European Commission

ANNEX 1

Horizon Europe (HORIZON)

Description of the action (DoA)

Part A

Part B

Associated with document Ref. Ares(2023)7965722 - 22/11/2023

DESCRIPTION OF THE ACTION (PART A)

COVER PAGE

Part A of the Description of the Action (DoA) must be completed directly on the Portal Grant Preparation screens.

PROJECT *Grant Preparation (General Information screen) — Enter the info.*	
Project number:	101138414
Project name:	Multidimensional Integrated Quantitative Approach To Assess Safety And Sustainability Of Nanomaterials In Real Case Life Cycle Scenarios Using Nanospecific Impact Categories
Project acronym:	INTEGRANO
Call:	HORIZON-CL4-2023-RESILIENCE-01
Topic:	HORIZON-CL4-2023-RESILIENCE-01-22
Type of action:	HORIZON-RIA
Service:	HADEA/B/03
Project starting date:	fixed date: 1 January 2024
Project duration:	48 months

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PROJECT SUMMARY

Project summary

Grant Preparation (General Information screen) — Provide an overall description of your project (including context and overall objectives, planned activities and main achievements, and expected results and impacts (on target groups, change procedures, capacities, innovation etc)). This summary should give readers a clear idea of what your project is about.

Use the project summary from your proposal.

In line with the current guidelines for Safe and Sustainable by Design (SSbD) chemicals and materials, INTEGRANO proposes a general assessment approach based on quantitative evidence to be applied in practice for specific Nano Materials (NMs) design cases referred to inorganic, organic and carbon NMs. The development NMs dedicated novel impact categories (ICs) for nano-toxicity and eco-nano-toxicity assessment will enable the integrated application of standardised assessment methodologies. The following four NMs Life Cycle Stages (LCS) are addressed: synthesis, incorporation, use phase and end-of-life. The application of the stage-gate SSbD process through the LCS addresses performance in the five dimensions (5D s): Safety, Environmental, Economic, Social and Functional. Generation of dedicated response functions will allow associating Key Decision Factors (KDFs, such as: concentrations, processing parameters, etc.) to Key Performance Indicators (KPIs, such as: occupational safety, CO2 emissions, job creation potential, NM cost, antibacterial functionality, etc.). SSbD NMs solutions will be obtained by Multi Objective Optimisation Design (MOOD) dedicated algorithm. A dedicated digital Decision Support Toolbox (DST) will elaborate design case specific data and run MOOD algorithm to sort the set of multi-optimal SSbD options, which are simultaneously complying with all the targeted KPIs referred to the 5Ds. The digital supported decision process will help scientists, material engineers, Nano-Enabled Products (NEPs) designers, policymakers and decision-makers to takle the SSbD challenge, allowing for dramatic reduction of Research & Development (RTD) and approval lead-time as well as minimising costs and increasing the transparency of the data, by making the industrial uptake of nanotechnologies more sustainable and viable.
INTEGRANO allows the integration with other existing SSbD frameworks by transposing results into other scoring metrics and enabling data exchange.

LIST OF PARTICIPANTS

PARTICIPANTS

Grant Preparation (Beneficiaries screen) — Enter the info.

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LIST OF WORK PACKAGES

Work packages *Grant Preparation (Work Packages screen) — Enter the info.*						
Work Package No	**Work Package name**	**Lead Beneficiary**	**Effort (Person-Months)**	**Start Month**	**End Month**	**Deliverables**
WP1	Definition of case studies, data management and digital DST	4 - CNR	61.00	1	36	D1.1 – First data management Plan D1.2 – Report on the goal and scope of addressed case studies, including KDFs and KPIs definition D1.3 – Digital Decision Support Toolbox for quantitative based integrated impact assessment towards SSbD solutions D1.4 – Final data management Plan
WP2	Experimental Data Generation: NMs provision and characterisation M-Measure (I)	3 - CENTI	185.00	1	42	D2.1 – Set of NMs samples D2.2 – INTEGRANO integrated database (DB) periodic release D2.3 – DB on NMs detection campaigns in real and simulated environment for Fate Factors assessment D2.4 – Report on Conditions of Safe Use
WP3	Nano Tox and nano eco-tox data generation	1 - UNIMIB	58.00	6	44	D3.1 – Quantitative assessment of Eco-toxicity endpoints for indication of suitable nano-specific EE for marine and terrestrial environment eco-toxicity ICs D3.2 – Relevant dose-response functions for the NMs in their different LC stages, for human and environmental toxicology outcomes supporting the definition of nano-specific EE for human and environmental toxicity ICs
WP4	Analysis, Assessment and Prediction Models	2 - ARCHE	66.00	12	44	D4.1 – Report on the modelling of NM

Work packages

Grant Preparation (Work Packages screen) — Enter the info.

Work Package No	Work Package name	Lead Beneficiary	Effort (Person-Months)	Start Month	End Month	Deliverables
						release and human/environmental exposure from relevant industrial case scenarios D4.2 – Integrated DB including characterisation, detection, modelling human and eco-toxicity relevant data based on FAIR principles D4.3 – In silico modelling of response functions D4.4 – Synthesis and incorporation models for integrated LCA, LCC and SLCA D4.5 – Report on social and economic modelling and externalities optimization
WP5	NMs Integrated Impact assessment for SSbD based solutions: Design and Validate	9 - PRJ	94.00	20	48	D5.1 – Report on proposed Impact model for determination of toxicity and eco-toxicity ICs scoring specifically related to NMs D5.2 – DB of Safe and sustainability assessment data (integrated LCA, LCC, SLCA) of targeted case studies based on integrated impact model and integrated LCIA D5.3 – Report on validated best SSbD solutions. D5.4 – Report on project interlaboratory validation
WP6	Stakeholders engagement, communication and dissemination	5 - AITEX	60.00	1	48	D6.1 – First PDER including communication activities, and updates D6.2 – Second PDER including communication activities, and updates

Work packages *Grant Preparation (Work Packages screen) — Enter the info.*						
Work Package No	**Work Package name**	**Lead Beneficiary**	**Effort (Person-Months)**	**Start Month**	**End Month**	**Deliverables**
						D6.3 – Final PDER including communication activities, and updates D6.4 – Guidelines for integrated assessment of health, social, economic, environmental sustainability. D6.5 – Project visual identity and website. D6.6 – First reports of stakeholder workshops and training plan D6.7 – Second reports of stakeholder workshops and training plan D6.8 – Final reports of stakeholder workshops and training plan D6.9 – IT platform for stakeholders engagement - SSbD Think tank D6.10 – First report on synergies and interaction with other EU projects and initiative D6.11 – Final report on synergies and interaction with other EU projects and initiative
WP7	Management and Coordination	1 - UNIMIB	48.00	1	48	D7.1 – Quality control plan D7.2 – Tools for operational, technical and contractual management periodic reporting

Work package WP1 – Definition of case studies, data management and digital DST

Work Package Number	WP1	**Lead Beneficiary**	4. CNR
Work Package Name	Definition of case studies, data management and digital DST		
Start Month	1	**End Month**	36

Objectives
This WP will achieve O-1: to develop a toolbox that enables easily identifying the set of safe and sustainable solutions (deign cases). The following specific objectives will be addressed: 1. To set robust data management plan to enable all project activities for data generation, curation and analysis [T1.1] 2. To implement Define phase in DMADV, set the specific project plan to implement the INTEGRANO IMM [T1.2] 3. To provide a suitable digital based decision support toolbox (DST) enabling SSbD [T1.3]

Description
The WP1 will set the basis for the INTEGRANO data generation and data flow management obtained in WP2, WP3, WP4 and WP5, enable achieving the addressed project objectives. WP1 will define goal and scope of specific design case studies for the implementation of the whole IMM. WP1 will develop and optimise the algorithms to enable the implementation of a digitalised decision support process via the decision support toolbox (DST) operated in WP5. Task 1.1. Data generation and management plan for impact assessment (M1-M18). Leader: CNR; Partners: UNIMIB, ARCHE, CENTI, PRJ, DRT. The task will first define and set a dedicated method and tool for data collection, storage and sharing in compliance with FAIR principles. INTEGRANO Database will be designed and developed in compliance with specific project needs and to assure data traceability and availability along the project development and after the project accomplishment. Task 1.1.1 Data management, quality assurance and architecture: Data quality and completeness (sufficiency of analysis) has been one of the primary concerns in the RA (human health and environmental) of NM/NEPs translating into a critical element of the SSbD notion.40 In this task, data completeness across the entire LCS will be ensured towards rationalized studies of SSbD cases. This task will involve the entire consortium into transforming raw scientific generated data to transparent and interoperable datasets.41 CNR will take advantage of the already developed FAIR data sets on field exposure campaigns, capturing data for exposure modelling,42 the tailor-made template to capture unctionality performance.43 It also promotes mentality shifting from individual scientists to the era of open data, digitisation, and sharing (Task 6.4). This task will also deliver a detailed and extended INTEGRANO data management plan (DMP). It includes capturing the input parameters, the outcomes to be predicted, information related to the protocol and instrumentation as well as the ontology scheme. The DMP will include and organize project data up-taking by INTEGRANO database but also by other EU databases already developed, such as eNanoMapper database or NanoCommons, contributing to the ongoing effort on data integration. For every data generating task agreed templates and data formats will be used to enable information and data bridging across the WPs.Sharing of data will be possible through a common repository with coded data records which will associate NMs samples, related: synthesis and incorporation process campaign, p-chem and functional characterisation data, emission sampling and safety assessment data. The data management principles and methodology will be applied throughout the project and will be also rendered available with project data generated also after the end of the project according to the fair open access philosophy (see methodology section). (Task output: D1.1) Task 1.1.2 Data Governance – Data Act and the Data Services Act. This Task will create a data governance architecture to ensure the sustainability of the related INTEGRANO output data. This is an interdisciplinary task that will generate important public policy outputs. For this output to be impactful, fair, trustworthy and open, data governance regimes will be required. Aligning INTEGRANO to wider strategic objective in EU data management will be a key objective of this task. The future regulatory framework will include the Data Act and the Data Services Act. The former is particularly important here, as EU states "The Data Act will ensure fairness in the digital environment, stimulate a competitive data market, open opportunities for data-driven innovation and make data more accessible for all". Building on previous EU projects in this area, INTEGRANO will make an important contribution on data governance around sustainability and safety around merging technologies. Task 1.2 Addressing case studies specific goal and scope. (M1-M18). Leader: CNR; Partners: UNIMIB, ARCHE, CENTI. For each design case, The Definition stage of DMADV method will be implemented. Specific goal and scope will be addressed considering the four NMs LCS along with planning of synthesis process and each incorporation processes, consideration of Use Phase and EoL options will be analysed. The relative functional units and system boundaries will

