decision aiding process: an operational perspective.* Annals of Operations Research, 2007. **154**(1): p. 3-27.

176. Vincke, P., *Multicriteria Decision-Aid*. 1992, Chichester: John Wiley & Sons.

177. PROSUITE. *Prospective Sustainability Assessment of technologies*. EU FP7 Project 2012. Accessed on 13/03/2016 at: http://www.prosuite.org/web/guest/home;jsessionid=8CDED0B55445A5232942EF9AE6B1E2F0].

178. Benoit, V. and P. Rousseaux, *Aid for aggregating the impacts in life cycle assessment.* International Journal of Life Cycle Assessment, 2003. **8**(2): p. 74-82.

179. Guitouni, A. and J.M. Martel, *Tentative guidelines to help choosing an appropriate MCDA method.* European Journal of Operational Research, 1998. **109**(2): p. 501-521.

180. Herva, M. and E. Roca, *Review of combined approaches and multi-criteria analysis for corporate environmental evaluation.* Journal of Cleaner Production, 2013. **39**: p. 355-371.

181. Greco, S., B. Matarazzo, and R. Słowiński, *Axiomatic characterization of a general utility function and its particular cases in terms of conjoint measurement and rough-set decision rules.* European Journal of Operational Research, 2004. **158**(2): p. 271-292.

182. Słowiński, R., S. Greco, and B. Matarazzo, *Axiomatization of utility, outranking and decision preference models for multiple-criteria classification problems under partial inconsistency with the dominance principle* Control and Cybernetics, 2002. **31**(4): p. 1005-1035.

183. Keeney, L.R. and H. Raiffa, *Decisions with Multiple Objectives: Preferences and Value Tradeoffs*. 1976, New York: Wiley.

184. Roy, B., *The outranking approach and the foundations of electre methods.* Theory and Decision, 1991(31): p. 49-73.

185. Greco, S., B. Matarazzo, and R. Słowiński, *Rough sets theory for multicriteria decision analysis.* European Journal of Operational Research, 2001. **129**(1): p. 1-47.

186. Wang, J.-J., et al., *Review on multi-criteria decision analysis aid in sustainable energy decision-making.* Renewable and Sustainable Energy Reviews, 2009. **13**(9): p. 2263-2278.

187. Linkov, I., et al., *For nanotechnology decisions, use decision analysis.* Nano Today, 2013. **8**(1): p. 5-10.

188. Govindan, K. and M.B. Jepsen, *ELECTRE: A comprehensive literature review on methodologies and applications.* European Journal of Operational Research, 2016. **250**(1): p. 1-29.

189. Razmak, J. and B. Aouni, *Decision Support System and Multi-Criteria Decision Aid: A State of the Art and Perspectives.* Journal of Multi-Criteria Decision Analysis, 2015. **22**(1-2): p. 101-117.

190. Pohekar, S.D. and M. Ramachandran, *Application of multi-criteria decision making to sustainable energy planning—A review.* Renewable and Sustainable Energy Reviews, 2004. **8**(4): p. 365-381.

191. Sadok, W., et al., *Ex ante assessment of the sustainability of alternative cropping systems: implications for using multi-criteria decision-aid methods. A review.* Agronomy for Sustainable Development, 2008. **28**(1): p. 163-174.

192. Sadok, W., et al., *MASC, a qualitative multi-attribute decision model for ex ante assessment of the sustainability of cropping systems.* Agronomy for Sustainable Development, 2009. **29**(3): p. 447-461.

193. Abastante, F., et al., *Addressing the Location of Undesirable Facilities through the Dominance-based Rough Set Approach.* Journal of Multi-Criteria Decision Analysis, 2013. **21**(1-2): p. 3-23.

194. Pałkowski, Ł., et al., *Antimicrobial Activity and SAR Study of New Gemini Imidazolium-Based Chlorides.* Chemical Biology & Drug Design, 2014. **83**(3): p. 278-288.

195. Boggia, A., et al., *Assessing Rural Sustainable Development potentialities using a Dominance-based Rough Set Approach.* Journal of Environmental Management, 2014. **144**: p. 160-167.

196. Zaras, K., J.-C. Marin, and B. Boudreau-Trude, *Dominance-Based Rough Set Approach in Selection of Portfolio of Sustainable Development Projects.* American Journal of Operations Research, 2012. **2**(4): p. 502-508.

197. Abastante, F., et al., *A Dominance-based Rough Set Approach Model for Selecting the Location for a Municipal Solid Waste Plant.* GEAM. GEOINGEGNERIA AMBIENTALE E MINERARIA, 2012. **137**(3): p. 43-54.

198. Keeney, L.R. and H. Raiffa, *Decisions with Multiple Objectives: Preferences and Value Tradeoffs*. 1993: Cambridge University Press.

199. Dillon, J.L. and C. Perry, *Multiattribute utility theory, multiple objectives and uncertainty in ex ante project evaluation.* Review of marketing and agricultural economics, 1977. **45**(1,2): p. 3-27.

200. De Montis, A., et al., *Assessing the quality of different MCDA methods*, in *Alternatives for Environmental Valuation*, M. Getzner, C. Spash, and S. Stagl, Editors. 2005, Routledge: Abingdon. p. 99-133.

201. Saaty, T.L., *The Analytic Hierarchy Process*. 1980, New York: McGraw-Hill.

202. Saaty, T.L., *The analytic hierarchy and analytic network processes for the measurement of intangible criteria and for decision-making*, in *Multi Criteria Decision Analysis: State of the Art Surveys*, J. Figueira, S. Greco, and M. Ehrgott, Editors. 2005, Springer: New York.

203. Figueira, J., V. Mousseau, and B. Roy, *ELECTRE methods*, in *Multi Criteria Decision Analysis: State of the Art Surveys*, J. Figueira, S. Greco, and M. Ehrgott, Editors. 2005, Springer: New York. p. 133-162.

204. Brans, J.P. and B. Mareschal, *PROMETHEE METHODS*, in *Multi Criteria Decision Analysis: State of the Art Surveys*, J. Figueira, S. Greco, and M. Ehrgott, Editors. 2005, Springer: New York. p. 163-186.

205. Brans, J.P., P. Vincke, and B. Mareschal, *How to select and how to rank projects. The PROMETHEE method.* European Journal of Operational Research, 1986. **24**: p. 228-238.

206. Behzadian, M., et al., *PROMETHEE: A comprehensive literature review on methodologies and applications.* European Journal of Operational Research, 2010. **200**(1): p. 198-215.

207. Greco, S., B. Matarazzo, and R. Słowiński, *A New Rough Set Approach to Evaluation of Bankruptcy Risk*, in *Operational Tools in the Management of Financial Risks*, C. Zopounidis, Editor. 1998, Springer US. p. 121-136.

208. Greco, S., B. Matarazzo, and R. Słowiński, *The Use of Rough Sets and Fuzzy Sets in MCDM*, in *Multicriteria Decision Making*, T. Gal, T. Stewart, and T. Hanne, Editors. 1999, Springer US. p. 397-455.

209. Słowiński, R., S. Greco, and B. Matarazzo, *Rough Sets in Decision Making*, in *Encyclopedia of Complexity and Systems Science*, A.R. Meyers, Editor. 2009, Springer New York: New York, NY. p. 7753-7787.

210. Roy, B. and R. Słowiński, *Questions guiding the choice of a multicriteria decision aiding method.* EURO Journal on Decision Processes, 2013. **1**(1-2): p. 69-97.

211. Augeri, M.G., et al., *Dominance-Based Rough Set Approach to Budget Allocation in Highway Maintenance Activities.* Journal of Infrastructure Systems, 2011. **17**(2): p. 75-85.

212. Greco, S., B. Matarazzo, and R. Słowiński, *Decision Rule Approach*, in *Multi Criteria Decision Analysis: State of the Art Surveys*, J. Figueira, S. Greco, and M. Ehrgott, Editors. 2005, Springer: New York. p. 507-555.

213. Dias, L.C. and V. Mousseau, *Inferring Electre's veto-related parameters from outranking examples.* European Journal of Operational Research, 2006. **170**(1): p. 172-191.

214. Colomb, B., et al., *Stockless organic farming: strengths and weaknesses evidenced by a multicriteria sustainability assessment model.* Agronomy for Sustainable Development, 2012. **33**(3): p. 593-608.

215. Stubelj Ars, M. and M. Bohanec, *Towards the ecotourism: a decision support model for the assessment of sustainability of mountain huts in the Alps.* J Environ Manage, 2010. **91**(12): p. 2554-64.

216. Bohanec, M., et al., *A qualitative multi-attribute model for economic and ecological assessment of genetically modified crops.* Ecological Modelling, 2008. **215**(1-3): p. 247-261.

217. Zheng, J., et al., *Learning criteria weights of an optimistic Electre Tri sorting rule.* Computers & Operations Research, 2014. **49**: p. 28-40.

218. Dias, L.C., et al., *An aggregation/disaggregation approach to obtain robust conclusions with ELECTRE TRI.* European Journal of Operational Research, 2002. **138**(2): p. 332-348.

219. Słowiński, R., S. Greco, and B. Matarazzo, *Rough set and rule-based multicriteria decision aiding.* Pesquisa Operacional, 2012. **32**(2): p. 213-270.

220. Zheng, J., *Preference Elicitation for Aggregation Models based on Reference Points: Algorithms and Procedures*. 2012, Ph.D. Thesis. Laboratoire Génie Industriel, Ecole Centrale Paris. Accessed on 22/09/2016 at: https://tel.archives-ouvertes.fr/tel-00740655/document.

221. Figueira, J.R., S. Greco, and R. Słowiński, *Building a set of additive value functions representing a reference preorder and intensities of preference: GRIP method.* European Journal of Operational Research, 2009. **195**(2): p. 460-486.

222. Greco, S., V. Mousseau, and R. Słowiński, *Ordinal regression revisited: Multiple criteria ranking using a set of additive value functions.* European Journal of Operational Research, 2008. **191**(2): p. 416-436.

223. Munda, G., P. Nijkamp, and P. Rietveld, *Qualitative multicriteria evaluation for environmental management.* Ecological Economics, 1994. **10**(2): p. 97-112.

224. Linkov, I. and T.P. Seager, *Coupling Multi-Criteria Decision Analysis, Life-Cycle Assessment, and Risk Assessment for Emerging Threats.* . Environmental Science & Technology, 2011. **45**: p. 5068-5074.

225. Yatsalo, B.I., et al., *Application of Multicriteria Decision Analysis Tools to Two Contaminated Sediment Case Studies.* Integrated Environmental Assessment and Management, 2007. **3**(2): p. 223-233.

226. Cinelli, M., et al., *A green chemistry-based classification model for the synthesis of silver nanoparticles.* Green Chemistry, 2015. **17**: p. 2825-2839.

227. Omann, I., *Multi-Criteria Decision Aid as an Approach for Sustainable Development Analysis and Implementation*. 2004, Ph.D. Thesis. University of Graz.

228. Buchholz, T., et al., *Multi Criteria Analysis for bioenergy systems assessments.* Energy Policy, 2009. **37**(2): p. 484-495.

229. Akadiri, P.O., P.O. Olomolaiye, and E.A. Chinyio, *Multi-criteria evaluation model for the selection of sustainable materials for building projects.* Automation in Construction, 2013. **30**(2): p. 113-125.

230. Huang, C.-C. and H.-W. Ma, *A multidimensional environmental evaluation of packaging materials.* Science of The Total Environment, 2004. **324**: p. 161-172.

231. Dhouib, D. and S. Elloumi, *A new multi-criteria approach dealing with dependent and heterogeneous criteria for end-of-life product strategy.* Applied Mathematics and Computation, 2011. **218**(5): p. 1668-1681.

232. Ghadimi, P., et al., *A weighted fuzzy approach for product sustainability assessment: a case study in automotive industry.* Journal of Cleaner Production, 2012. **33**(0): p. 10-21.

233. Herva, M., et al., *Application of fuzzy logic for the integration of environmental criteria in ecodesign.* Expert Systems with Applications, 2012. **39**(4): p. 4427-4431.

234. Remery, M., C. Mascle, and B. Agard, *A new method for evaluating the best product end-of-life strategy during the early design phase.* Journal of Engineering Design, 2011. **23**(6): p. 419-441.

235. Khan, F.I., R. Sadiq, and B. Veitch, *Life cycle iNdeX (LInX): a new indexing procedure for process and product design and decision-making.* Journal of Cleaner Production, 2004. **12**(1): p. 59-76.

236. Chiou, H.-K. and G.-H. Tzeng, *Fuzzy Multiple-Criteria Decision-Making Approach for Industrial Green Engineering.* Environmental Management, 2002. **30**(6): p. 0816-0830.

237. Malloy, T.F., et al., *Use of multi-criteria decision analysis in regulatory alternatives analysis: A case study of lead free solder.* Integrated Environmental Assessment and Management, 2013. **9**(4): p. 652-664.

238. Teghem, J., C. Delhaye, and P.L. Kunsch, *An interactive decision support system for multicriteria decision aid.* Mathematical and Computer Modelling, 1989. **12**(10-11): p. 1311-1320.

239. Munda, G., *The Issue of Consistency: Basic Discrete Multi-Criteria "Methods"*, in *Social Multi-Criteria Evaluation for a Sustainable Economy*. 2008, Springer Berlin Heidelberg: Berlin. p. 85-109.

240. Bockstaller, C., et al., *Comparison of methods to assess the sustainability of agricultural systems. A review.* Agronomy for Sustainable Development, 2009. **29**(1): p. 223-235.

241. Reuters, T. *Web of Science*. 2015.

242. Belton, V. and T.J. Stewart, *Outranking methods*, in *Multiple criteria decision analysis; an integrated approach*. 2002, Kluwer Academic Publisher. p. 233-260.

243. Munda, G. and M. Nardo, *Constructing Consistent Composite Indicators: the Issue of Weights* 2005, Institute for the Protection and Security of the Citizen. p. 1-12.

244. Belton, V. and T.J. Stewart, *Preference modelling*, in *Multiple criteria decision analysis; an integrated approach*. 2002, Kluwer Academic Publisher. p. 79-118.

245. Mendoza, G.A. and H. Martins, *Multi-criteria decision analysis in natural resource management: A critical review of methods and new modelling paradigms.* Forest Ecology and Management, 2006. **230**(1-3): p. 1-22.

246. Danielson, M., et al., *Using a Software Tool for Public Decision Analysis: The Case of Nacka Municipality.* Decision Analysis, 2007. **4**(2): p. 76-90.

247. De Montis, A., et al., *Criteria for quality assessment of MCDA methods*, in *3rd Biennial Conference of the European Society for Ecological Economics*. 2000: Vienna.

248. Raju, K.S. and C.R.S. Pillai, *Multicriterion decision making in performance evaluation of an irrigation system.* European Journal of Operational Research, 1999. **3**(1): p. 479–488.

249. InfoHarvest. *Criterium Decision Plus 3.0*. 2016. Accessed on 11/03/2016 at: http://www.infoharvest.com/ihroot/index.asp].

250. Merad, M., et al., *Using a multi-criteria decision aid methodology to implement sustainable development principles within an organization.* European Journal of Operational Research, 2013. **224**(3): p. 603-613.

251. Geldermann, J. and K. Zhang, *Software review: "Decision Lab 2000".* Journal of Multi-Criteria Decision Analysis, 2001. **10**(6): p. 317-323.

252. Fernandez, A., *Software review: Expert choice.* OM/MS Today, 1996. **23**: p. 80-83.

253. Greco, S., B. Matarazzo, and R. Słowiński, *Rough Set Approach to Decisions under Risk*, in *Rough Sets and Current Trends in Computing*, W. Ziarko and Y. Yao, Editors. 2001, Springer Berlin Heidelberg. p. 160-169.

254. Dembczyński, K., S. Greco, and R. Słowiński, *Rough set approach to multiple criteria classification with imprecise evaluations and assignments.* European Journal of Operational Research, 2009. **198**(2): p. 626-636.

255. Błaszczyński, J., et al., *jMAF - Dominance-Based Rough Set Data Analysis Framework*, in *Rough Sets and Intelligent Systems - Professor Zdzisław Pawlak in Memoriam*, A. Skowron and Z. Suraj, Editors. 2013, Springer Berlin Heidelberg. p. 185-209.

256. Szeląg, M., et al., *jRank - Ranking using Dominance-based Rough Set Approach*, in *Research Report RA-07/10*. 2013, Poznan University of Technology.

257. Słowiński, R. and J. Błaszczyński. *JMAF software*. 2016. Accessed on 14/03/2016 at: http://idss.cs.put.poznan.pl/site/142.html].

258. Słowiński, R. and M. Szeląg. *JRank software*. 2016.

259. Tervonen, T., *JSMAA: open source software for SMAA computations.* International Journal of Systems Science, 2014. **45**(1): p. 69-81.

260. Tylock, S.M., et al., *Energy management under policy and technology uncertainty.* Energy Policy, 2012. **47**(0): p. 156-163.

261. Prado-Lopez, V., et al., *Stochastic multi-attribute analysis (SMAA) as an interpretation method for comparative life-cycle assessment (LCA).* The International Journal of Life Cycle Assessment, 2014. **19**(2): p. 405-416.

262. Weistroffer, H.R., C.H. Smith, and S.C. Narula, *Multi Criteria Decision Support Software*, in *Multi Criteria Decision Analysis: State of the Art Surveys*, J. Figueira, S. Greco, and M. Ehrgott, Editors. 2005, Springer: New York. p. 989-1009.

263. Le Teno, J.F. and B. Mareschal, *An interval version of PROMETHEE for the comparison of building products' design with ill-defined data on environmental quality.* European Journal of Operational Research, 1998. **109**: p. 522-529.

264. De Keyser, W. and P. Peeters, *A note on the use of PROMETHEE multicriteria methods.* European Journal of Operational Research, 1996. **89**: p. 457-461.

265. Meyer, P. and S. Bigaret, *Diviz: A software for modeling, processing and sharing algorithmic workflows in MCDA.* Intelligent Decision Technologies, 2012. **6**(4): p. 283-296.

266. Dias, L.C. and J.N. Climaco, *Additive Aggregation with Variable Interdependent Parameters: The VIP Analysis Software.* The Journal of the Operational Research Society, 2000. **51**(9): p. 1070-1082.

267. Kadziński, M., R. Słowiński, and S. Greco, *Robustness analysis for decision under uncertainty with rule-based preference model.* Information Sciences, 2016. **328**: p. 321-339.

268. Figueira, J. and B. Roy, *A note on the paper, "Ranking irregularities when evaluating alternatives by using some ELECTRE methods", by Wang and Triantaphyllou, Omega (2008).* Omega, 2009. **37**(3): p. 731-733.

269. Mareschal, B., Y. De Smet, and P. Nemery, *Rank Reversal in the PROMETHEE II Method. Some New Results*, in *International Conference on Industrial Engineering and Engineering Management*. 2008: Singapore, December 8-11.

270. Roland, J., Y. De Smet, and C. Verly. *Rank Reversal as a Source of Uncertainty and Manipulation in the PROMETHEE II Ranking. A First Investigation*. in *14th International Conference on Information Processing and Management of Uncertainty in Knowledge-Based Systems*. 2012. Catania, Italy, July 9-13, 2012.

271. Wang, X. and E. Triantaphyllou, *Ranking irregularities when evaluating alternatives by using some ELECTRE methods.* Omega, 2008. **36**(1): p. 45-63.

272. Zopounidis, C. and M. Doumpos, *Multicriteria classification and sorting methods: A literature review.* European Journal of Operational Research, 2002. **138**(2): p. 229-246.

273. Maleki, H. and S. Zahir, *A Comprehensive Literature Review of the Rank Reversal Phenomenon in the Analytic Hierarchy Process.* Journal of Multi-Criteria Decision Analysis, 2013. **20**(3-4): p. 141-155.

274. Saaty, T.L., *An Exposition on the AHP in Reply to the Paper "Remarks on the Analytic Hierarchy Process".* Management Science, 1990. **36**(3): p. 259-268.