be specified with declaration of assumptions and cut offs and management of data uncertainties along the SSbD process. For each desing case study the relevant set of relevant KDFs will be pecified and the relevant KPIs referred to the five dimensions of safety, sustainability and functionality will be defined. Dedicated design of experiments (DoE) will be specified and the samples generation plan implemented for producing a suitable number of samples for assessing the: (a) P-Chem NMs features (p-chem KPIs) and functionality, (b) Nanocomposite materials (multi-) functional KPIs levels, (c) Eco-toxicity profile by obtaining dose-response curves, (effect factors-EE and related ecotox levels, (d)Human toxicity profile by devising dose-response curves to obtain LOAEL, and NOAEL values. The DoE plan will also consider the emission sampling campaigns associated to the selected (synthesis and incorporation) processing conditions and the (NEPs) samples generation plan will consider the emission assessment that will be also investigated throughout the use phase and end-of-life (EoL) phases by sampling NMs release into the environment (e.g. by airborne NPs sampling, leaching, abrasion, tests, dispersion and transport models…). (Task output: D1.2)
Task 1.3. Dedicated Algorithms and digital Decision Support Toolbox implementation for NMs SSbD (M1-M36). Leader: PRJ; Participants: AllCNR, UNIMIB, ARCHE, CENTI, DRT.
PRJ will design and implement the INTEGRANO digital DST that will implement algorithms for: (1) assessing correlation between set KDFs values in the DoE matrices and obtained KPIs values from experimental measurement and computation referred to the 5Ds for each NMs LCS (2) Multi-Objective Optimisation Design (MOOD) to sort among all possible design cases the multi-optimal ones, simultaneously complying with safety, sustainability and functional KPIs requirements The MOOD algorithm that will be developed within INTEGRANO will evolve the one proposed in ASINA48. Indeed, INTEGRANO will enable integrating the safety and nano-safety dimensions that will be computed exploiting standardised LCA and SCLA frameworks. The new MOOP algorithm will be implemented in the digital DST dedicated to material engineers and products designers, and regulators. PRJ will design and implement the DST architecture to allow a web-based interface for future industrial implementations and will enable different user levels from nanotechnology non-experienced to nano-material engineering expert. The DST will receive specific input by the expert end-user on relevant KDFs affecting the KPIs. The input data will refer to the specific design of experiment (DoE) matrix (T1.2). providing a limited number of KDFs combinations associated design cases data, the DST will be programmed to obtain response functions (correlating KDFs-KPIs). The DST computational kernel will operate the new INTEGRANO MOOD algorithm to select a sub-set of optimal design cases simultaneously complying with the KPIs technical specifications (i.e. low environmental impact and cost, high degree of safety and functionality). Finally, the DST will suggest the end-user the selected sub-set of potentially viable SSbD cases via graphic user interface (GUI) enabling the DST user to operate the (implicit or explicit) weighting and to select among the suggested multi-optimal design cases. The DST will enable direct correspondence between selected design case and expected performance (KPIs expected values). The set of design cases investigated within INTEGRANO will be stored in DST DB, also available for non-expert users. Access to the DST prototype will be given to INTEGRANO industrial partners to assess user experience for future industrial developments and to allow industrial partners to practice for future products design and development. The prototype and a report targeting national/international authorities, and relevant industrial sectors will be issued after DST validation with a limited set of NMs and NEPs design cases. It will include feedback gathered during a workshop organised to test the tool with industrial stakeholders (T6.2). (Task output : D1.3)

Work package WP2 – Experimental Data Generation: NMs provision and characterisation M-Measure (I)

Work Package Number	WP2	**Lead Beneficiary**	3. CENTI
Work Package Name	Experimental Data Generation: NMs provision and characterisation M-Measure (I)		
Start Month	1	**End Month**	42

Objectives
WP2 will address O-7: to apply the SSbD to materials defining a representative set of NMs. WP specific objectives: 1. to provide the type and amount of NMs for p-chem and functional characterisation and tox and ecotox assays and to obtain new data on functional properties of selected NMs and NEPs (T2.1, T2.2,T2.3) 2. to use and adapt existing RA frameworks to the INTEGRANO context, providing practical indication for read-across (identification of similar materials), to obtain relevant data to facilitate the decision process (identification of cut-off values), satisfy regulatory requirements and predict potential risk of NMs (T2.2) 3. to provide experimental supporting evidence NMs fate models validation (T2.4) 4. to quantify safe CoU for manufacturing processes, use of products and EoL (T2.5)

Description
Starting from the selected group of representative NMs industrial potential applications leading to innovative NEPs, an appropriate quantitative characterisation program will be set out and implemented to provide a detailed profile of the NMs along their LC, also supporting grouping and read-across methodology. NMs p-chem and functional characterisation will be carried out to assess NMs features and technical performance. Detection and sampling of NMs emitted in different environmental compartments will be covered to better interpret the NMs LC pathways, and to validate the models proposed in WP3 for fatefactors (FF), exposure-factors (EF) and effect-factors (EE). Activities will also focus on performing RA and establishing safe CoU, as well as assessment of NMs EoL and circularity options for some products. Task 2.1. Synthesis and Provision of the NM groups for targeted applications (M3-M24). Task Leader: CENTI; Participants: UNITO, CNR, BIU, AITEX. The selected group of NMs will be obtained by various synthesis processes provided by partners (CNR, CENTI, BIU, UniTO, AITEX) based on previous project experience and scientific research. The synthesis parameters will be set to obtain specific NMs properties for the required functionalities in the addressed applications (see Table 1.2.2b). Other sources of NMs procurement may be considered according to specific needs and industrial relevance for the targeted applications. The achievement of targeted NMs functionalities and their assessment will support the comparative analysis for functional substitution of conventional chemicals either by direct substitution with (e.g. antibacterial) NMs or by considering the addressed NMs an enabling factor for functional substitution of conventional (e.g. fossil-based) materials with other more sustainable and safer (e.g. bio-based) materials. The NMs Provision will be rationalised and planned according to the samples requirements for carrying out characterisation and assays specified in the DoE matrices provided in WP1. The selected and implemented synthesis processes for obtaining the NMs samples will be described in detail to allow analysis and modelling to be carried out in WP4 for process virtualisation. (Task output: D2.1) Task 2.2. Data mining (M1-M18) Task Leader: CNR; Participants: UNITO, CENTI, BIU, AITEX Given the selected group of NMs identification of reference literature and NMs open access databases (e.g., caNanoLab,eNanoMapper, NR, Nanowerk, NBIK, NIL, NKB, PubVINAS) quantitative data will be searched through a data mining process, including NMs samples availability (e.g., Fraunhofer and JRC NMs repositories). INTEGRANO will also enrich such databases, supporting the setting of a proper general recognised classification of selected NMs. This task will capture basic features properties and information of selected NMs enabling grouping and read-across methodologies to extend INTEGRANO results to a broader set of industrially oriented applications. Results will be associated to other NMs families with common features: behaviour in environmental interactions, eco-/toxicity effects. Data mining will also support the identification of suitable NMs reference ICs based on NMs-specific EE referred to eco-/toxicity ICs. The obtained data will be also useful for (WP2, WP3). Functional substitution among NMs options with comparable features will also be considered. Task 2.3. NMs Characterisation program for selected NMs: size, morphology, p-chem properties (M7-M36). Task Leader: CNR; Participants: UNITO, CENTI, BIU, AITEX This task will set the basis for the whole NMs characterisation program by analysing NMs and their behaviour through their entire LC. NMs p-chem identification and information gathering will be aimed at obtaining (a) chemical substance (compound) information, (b) particle sizes and (c) surface properties according to the OECD GP 49,50. Given the selected NMs classes, an extensive review of existing characterisation methods will be provided to identify the criticalities and gaps to better characterise the size, morphology, and nature of NMs in connection to the attribution of their: p-chem properties, interaction with complex matrices, and potential eco-/toxicological risk. Furthermore, the INTEGRANO characterisation plan will be set out to fill in the SoA gaps and propose advanced characterisation methodologies. This will be obtained by integrating the characterisation techniques, described in detail in the Scientific Methodology (1.2.2) in an innovative way in order to better assess and interpret characterisation results also by means of post processing data analysis and correlation methods supported by digital tools for multifactorial analysis. NMs basic properties are expected to suggest further parameters that may affect functional performance, exposure, environmental fate and related AOPs. Partners will also identify alternative characterisation techniques or related techniques improvements by combination of cross characterisation techniques, e.g., TEM-SEM microscopy with DLS and ICPMS to find data correlations of NMs size measurement applied to composite inorganic-inorganic NMs (e.g., TiO_2/SiO_2 core shell NPs) or inorganic-organic NMs (e.g., Ag-HEC). Experimental data will be correlated to provide full characterisation of NMs through their LC considering their interaction with complex environmental matrices, also for extensive grouping and read-across processes. In combination with the NMs detection campaigns (Task 1.3), comparative characterisation of native NMs with NMs that interacted/reacted with environmental complex matrices will be provided to track NMs features and nature potential changes and to better interpret of eco-/tox outcomes that will be assessed in WP3. Interlaboratory p-chem characterisation will be performed in order to agree on obtained results based on complementary techniques (see task 5.4) (Task output: D2.2) Task 2.4. Characterisation and Detection of NMs and NEPs in real-case LC scenarios (M13-M42). Task Leader: CNR; Participants: PRJ, CENTI, UNITO, ARCHE, B4C, UniMIB, RoV, DRT, VERL

Task 2.4.1 NMs characterisation in their native form and after environmental interaction. Characterisation of NMs will be at: (A) their native state (B) incorporated (into matrices or coatings) (C) after emission to environmental compartments. A) The Synthesised group of NMs at their native state will be characterised (synthesis stage gate, 1st step of NMs LC) in order to identify and quantify their size, morphology, p-chem features, Zeta potential. (CNR, UNITO, UniMIB). The obtained results will enable detailed grouping and read across process as well as anticipating the potential interaction with complex environmental matrices. B) The composite NMs obtained by NPs incorporation (2nd stage of NMs LC) will be characterised to assess the level of intended functionality (i.e., photoluminescence, antibacterial activity, photocatalytic activity, …) for the targeted NEPs applications supporting their industrial and commercial relevance (CNR) C) The NMs emitted in different environmental compartments at different stages of their LC will be (i) detected and (ii) characterised. The NMs interaction with complex environmental matrices will be assessed by measurement of potential NPs size, morphology, and nature change due to processes such as: chemical degradation, hetero-agglomeration, dissolution… by employing methods and characterisation techniques used in Task 1.2. The comprehensive characterisation results of native NMs and read-across outcomes will corroborate the interpretation of the eco-/toxicology effects assessed in WP2. The comparative analysis obtained by the characterisation of native NMs (Task1.3.1) with NMs emitted in the environment (Task1.3.2) will allow better interpretation of EE obtained for eco-/toxicity assessment in WP2. Interlaboratory characterisation will be performed in order to agree on obtained results (UNIMIB, CNR) (Task 5.4) Task 2.4.2 Detection of NMs emitted into the environment (synthesis & incorporation). Dedicated campaigns will be set up to assess NMs emission to environmental compartments at (a) synthesis, (b) incorporation, (c) (modelled) use, (d) (modelled) EoL LC stages. For synthesis and incorporation NMs detection and sampling will be run at pilot sites (CENTI, CNR, UniTO, AITEX, BIU). For use phase and EoL specific experimental simulation tests will be carried out in order to enable detection and quantification of emitted NMs. Detection of emitted NMs will be focussed on (a) Airborn NMs and (b) waterborne NMs according to the methods reported in the methodology section. Task 2.4.3 Experimental simulation of NMs Emission in environmental compartments with complex matrices (use & EoL). NMs samples interacting with environmental compartments will be obtained through experimental tests simulating environmental stressors in use- and EoL-LC stages. Standardised tests and methodologies51 will be used to simulate NMs emission and interaction with the environment referred to the use-maintenance phase stress modelling (methods reported in the methodology): such as abrasion, weathering, washing. These and other simulation tests will allow detecting airborne NPs, as well as NPs leachates due to potential release of NPs in water medium by water filtration SiC membranes as NEPs (B4C, CNR) during use phase by applying the techniques established in the characterisation program (Task 1.2). The fourth stage of NMs LC will be considered by investigating, different EoL scenarios, landfilling, incineration, recycling, connected to specific NMs and NEPs design options. The EoL stage will include characterisation of NMs released into the environment by leaching, dissolving, diffusion and transport processes due to combustion, handling, disassembly, cutting, grinding, drilling, etc. The experimental measurements obtained will be employed to increase knowledge of NMs environmental pathways for validating emissions models aimed at providing Fate Factors (FF) computations. (Task output: D2.3) Task 2.5 Determination of safe condition of Use (CoU) and Risk Assessment (RA) (M19-42). Task Leader. ARCHE; Participants CNR, UniMIB The release of NMs during all stages of the occupational NEP LC will be assessed with specific focus on exposure for synthesis and incorporation52 and for consumer exposure in use phase, EoL release assessment will involve detailed analysis of NEPs disassembly and management NMs, possibly including mechanical and chemical treatment of NMs at EoL, potential release connected to disposal and landfilling practices or emissions due to combustion in incineration processes. Safe CoU are specified according to ECHA Chapter R.14 for processes and product considering occupational, consumer and environmental exposure. Emission factors in relevant EoL scenarios will be quantified for occupational and environmental exposure assessment. Circularity options will be considered by possible reuse or recycling of NMs in subsequent LCs. (Task output: D2.4)