275. Haerer, W., *Software review: Criterium Decision Plus 3.0.* OR/MS Today, 2000. **27**(1).

276. LAMSADE. *ELECTRE software*. 2016. Accessed on 11/03/2016 at: http://www.lamsade.dauphine.fr/spip.php?rubrique64&lang=en].

277. Hokkanen, J. and P. Salminen, *Locating a Waste Treatment Facility byMulticriteria Analysis.* journal of Multi-Criteria Decision Analysis, 1997. **6**: p. 175-184.

278. Khalili, N.R. and S. Duecker, *Application of multi-criteria decision analysis in design of sustainable environmental management system framework.* Journal of Cleaner Production, 2013. **47**: p. 188-198.

279. De Smet, Y. *D-SIGHT*. 2016. Accessed on 11/03/2016 at: http://www.d-sight.com].

280. Mareschal, B. *PROMETHEE-GAIA*. 2016. Accessed on 11/03/2016 at: http://www.promethee-gaia.net/software.html].

281. Keeney, L.R. and E.F. Wood, *An illustrative example of the use of multiattribute utility theory for water resource planning.* Water resources research, 1977. **13**(4): p. 705-712.

282. van der Werf, H.M.G. and J. Petit, *Evaluation of the environmental impact of agriculture at the farm level: a comparison and analysis of 12 indicator-based methods.* Agriculture, Ecosystems & Environment, 2002. **93**(1–3): p. 131-145.

283. Akadiri, P.O. and P.O. Olomolaiye, *Development of sustainable assessment criteria for building materials selection.* Engineering, Construction and Architectural Management, 2012. **19**(6): p. 666-687.

284. Gibson, R.B., et al., *Specification of sustainability based environmental assessment decision criteria and implications for determining "significance" in environmental assessment*, in *Research and Development Monograph Series*. 2001, Canadian Environmental Assessment Agency. Accessed on 22/09/2016 at: http://static.twoday.net/NE1BOKU0607/files/Gibson_Sustainability-EA.pdf.

285. Hoffman, R.R. and G. Lintern, *Eliciting and representing the knowledge of experts*, in *Cambridge handbook of expertise and expert performance*, K.A. Ericsson, et al., Editors. 2006, Cambridge University Press: New York. p. 203-222.

286. Ford, D.N. and J.D. Sterman, *Expert knowledge elicitation to improve formal and mental models.* System Dynamics Review, 1998. **14**(4): p. 309-340.

287. Hoffman, R.R., B. Crandall, and N. Shadbolt, *Use of the Critical Decision Method to Elicit Expert Knowledge: A Case Study in the Methodology of Cognitive Task Analysis.* Human Factors, 1998. **40**(2): p. 254-276.

288. Hoffman, R.R., et al., *Eliciting Knowledge from Experts: A Methodological Analysis.* Organizational Behavior and Human Decision Processes, 1995. **62**(2): p. 129-158.

289. Burton, A.M., et al., *The efficacy of knowledge elicitation techniques: a comparison across domains and levels of expertise.* Knowledge Acquisition, 1990. **2**(2): p. 167-178.

290. Hoffman, R.R., *The Problem of Extracting the Knowledge of Experts from the Perspective of Experimental Psychology.* AI Applications, 1987. **1**(2): p. 35-48.

291. Creswell, W.J., *Quantitative methods*, in *Research Design. Qualitative, Quantitative, and Mixed Methods Approaches. 4th Edition*. 2014, SAGE Publications. p. 155-182.

292. Bourque, L.B. and E.P. Fielder, *How to Conduct Self-Administered and Mail Surveys*. The Survey Kit 3. 1995: SAGE Publications.

293. Amer, M. and T. Daim, *Expert Judgment Quantification*, in *Research and Technology Management in the Electricity Industry*, D. Tugrul, O. Terry, and K. Jisun, Editors. 2013, Springer-Verlag: London. p. 31-65.

294. Choi, J.Y. and G. Ramachandran, *Review of the OSHA Framework for Oversight of Occupational Environments.* The Journal of law, medicine & ethics, 2009. **37**(4): p. 633-650.

295. Berube, D., et al., *Characteristics and classification of nanoparticles: Expert Delphi survey.* Nanotoxicology, 2011. **5**(2): p. 236-243.

296. Besley, J.C., V.L. Kramer, and S.H. Priest, *Expert opinion on nanotechnology: risks, benefits, and regulation.* Journal of Nanoparticle Research, 2007. **10**(4): p. 549-558.

297. Basto, M. and J.M. Pereira, *An SPSS R-Menu for Ordinal Factor Analysis.* Journal of Statistical Software, 2012. **46**(4): p. 1-29.

298. Siegel, S. and N.J.J. Castellan, *Choosing an Appropriate Statistical Test*, in *Nonparametric Statistics for the Behavioral Sciences*. 1988, McGraw-Hill International Editions: Sydney. p. 6-18.

299. Braimah, N. and I. Ndekugri, *Consultants' Perceptions on Construction Delay Analysis Methodologies.* Journal of Construction Engineering and Management, 2009. **135**(12): p. 1279-1288.

300. Siegel, S. and N.J.J. Castellan, *Non Parametric Statistics for the Behavioral Sciences*. Statistics Series. 1988, Sydney: McGraw-Hill International Editions.

301. Sarantakos, S., *A Toolkit for Quantitative Data Analysis Using SPSS*. 2007: Palgrave Macmillan.

302. Field, A.P., *Non-parametric tests*, in *Discovering statistics using IBM SPSS Statistics (and sex and drugs and rock 'n' roll), 3rd Edition*. 2011, Sage publications: London. p. 539-583.

303. Furr, M.R., *Scale Construction and Psychometrics for Social and Personality Psychology*. 2011: SAGE Publications.

304. Litwin, M.S., *How to measure survey reliabiliy and validity*. 1995: SAGE Publications.

305. Zumbo, B.D., A.M. Gadermann, and C. Zeisser, *Ordinal Versions of Coefficients Alpha and Theta For Likert Rating Scales.* Journal of Modern Applied Statistical Methods, 2007. **6**: p. 21-29.

306. Gadermann, A.M., M. Guhn, and B.D. Zumbo, *Estimating ordinal reliability for Likert-type and ordinal item response data. A conceptual, empirical and practical guide.* Practical Assessment, Research & Evaluation, 2012. **17**(3): p. 1-13.

307. Garson, G.D., *Scales and Measures*. 2013, Asheboro, NC: Statistical Associates Publishers.

308. Pallant, J., *SPSS Survival Manual. A step by step guide to data analysis using SPSS - 4th edition*. 2011: McGraw-Hill.

309. Oppenheim, A.N., *Questionnaire Design, Interviewing and Attitude Measurement*. 1992: Pinter Publications.

310. Chinyio, E., P. Olomolaiye, and P. Corbett, *Quantification of Construction Clients' Needs through Paired Comparisons.* Journal of Management in Engineering, 1998. **14**(1): p. 87-92.

311. Buckingham, A. and P. Saunders, *The Survey Methods Workbook: From Design to Analysis*. 2004: Polity.

312. Babbie, E., et al., *Measures of Association for Nominal and Ordinal Variables*, in *Adventures in Social Research: Data Analysis Using IBM SPSS Statistics, 8th Edition*. 2013, SAGE Publications. p. 219-246.

313. Meyers, L.S., G.C. Gamst, and A.J. Guarino, *Reliability Analysis: Assessing Rater Consistency*, in *Performing Data Analysis Using IBM SPSS*. 2013, John Wiley & Sons. p. 319-329.

314. Meyers, L.S., G.C. Gamst, and A.J. Guarino, *Reliability Analysis: Internal Consistency*, in *Performing Data Analysis Using IBM SPSS*. 2013, John Wiley & Sons. p. 311-318.

315. Pallant, J., *Checking the reliability of a scale*, in *SPSS Survival Manual. A step by step guide to data analysis using SPSS - 4th edition*. 2011, McGraw-Hill. p. 97-101.

316. Komanduri, R., et al. *NSF-EC workshop on nanomanufacturing and processing: a summary report*. in *Nano- and Microtechnology: Materials, Processes, Packaging, and Systems, 446 (November 1, 2002); doi:10.1117/12.484270*. 2002.

317. van Lente, H. and J.I. van Til, *Articulation of sustainability in the emerging field of nanocoatings.* Journal of Cleaner Production, 2008. **16**(8-9): p. 967-976.

318. Hohenthal, C., et al., *Final assessment of nano enhanced new products*. 2012, Accessed on October 1, 2015 at: http://sunpap.vtt.fi/pdf/SUNPAP_WP2_DEL2_5_20121031_VTT.pdf: SUNPAP project.

319. Spence, K.L., et al., *A comparative study of energy consumption and physical properties of microfibrillated cellulose produced by different processing methods.* Cellulose, 2011. **18**(4): p. 1097-1111.

320. Jonoobi, M., A.P. Mathew, and K. Oksman, *Producing low-cost cellulose nanofiber from sludge as new source of raw materials.* Industrial Crops and Products, 2012. **40**: p. 232-238.

321. Oksman, K., et al., *Cellulose nanowhiskers separated from a bio-residue from wood bioethanol production.* Biomass & Bioenergy, 2011. **35**(1): p. 146-152.

322. Leistritz, F.L., et al., *Preliminary Feasibility Analysis for an integrated biomaterials and ethanol biorefinery using wheat straw feedstock*. 2006, Agribusiness & Applied Economics Report No. 590. Accessed on 22/09/2016: http://ageconsearch.umn.edu/bitstream/23500/1/aer590.pdf.

323. Leistritz, F.L., et al., *Use of Agricultural Residue Feedstock In North Dakota Biorefineries* Journal of Agribusiness, 2009. **27**: p. 17-32.

324. Duran, N., et al., *A minireview of cellulose nanocrystals and its potential integration as co-product in bioethanol production.* Journal of the Chilean Chemical Society, 2011. **56**: p. 672-677.

325. Busnaina, A., et al., *Nanomanufacturing and sustainability: opportunities and challenges.* Journal of Nanoparticle Research, 2013. **15**(10): p. 1-6.

326. Chiota, J., et al., *Multiscale Directed Assembly of Polymer Blends Using Chemically Functionalized Nanoscale-Patterned Templates.* Small, 2009. **5**(24): p. 2788-2791.

327. Makaram, P., et al., *Scalable nanotemplate assisted directed assembly of single walled carbon nanotubes for nanoscale devices.* Applied Physics Letters, 2007. **90**(243108): p. 1-3.

328. Dalton-Brown, S., *Global Ethics and Nanotechnology: A Comparison of the Nanoethics Environments of the EU and China.* NanoEthics, 2012. **6**(2): p. 137-150.

329. Furr, M.R., *Evaluating Psychometric Properties: Dimensionality and Reliability*, in *Scale Construction and Psychometrics for Social and Personality Psychology*. 2011, SAGE Publications. p. 25-51.

330. Robichaud, C.O., et al., *Relative Risk Analysis of Several Manufactured Nanomaterials- An Insurance Industry Context.* Environmental Science & Technology, 2005. **39**(22): p. 8985-8984.

331. Theis, T.L., et al., *A life cycle framework for the investigation of environmentally benign nanoparticles and products.* physica status solidi (RRL) - Rapid Research Letters, 2011. **5**(9): p. 312-317.

332. Dahlben, L.J., et al., *Environmental Life Cycle Assessment of a Carbon Nanotube-Enabled Semiconductor Device.* Environmental Science & Technology, 2013. **47**(15): p. 8471-8478.

333. Nyström, A.M. and B. Fadeel, *Safety assessment of nanomaterials: Implications for nanomedicine.* Journal of Controlled Release, 2012. **161**(2): p. 403-408.

334. OECD, *Ecotoxicology and Environmental Fate of Manufactured Nanomaterials: Test Guidelines*. 2014: ENV/JM/MONO(2014)1. Series on Safety of Manufactured Nanomaterials. Available at: http://www.oecd.org/science/nanosafety/publications-series-safety-manufactured-nanomaterials.htm.

335. Gilbertson, L.M., et al., *Coordinating modeling and experimental research of engineered nanomaterials to improve life cycle assessment studies.* Environmental Science: Nano, 2015. **2**: p. 669-682.

336. Baun, A., et al., *Ecotoxicity of engineered nanoparticles to aquatic invertebrates: a brief review and recommendations for future toxicity testing.* Ecotoxicology, 2008. **17**(5): p. 387-395.

337. Hou, W.-C., P. Westerhoff, and J.D. Posner, *Biological accumulation of engineered nanomaterials: a review of current knowledge.* Environmental Science: Processes & Impacts, 2013. **15**(1): p. 103-122.

338. Schreiner, K.M., et al., *White-Rot Basidiomycete-Mediated Decomposition of C60 Fullerol.* Environmental Science & Technology, 2009. **43**(9): p. 3162-3168.

339. Allen, B.L., et al., *Biodegradation of Single-Walled Carbon Nanotubes through Enzymatic Catalysis.* Nano Letters, 2008. **8**(11): p. 3899-3903.

340. Petersen, E.J., et al., *Adapting OECD Aquatic Toxicity Tests for Use with Manufactured Nanomaterials: Key Issues and Consensus Recommendations.* Environmental Science & Technology, 2015. **49**(16): p. 9532-9547.

341. OECD, *Report of the OECD expert meeting on the physical chemical properties of manufactured nanomaterials and test guidelines*. 2014: ENV/JM/MONO 15. Series on Safety of Manufactured Nanomaterials. Available at: http://www.oecd.org/science/nanosafety/publications-series-safety-manufactured-nanomaterials.htm.

342. Upadhyayula, V.K.K., et al., *Life cycle assessment as a tool to enhance the environmental performance of carbon nanotube products: a review.* Journal of Cleaner Production, 2012. **26**(0): p. 37-47.

343. Wiesner, M.R., et al., *Decreasing Uncertainties in Assessing Environmental Exposure, Risk, and Ecological Implications of Nanomaterials.* Environmental Science & Technology, 2009. **43**(17): p. 6458-6462.

344. OECD, *Preliminary Review of OECD Test Guidelines for their Applicability to Manufactured Nanomaterials*. 2009: ENV/JM/MONO 21. Series on Safety of Manufactured Nanomaterials. Available at: http://www.oecd.org/science/nanosafety/publications-series-safety-manufactured-nanomaterials.htm.

345. Kennedy, A.J., et al., *Gaining a Critical Mass: A Dose Metric Conversion Case Study Using Silver Nanoparticles.* Environmental Science & Technology, 2015. **49**(20): p. 12490-12499.

346. Godwin, H., et al., *Nanomaterial Categorization for Assessing Risk Potential To Facilitate Regulatory Decision-Making.* ACS Nano, 2015. **9**(4): p. 3409-3417.

347. ECHA, *Human health and environmental exposure assessment and risk characterisation of nanomaterials - Best practice for REACH registrants*. 2014, European Chemicals Agency. Accessed on 22/09/2016 at: https://echa.europa.eu/documents/10162/5399565/best_practices_human_health_environment_nano_3rd_en.pdf.

348. REACH, *Implementation Project on Nanomaterials: Specific Advice on Exposure Assessment and Hazard/Risk Characterisation for Nanomaterials under REACH (RIPoN 3)* http://ec.europa.eu/environment/chemicals/nanotech/pdf/report_ripon3.pdf, Editor. 2011.

349. Brouwer, D., et al., *Harmonization of Measurement Strategies for Exposure to Manufactured Nano-Objects; Report of a Workshop.* Annals Occupational Hygiene, 2012. **56**(1): p. 1-9.

350. OECD, *Report of an OECD Workshop on Exposure Assessment and Exposure Mitigation: Manufactured Nanomaterials*. 2009: ENV/JM/MONO18. Series on Safety of Manufactured Nanomaterials. Available at: http://www.oecd.org/science/nanosafety/publications-series-safety-manufactured-nanomaterials.htm.

351. OECD, *Compilation and Comparison of Guidelines Related to Exposure to Nanomaterials in Laboratories*. 2010: ENV/JM/MONO47. Series on Safety of Manufactured Nanomaterials. Available at: http://www.oecd.org/science/nanosafety/publications-series-safety-manufactured-nanomaterials.htm.

352. OECD, *Harmonized Tiered Approach to Measure and Assess the Potential Exposure to Airborne Emissions of Engineered Nano-Objects and their Agglomerates and Aggregates at Workplaces*. 2015: ENV/JM/MONO 19. Series on Safety of Manufactured Nanomaterials. Available at: http://www.oecd.org/science/nanosafety/publications-series-safety-manufactured-nanomaterials.htm.

353. OECD, *Guidance on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials*. 2012: ENV/JM/MONO 40. Series on Safety of Manufactured Nanomaterials. Available at: http://www.oecd.org/science/nanosafety/publications-series-safety-manufactured-nanomaterials.htm.

354. Braakhuis, H.M., et al., *Physicochemical characteristics of nanomaterials that affect pulmonary inflammation.* Particle and Fibre Toxicology, 2014. **11**(18): p. 1-25.

355. OECD, *List of Manufactured Nanomaterials and List of Endpoints for Phase One of the Sponsorship Programme for the Testing of Manufactured Nanomaterials: Revision*. 2010: ENV/JM/MONO 46. Series on Safety of Manufactured Nanomaterials. Available at: http://www.oecd.org/science/nanosafety/publications-series-safety-manufactured-nanomaterials.htm.

356. Albanese, A., P.S. Tang, and W.C.W. Chan, *The Effect of Nanoparticle Size, Shape, and Surface Chemistry on Biological Systems.* Annual Review of Biomedical Engineering, 2012. **14**(1): p. 1-16.

357. Kendall M. and H. S., *Health impact and toxicological effects of nanomaterials in the lung.* Respirology, 2012. **17**(743-758).

358. Zhang, J., et al., *Impacts of a Nanosized Ceria Additive on Diesel Engine Emissions of Particulate and Gaseous Pollutants.* Environmental Science &Technology, 2013. **47**(22): p. 13077-13085.

359. Changseok, H., et al., *Green Nanotechnology: Development of Nanomaterials for Environmental and Energy Applications*, in *Sustainable Nanotechnology and the Environment: Advances and Achievements*. 2013, American Chemical Society. p. 201-229.

360. Jie, H., R.P.-V. Jose, and L.G.-T. Jorge, *Nanomaterials in Agricultural Production: Benefits and Possible Threats?*, in *Sustainable Nanotechnology and the Environment: Advances and Achievements*. 2013, American Chemical Society. p. 73-90.

361. Panagiotis, D., K. Antonios, and P.G. Emmanuel, *Nanostructured Materials for Environmentally Conscious Applications*, in *Sustainable Nanotechnology and the Environment: Advances and Achievements*. 2013, American Chemical Society. p. 59-72.

362. Kermisch, C., *Do new Ethical Issues Arise at Each Stage of Nanotechnological Development?* NanoEthics, 2012. **6**(1): p. 29-37.

363. Altmann, J., *Military Uses of Nanotechnology: Perspectives and Concerns.* Security Dialogue, 2004. **35**(1): p. 61-79.

364. Malsch, I., *Governing Nanotechnology in a Multi-Stakeholder World.* NanoEthics, 2013. **7**(2): p. 161-172.

365. Lisziewicz, J. and E.R. Tőke, *Nanomedicine applications towards the cure of HIV.* Nanomedicine : nanotechnology, biology, and medicine, 2013. **9**(1): p. 28-38.

366. Fluri, F., *Clinical Nanomedicine: Nanomedical approaches in Alzheimer's disease.* European Journal of Nanomedicine, 2010. **3**(1): p. 7-12.

367. Brignon, J.-M., *Socio-economic analysis: a tool for assessing the potential of nanotechnologies.* Journal of Physics: Conference Series, 2011. **304**: p. 1-8.

368. Benjamin, A.W., et al., *Anticipatory Governance and Anticipatory Life Cycle Assessment of Single Wall Carbon Nanotube Anode Lithium ion Batteries.* Nanotechnology, Law and Business, 2013. **9**(3): p. 101-118.