Work package WP3 – Nano Tox and nano eco-tox data generation

Work Package Number	WP3	**Lead Beneficiary**	1. UNIMIB
Work Package Name	Nano Tox and nano eco-tox data generation		
Start Month	6	**End Month**	44

Objectives

WP3 will achieve O-2 to develop and validate new toxicological and eco-toxicological assessment methods to develop and validate new toxicological methods; O-4 to gain insights and predict mid- and endpoint toxicology of selected NMs as a function of their properties and use scenarios. The following specific objectives will be addressed: 1. to assess eco-toxicology of investigated composite NMs groups (T3.1) 2. to provide (eco-)toxicological EE based on dose-response experimental outcomes (T3.1) 3. to identify and correlate dimension, morphology and other p-chem features modulating impact on AOPs (T3.2) 4. to assess exposure scenario and carry out studies on NMs persistence and bioaccumulation even in low concentration doses at prolonged simulated exposure (T3.1)

Description
WP3 is targeted to measurement and data generation related to nano-eco-toxicity and nano-toxicity for obtaining specific information based on experimental tests and measurements on specific effects related to human toxicity and eco-toxicity, supporting INTEGRANO framework for the assessment of safety and sustainability of NMs along their LCS, based on a quantitative approach. The outputs of WP3 will enable defining new nano-specific EF and EE to obtain new CFs for toxicological dedicated nano-ICs for the LCIA (WP4) Task 3.1. Ecotoxicity: Fate and effects in biological and environmental relevant matrices (M6-M44). Task Leader: CNR; Participants: UNIMIB, BIU, UniTO In this task NMs study of release into the environment that will determine the ultimate exposure's form and level to living organisms in the environment, taking into account eco-toxicity effects. Prior information will be exploited, in a read-across scheme, and benefitting of detection campaigns (Task 1.3). to facilitate the understanding of the overall distribution, fate and exposure of NMs, while limiting and prioritizing testing. The interaction of NMs as incorporated into NEPs with complex environmental matrices will be investigated by considering mechanisms of environmental p-chem transformations (e.g. hetero-clustering, morphology and chemical changes) to correlate with ecotoxicity assessment. These key parameters will be derived by SoA assessment models and models developed in Task 3.1 that consider also transport, transformation and fate of NMs. Following the fit-to-purpose OECD PCDF, INTEGRANO will estimate environmental exposure and feed this information to dosimetry and environmental fate models, also taking into consideration long term effects due to low doses exposure and persistence. NMs features in the environmental matrices will be correlated to the characterising factors that link to likelihood, route and organism (dose) exposure. CNR will perform specific ecotoxicological assessments to check the ecosafety of NMs and NEPs through their (modelled) LC, to prevent toxicity effects in the marine (water, sediments) and terrestrial (water, soil) environments by using standard and innovative bioassays. (see methodology). Acute and behavioural responses will be considered. (Task output: D3.1) Task 3.2. Collecting toxicity data and filling gaps for an early identification of hazard potential. CFs for toxicological assessment by in-vitro advanced models (M6-M44). Task Leader: UNIMIB; Participants, CNR, , AITEX, RoV, B4C, DRT , PRJ In-vitro and in silico testing/modelling of the hazardous properties of the NMs and NEPs will be performed to detect the relationships between the p-chem properties and the toxicity outcomes. In INTEGRANO, the following new methodological approach is proposed: the NMs/NEPs hazard assessment will be performed for every step of the NMs life cycle by using in-vitro realistic exposure, using human lung and skin cell/tissue cultures exposed at the air-liquid interface (ALI), or in submerged condition. When relevant NMs/NEPs will be also tested after aging. To move towards a higher representativeness of in-vivo doseresponse relationships, the in-vitro data can be coupled with the Multiple-Path Particle Dosimetry (MPPD) model applied to the environmental monitoring campaigns aimed at determining the airborne released NMs, to link a response in-vitro to possible occupational hazards. In this perspective, three main nano-specific indicators/nano specific characterizing factors have been identified:(1) oxidative potential (OP), (2) inflammation, and (3) DNA damage. Related biological markers, linkable to KEs along putative or established AOPs, will be also measured by molecular techniques. The use of zebrafish embryos – a well-established model for both environmental and human hazard assessment - will complement the in vitro studies to make the results more consistent at the organismic level. Correlation between the NMs p-chem properties with the analysed biological outcomes for the different indicators will be performed. The correlation will be explored also by PCA and, if applicable, with multivariate correlation models to obtain a comprehensive evaluation of the NMs' properties that drive the toxicological outcomes, as well as the design and re-design of the materials. (Task output: D3.2)

Work package WP4 – Analysis, Assessment and Prediction Models

Work Package Number	WP4	Lead Beneficiary	2. ARCHE

Work Package Name	Analysis, Assessment and Prediction Models		
Start Month	12	**End Month**	44

Objectives
This WP will achieve O-3: to gain insights and predict mid-point toxicity and eco-toxicity of selected NMs as a function of their properties and use scenario. The following specific objectives will be addressed: 1. To identify relevant emission and exposure determinants and establish a mechanistic exposure model that is applicable for regulatory chemical safety decision making for indoor and outdoor environments (T4.1) 2. To assess environmental risks in each LC step by predicting waste mass flows and accumulation in air, water (marine, fresh and groundwater) and soil, and compare with the ecotoxicological profiles (T4.1)

Description

Fate and exposure modelling to estimate fate and exposure factors will be developed to support nano specific CFs development. FAIRification and harmonisation of data generated within the project and collected from external sources will be performed in order to guarantee accessibility and usability. In silico modelling for leveraging generated and collected data will be carried out to generate response functions supporting input for the MCDA.

Specific activities will include the application of in-silico methods to model performance and predict specific toxicological effects of NMs. They will include grouping and read across methods to expand the pool of data on the selected NMs and modelling of the environmental transfer processes of NMs and NEPs. Data will be cross checked with the in-vitro tests as described in WP2.

Task 4.1. Modelling of environmental NMs fate and exposure (M12-M44). Task Leader: ARCHE; Partners: UNIMIB, CNR

Pollution mass flows are predicted by using well-established mechanistic models that take into account the use patterns in each life-cycle stage. Emission factors are quantified in relevant units with respective to the release scenario.51 Existing biological and environmental fate exposure data and factors will be collected regarding release mechanisms and hot-spots, life-cycle scenarios, NMs properties and exposure routes and patterns (duration and frequency). The data will be documented by following FAIR principles to easy-to-use emission library and utilised using novel parsimonious computational models covering the whole NM lifeline, from manufacturing and processing of the NM to application and disposal of the nano-enabled relevant product. Air, water (marine, fresh and groundwater) and soil concentrations are predicted according to the life-cycle release assessment.53

Dispersion of air emissions in manufacturing are predicted by using well-established Gaussian dispersion model for stack and fugitive emissions. As a starting point, open access databases and models will be considered for Environmental fate and exposure predictions such as NanoFASE model and SimpleBox4nano, depending on the spatial and temporal resolution required to assess NMs emissions in specified environmental compartments during NMs LC. The NanoFASE model will be required for multimedia spatiotemporal resolution for NMs fate and exposure modelling. The approach used is to partition a defined geographical region into a grid, each grid cell representing one or more environmental compartments - soils, surface waters and bed sediments.

NanoFASE is driven by NM emissions data, and predicts spatio-temporal environmental concentrations in soils, surface waters and sediments (PECs). SimpleBox4nano, being a regulatory-relevant box-type multimedia model, will be considered for mesoand global-scale modelling to simulate environmental fate of chemicals as fluxes (mass flows) between a series of well-mixed boxes of air, water, sediment and soil on regional, continental and global spatial scales.

Primary NMs emissions into the environment will be considered for synthesis and incorporation LC stages by specific modelling of the processes, NMs emission sources, and their interaction with the working environment. This will include modelling of workers exposure. Emission models will be validated and calibrated based on results of dedicated campaigns for NMs detection and quantification obtained in Task 1.3. Airborne NPs specific mass concentrations will be simulated using the Near field/Fear field model, including parametrization of NMs features (mass, volume, density distributions) and of the work environment. This will include processing environment volume, flow rates, air mixing between Near field and Far field environmental compartments, and local Exhaust Ventilation (LEV). For NMs incorporation processes, transfer efficiency parameters will be considered. Quantification of the CoU will be possible by considering Recommended Exposure Limits (RELs) for specified respiratory fractions referred to Time Weighted average (TAW) of the selected NMs. A similar approach will be considered to assess NMs emission during NEPs use phase. Models will be validated and calibrated based on emission data obtained through experimental simulation of use phase environmental stressors.

Fate and exposure modelling connected to the EoL will be carried out applying the same modelling approach, which starts from the detailed description of the NMs handling and management for the considered EoL options, for which specific experimental conditions will be considered (Task 1.3). Calibrated models will be also useful to extend the

application of the model for quantification of emission factors to other design cases (by changing the NMs, processing and work environment parametrization). The numerical implementation of the emission and exposure models will allow to carry out a sensitivity assessment related to synthesis and incorporation processing parameters and to use phase conditions close to regime operation, by applying the DST multi-optimisation algorithm, which will allow to obtain the most favourable conditions (lowest attainable emissions factors), complying with the required technical performance of NMs and incorporated composite NMs. (Task output: D4.1) Task 4.2. In silico-modelling: training of ML tool and response functions generation (M12-M44). Task Leader: CNR; Partners: PRJ, CNR, ARCHE, UniMIB, BIU, AITEX This Task will: (1) use the limited amount of sufficient project-generated data to obtain response functions associating KDFs and KPIs obtained experimental data and by deterministic-mechanistic modelling, (2) use external FAIRified (big) data obtained from data mining task (Task 1.2) to train and validate ML algorithms. The project-generated data will be treated by a dedicated curation and interpolation algorithm which will capture non-linear functional dependence of KPIs on KDFs by interconnecting decision and performance spaces54. The ML models will be used to generate response functions describing the dependence of NMs p-chem features and toxicity effects levels as a function of synthesis, incorporation parameters, use conditions and EoL options. Iterating through sensitivity analysis scenarios they can provide data to optimize a multicriteria algorithm,55,56,57 as it has been leveraged in previous developed SSbD frameworks and adopted by the recently created draft proposed in the context of an Administrative Arrangement between DG RTD and the JRC.58 A number of regressors will be considered from Support Vector Machines or Neural Networks to Linear Trees, Xboost and Random Forests and those providing the highest predictive performance while capturing non-linearities between important features59,60 will be explored and selected. Model validation will occur though goodness of fit and robustness metrics. This task will also provide insights into the features across the desired dimensionalities. (A) Dimensional, morphological, p-chem characterisation of NMs and NMs functionality assessment, (B) Release/ Emission, EF, (C) NMs Eco-Toxicity EE, (D) Human Toxicity EE. Response functions obtained by in-silico modelling will complement those obtained by deterministic-mechanistic modelling and from direct experimental measurements. The ML model will be based on a large number of hypothetical implementations of the exposure/release models of WP3. Predictive ML models can outperform read across techniques if enough data can be compiled. The two approaches will be combined in a supplementary fashion (Task output: D4.2, D4.3) Task 4.3. Modelling and Virtualisation of the synthesis and incorporation processes (M12-M30) Task leader: PRJ, Partners: CENTI, AITEX, BIU, UniTO, CNR. In this task the all synthesis and incorporation processes will be analysed and duly modelled, by mapping the energy-mass balance as a function of specific values of the set processing parameters in accordance to the specified DoE matrices. This will allow virtualising the process in such a way to obtain values for environmental, social economic, impact categories when processing set (KDFs) values are specified. For each addressed process in the project a process specific digital module will be generated to be integrated in the DST (WP5), thus enabling the SSbD integrated assessment by performing integrated LCA, SCLA, LCC. (Task output: D4.4) Task 4.4 Economic and social modelling (12-44) Task leader: BIU, Partners: UniMIB, CENTI, AITEX, UniTO, CNR, B4C, RoV, VERL, PRJ, DRT Economic and social modelling and monetization of externalities to identify and quantify the negative externalities that can be avoided through the implementation of NMs, assessing the multiple sustainability criteria using mathematical models. Monetization of the negative externalities, which will involve assigning a monetary value to the avoided impacts. This will enable the internalization of externalities into the market price of NMs, providing incentives for its development, production, and use. (Task output: D4.5)