369. Hubbe, M.A., et al., *Cellulosic nanocomposites. A review.* BioResources, 2008. **3**: p. 929-980.

370. Nadagouda, M.N., et al., *Synthesis of Silver and Gold Nanoparticles Using Antioxidants from Blackberry, Blueberry, Pomegranate and Turmeric Extracts.* ACS Sustainable Chemistry & Engineering, 2014. **2**: p. 1717-1723.

371. Wei, F., et al., *The mass production of carbon nanotubes using a nano-agglomerate fluidized bed reactor: A multiscale space–time analysis.* Powder Technology, 2008. **183**(1): p. 10-20.

372. Northeastern. *Centre for High-rate Nanomanufacturing* 2015. Accessed on 11/03/2016 at: http://nano.server281.com/].

373. Luque, R., *Sustainable Nanomaterials: A Greener Future Avenue?* Materials Science & Nanotechnology, 2013. **1**(1): p. 1-2.

374. Virkutyte, J. and R.S. Varma, *Environmentally Friendly Preparation of Metal Nanoparticles*, in *Sustainable Preparation of Metal Nanoparticles: Methods and Applications*. 2013, The Royal Society of Chemistry. p. 7-33.

375. Virkutyte, J. and R.S. Varma, *Green Synthesis of Nanomaterials: Environmental Aspects*, in *Sustainable Nanotechnology and the Environment: Advances and Achievements*. 2013, American Chemical Society. p. 11-39.

376. Das, S.K. and E. Marsili, *Bioinspired Metal Nanoparticle: Synthesis, Properties and Application*, in *Nanomaterials*, M. Rahman, Editor. 2011, InTech. p. 253-278.

377. Wang, H., et al., *Mechanisms of PVP in the preparation of silver nanoparticles.* Materials Chemistry and Physics, 2005. **94**(2–3): p. 449-453.

378. Iravani, S., *Green synthesis of metal nanoparticles using plants.* Green Chemistry, 2011. **13**(10): p. 2638-2650.

379. Guzmán, M.G., J. Dille, and S. Godet, *Synthesis of silver nanoparticles by chemical reduction method and their antibacterial activity.* Engineering and Technology, 2008. **2**: p. 315-322.

380. Chou, K.-S. and C.-Y. Ren, *Synthesis of nanosized silver particles by chemical reduction method.* Materials Chemistry and Physics, 2000. **64**(3): p. 241-246.

381. Liu, Y.-C. and L.-H. Lin, *New pathway for the synthesis of ultrafine silver nanoparticles from bulk silver substrates in aqueous solutions by sonoelectrochemical methods.* Electrochemistry Communications, 2004. **6**(11): p. 1163-1168.

382. Sandmann, G., H. Dietz, and W. Plieth, *Preparation of silver nanoparticles on ITO surfaces by a double-pulse method.* Journal of Electroanalytical Chemistry, 2000. **491**(1–2): p. 78-86.

383. Mallick, K., M.J. Witcomb, and M.S. Scurrell, *Self-assembly of silver nanoparticles in a polymer solvent: formation of a nanochain through nanoscale soldering.* Materials Chemistry and Physics, 2005. **90**(2–3): p. 221-224.

384. Zhu, J., et al., *Shape-Controlled Synthesis of Silver Nanoparticles by Pulse Sonoelectrochemical Methods.* Langmuir, 2000. **16**(16): p. 6396-6399.

385. Bae, C.H., S.H. Nam, and S.M. Park, *Formation of silver nanoparticles by laser ablation of a silver target in NaCl solution.* Applied Surface Science, 2002. **197–198**(0): p. 628-634.

386. Dong, C., et al., *Facile and one-step synthesis of monodisperse silver nanoparticles using gum acacia in aqueous solution.* Journal of Molecular Liquids, 2014. **196**(0): p. 135-141.

387. Raveendran, P., J. Fu, and S.L. Wallen, *A simple and "green" method for the synthesis of Au, Ag, and Au-Ag alloy nanoparticles.* Green Chemistry, 2006. **8**(1): p. 34-38.

388. Anastas, P.T. and J.C. Warner, *Green Chemistry: Theory and Practice*. 1998, New York: Oxford University Press.

389. Anastas, P.T. and J.B. Zimmerman, *Peer Reviewed: Design Through the 12 Principles of Green Engineering.* Environmental Science & Technology, 2003. **37**(5): p. 94A-101A.

390. Patete, J.M., et al., *Viable methodologies for the synthesis of high-quality nanostructures.* Green Chemistry, 2011. **13**(3): p. 482-519.

391. Kaviya, S., et al., *Biosynthesis of silver nanoparticles using citrus sinensis peel extract and its antibacterial activity.* Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2011. **79**(3): p. 594-8.

392. Eckelman, M.J., J.B. Zimmerman, and P.T. Anastas, *Toward Green Nano. E-factor Analysis of Several Nanomaterial Syntheses.* Journal of Industrial Ecology, 2008. **12**(3): p. 316-328.

393. Korbekandi, H. and S. Iravani, *Silver Nanoparticles*, in *The Delivery of Nanoparticles*, A.A. Hashim, Editor. 2012, InTech. p. 3-36.

394. Pourzahedi, L. and M.J. Eckelman, *Environmental Life Cycle Assessment of Nanosilver-Enabled Bandages.* Environmental Science & Technology, 2014. **49**(1): p. 361-368.

395. Gawande, M.B., et al., *Microwave-Assisted Chemistry: Synthetic Applications for Rapid Assembly of Nanomaterials and Organics.* Accounts of Chemical Research, 2014. **47**(4): p. 1338-1348.

396. Varma, R.S., *Journey on greener pathways: from the use of alternate energy inputs and benign reaction media to sustainable applications of nano-catalysts in synthesis and environmental remediation.* Green Chemistry, 2014. **16**(4): p. 2027-2041.

397. Varma, R.S., *Green Chemistry with Microwave Energy*, in *Innovations in Green Chemistry and Green Engineering*, P.T. Anastas and J.B. Zimmerman, Editors. 2013, Springer New York. p. 115-156.

398. C. Hulteen, J. and C.R. Martin, *A general template-based method for the preparation of nanomaterials.* Journal of Materials Chemistry, 1997. **7**(7): p. 1075-1087.

399. Gedanken, A., *Using sonochemistry for the fabrication of nanomaterials.* Ultrasonics Sonochemistry, 2004. **11**(2): p. 47-55.

400. Su, C.-H., P.-L. Wu, and C.-S. Yeh, *Sonochemical Synthesis of Well-Dispersed Gold Nanoparticles at the Ice Temperature.* The Journal of Physical Chemistry B, 2003. **107**(51): p. 14240-14243.

401. Tsuji, M., et al., *Microwave-Assisted Synthesis of Metallic Nanostructures in Solution.* Chemistry – A European Journal, 2005. **11**(2): p. 440-452.

402. Nadagouda, M.N. and R.S. Varma, *Microwave-Assisted Shape-Controlled Bulk Synthesis of Noble Nanocrystals and Their Catalytic Properties.* Crystal Growth & Design, 2007. **7**(4): p. 686-690.

403. Nirmala Grace, A. and K. Pandian, *One pot synthesis of polymer protected Pt, Pd, Ag and Ru nanoparticles and nanoprisms under reflux and microwave mode of heating in glycerol—A comparative study.* Materials Chemistry and Physics, 2007. **104**(1): p. 191-198.

404. Komarneni, S., et al., *Microwave−Polyol Process for Pt and Ag Nanoparticles.* Langmuir, 2002. **18**(15): p. 5959-5962.

405. Moseley, J.D. and C.O. Kappe, *A critical assessment of the greenness and energy efficiency of microwave-assisted organic synthesis.* Green Chemistry, 2011. **13**(4): p. 794-806.

406. Li, Z., et al., *Synthesis of Single-Crystal Gold Nanosheets of Large Size in Ionic Liquids.* The Journal of Physical Chemistry B, 2005. **109**(30): p. 14445-14448.

407. Kim, T.Y., et al., *Shape-controlled synthesis of silver crystals mediated by imidazolium-based ionic liquids.* Physical Chemistry Chemical Physics, 2011. **13**(36): p. 16138-16141.

408. Zhao, Y., et al., *Effects of Ionic Liquids on the Characteristics of Synthesized Nano Fe(0) Particles.* Inorganic Chemistry, 2009. **48**(21): p. 10435-10441.

409. Anja-Verena, M., et al., *Nanoparticle Synthesis in Ionic Liquids*, in *Ionic Liquids: From Knowledge to Application*. 2009, American Chemical Society. p. 177-188.

410. Korbekandi, H., S. Iravani, and S. Abbasi, *Production of nanoparticles using organisms.* Critical Reviews in Biotechnology, 2009. **29**(4): p. 279-306.

411. Hebbalalu, D., et al., *Greener Techniques for the Synthesis of Silver Nanoparticles Using Plant Extracts, Enzymes, Bacteria, Biodegradable Polymers, and Microwaves.* ACS Sustainable Chemistry & Engineering, 2013. **1**(7): p. 703-712.

412. Bharde, A., et al., *Extracellular Biosynthesis of Magnetite using Fungi.* Small, 2006. **2**(1): p. 135-141.

413. Bansal, V., et al., *Bioleaching of Sand by the Fungus Fusarium oxysporum as a Means of Producing Extracellular Silica Nanoparticles.* Advanced Materials, 2005. **17**(7): p. 889-892.

414. Uddin, I., et al., *Structure and Microbial Synthesis of Sub-10 nm Bi2O3 Nanocrystals.* Journal of Nanoscience and Nanotechnology, 2008. **8**(8): p. 3909-3913.

415. Bansal, V., et al., *Room-Temperature Biosynthesis of Ferroelectric Barium Titanate Nanoparticles.* Journal of the American Chemical Society, 2006. **128**(36): p. 11958-11963.

416. Fayaz, A.M., et al., *Biogenic synthesis of silver nanoparticles and their synergistic effect with antibiotics: a study against gram-positive and gram-negative bacteria.* Nanomedicine: Nanotechnology, Biology and Medicine, 2010. **6**(1): p. 103-109.

417. Mukherjee, P., et al., *Fungus-Mediated Synthesis of Silver Nanoparticles and Their Immobilization in the Mycelial Matrix: A Novel Biological Approach to Nanoparticle Synthesis.* Nano Letters, 2001. **1**(10): p. 515-519.