Work package WP5 – NMs Integrated Impact assessment for SSbD based solutions: Design and Validate

Work Package Number	WP5	**Lead Beneficiary**	9. PRJ
Work Package Name	NMs Integrated Impact assessment for SSbD based solutions: Design and Validate		
Start Month	20	**End Month**	48

Objectives
This WP will achieve O-2 to develop and validate new toxicological and eco-toxicological assesmsent methods; O-5 to promote the integration of existing assessment frameworks, standards and practices; O-7 to apply the SSbD integrated

approach to materials defining a representative set of NMs classes, including their applications and referring to different sectors and implied value chains (VCs); The WP specific objectives are:
1- To allow a SSbD quantitative based impact assessment, providing measurable and comparable outputs (T5.2)
2- To implement an holistic approach including environmental, human safety, economic, social as well as functional dimensions simultaneously (T5.1,T5.3)
3- To exploit the a SSbD digital DST which supports and facilitates the analysis and selection of competitive solutions (T5.3)

Description

WP5 addresses the integrated impact assessment by proposing novel nano-specific impact categories that will enable the application of assessed standards: ISO14040-44 for life cycle assessment (LCA) and ISO14067 for Carbon FootPrint (CFP). WP5 will also enable integrated assessment of hazard, environmental, social, and economic impact considering functional performance at the same time. WP5 will implement the last two phases of the DMADV: Design and Verify-Validate. WP5 will implement the project integrated approach to the SSbD aggregating and elaborating all project acquired and generated data into proposed SSbD solutions to the considered design cases. Design and redesign of new bio based chemicals, NMs and nanocomposite materials will be supported by the SSbD Decision SupportToolbox. The DMADV method will be recursively operated according to the stage-gate process (see methodology) through the four life cycle stages (LCS): (1) NM synthesis, (2) NM incorporation in nanocomposite materials (NCM) and Nano-enable products (NEPs), (3) use phase, (4) End-of-Life with recycling options.
Task 5.1. Integrated safe and Sustainability assessments (M20-M42). Task leader: UniMIB; Participants: PRJ, CENTI, BIU, AITEX, UniTO, ARCHE, PRJ, B4C, DRT , CNR
The INTEGRANO integrated impact assessment framework is the scientific breakthrough that will enable comprehensive LCIA addressing hazard, environmental, economic, and social dimensions by exploiting existing standards. This will be accomplished by performing the integrated LCA, SCLA and LCC for the selected group of NMs along their life cycle analysed according to a cradle-to-grave or cradle-to-cradle approach, according to the NM circularity model. Task 5.3 will enable the integrated approach by proposing the definition of novel impact categories (ICs) for the toxicity potentials and the eco-toxicity potentials associated to the NMs. This will be possible thanks to the assessment of emission, fate, exposure-intake and effects factors and by the definition of suitable characterisation factors for the addressed NMs. In this way the already standardised procedure for environmental impacts assessment provided by LCA 10040-44 standards may be directly transferred to the NMs hazard assessment by providing the NM safety performance.
The multi-dimensional impact assessment will be performed with a modular approach according to the described stage-gate process. Each NM LCS stage will be considered as autonomous functional system. This will enable defining specific system boundaries and functional units associated to the addressed functional KPI (Task1.1).
The impact assessment for the safety and sustainability dimensions will be performed in accordance with the standards61 assessment phases (1) Goal and Scope definition, specifying: the boundaries of each functional system associated to each NM-LCS, the assumptions and cut-offs applied to the system model, the functional unit (based on NMs and NEPs functionalities) (2) Inventory, providing a comprehensive functional system energy and mass balance accounting for flows across the system boundaries, including NMs emissions (as per the dedicated sampling and modelling results (T2.4, T4.1) (3) LCIA performed according to INTEGRANO proposed impact method integrated with NMs-specific eco-/toxicology ICs (4) Interpretation of results The LCA, LCC and SLCA will be carried out by using OpenLCA SW, which allows for specific programming and integration of computational framework; primary data will be collected from partners by experimental and processing data; secondary data will be derived by standard databases (Ecoinvent 3.8 for LCA, PSILCA for SLCA, available economic data from and social data from EUROSTAT and other official data sources). The considered ICs for LCA will involve conventional local and global impacts such as potential for climate change (GWP), eutrophication EP), acidification (AP), resources depletion (ADP, ADP-En), ozone (ODP, POCP), human toxicity (HTTP), ecotoxicity (MAETP, FAETP, TETP) to which the nano-toxicity and nano-eco-toxicity new NMsspecific ICs proposed by INTEGRANO will be added. Within the proposed integrated framework, the SLCA ICs will include the UNEP recommended stakeholders categories62: workers, local communities, consumers, value chain actors, society and children. In particular: safety, human rights, working conditions, socio-economic repercussions, cultural heritage and governance connected to the production-, use- and management of NMs at EoL will be considered. The SLCA will be imply addressing subcategories like percentage of employees, working conditions (in connection to occupational exposure). As specified by ISO standards The Functional systems and related Inventories will be referred to specific location (regionalised assessment) and reference time frame in order to properly select energy mixes, emissions effects, specific raw material and energy costs, social impacts. (Task output: D5.1)
Task 5.2. Data completeness and integration (M20-M30). Task Leader: CNR; Partners: CENTI, BIU, AITEX, UniTO, UNIMIB, ARCHE, PRJ, B4C, DRT
Collection of data generated in the previous WPs will allow the creation of case study specific datasets relating

to safety, sustainability and performance. Base on the data mining process carried out in WP1, results (FARIfied datasets63,64) generated from previous and ongoing EU projects will be leveraged and integrated in the data generated within the project. Data capturing will ensure transparency for detailed information or the protocols, instrumentations and measurement matrix, allowing future data re-use. Besides exploring and leveraging datasets. Based on previous project results predictive ML models will be used as a proxy of deterministic models and will be used as such under the INTEGRANO framework to simplify exposure and release estimations.
Task 5.3 Design Safe and Sustainable NMs (M25-M48) Task Leader: PRJ; Partners: CNR, CENTI, BIU, AITEX, UniTO, UniMIB
Task 5.3 is characterised by the digital assisted selection of the multioptimal SSbD cases. Within INTEGRANO proposed IMM framework the SSbD strategy is developed to maximise all KPIs associated to each of the five dimensions considered (environmental, social, safety, economic, functional). As a consequence of the KDFs values changing e.g. by selecting different synthesis or incorporation set processing parameters, different synthesis recipes, the resulting NMs, NCMs and NEPs KPIs will be affected. Considering to test manually all possible KDFs combinations and checking for multiple KPIs symultaneous maximisation would be inapplicable: exceedingly time consuming and expensive. For this purpose, the digital DST to be delivered in Task 1.3 will operate the algorithms to (1) find functional dependence of KPIs on KDFs and to sort among all possible KDFs combinations the ones that simultaneously maximise the KPIs. This way the automatic digital assisted multi-objective optimisation design will be applied for each design case. This will be performed by the DST user that will provide the required input: (a) selection of the life cycle stage among (1) synthesis, (2)incorporation, (3) use phase, (4) End of Life options; declare: (b) the number of KDFs, (c) the specific quantity and unit of measurements of each KDF, (d) the range in which the KDF will span; the number of KPIs, (e) the specific quantity and unit of measurements of each KPI; for each reference design case (associated to a produced sample) according to the DoE matrix the user will insert: (f) the associated KDFs values, (g) the corresponding KPIs values associated to the design case. The DST will run the algorithm and return a set of selected multi-optimal design cases that simultaneously comply with the maximisation of the addressed KPIs. Each multi-optimal design case is associated to unique set of KDFs values (which do not necessarily correspond to the reference design cases KDFs set values). This automatic sorting process basically filters all possible design cases that will not comply with the KPIs multi-optimisation, which need to be discarded. The procedure does not arbitrarily restrict the set of potentially viable SSbD solutions, on the contrary it keeps all the suitable options available for the sorting process assigned to the verification and validation final step.
Task 5.4 Verify and Validate (M25-M48) Task Leader: CNR; Partners: CENTI, BIU, AITEX, UniTO, VERL, RoV,
Verification and validation is the final step in the DMADV. The DST through the DST GUI will provide the set of multi-optimal design cases, among which the DST user will operate the selection of the best SSbD option. This process will be digitally assisted but the final decision is in charge of the DST user. Indeed the DST will support informed decisions. This will be worked out through the DST user weighting procedure: by setting weights to the addressed KPIs the user will be able to select the best SSbD case.
For each tentative weighting, the user will be provided the expected KPIs values associated to the KPIs weights selection. This way the DST user will be informed about consequences on each attainable performance (KPIs values) due to his selection (weighting option). When the best SSbD case will be sorted the associated KDFs values are specified by the DST. With the obtained quantitative information on the best KDFs choice the testing and validation process will be started by producting a suitable number of samples subject to final functional testing and toxicity and eco-toxicity assays to assess actual effects of expected KPIs values for the fixed KDFs values. Interlaboratory testing and validation will be done (Task outptut: D5.3, D5.4)

Work package WP6 – Stakeholders engagement, communication and dissemination

Work Package Number	WP6	**Lead Beneficiary**	5. AITEX
Work Package Name	Stakeholders engagement, communication and dissemination		
Start Month	1	**End Month**	48

Objectives
This WP will achieve O-8 To provide recommendations and decision support for standards and policies for safe and sustainable design of NMs and NEPs; O-9: to transfer knowledge and valorise project results. Specific objectives of WP5: 1. To establish a forum for the cooperation with the standardisation and regulation bodies and exploit integration of INTEGRANO data in the existing policies and standards (T6.2) 2. To provide recommendations on specific policies regarding NMs characterisation protocols or addressing specific adverse effects of the studied materials (T6.3)

3. To support chemical and advanced materials manufacturers in addressing SSbD approach for selected materials (T6.2, T6.4) To establish an efficient platform for engaging with a wider community and adopt concrete measures for communicating INTEGRANO scientific results, sharing general knowledge and facilitating capacity building, education and networking in the field of SSbD of chemicals and advanced materials (T6.2)

Description
WP6 is aimed at opening up the scientific and technological value generated within the project, to promote specific results and methodology dissemination and exploitation to facilitate engagement of all relevant stakeholders along the involved value chains. An open approach will be implemented to foster acceptance and effective uptake of the developed methodology and DST in different industrial sectors, also promoting the interaction and mutual data feed with other funded projects and collaboration with relevant player in SSbD such as JRC and PARC. Task 6.1. Developing, updating and implementing the INTEGRANO PDER (M1-M48). Task Leader: PRJ; Participants: all A preliminary PDER will be published by M3 to set out a general roadmap for activities and expected results, indicating specific formats, assignments for partners, ownership or co-ownership (incl. external partners), forecasted timelines, target stakeholder groups and dissemination tools/channels. It will also contain a communication plan, where specific communication needs of the users will be analysed and proposed (e.g., schedule of project meetings and external related meetings), along with the strategy to monitor impacts and collect feedbacks. The first PDER will undergo periodic updates. Task 6.1.1 Dissemination Activities: Dissemination to the international scientific and technological community will be achieved through scientific publications and presentations at relevant conferences and events, leading events at national as well as international level, to address different audiences. This will increase the visibility of the project's outcomes and will instigate the necessary feedback in accordance with confidentiality levels agreed by the consortium and the IPR specified in the CA. A set of specific conferences and event for disseminated results will be provide buy the DCE manager and partners invited to participte and contribute. Task 6.1.2 Communication Activities and Tools: The communication activities and tools will target general public/ consumers and will support the dissemination actives toward industrial and citizen target groups. The project visual identity will be defined together will all the necessary templates and materials (logo, ppt, brochure, rollup, social media, press releases..)needed to maximize the diffusion of project challenges and results. An interactive project website will be created and used both for internal communication and management purpose (private section) as for reaching the public. The private section will include: updated project documents, notifications, calendar of deliverables, milestones, technical and financial reporting, meetings, private chat forum and databases. The public section will include links to partners, gallery of topics of interest, links to events organised bythe consortium and forum for discussions. INTEGRANO will engage journalists and ensure media coverage of the project throughout its course via social media content, news and press releases. (Task output D6.5) Task 6.2. Stakeholders identification and engagement (M5-M48). Task Leader: AITEX Participants: UNIMIB, PRJ, DRT, UNITO, ARCHE, CENTI, CNR, BIU, VERL, RoV, B4C, and DRT Task 6.2.1 Stakeholders mapping and identification: INTEGRANO will map the various stakeholders involved in the valued chains involved in the project and large set of stakeholder in EU linked to chemicals and advanced material sectors, as well as policy makers, public authorities, Innovation hubs and incubators, and NGOs of for optimal dissemination of results, obtaining feedback and advice, establishing cooperation activities related to project implementation, networking and maintaining a continuous dialogue to ensure their access to developed methodology, guidelines and decision support tool during and beyond project lifetime. A set of selected stakeholders representing largely involved sectors and authorities will be invited to participate to the project Advisory Board. Task 6.2.2 Stakeholders engagement and development of a shared support and agreement. A communication platform will be set up for the continuous interaction of stakeholders involved the value chains and in public authorities and standard bodies. An IT portal will be set to invite different participants to share their vision, data, needs relate to SSbD approach and will serve as Think Tank also for sharing experience, expertise and public result for the EU funded project, periodic webinar will be organized to assess needs, requests, insight related to possible conflict of interest and potential impact affecting each stakeholders group. At least one f2f workshop dedicated to each involved value chain and industrial sectors (cosmetics, water treatment, textile) will be organized and a general event dedicated to SSbD applied to chemicals and advance materials, involving representatives from different industrial sectors, international governing and standardization organizations, academia and JRC and PARC representatives. The platform will serve also for training dedicated to students, PhD, young researchers and industry representatives. Presentation and participation to major sectorial events and conference in EU will support the engagement and the involvement in the SSbD Think Tank platform. (Task output D6.6) Task 6.2.3 Synergies with other funded project: specific yearly event online or f2f will be organize to connect, create

synergies and share insights projects funded under the same call and from the following topics: CE-NMBP-42-2020, HORIZON-CL4-2023-RESILIENCE-01-21 and HORIZON-HLTH-2022-ENVHLTH-04-01. A dedicated area of the IT platform will be developed for EU funded project interaction, information and results exchange. (Task output D6.10) Task 6.3. Development of Guidelines for integrative impact assessment and SSbD methodology application (M12-48). Task Leader: UNIMIB Participants: ARCHE, PRJ, CNR, AITEX, CENTI. Guidelines for use of SSbD methodology will be developed addressing policy maker, standardization organization, industry with specific recommendation for different users/stakeholders and industries. This task will also analyse the feasibility of broader use of integrated SSbD models across EU legislation. The task will integrate technical-performance data and environmental-health and additional social and economic data generated through the consultation process, producing as a result a document of guidance to be shared with ISO Committees, OECD and PARC. In the task JRC will be invited to collaborate. In addition this task will: (i) conduct an assessment of the implications of INTEGRANO approach with respect to the invocation of the precautionary principle (PP; Art. 191, EU Treaty) across all the relevant pieces of legislation (EU-Commission, 2000); (ii) review recent case law involving the application of PP in the domain of safety; (iii) conduct a literature review focusing on the application of the principles of PP and evidence-based policy in the domain of chemical regulation, (iv) review the literature that applies the PP to the use of AI to resolve social problems. (Task output: D6.4)

Work package WP7 – Management and Coordination

Work Package Number	WP7	**Lead Beneficiary**	1. UNIMIB
Work Package Name	Management and Coordination		
Start Month	1	**End Month**	48

Objectives
The WP will assure quality control, management, internal communication and risk control in order to properly achieve the implementation objective and expected outcomes. The specific objectives of WP5 are 1. To provide administrative, legal and secretariat services for the day-to day project management, implement financial and resource planning and monitor timelines and budget of the project implementation (T7.1 T7.2) 2. To ensure quality of project deliverables, monitor and mitigate risks along the project implementation. To facilitate internal communication and decision mechanisms for substantial revisions and provide an internal data management system and a centralized communication channel with the Commission and key external partners (T7.3)

Description
WP7 will consider operational and administrative management, training and education, data management, governance and internal communication, management of risks and IPR. Task 7.1. Operational management and quality control of the project and consortium (M1-M48). Task Leader: UNIMIB; Participants: PRJ The activities will include day-to-day project management and secretariat support to the project, including management of deliverables, minutes, legal documents pertinent to the project. Providing internal communication helpdesk on administrative and financial issues and support to partners regarding use of EC web platform, templates, etc., UNIMIB and PRJ (Project Management Team) will keep continuous record with dedicated working documents on project budget, specific WPs and tasks implementation monitoring. They will keep record of Consortium queries to be addressed by decision making mechanism and ensure that other partners are provided with up-to date information and instructions regarding their inputs to administrative processes. It will also include logistic and administrative support to monitoring/ planning meetings. (Task outputs: D7.1) Task 7.2 Financial management Leader: UNIMIB Participants: PRJ (M1-M48). UNIMIB will advise the partners on Horizon Europe financial guidelines. The PMT will be the main contact for the partners to clarify issues regarding costs eligibility and EC reporting guidelines, contractual and legal status, and technical reporting. The Coordinator will evaluate and validate the technical performance of the partners vs. the stated costs for the respective periods. and will also inform partners about irregularities and modifications. Templates for internal follow up of person months, equipment and consumable costs will be designed and delivered to all partners. Task 7.3. Internal coordination, communication and relation with the Commission (M1-M48). Task Leader: UNIMIB; Participants: all In order to facilitate internal collaboration and communication a collaborative platform and repository for knowledge

management will be set up supporting the secure and updated exchange of larger project information (reports, data, etc.), management of communication procedures and tools will be implemented to facilitate exchange among partners (internal communication) and with interested entities outside the consortium (external communication). The internal communication will be supported by organization of meeting on regular and periodic basis: (a) General Assembly every 6 months. These meetings will include an overview of the last period achievements (b) Executive Committee 6-monthly to report on the consortium management, changes in the work programme, dissemination and exploitation issues will be raised, (c) WP technical meetings (online) every 2 months for coordinating the work at WP level (one meting for each WP) (d) WP leaders meetings (online) every 3 month – organised and followed by the Coordinator and PMT, to discuss the planning of WP's interactions and the definition and follow-up of internal deliverables and meetings. (e) The management team meeting (online) every 2 weeks to discuss managerial issues.

STAFF EFFORT

Staff effort per participant *Grant Preparation (Work packages - Effort screen) — Enter the info.*								
Participant	**WP1**	**WP2**	**WP3**	**WP4**	**WP5**	**WP6**	**WP7**	**Total Person-Months**
1 - UNIMIB	8.00	1.00	33.00	2.00	4.00	6.00	16.00	70.00
2 - ARCHE	2.00	3.00		10.00	2.00	2.00	1.00	20.00
3 - CENTI	8.00	31.00		6.00	8.00	2.00	2.00	57.00
4 - CNR	30.00	38.00	3.00	15.00	5.00	7.00	2.00	100.00
5 - AITEX		20.00	5.00	6.00	8.00	10.00	2.00	51.00
6 - BIU		22.00	1.00	8.00	26.00	6.00	2.00	65.00
7 - VERL		10.00		6.00	6.00	2.00	2.00	26.00
8 - UNITO		32.00	1.00	2.00	3.00	5.00	2.00	45.00
9 - PRJ	12.00	2.00	2.00	3.00	25.00	12.00	11.00	67.00
10 - ROV		9.00	3.00	4.00	2.00	2.00	4.00	24.00
11 - B4C		10.00	3.00	2.00	2.00	3.00	2.00	22.00
12 - DRT	1.00	7.00	7.00	2.00	3.00	3.00	2.00	25.00
Total Person-Months	61.00	185.00	58.00	66.00	94.00	60.00	48.00	572.00

LIST OF DELIVERABLES

Deliverables

Grant Preparation (Deliverables screen) — Enter the info.

The labels used mean:

Public — fully open (⚠ automatically posted online)
Sensitive — limited under the conditions of the Grant Agreement
EU classified —RESTREINT-UE/EU-RESTRICTED, CONFIDENTIEL-UE/EU-CONFIDENTIAL, SECRET-UE/EU-SECRET under Decision 2015/444

Deliverable No	Deliverable Name	Work Package No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
D1.1	First data management Plan	WP1	4 - CNR	R — Document, report	PU - Public	3
D1.2	Report on the goal and scope of addressed case studies, including KDFs and KPIs definition	WP1	9 - PRJ	R — Document, report	SEN - Sensitive	18
D1.3	Digital Decision Support Toolbox for quantitative based integrated impact assessment towards SSbD solutions	WP1	9 - PRJ	OTHER	SEN - Sensitive	24
D1.4	Final data management Plan	WP1	4 - CNR	R — Document, report	PU - Public	18
D2.1	Set of NMs samples	WP2	3 - CENTI	OTHER	PU - Public	24
D2.2	INTEGRANO integrated database (DB) periodic release	WP2	3 - CENTI	OTHER	PU - Public	36
D2.3	DB on NMs detection campaigns in real and simulated environment for Fate Factors assessment	WP2	4 - CNR	OTHER	PU - Public	42
D2.4	Report on Conditions of Safe Use	WP2	2 - ARCHE	R — Document, report	PU - Public	42
D3.1	Quantitative assessment of Eco-toxicity endpoints for indication of suitable nano-	WP3	4 - CNR	R — Document, report	PU - Public	44

Deliverables

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Deliverable No	Deliverable Name	Work Package No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
	specific EE for marine and terrestrial environment eco-toxicity ICs					
D3.2	Relevant dose-response functions for the NMs in their different LC stages, for human and environmental toxicology outcomes supporting the definition of nano-specific EE for human and environmental toxicity ICs	WP3	1 - UNIMIB	R — Document, report	PU - Public	44
D4.1	Report on the modelling of NM release and human/environmental exposure from relevant industrial case scenarios	WP4	2 - ARCHE	R — Document, report	PU - Public	36
D4.2	Integrated DB including characterisation, detection, modelling human and eco-toxicity relevant data based on FAIR principles	WP4	4 - CNR	OTHER	PU - Public	44
D4.3	In silico modelling of response functions	WP4	4 - CNR	OTHER	SEN - Sensitive	30
D4.4	Synthesis and incorporation models for integrated LCA, LCC and SLCA	WP4	9 - PRJ	R — Document, report	PU - Public	36
D4.5	Report on social and economic modelling and externalities optimization	WP4	6 - BIU	R — Document, report	SEN - Sensitive	36
D5.1	Report on proposed Impact model for determination of toxicity and eco-toxicity ICs scoring specifically related to NMs	WP5	1 - UNIMIB	OTHER	PU - Public	42

Deliverables

Grant Preparation (Deliverables screen) — Enter the info.