418. Nair, B. and T. Pradeep, *Coalescence of Nanoclusters and Formation of Submicron Crystallites Assisted by Lactobacillus Strains.* Crystal Growth & Design, 2002. **2**(4): p. 293-298.

419. Mandal, D., et al., *The use of microorganisms for the formation of metal nanoparticles and their application.* Applied Microbiology and Biotechnology, 2006. **69**(5): p. 485-492.

420. Sweeney, R.Y., et al., *Bacterial Biosynthesis of Cadmium Sulfide Nanocrystals.* Chemistry & Biology, 2004. **11**(11): p. 1553-1559.

421. Konishi, Y., et al., *Bioreductive deposition of platinum nanoparticles on the bacterium Shewanella algae.* Journal of Biotechnology, 2007. **128**(3): p. 648-653.

422. Govindaraju, K., et al., *Silver, gold and bimetallic nanoparticles production using single-cell protein (Spirulina platensis) Geitler.* Journal of Materials Science, 2008. **43**(15): p. 5115-5122.

423. Shankar, S.S., et al., *Bioreduction of chloroaurate ions by geranium leaves and its endophytic fungus yields gold nanoparticles of different shapes.* Journal of Materials Chemistry, 2003. **13**(7): p. 1822-1826.

424. Kahrilas, G.A., et al., *Microwave-Assisted Green Synthesis of Silver Nanoparticles Using Orange Peel Extract.* ACS Sustainable Chemistry & Engineering, 2013. **2**(3): p. 367-376.

425. Baruwati, B. and R.S. Varma, *High Value Products from Waste: Grape Pomace Extract—A Three-in-One Package for the Synthesis of Metal Nanoparticles.* ChemSusChem, 2009. **2**(11): p. 1041-1044.

426. Zhang, X., et al., *Synthesis of nanoparticles by microorganisms and their application in enhancing microbiological reaction rates.* Chemosphere, 2011. **82**(4): p. 489-494.

427. Kavitha, K.S., et al., *Plants as Green Source towards Synthesis of Nanoparticles.* International Research Journal of Biological Sciences, 2013. **2**(6): p. 66-76.

428. Kou, J., C. Bennett-Stamper, and R.S. Varma, *Green Synthesis of Noble Nanometals (Au, Pt, Pd) Using Glycerol under Microwave Irradiation Conditions.* ACS Sustainable Chemistry & Engineering, 2013. **1**(7): p. 810-816.

429. Dubey, S.P., M. Lahtinen, and M. Sillanpää, *Green synthesis and characterizations of silver and gold nanoparticles using leaf extract of Rosa rugosa.* Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2010. **364**(1-3): p. 34-41.

430. de Figueirêdo, M.C.B., et al., *Life cycle assessment of cellulose nanowhiskers.* Journal of Cleaner Production, 2012. **35**: p. 130-139.

431. Som, C., et al., *The importance of life cycle concepts for the development of safe nanoproducts.* Toxicology, 2010. **269**(2-3): p. 160-9.

432. Köhler, A.R., et al., *Studying the potential release of carbon nanotubes throughout the application life cycle.* Journal of Cleaner Production, 2008. **16**(8-9): p. 927-937.

433. Bauer, C., et al., *Towards a framework for life cycle thinking in the assessment of nanotechnology.* Journal of Cleaner Production, 2008. **16**(8-9): p. 910-926.

434. Ahmad, N., et al., *Rapid synthesis of silver nanoparticles using dried medicinal plant of basil.* Colloids and Surfaces B: Biointerfaces, 2010. **81**(1): p. 81-86.

435. Vidhu, V.K., S.A. Aswathy, and D. Philip, *Green synthesis of silver nanoparticles using Macrotyloma uniflorum.* Spectrochim Acta A Molecular and Biomolecular Spectroscopy, 2011. **83**: p. 392-397.

436. Santos, S.A.O., et al., *Unveiling the Chemistry behind the Green Synthesis of Metal Nanoparticles.* ChemSusChem, 2014. **7**(9): p. 2704-2711.

437. Belton, V. and T. Stewart, *Problem Structuring and Multiple Criteria Decision Analysis*, in *Trends in Multiple Criteria Decision Analysis*, M. Ehrgott, J.R. Figueira, and S. Greco, Editors. 2010, Springer US. p. 209-239.

438. Cinelli, M., S.R. Coles, and K. Kirwan, *Analysis of the Potentials of Multi Criteria Decision Analysis Methods to Conduct Sustainability Assessment.* Ecological Indicators, 2014. **46**: p. 138-148.

439. Dent, J.B., G. Edwards-Jones, and M.J. McGregor, *Simulation of ecological, social and economic factors in agricultural systems.* Agricultural Systems, 1995. **49**(4): p. 337-351.

440. Slowinski, R., S. Greco, and B. Matarazzo, *Rough set and rule-based multicriteria decision aiding.* Pesquisa Operacional, 2012. **32**: p. 213-270.

441. Crandall, B., G. Klein, and R.R. Hoffman, *Working Minds: A Practitioner's Guide to Cognitive Task Analysis*. 2006, Cambridge, MA: The MIT Press.

442. Naidu, S.R., *Towards Sustainable Development of Nanomanufacturing*. 2012, PhD thesis. University of Tennessee. Accessed on 22/09/2016 at: http://trace.tennessee.edu/cgi/viewcontent.cgi?article=2413&context=utk_graddiss.

443. Nadagouda, M.N. and R.S. Varma, *Green synthesis of silver and palladium nanoparticles at room temperature using coffee and tea extract.* Green Chemistry, 2008. **10**(8): p. 859-862.

444. Baruwati, B., V. Polshettiwar, and R.S. Varma, *Glutathione promoted expeditious green synthesis of silver nanoparticles in water using microwaves.* Green Chemistry, 2009. **11**(7): p. 926-930.

445. Nadagouda, M.N. and R.S. Varma, *Green Synthesis of Ag and Pd Nanospheres, Nanowires, and Nanorods Using Vitamin B2: Catalytic Polymerisation of Aniline and Pyrrole.* Journal of Nanomaterials, 2008. **doi:10.1155/2008/782358**.

446. Gill, N.K., et al., *Quantification of power consumption and oxygen transfer characteristics of a stirred miniature bioreactor for predictive fermentation scale-up.* Biotechnology and Bioengineering, 2008. **100**(6): p. 1144-1155.

447. Razzaq, T. and C.O. Kappe, *On the Energy Efficiency of Microwave-Assisted Organic Reactions.* ChemSusChem, 2008. **1**(1-2): p. 123-132.

448. Gronnow, M.J., et al., *Energy Efficiency in Chemical Reactions: A Comparative Study of Different Reaction Techniques.* Organic Process Research & Development, 2007. **11**(2): p. 293-293.

449. Gronnow, M.J., et al., *Energy Efficiency in Chemical Reactions: A Comparative Study of Different Reaction Techniques.* Organic Process Research & Development, 2005. **9**(4): p. 516-518.

450. Panáček, A., et al., *Silver Colloid Nanoparticles: Synthesis, Characterization, and Their Antibacterial Activity.* The Journal of Physical Chemistry B, 2006. **110**(33): p. 16248-16253.

451. DuránI, N., et al., *Potential use of silver nanoparticles on pathogenic bacteria, their toxicity and possible mechanisms of action.* Journal of the Brazilian Chemical Society, 2010. **21**(6): p. 949-959.

452. Mohan, Y.M., et al., *Hydrogel networks as nanoreactors: A novel approach to silver nanoparticles for antibacterial applications.* Polymer, 2007. **48**(1): p. 158-164.

453. Martínez-Castañón, G.A., et al., *Synthesis and antibacterial activity of silver nanoparticles with different sizes.* Journal of Nanoparticle Research, 2008. **10**(8): p. 1343-1348.

454. Greco, S., B. Matarazzo, and R. Słowiński, *Rough sets methodology for sorting problems in presence of multiple attributes and criteria.* European Journal of Operational Research, 2002. **138**(2): p. 247-259.

455. Błaszczyński, J., S. Greco, and R. Słowiński, *Multi-criteria classification – A new scheme for application of dominance-based decision rules.* European Journal of Operational Research, 2007. **181**(3): p. 1030-1044.

456. Greco, S., B. Matarazzo, and R. Słowiński, *Dominance-Based Rough Set Approach to Decision Involving Multiple Decision Makers*, in *Rough Sets and Current Trends in Computing*, S. Greco, et al., Editors. 2006, Springer Berlin Heidelberg. p. 306-317.

457. Chakhar, S. and I. Saad, *Dominance-based rough set approach for groups in multicriteria classification problems.* Decision Support Systems, 2012. **54**(1): p. 372-380.

458. Mindjet, *Mindjet Software*. 2016: Accessed on 13/03/2016 at: http://www.mindjet.com.

459. Cruz, D., et al., *Preparation and physicochemical characterization of Ag nanoparticles biosynthesized by Lippia citriodora (Lemon Verbena).* Colloids and Surfaces B: Biointerfaces, 2010. **81**(1): p. 67-73.

460. Sheny, D.S., J. Mathew, and D. Philip, *Phytosynthesis of Au, Ag and Au–Ag bimetallic nanoparticles using aqueous extract and dried leaf of Anacardium*

*occidentale.* Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2011. **79**(1): p. 254-262.

461. Raveendran, P., J. Fu, and S.L. Wallen, *Completely "Green" Synthesis and Stabilization of Metal Nanoparticles.* Journal of the American Chemical Society, 2003. **125**(46): p. 13940-13941.

462. Gao, X., et al., *Green synthesis and characteristic of core-shell structure silver/starch nanoparticles.* Materials Letters, 2011. **65**(19–20): p. 2963-2965.

463. Singhal, G., et al., *Biosynthesis of silver nanoparticles using Ocimum sanctum (Tulsi) leaf extract and screening its antimicrobial activity.* Journal of Nanoparticle Research, 2011. **13**(7): p. 2981-2988.

464. Jha, A.K., et al., *Plant system: Nature's nanofactory.* Colloids and Surfaces B: Biointerfaces, 2009. **73**(2): p. 219-223.