The labels used mean:

Public — fully open (⚠ automatically posted online)
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EU classified —RESTREINT-UE/EU-RESTRICTED, CONFIDENTIEL-UE/EU-CONFIDENTIAL, SECRET-UE/EU-SECRET under Decision 2015/444

Deliverable No	Deliverable Name	Work Package No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
D5.2	DB of Safe and sustainability assessment data (integrated LCA, LCC, SLCA) of targeted case studies based on integrated impact model and integrated LCIA	WP5	9 - PRJ	DEM — Demonstrator, pilot, prototype	PU - Public	42
D5.3	Report on validated best SSbD solutions.	WP5	4 - CNR	R — Document, report	PU - Public	48
D5.4	Report on project interlaboratory validation	WP5	4 - CNR	R — Document, report	PU - Public	42
D6.1	First PDER including communication activities, and updates	WP6	9 - PRJ	R — Document, report	SEN - Sensitive	3
D6.2	Second PDER including communication activities, and updates	WP6	9 - PRJ	R — Document, report	SEN - Sensitive	18
D6.3	Final PDER including communication activities, and updates	WP6	9 - PRJ	R — Document, report	SEN - Sensitive	36
D6.4	Guidelines for integrated assessment of health, social, economic, environmental sustainability.	WP6	1 - UNIMIB	R — Document, report	PU - Public	48
D6.5	Project visual identity and website.	WP6	9 - PRJ	DEC —Websites, patent filings, videos, etc	PU - Public	3
D6.6	First reports of stakeholder workshops and training plan	WP6	5 - AITEX	R — Document, report	PU - Public	24

Deliverables

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Deliverable No	Deliverable Name	Work Package No	Lead Beneficiary	Type	Dissemination Level	Due Date (month)
D6.7	Second reports of stakeholder workshops and training plan	WP6	5 - AITEX	R — Document, report	PU - Public	36
D6.8	Final reports of stakeholder workshops and training plan	WP6	5 - AITEX	R — Document, report	PU - Public	48
D6.9	IT platform for stakeholders engagement - SSbD Think tank	WP6	9 - PRJ	DEC —Websites, patent filings, videos, etc	PU - Public	8
D6.10	First report on synergies and interaction with other EU projects and initiative	WP6	5 - AITEX	R — Document, report	PU - Public	36
D6.11	Final report on synergies and interaction with other EU projects and initiative	WP6	5 - AITEX	R — Document, report	PU - Public	48
D7.1	Quality control plan	WP7	1 - UNIMIB	R — Document, report	SEN - Sensitive	6
D7.2	Tools for operational, technical and contractual management periodic reporting	WP7	1 - UNIMIB	R — Document, report	SEN - Sensitive	9

Deliverable D1.1 – First data management Plan

Deliverable Number	D1.1	**Lead Beneficiary**	4. CNR
Deliverable Name	First data management Plan		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	3	**Work Package No**	WP1

Description
Data management Plan

Deliverable D1.2 – Report on the goal and scope of addressed case studies, including KDFs and KPIs definition

Deliverable Number	D1.2	**Lead Beneficiary**	9. PRJ
Deliverable Name	Report on the goal and scope of addressed case studies, including KDFs and KPIs definition		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	18	**Work Package No**	WP1

Description
Report on the goal and scope of addressed case studies, including KDFs and KPIs definition

Deliverable D1.3 – Digital Decision Support Toolbox for quantitative based integrated impact assessment towards SSbD solutions

Deliverable Number	D1.3	**Lead Beneficiary**	9. PRJ
Deliverable Name	Digital Decision Support Toolbox for quantitative based integrated impact assessment towards SSbD solutions		
Type	OTHER	**Dissemination Level**	SEN - Sensitive
Due Date (month)	24	**Work Package No**	WP1

Description
Digital Decision Support Toolbox for quantitative based integrated impact assessment towards SSbD solutions

Deliverable D1.4 – Final data management Plan

Deliverable Number	D1.4	**Lead Beneficiary**	4. CNR
Deliverable Name	Final data management Plan		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	18	**Work Package No**	WP1

Description

Final data management Plan

Deliverable D2.1 – Set of NMs samples

Deliverable Number	D2.1	**Lead Beneficiary**	3. CENTI
Deliverable Name	Set of NMs samples		
Type	OTHER	**Dissemination Level**	PU - Public
Due Date (month)	24	**Work Package No**	WP2

Description
Set of NMs samples

Deliverable D2.2 – INTEGRANO integrated database (DB) periodic release

Deliverable Number	D2.2	**Lead Beneficiary**	3. CENTI
Deliverable Name	INTEGRANO integrated database (DB) periodic release		
Type	OTHER	**Dissemination Level**	PU - Public
Due Date (month)	36	**Work Package No**	WP2

Description
INTEGRANO integrated database (DB) periodic release

Deliverable D2.3 – DB on NMs detection campaigns in real and simulated environment for Fate Factors assessment

Deliverable Number	D2.3	**Lead Beneficiary**	4. CNR
Deliverable Name	DB on NMs detection campaigns in real and simulated environment for Fate Factors assessment		
Type	OTHER	**Dissemination Level**	PU - Public
Due Date (month)	42	**Work Package No**	WP2

Description
DB on NMs detection campaigns in real and simulated environment for Fate Factors assessment

Deliverable D2.4 – Report on Conditions of Safe Use

Deliverable Number	D2.4	**Lead Beneficiary**	2. ARCHE
Deliverable Name	Report on Conditions of Safe Use		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	42	**Work Package No**	WP2

Description

Report on Conditions of Safe Use

Deliverable D3.1 – Quantitative assessment of Eco-toxicity endpoints for indication of suitable nano-specific EE for marine and terrestrial environment eco-toxicity ICs

Deliverable Number	D3.1	**Lead Beneficiary**	4. CNR
Deliverable Name	Quantitative assessment of Eco-toxicity endpoints for indication of suitable nano-specific EE for marine and terrestrial environment eco-toxicity ICs		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	44	**Work Package No**	WP3

Description
Quantitative assessment of Eco-toxicity endpoints for indication of suitable nano-specific EE for marine and terrestrial environment eco-toxicity ICs

Deliverable D3.2 – Relevant dose-response functions for the NMs in their different LC stages, for human and environmental toxicology outcomes supporting the definition of nano-specific EE for human and environmental toxicity ICs

Deliverable Number	D3.2	**Lead Beneficiary**	1. UNIMIB
Deliverable Name	Relevant dose-response functions for the NMs in their different LC stages, for human and environmental toxicology outcomes supporting the definition of nano-specific EE for human and environmental toxicity ICs		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	44	**Work Package No**	WP3

Description
Relevant dose-response functions for the NMs in their different LC stages, for human and environmental toxicology outcomes supporting the definition of nano-specific EE for human and environmental toxicity ICs

Deliverable D4.1 – Report on the modelling of NM release and human/environmental exposure from relevant industrial case scenarios

Deliverable Number	D4.1	**Lead Beneficiary**	2. ARCHE
Deliverable Name	Report on the modelling of NM release and human/environmental exposure from relevant industrial case scenarios		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	36	**Work Package No**	WP4

Description
Report on the modelling of NM release and human/environmental exposure from relevant industrial case scenarios

Deliverable D4.2 – Integrated DB including characterisation, detection, modelling human and eco-toxicity relevant data based on FAIR principles

Deliverable Number	D4.2	**Lead Beneficiary**	4. CNR
Deliverable Name	Integrated DB including characterisation, detection, modelling human and eco-toxicity relevant data based on FAIR principles		
Type	OTHER	**Dissemination Level**	PU - Public
Due Date (month)	44	**Work Package No**	WP4

Description
Integrated DB including characterisation, detection, modelling human and eco-toxicity relevant data based on FAIR principles

Deliverable D4.3 – In silico modelling of response functions

Deliverable Number	D4.3	**Lead Beneficiary**	4. CNR
Deliverable Name	In silico modelling of response functions		
Type	OTHER	**Dissemination Level**	SEN - Sensitive
Due Date (month)	30	**Work Package No**	WP4

Description
In silico modelling of response functions

Deliverable D4.4 – Synthesis and incorporation models for integrated LCA, LCC and SLCA

Deliverable Number	D4.4	**Lead Beneficiary**	9. PRJ
Deliverable Name	Synthesis and incorporation models for integrated LCA, LCC and SLCA		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	36	**Work Package No**	WP4

Description
Synthesis and incorporation models for integrated LCA, LCC and SLCA

Deliverable D4.5 – Report on social and economic modelling and externalities optimization

Deliverable Number	D4.5	**Lead Beneficiary**	6. BIU
Deliverable Name	Report on social and economic modelling and externalities optimization		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	36	**Work Package No**	WP4

Description
Report on social and economic modelling and externalities optimization

Deliverable D5.1 – Report on proposed Impact model for determination of toxicity and eco-toxicity ICs scoring specifically related to NMs

Deliverable Number	D5.1	**Lead Beneficiary**	1. UNIMIB
Deliverable Name	Report on proposed Impact model for determination of toxicity and eco-toxicity ICs scoring specifically related to NMs		
Type	OTHER	**Dissemination Level**	PU - Public
Due Date (month)	42	**Work Package No**	WP5

Description
Report on proposed Impact model for determination of toxicity and eco-toxicity ICs scoring specifically related to NMs

Deliverable D5.2 – DB of Safe and sustainability assessment data (integrated LCA, LCC, SLCA) of targeted case studies based on integrated impact model and integrated LCIA

Deliverable Number	D5.2	**Lead Beneficiary**	9. PRJ
Deliverable Name	DB of Safe and sustainability assessment data (integrated LCA, LCC, SLCA) of targeted case studies based on integrated impact model and integrated LCIA		
Type	DEM — Demonstrator, pilot, prototype	**Dissemination Level**	PU - Public
Due Date (month)	42	**Work Package No**	WP5

Description
DB of Safe and sustainability assessment data (integrated LCA, LCC, SLCA) of targeted case studies based on integrated impact model and integrated LCIA

Deliverable D5.3 – Report on validated best SSbD solutions.

Deliverable Number	D5.3	**Lead Beneficiary**	4. CNR
Deliverable Name	Report on validated best SSbD solutions.		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	48	**Work Package No**	WP5

Description
Report on validated best SSbD solutions.

Deliverable D5.4 – Report on project interlaboratory validation

Deliverable Number	D5.4	**Lead Beneficiary**	4. CNR
Deliverable Name	Report on project interlaboratory validation		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	42	**Work Package No**	WP5

Description
Report on project interlaboratory validation

Deliverable D6.1 – First PDER including communication activities, and updates

Deliverable Number	D6.1	**Lead Beneficiary**	9. PRJ
Deliverable Name	First PDER including communication activities, and updates		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	3	**Work Package No**	WP6

Description
PDER including communication activities, and updates

Deliverable D6.2 – Second PDER including communication activities, and updates

Deliverable Number	D6.2	**Lead Beneficiary**	9. PRJ
Deliverable Name	Second PDER including communication activities, and updates		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	18	**Work Package No**	WP6

Description
PDER including communication activities, and updates

Deliverable D6.3 – Final PDER including communication activities, and updates

Deliverable Number	D6.3	**Lead Beneficiary**	9. PRJ
Deliverable Name	Final PDER including communication activities, and updates		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	36	**Work Package No**	WP6

Description
III° PDER including communication activities, and updates

Deliverable D6.4 – Guidelines for integrated assessment of health, social, economic, environmental sustainability.

Deliverable Number	D6.4	**Lead Beneficiary**	1. UNIMIB
Deliverable Name	Guidelines for integrated assessment of health, social, economic, environmental sustainability.		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	48	**Work Package No**	WP6

Description
Guidelines for integrated assessment of health, social, economic, environmental sustainability.

Deliverable D6.5 – Project visual identity and website.

Deliverable Number	D6.5	Lead Beneficiary	9. PRJ
Deliverable Name	Project visual identity and website.		
Type	DEC —Websites, patent filings, videos, etc	Dissemination Level	PU - Public
Due Date (month)	3	Work Package No	WP6

Description
Project visual identity and website.

Deliverable D6.6 – First reports of stakeholder workshops and training plan

Deliverable Number	D6.6	Lead Beneficiary	5. AITEX
Deliverable Name	First reports of stakeholder workshops and training plan		
Type	R — Document, report	Dissemination Level	PU - Public
Due Date (month)	24	Work Package No	WP6

Description
Reports of stakeholder workshops and training plan

Deliverable D6.7 – Second reports of stakeholder workshops and training plan

Deliverable Number	D6.7	Lead Beneficiary	5. AITEX
Deliverable Name	Second reports of stakeholder workshops and training plan		
Type	R — Document, report	Dissemination Level	PU - Public
Due Date (month)	36	Work Package No	WP6

Description
Reports of stakeholder workshops and training plan

Deliverable D6.8 – Final reports of stakeholder workshops and training plan

Deliverable Number	D6.8	Lead Beneficiary	5. AITEX
Deliverable Name	Final reports of stakeholder workshops and training plan		
Type	R — Document, report	Dissemination Level	PU - Public
Due Date (month)	48	Work Package No	WP6

Description
Reports of stakeholder workshops and training plan

Deliverable D6.9 – IT platform for stakeholders engagement - SSbD Think tank

Deliverable Number	D6.9	**Lead Beneficiary**	9. PRJ
Deliverable Name	IT platform for stakeholders engagement - SSbD Think tank		
Type	DEC —Websites, patent filings, videos, etc	**Dissemination Level**	PU - Public
Due Date (month)	8	**Work Package No**	WP6

Description
IT platform for stakeholders engagement - SSbD Think tank

Deliverable D6.10 – First report on synergies and interaction with other EU projects and initiative

Deliverable Number	D6.10	**Lead Beneficiary**	5. AITEX
Deliverable Name	First report on synergies and interaction with other EU projects and initiative		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	36	**Work Package No**	WP6

Description
Report on synergies and interaction with other EU projects and initiative

Deliverable D6.11 – Final report on synergies and interaction with other EU projects and initiative

Deliverable Number	D6.11	**Lead Beneficiary**	5. AITEX
Deliverable Name	Final report on synergies and interaction with other EU projects and initiative		
Type	R — Document, report	**Dissemination Level**	PU - Public
Due Date (month)	48	**Work Package No**	WP6

Description
Report on synergies and interaction with other EU projects and initiative

Deliverable D7.1 – Quality control plan

Deliverable Number	D7.1	**Lead Beneficiary**	1. UNIMIB
Deliverable Name	Quality control plan		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive

Due Date (month)	6	**Work Package No**	WP7

Description
Quality control plan

Deliverable D7.2 – Tools for operational, technical and contractual management periodic reporting

Deliverable Number	D7.2	**Lead Beneficiary**	1. UNIMIB
Deliverable Name	Tools for operational, technical and contractual management periodic reporting		
Type	R — Document, report	**Dissemination Level**	SEN - Sensitive
Due Date (month)	9	**Work Package No**	WP7

Description
Tools for operational, technical and contractual management periodic reporting

LIST OF MILESTONES

Milestones *Grant Preparation (Milestones screen) — Enter the info.*					
Milestone No	**Milestone Name**	**Work Package No**	**Lead Beneficiary**	**Means of Verification**	**Due Date (month)**
1	Digital Decision Support Toolbox for NMs SSbD	WP1	9-PRJ	DST ready and operating	36
2	Accomplishment of NMs Characterisation dataset	WP2	3-CENTI	Experimental generated data available	30
3	NMs/NEPs hazard and ecotox assessment	WP3	1-UNIMIB	Available NMs tox and ecotox profiles	44
4	Modelling and Virtualisation of the synthesis and incorporation processes	WP4	2-ARCHE	Availability of generated data by modelling	44
5	Performing the integrated LCA, SCLA and LCC for the selected group of NMs	WP5	9-PRJ	Availability of first INTEGRANO dataset of SSbD studied design cases with DST	36
6	Development of Guidelines for integrative impact assessment and SSbD methodology application	WP5	1-UNIMIB	IT platform for stakeholders engagement ready with SSbD guidelines	48

LIST OF CRITICAL RISKS

Critical risks & risk management strategy *Grant Preparation (Critical Risks screen) — Enter the info.*			
Risk number	**Description**	**Work Package No(s)**	**Proposed Mitigation Measures**
1	Failing availability of any unit, service, infrastructure, lab for synthesis, incorporation,	WP2	In case of any missing resource, the broad science and technology network linked with project

Critical risks & risk management strategy *Grant Preparation (Critical Risks screen) — Enter the info.*			
Risk number	**Description**	**Work Package No(s)**	**Proposed Mitigation Measures**
	characterisation or assaying Severity: high; likelihood: low		partners will be activated to cover the temporary gaps in order to assure smooth development of project tasks.
2	Failing availability of any unit, service, infrastructure, lab for synthesis, incorporation, characterisation or assaying Severity: high; likelihood: low	WP3	In case of any missing resource, the broad science and technology network linked with project partners will be activated to cover the temporary gaps in order to assure smooth development of project tasks.
3	Failing availability of raw materials and reagents, facilities or services. Severity: medium; likelihood: low	WP2	Alternative external partners or suppliers will be identified to assure the due procurements and assure materials flow for addressed synthesis, incorporation, hazard and eco-toxicity assessment, testing and validation.
4	Failing availability of raw materials and reagents, facilities or services. Severity: medium; likelihood: low	WP3	Alternative external partners or suppliers will be identified to assure the due procurements and assure materials flow for addressed synthesis, incorporation, hazard and eco-toxicity assessment, testing and validation.
5	Primary and/or secondary data gaps slow down the process for attaining new impact categories and characterisation factors. Severity: medium; likelihood: low	WP4	Consideration of conventional models for FF and EF computation and literature data on effect factors from data mining will be considered as first modelling and data proxies. Extrapolation of sampled emissions data to other environmental compartments will be applied.
6	Primary and/or secondary data gaps slow down the process for attaining new impact categories and characterisation factors. Severity: medium; likelihood: low	WP5	Consideration of conventional models for FF and EF computation and literature data on effect factors from data mining will be considered as first modelling and data proxies. Extrapolation of sampled emissions data to other environmental compartments will be applied.
7	Complicated Design case imply computational limitations to DST use, MOOD miss to find multi-optimal solutions. Severity: medium; likelihood: low	WP5	Parallel and multilevel use of the DST will allow splitting the complicated SSbD into smaller and lower dimensionality MOOD analyses for further integration and correlation of results
8	Outreach and open science practices receive little feedback. Severity: low; likelihood medium	WP6	Partnerships with organizations with a good outreach to the community (academies of sciences, associations), increasing activity through established social media

PROJECT REVIEWS

Project Reviews *Grant Preparation (Reviews screen) — Enter the info.*			
Review No	**Timing** (month)	**Location**	**Comments**
RV1	18	On spot or online	
RV2	36	On spot or online	
RV3	48	On spot or online	

MULTIDIMENSIONAL INTEGRATED QUANTITATIVE APPROACH TO ASSESS SAFETY AND SUSTAINABILITY OF NANOMATERIALS IN REAL CASE LIFE CYCLE SCENARIOS USING NANOSPECIFIC IMPACT CATEGORIES

INTEGRANO

History of Change

Version 1.0		Page
Data	**PART A**	
02/08/2023	All the CNR departments involved in the project have been specifies in the beneficiary data	
	D1.1 Split in D1.1 First data Management Plan and D1.4 Final data Management Plan	
	D6.1 Split in D6.1 First PDER including communication activities and updates, D6.2 Second PDER including communication activities, and updates, D6.3 Final PDER including communication activities, and updates	
	D6.2 renamed D6.4	
	D6.3 renamed D6.5	
	D6.4 renamed D6.6	
	D6.5 renamed D6.9	
	D6.6 Split in D6.10 First report on synergies and interaction with other EU projects and initiative and D6.11 Final report on synergies and interaction with other EU projects and initiative	
Data	**PART B**	
02/08/2023	Section 4 Ethics added	
	GANTT chart updated with new named deliverables	
	Table 3.1h, purchase costs specified	
	CNR departments described and specified	Page 37
Version 1.1		
Data	**PART A**	
18/09/20232		
	Equipment costs moved to other goods and services category cost for B4C	
Data	**PART B**	
18/09/20232	The role of JRC has been specified	Page 37
	Tables 3.1i has been added	Page 37 - 38
Version 1.2		
Data	**PART A**	
05/10/2023	Staff effort corrected: total UNIMIB 70 PMs and CeNTI 57 PMs	
	PMs redistribution to increase staff effort in WP4 and WP7, from 48 to 66 and from 36 to 48 respectively	
	D1.3 correction of due date from M36 to M24, since the related task ends at M24	
	D2.2 corrected with the right title, due date and leader	
	D4.1 anticipated due date to M36 from M44	
	D4.4 anticipated due date to M36 from M44	
	D4.5 anticipated due date to M36 from M44	
	D6.9 delivery date correction Delivery date to M8 instead of M48	
	Correction of staff effort	
Data	**PART B**	
05/10/2023	Table of content included	Page 2
	Additional information "State of the Art and Addressed problems and needs"	Page 3-4
	Additional information "MCDA for evaluation and weighting of multiple sustainability criteria and	Page 5-6

	impacts estimations at EU and global level."	
	Numbering of specific objective corrected, adding the missing O-6; following numbers modified.	Page 7
	A table related to specific objectives, the KPIs to assess their achievement and the means of verification is provided	Page 8-9
	Deleted all **#s** next to tables and titles	All pages
	Additional information on quantification of environmental outcomes and on management of environmental impacts has been added	Page 24
	Additional information has been added in paragraph "2.1.1 Expected Outcomes and Wider Impacts"	Page 24
	Additional information has been added. Barriers to Expected Outcomes (BEOs)	Page 24
	Additional information has been added: BEO1, BEO2, BE03	Page 25 - 26
	Deleted repeated content and footnote in SO1	Page 26
	In the Impact section the Key strategic orientations are addressed and added	Page 29
	Correction in Gantt diagram tasks and deliverables due dates in coherence with a.m. changes	Page35
	Detailed purchase cost for each partner specified and corrected	Page 36
	Additional information on the contribution of SSH have been added in the description of the consortium	Pag 37
	Additional information on competence on LCA have been included	Pag 37
	Added content in "Ethics"	Pag 38

Summary

List of most commonly used abbreviations in the proposal and their definition

Abb.	Full name	Abb.	Full name	Abb.	Full name
ALI	Air-liquid-interface	ICs	Impact categories	NPs	Nanoparticles
AOPs	Adverse Outcomes Pathways	KPIs	Key performance Indicators	NSC	Nano-safety Cluster
CF	Characterisation factor	LC	Life Cycle	OP	Oxidative potential
CoU	Conditions of Use	LCA	Life Cycle Assessment	p-chem	Physico Chemical
DST	Decision support tool	LCC	Life Cycle Costing	PDER	Plan for the Dissemination and Exploitation of Results
EE	Effect factors	LCIA	Life Cycle Impact Assessment	RA	Risk Assessment
EF	Exposure factors	MOOD	Multi Objective Optimisation Design	SLCA	Social Life Cycle Assessment
EoL	End of Life	NCMs	Nano Composite Materials	SoA	State of Art
FAIR	Findability, Accessibility, Interoperability, and Reusability	NEPs	Nano-enabled products	SSbD	Safe and sustainable by design
FF	Fate factor	NMs	Nanomaterials	SSNMR	Solid-State Nuclear Magnetic Resonance

1. Excellence

1.1 Objectives and ambition

Important efforts have been done to pave the way towards the safety and sustainability of chemicals and materials clarifying framework, concepts and methodologies as well as providing reference guidelines and criteria on how to tackle this challenge[1,2]. The principles of nanomaterials (NMs) safety have been extensively addressed in the last years by research and regulatory communities due to the increasing number of applications and formulations of nano-enabled products (NEPs). This required conduction of downstream risk analysis during the NMs Life Cycle (LC) for safer management and a more sustainable intrinsic design of NMs properties, or the design at source[3]. Despite existing obtained advantages and knowledge base, due to ambiguity of potential adverse effects of NMs on humans and the environment, the Safe and Sustainable-by-Design (SSbD) concept was introduced in the field[4]. Its implementation for NEPs has been recently subject to EU funding from Nano-safety Cluster (NSC)[5], providing tools, databases, approaches and frameworks for assessment and decision support to make the growing use of NMs and NEPs safer. Design of Safe and Sustainable chemicals and materials requires a paradigm shift into concrete implementation of existing guidelines into a general methodology open to the integration of developed frameworks and applicable to specific and case studies. This would allow benefitting from the integration of available data with case-specific data obtainable by: cutting edge characterisation techniques, comprehensive hazard assessment methodologies and application of sustainability assessment standardised methodologies. This would promote efficient and effective functional substitution of chemicals of emerging concern as well as their efficient removal from the environment by generating novel, safer and more sustainable chemicals and materials supporting bioeconomy and circularity. INTEGRANO promotes a general methodology applicable to specific case studies, which overcomes time, costs, and resource limitations associated to experimental data generation by offering a rationalised methodology requiring a minimum amount of reference data. The elaboration of reference data will dramatically shorten the new safe and sustainable chemicals and materials development lead time and reduce the associated Research and Technology Development (RTD) costs. INTEGRANO ambitious program addresses the need to cover the gaps associated to the nanomaterials (NMs) safety and sustainability assessment through their life cycle. The proposal of new toxicity and eco-toxicity impact categories will enable and integrated safety and sustainability assessment by exploiting existing standards. The design and re-design of safer and more sustainable addressed groups of NMs would enable functional substitution of chemicals that are contaminants of emerging concern, their removal from the environment, and would enable the use of bio-based and recyclable polymer materials offering positive impacts in applications referred to several sample applications and related value chains.