465. Hu, B., et al., *Microwave-Assisted Rapid Facile "Green" Synthesis of Uniform Silver Nanoparticles: Self-Assembly into Multilayered Films and Their Optical Properties.* The Journal of Physical Chemistry C, 2008. **112**(30): p. 11169-11174.

466. Nadagouda, M.N., T.F. Speth, and R.S. Varma, *Microwave-Assisted Green Synthesis of Silver Nanostructures.* Accounts of Chemical Research, 2011. **44**(7): p. 469-478.

467. Pal, A., S. Shah, and S. Devi, *Microwave-assisted synthesis of silver nanoparticles using ethanol as a reducing agent.* Materials Chemistry and Physics, 2009. **114**(2–3): p. 530-532.

468. Liou, J.J.H. and G.-H. Tzeng, *A Dominance-based Rough Set Approach to customer behavior in the airline market.* Information Science, 2010. **180**(11): p. 2230-2238.

469. Flari, V., et al., *Expert judgment based multi-criteria decision model to address uncertainties in risk assessment of nanotechnology-enabled food products.* Journal of Nanoparticle Research, 2011. **13**(5): p. 1813-1831.

470. Tervonen, T., et al., *A stochastic method for robustness analysis in sorting problems.* European Journal of Operational Research, 2009. **192**(1): p. 236-242.

471. Dias, L.C., *A note on the role of robustness analysis in decision-aiding processes*, in *Rubustness in OR-DA*, B. Roy, M.A. Aloulou, and R. Kalaï, Editors. 2007, LAMSADE: Paris. p. 53-70.

472. Antunes, C.H. and L.C. Dias, *Managing uncertainty in decision support models.* European Journal of Operational Research, 2007. **181**(3): p. 1425-1426.

473. Tobiszewski, M. and A. Orłowski, *Multicriteria decision analysis in ranking of analytical procedures for aldrin determination in water.* Journal of Chromatography A, 2015. **1387**(0): p. 116-122.

474. Linkov, I., et al., *Classifying Nanomaterial Risks Using Multi-Criteria Decision Analysis*, in *Nanomaterials: Risks and Benefits*, I. Linkov and J. Steevens, Editors. 2009, Springer Netherlands. p. 179-191.

475. Tervonen, T. and R. Lahdelma, *Implementing stochastic multicriteria acceptability analysis.* European Journal of Operational Research, 2007. **178**(2): p. 500-513.

476. Tervonen, T., et al., *Applying Multiple Criteria Decision Analysis to Comparative Benefit-Risk Assessment: Choosing Among Statins in Primary Prevention.* Medical Decision Making, 2015. **35**(7): p. 859-871.

477. Tervonen, T., et al., *A stochastic multicriteria model for evidence-based decision making in drug benefit-risk analysis.* Statistics in Medicine, 2011. **30**(12): p. 1419-1428.

478. Rogers, K. and T.P. Seager, *Environmental Decision-Making Using Life Cycle Impact Assessment and Stochastic Multiattribute Decision Analysis: A Case Study on Alternative Transportation Fuels.* Environmental Science & Technology, 2009. **43**(6): p. 1718-1723.

479. Merad, M., et al., *Use of multi-criteria decision-aids for risk zoning and management of large area subjected to mining-induced hazards.* Tunnelling and Underground Space Technology, 2004. **19**(2): p. 125-138.

480. Tervonen, T., et al., *SMAA-TRI: A Parameter Stability Analysis Method for ELECTRE TRI*. 2005: Research Report 6/2005 of The Institute of Systems Engineering and Computers (INESC Coimbra), Coimbra, Portugal.

481. Figueira, J. and B. Roy, *Determining the weights of criteria in the ELECTRE type methods with a revised Simos' procedure.* European Journal of Operational Research, 2002. **139**(2): p. 317-326.

482. Słowiński, R., C. Zopounidis, and A.I. Dimitras, *Prediction of company acquisition in Greece by means of the rough set approach.* European Journal of Operational Research, 1997. **100**: p. 1-15.

483. Dimitras, A.I., et al., *Business failure prediction using rough sets.* European Journal of Operational Research, 1999. **114**(2): p. 263-280.

484. Slowínski, R., C. Zopounidis, and A.I. Dimitras, *Prediction of company acquisition in Greece by means of the rough set approach.* European Journal of Operational Research, 1997. **100**(1): p. 1-15.

485. Cinelli, M., et al., *A Framework of Criteria for the Sustainability Assessment of Nanoproducts.* Journal of Cleaner Production, 2016. **126**: p. 277-287.

486. Cinelli, M., et al., *Multiple Criteria Decision Aiding Moves Sustainable Nanotechnology Forward*, in *82nd European Working Group on Multiple Criteria Decision Aiding*. 2015: Odense, Denmark.

487. Wiek, A., D.J. Lang, and M. Siegrist, *Qualitative system analysis as a means for sustainable governance of emerging technologies: the case of nanotechnology.* Journal of Cleaner Production, 2008. **16**(8-9): p. 988-999.

488. Morose, G., *The 5 principles of “Design for Safer Nanotechnology”.* Journal of Cleaner Production, 2010. **18**(3): p. 285-289.

489. Osterwalder, N., et al., *Energy Consumption During Nanoparticle Production: How Economic is Dry Synthesis?* Journal of Nanoparticle Research, 2006. **8**(1): p. 1-9.

490. Wender, B.A., et al., *Anticipatory governance and anticipatory life cycle assessment of single wall carbon nanotube anode lithium ion batteries.* Nanotechnology Law and Business, 2012. **9**(3): p. 201-.

491. Klemm, D., et al., *Nanocelluloses: a new family of nature-based materials.* Angewandte Chemie International Edition, 2011. **50**(24): p. 5438-5466.

492. Abdul Khalil, H.P.S., A.H. Bhat, and A.F. Ireana Yusra, *Green composites from sustainable cellulose nanofibrils: A review.* Carbohydrate Polymers, 2012. **87**(2): p. 963-979.

493. Oksman, K., A.P. Mathew, and M. Sain, *Novel bionanocomposites: processing, properties and potential applications.* Plastics, Rubber and Composites, 2009. **38**(9): p. 396-405.

494. Dufrense, A., *Polymer Nanocomposites from Biological Sources*, in *Encyclopedia of Nanoscience and Nanotechnology*, H.S. Nalwa, Editor. 2010, Americal Scientific Publishers. p. 219-250.

495. Vaananen, V., et al., *Evaluation of the suitability of the developed methdology for nanoparticle health and safety studies*. 2012, Scaling Up Nanoparticles in Modern Paper Making - SUNPAP Project. Accessed on 22/09/2016 at: http://sunpap.vtt.fi/pdf/SUNPAP_WP10_DEL10_5_20120827_FIOH.pdf.

496. Kuemmerer, K., et al., *Biodegradability of organic nanoparticles in the aqueous environment.* Chemosphere, 2011. **82**(10): p. 1387-1392.

497. Bras, J., et al., *Mechanical, barrier, and biodegradability properties of bagasse cellulose whiskers reinforced natural rubber nanocomposites.* Industrial Crops and Products, 2010. **32**(3): p. 627-633.

498. Hassan, M.L., et al., *Polycaprolactone/modified bagasse whisker nanocomposites with improved moisture-barrier and biodegradability properties.* Journal of Applied Polymer Science, 2012. **125**: p. E10-E19.

499. Maiti, S., et al., *Structural changes of starch/polyvinyl alcohol biocomposite films reinforced with microcrystalline cellulose due to biodegradation in simulated aerobic compost environment.* Journal of Applied Polymer Science, 2011. **122**(4): p. 2503-2511.

500. Taipale, T., et al., *Effect of microfibrillated cellulose and fines on the drainage of kraft pulp suspension and paper strength.* Cellulose, 2010. **17**(5): p. 1005-1020.

501. Tejado, A., et al., *Energy requirements for the disintegration of cellulose fibers into cellulose nanofibers.* Cellulose, 2012. **19**(3): p. 831-842.

502. Siró, I. and D. Plackett, *Microfibrillated cellulose and new nanocomposite materials: a review.* Cellulose, 2010. **17**(3): p. 459-494.

503. Zimmermann, T., N. Bordeanu, and E. Strub, *Properties of nanofibrillated cellulose from different raw materials and its reinforcement potential.* Carbohydrate Polymers, 2010. **79**(4): p. 1086-1093.

504. Eriksen, O., K. Syverud, and O. Gregersen, *The use of microfibrillated cellulose produced from kraft pulp as strength enhancer in TMP paper.* Nordic Pulp & Paper Research Journal, 2008. **23**(3): p. 299-304.

505. Isogai, T., T. Saito, and A. Isogai, *Wood cellulose nanofibrils prepared by TEMPO electro-mediated oxidation.* Cellulose, 2011. **18**(2): p. 421-431.

506. Zhou, Y., et al., *Recyclable organic solar cells on cellulose nanocrystal substrates.* Scientific Reports, 2013. **3**: p. 1536.

507. Korhonen, J.T., et al., *Hydrophobic nanocellulose aerogels as floating, sustainable, reusable, and recyclable oil absorbents.* ACS Appl Mater Interfaces, 2011. **3**(6): p. 1813-6.

508. Wang, M., et al., *Electrospun 1,4-DHAQ-Doped Cellulose Nanofiber Films for Reusable Fluorescence Detection of Trace Cu2+ and Further for Cr3+.* Environmental Science & Technology, 2012. **46**(1): p. 367-373.

509. Roman, M., et al., *Cellulose nanocrystals for drug delivery*, in *Polysaccharide Materials: Performance by Design*. 2009, ACS Symposium Series. p. 81-91.

510. Pereira, M.M., et al., *Cytotoxicity and expression of genes involved in the cellular stress response and apoptosis in mammalian fibroblast exposed to cotton cellulose nanofibers.* Nanotechnology, 2013. **24**(7): p. 1-8.

511. Roman, M., et al., *Cellulose nanocrystals for targeted drug delivery applications*, in *235th ACS National Meeting*. 2008: New Orleans, LA.

512. Ni, H., et al., *Cellulose nanowhiskers: preparation, characterization and cytotoxicity evaluation.* Biomedical Materials Engineering, 2012. **22**(1-3): p. 121-7.

513. Dong, S., et al., *Cytotoxicity and Cellular Uptake of Cellulose Nanocrystals.* Nano LIFE, 2012. **02**(03): p. 1-11.

514. Gougen, R., *EHS practices for safe production of nancrystalline cellulose*, in *TAPPI International Conference on Nanotechnology for Renewable Materials*. 2012: Montreal, Canada.

515. O'Connor, B., *Ensuring the Safety of Manufactured Nanocrystalline Celulose. A Risk Assessment under Canada's New Substances Notification Regulations*, in *TAPPI International Conference on Nanotechnology for Renewable Materials*. 2011: Washington D.C., USA.

516. Clift, M.J.D., et al., *Investigating the Interaction of Cellulose Nanofibers Derived from Cotton with a Sophisticated 3D Human Lung Cell Coculture.* Biomacromolecules, 2011. **12**(10): p. 3666-3673.

517. O'Connor, B., *NCC. Environmental and safety update*, in *TAPPI International Conference on Nanotechnology for Renewable Materials*. 2012: Montreal, Canada.

518. Hirani, A., *Targeting brain inflammation with bioconjugated nanoparticles*. 2009, Biomedical Engineering and Sciences. Virginia Polytechnic Institute.

519. Vartiainen, J., et al., *Health and environmental safety aspects of friction grinding and spray drying of microfibrillated cellulose.* Cellulose, 2011. **18**: p. 775-786.

520. Vartiainen, J., et al., *Health and environmental safety aspects of nanofibrillated cellulose*, in *NANOCON*. 2011: Brno, Czech Republic.

521. Pitkanen, M., et al., *Nanofibrilar cellulose - Assessment of cytotoxic and genotoxic properties in vitro*, in *TAPPI International Conference on Nanotechnology for Renewable Materials, 27-29.09.2010*. 2010: Espoo, Finland.

522. Norppa, H., *Nanofibrillated cellulose. Results of in vitro and in vivo toxicological assays*, in *Final conference. Scaling Up Nanoparticles in Modern Paper Making - SUNPAP Project*. 2012: Milan, Italy.

523. Kovacs, T., et al., *An ecotoxicological characterization of nanocrystalline cellulose (NCC).* Nanotoxicology, 2010. **2010**: p. 255-270.

524. O'Connor, B., *Ensuring the Safety of Manufactured Nanocrystalline Celulose*, in *OECD conference*. 2009: Paris, France.

525. Male, K.B., et al., *Probing inhibitory effects of nanocrystalline cellulose: inhibition versus surface charge.* Nanoscale, 2012. **4**(4): p. 1373-1379.

526. Kapanen, A., et al., *Toxicity and characteristics of microfibrillated cellulose in kinetic luminiscent bacteria test environment*, in *6th International Conference on the Environmental Effects of Nanoparticles and Nanomaterials*. 2011: London, UK.

527. Rushton, E.K., et al., *Concept of Assessing Nanoparticle Hazards Considering Nanoparticle Dosemetric and Chemical/Biological Response-metrics.* Journal of toxicology and environmental health. Part A, 2010. **73**(5): p. 445-461.

528. Hankin, S.M., et al., *Specific Advice on Fulfilling Information Requirements for Nanomaterials under REACH (RIP-oN 2) – Final Project Report*. 2011: RNC/RIP-oN2/FPR/1/FINAL. Accessed on 22/09/2016 at: http://ec.europa.eu/environment/chemicals/nanotech/pdf/report_ripon2.pdf.

529. OECD, *Report of the Workshop on Risk Assessment of Manufactured Nanomaterials in a regulatory context*. 2010: ENV/JM/MONO 10. Series on Safety of Manufactured Nanomaterials. Available at: http://www.oecd.org/science/nanosafety/publications-series-safety-manufactured-nanomaterials.htm.

530. IPCS, *Risk Assessment Terminology*, in *International Programme on Chemical Safety.* 2004, World Health Organization. Accessed on 22/09/2016 at: http://www.inchem.org/documents/harmproj/harmproj/harmproj1.pdf.

531. Sun, Y., B. Mayers, and Y. Xia, *Transformation of Silver Nanospheres into Nanobelts and Triangular Nanoplates through a Thermal Process.* Nano Letters, 2003. **3**(5): p. 675-679.

532. Al-Thabaiti, S.A., et al., *Formation and characterization of surfactant stabilized silver nanoparticles: A kinetic study.* Colloids and Surfaces B: Biointerfaces, 2008. **67**(2): p. 230-237.

533. He, S., et al., *Formation of Silver Nanoparticles and Self-Assembled Two-Dimensional Ordered Superlattice.* Langmuir, 2001. **17**(5): p. 1571-1575.

534. Moulton, M.C., et al., *Synthesis, characterization and biocompatibility of "green" synthesized silver nanoparticles using tea polyphenols.* Nanoscale, 2010. **2**(5): p. 763-770.

535. Krishnaraj, C., et al., *Synthesis of silver nanoparticles using Acalypha indica leaf extracts and its antibacterial activity against water borne pathogens.* Colloids and Surfaces B: Biointerfaces, 2010. **76**(1): p. 50-56.

536. Narayanan, K.B. and N. Sakthivel, *Extracellular synthesis of silver nanoparticles using the leaf extract of Coleus amboinicus Lour.* Materials Research Bulletin, 2011. **46**: p. 1708-1713.

537. Gao, F., Q. Lu, and S. Komarneni, *Interface Reaction for the Self-Assembly of Silver Nanocrystals under Microwave-Assisted Solvothermal Conditions.* Chemistry of Materials, 2005. **17**(4): p. 856-860.

538. Tsuji, M., et al., *Rapid Preparation of Silver Nanorods and Nanowires by a Microwave-Polyol Method in the Presence of Pt Catalyst and Polyvinylpyrrolidone.* Crystal Growth & Design, 2006. **7**(2): p. 311-320.

539. Das, R., S. Gang, and S.S. Nath, *Preparation and Antibacterial Activity of Silver Nanoparticles.* Journal of Biomaterials and Nanobiotechnology, 2011. **2**(472-475).

540. Zhao, T., et al., *Size-controlled preparation of silver nanoparticles by a modified polyol method.* Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2010. **366**(1–3): p. 197-202.

541. Sreeram, K.J., M. Nidhin, and B.U. Nair, *Microwave assisted template synthesis of silver nanoparticles.* Bulletin of Materials Science, 2009. **31**(7): p. 937-942.

542. Luo, Y. and X. Sun, *Rapid, single-step preparation of dendrimer-protected silver nanoparticles through a microwave-based thermal process.* Materials Letters, 2007. **61**(8–9): p. 1622-1624.

543. Huang, H. and X. Yang, *Synthesis of polysaccharide-stabilized gold and silver nanoparticles: a green method.* Carbohydrate Research, 2004. **339**(15): p. 2627-2631.

544. Kundu, S., K. Wang, and H. Liang, *Size-Controlled Synthesis and Self-Assembly of Silver Nanoparticles within a Minute Using Microwave Irradiation.* The Journal of Physical Chemistry C, 2008. **113**(1): p. 134-141.

545. Bar, H., et al., *Green synthesis of silver nanoparticles using seed extract of Jatropha curcas.* Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2009. **348**(1-3): p. 212-216.

546. Kou, J. and R.S. Varma, *Beet juice utilization: Expeditious green synthesis of noble metal nanoparticles (Ag, Au, Pt, and Pd) using microwaves.* RSC Advances, 2012. **2**(27): p. 10283-10290.

547. Prasad, T. and E.K. Elumalai, *Biofabrication of Ag nanoparticles using Moringa oleifera leaf extract and their antimicrobial activity.* Asian Pacific Journal of Tropical Biomedicine, 2011. **1**(6): p. 439-442.

548. Philip, D., et al., *Murraya Koenigii leaf-assisted rapid green synthesis of silver and gold nanoparticles.* Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2011. **78**(2): p. 899-904.

549. Pal, A., S. Shah, and S. Devi, *Synthesis of Au, Ag and Au–Ag alloy nanoparticles in aqueous polymer solution.* Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2007. **302**(1–3): p. 51-57.

550. Chandran, S.P., et al., *Synthesis of Gold Nanotriangles and Silver Nanoparticles Using Aloevera Plant Extract.* Biotechnology Progress, 2006. **22**(2): p. 577-583.

551. Nune, S.K., et al., *Green Nanotechnology from Tea: Phytochemicals in Tea as Building Blocks for Production of Biocompatible Gold Nanoparticles.* Journal of materials chemistry, 2009. **19**(19): p. 2912-2920.

552. Virkutyte, J. and R.S. Varma, *Green synthesis of metal nanoparticles: Biodegradable polymers and enzymes in stabilization and surface functionalization.* Chemical Science, 2011. **2**(5): p. 837-846.

553. Murphy, C.J., *Sustainability as an emerging design criterion in nanoparticle synthesis and applications.* Journal of Materials Chemistry, 2008. **18**(19): p. 2173-2176.

554. Valodkar, M., et al., *Euphorbiaceae latex induced green synthesis of non-cytotoxic metallic nanoparticle solutions: A rational approach to antimicrobial applications.* Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2011. **384**(1–3): p. 337-344.

555. Moseley, J.D. and E.K. Woodman, *Energy Efficiency of Microwave- and Conventionally Heated Reactors Compared at meso Scale for Organic Reactions.* Energy & Fuels, 2009. **23**(11): p. 5438-5447.

556. Durán, N., et al., *Potential use of silver nanoparticles on pathogenic bacteria, their toxicity and possible mechanisms of action.* Journal of the Brazilian Chemical Society, 2010. **21**: p. 949-959.

557. Kou, J. and R.S. Varma, *Beet Juice-Induced Green Fabrication of Plasmonic AgCl/Ag Nanoparticles.* ChemSusChem, 2012. **5**(12): p. 2435-2441.

558. Gogoi, S.K., et al., *Green Fluorescent Protein-Expressing Escherichia coli as a Model System for Investigating the Antimicrobial Activities of Silver Nanoparticles.* Langmuir, 2006. **22**(22): p. 9322-9328.