State of the Art and Addressed problems and needs. Several diversified efforts have been carried out in EU to develop safe and sustainability assessments. In the following we provide a non-comprehensive survey of major assessments methods and tools as a results of EU projects under NMPB 15 and 16 calls.

- DIAGONAL[6]: This project focuses on providing a system for nanomaterial safety and sustainability assessment, targeting various industries, including textiles and cosmetics. Their platform could utilize advanced toxicology data and risk assessment models. The Tool is not available for cross comparison. The selection of the KPIs will ultimately determine the selection of a tool over another. The project aims to bring new methodologies to guarantee long-term Nano safety.
- HARMLESS[7]: this project that emphasizes New Approach Methodologies and AI, aiming to help businesses make safe and eco-friendly choices. It offers life cycle analysis tools and environmental impact metrics covering also social aspects. However, the target segments differ.
- SABYDOMA[8]: this project has the goal of optimizing nanomaterials' safety, especially in synthesis process. The projects employs a high-throughput data flow through platform for screening NM using multiple sensor elements for specific applications.
- SAbyNA[9]: this project provides a technological solutions, user-friendly, customized and integrative guidance platform to support the development of safe-by-design NM and Nano-enabled products targeting different industrial sectors.

[1] Caldeira C, et al Safe and Sustainable by Design chemicals and materials, JRC Technical Report, 2022, ISBN 978-92-76-53264-4
[2] European Commission, Strategic Research and Innovation Plan for Safe and Sustainable Chemicals and Materials, , 2022, ISBN 978-92-76-49115-6
[3]. DOI:10.1007/978-3-319-32392-3_10
[4]. doi: 10.3390/nano121118109; Gottardo, S. et al. (2021) NanoImpact 100297; Falinski, M et al. (2018) Nat. Nanotechnol 13; Tavernaro, I. et al. (2021) NanoImpact 24.
[5]. Falk, A. et al. (2021) Safe-by-design and EU funded NanoSafety projects. 10.5281/zenodo.4652587;
[6] https://www.diagonalproject.eu/
[7] https://www.harmless-project.eu/
[8] https://www.sabydoma.eu/
[9] https://www.sabyna.eu/

- SbD4Nano[10]: this project approach is based on a new e-infrastructure developed as a decision-making tool for the automatic generation of a Safe-by-Design performance index. SbD4Nano does not explicitly deals with sustainability.
- SUNSHINE[11]: this project aims to provide an expert system specifically for safe and sustainable nanomaterial selection. The SUNSHINE platform might integrate life cycle assessment data, allowing businesses to choose environmentally-friendly alternatives.
- ASINA[12]: this project aims at providing a framework based on quantitative approach for on SSbD, implementing specific case studies. The project does not address the social impacts and does not develop nano-specific impact categories to measure toxicity and eco-toxicity, safety and sustainability dimensions along with the relative impact categories are separated.

New approach methodologies (NAMs),, according to ECHA's definition, include in silico approaches, in chemical and in vitro assays, as well as the inclusion of information from the exposure of chemicals in the context of hazard assessment. They also include a variety of new testing tools, such as "high-throughput screening" and "high-content methods" e.g. genomics, proteomics, metabolomics; as well as some "conventional" methods that aim to improve understanding of toxic effects, either through improving toxicokinetic or toxicodynamic knowledge for substances. Several funding programs supported and are supporting NAMs, such as: Horizon 2020 / Horizon Europe (European Union), Long-Range Research Initiative (-LRI, Cefic-lri Programme | European Chemical Industry Council), Long Range Science Strategy (LRSS) (Cosmetics Europe), Crack-IT NC3Rs (The UK national centre for the replacement, refinement & reduction of animals in research), EPAA (The European Partnership for Alternative Approaches to Animal Testing). A list of reference initiatives and projects addressing NAMs are reported:

- VHP4Safety: the mission of the Virtual Human Platform is to improve the prediction of the potential harmful effects of chemicals and pharmaceuticals based on a holistic, interdisciplinary definition of human health by developing the Virtual Human Platform and accelerating the transition from animal-based testing to innovative safety assessment.
- EU-ToxRisk: the vision of EU-ToxRisk is to drive the required paradigm shift in toxicological testing away from 'black box' animal testing towards a toxicological assessment based on human cell responses and a comprehensive mechanistic understanding of cause-consequence relationships of chemical adverse effects. EU-ToxRisk will integrate advancements in cell biology, omics technologies, systems biology and computational modelling to define the complex chains of events that link chemical exposure to toxic outcome.
- ASPIS cluster: this cluster is led by the European Commission and aims to synergise efforts and increase visibility of three EU-supported projects focused on improving safety assessment without animal testing (RISK-HUNT3RONTOXPRECISIONTOX).
- PANORAMIX: will use a mixture modelling, case studies and experimental data to deliver a web-based interface for calculating risks to chemical mixtures and to define effect-based trigger values for in vitro effects that can be directly measured in water, food, and blood to identify when mixture exposure poses a health threat.
- EURION CLUSTER: is a cluster group of eight research projects (e.g. FREIA, GOLIATH, ENDpoiNTS) from the Call SC1-BHC-27-2018 – New testing and screening methods to identify endocrine disrupting chemicals (EDCs).
- PARC: is an EU-wide research and innovation programme to support EU and national chemical risk assessment and risk management bodies with new data, knowledge, methods, networks and skills to address current, emerging and novel chemical safety challenges. It will facilitate the transition to next generation risk assessment to letter protect human health and the environment, in line with the Green Deal's zero-pollution ambition for a toxic free environment and will be an enabler for the EU Chemicals Strategy for sustainability.

INTEGRANO addresses shortcomings and gaps emerging from the analysis of the **current state-of-the-art (SoA**) in safe and sustainability assessment, which indicates that industrial production of NMs and NEPs is still struggling to activate the SSbD approach and fast industrial uptake of engineered NMs[13]. Indeed, NMs safety and sustainability assessment methods **lacks quantitative dimension**. Currently more efficient approaches are required to: (1) **monitor emissions**, **assess** the toxicological and eco-toxicological **effects** of NMs based on their environmental fate, (2) **integrate** their safety, environmental, social, functional and economic performances, (3) strengthen and **facilitate** the **decision-making process** based on objective, quantitative information proving transparent data and evidence on the safety and sustainability of NMs throughout their whole life cycle. This implies obtaining NM-specific quantifiable performance profile by **reducing** research and development **lead-time** and **costs**, which in turn requires relying on a minimum and sufficient set of specific data providing relevant information on which the decision-making process can be based.

[10] https://www.sbd4nano.eu/
[11] https://www.h2020sunshine.eu/
[12] https://www.asina-project.eu/
[13]. doi.org/10.1155/2014/498420; doi.org/10.3390/nano5031351; DOI: 10.1016/j.biotechadv.2013.11.006; doi.org/10.1039/C8NR02278J.

Lack of nano-specific impact categories, and attention toward the nano-toxicity and nano-eco-toxicity effects limits the possibility of achieving and integrating environmental and safety assessment, which currently may be obtained with standard LCA methodologies addressing eco-toxicity and human toxicity impact categories referred to bulk materials only.

Life Cycle Assessment of NMs has received steadily growing attention, but only few studies address toxicity indicators, mainly due to the knowledge-gap in the field of NMs Risk Assessment (RA) and toxicity profiling. The **lack** of the **definition** of suitable **effect factors** (EEs) for the human nano-toxicity and nano-eco-toxicity affecting soil and water **hampers** the **use of** current assessed **standards** in health and environmental impact assessment for SSbD.

Nanotoxicology presents an unfold potential, as the *in-silico* and *in-vitro* approaches are gradually replacing traditional *in-vivo* models in RA and LCA[14]. Various initiatives proposed advanced frameworks for human toxicity of chemicals[15], but there is still room for improvement regarding methodology and integration efforts in this field. Similarly, several frameworks have been proposed to tackle NMs safety providing more specific hazard assessing tools. Some are qualitative or semi quantitative due to lacking information on specific NMs. A comprehensive quantitative approach to NMs safety and sustainability profile characterisation is needed to integrate standard (bulk chemicals) life cycle sustainability and assessment of specific (nano-induced) safety, environmental and social impacts.

The **lack of available harmonised or specific data** related to the safety of selected NMs groups and the availability of only few datasets, especially including environmental analysis[16], poses a challenge to the design of safe and sustainable NMs and their incorporation in nano-composite materials (NCMs) and NEPs. Moreover the time needed and the economic burden associated to the characterisation of NMs Physico-chemical (p-chem) features and to toxicity and eco-toxicity assaying, requires a **rationalised integrated approach** to leverage the **extraction of relevant information from a limited amount of characterised reference samples**.

In line with the current guidelines for Safe and Sustainable by Design (SSbD) chemicals and materials, INTEGRANO proposes a general assessment approach based on quantitative evidence to be applied in practice for specific Nano Materials (NMs) design cases referred to inorganic, organic and carbon NMs. The development NMs dedicated novel impact categories (ICs) for nano-toxicity and eco-nano-toxicity assessment will enable the integrated application of standardised assessment methodologies. The following four NMs Life Cycle Stages (LCS) are addressed: synthesis, incorporation, use phase and end-of-life. The application of the stage-gate SSbD process through the LCS addresses performance in the five dimensions (5Ds): Safety, Environmental, Economic, Social and Functional. Generation of dedicated response functions will allow associating Key Decision Factors (KDFs, such as: concentrations, processing parameters, etc.) to Key Performance Indicators (KPIs, such as: occupational safety, CO2 emissions, job creation potential, NM cost, antibacterial functionality, etc.). SSbD NMs solutions will be obtained by Multi Objective Optimisation Design (MOOD) dedicated algorithm, which operates within the framework of the Multi-Criteria Decision Analysis (MCDA). A dedicated digital Decision Support Toolbox (DST) will elaborate design case specific data and run MOOD algorithm to sort the set of multi-optimal SSbD options, which are simultaneously complying with all the targeted KPIs referred to the 5Ds. Thus the SSbD challenge will be tackled with the DST that will enable decision-makers at all levels. The digital supported decision process will help (scientists, material engineers, Nano-Enabled Products (NEPs) designers, policymakers) taking informed decisions based on comparative quantitative evidence, and at the same time to tackle the SSbD challenge,allowing for dramatic reduction of Research & Development (RTD) effort, and approval lead-time as well as minimising costs and increasing the transparency of the data, by making the industrial uptake of nanotechnologies more sustainable and viable.

INTEGRANO allows the integration with other existing SSbD frameworks by transposing results into other scoring metrics and enabling data exchange.

MCDA for evaluation and weighting of multiple sustainability criteria and impacts estimations at EU and global level. As absolute safety and absolute sustainability of a real case specific solution may be only accepted by assuming *not applying* or *not implementing* that solution at all, we are left with the only possible definition of the attributes 'Safe' and 'Sustainable' which qualifies them as relative (multi-)attributes, associated to the best available technologies (BATs), to the solution implementation time and location.

Furthermore, sustainability and safety are intrinsically multicriteria interrelated performance concepts that may be explicitly and quantitatively rendered with explicit attributes. For this purpose, standard methodologies for environmental (e.g. ISO14040-44) and social sustainability assessment employ impact categories, which represent the Key Performance Indicators (KPIs) accounting for sustainability of the addressed solutions. To the same pace, INTEGRANO addresses the nano-enabled solution safety and sustainability through the assessment of quantitative KPIs, by integrating existing standards, metrics, and assessment methods as well as by investigating the possibility of devising nanoforms-specific toxicity and eco-toxicity impact categories, which account for peculiar effects induced by nanoforms (NFs).

Given the relative nature of Safety and Sustainability attributes, the SSbD evaluation criteria imply adopting a quantitative

[14]. D. Romeo et al. (2020) Environment International 137, 105505.
[15]. B. Salieri et al. (2020) Nanotoxicology v.14, 2, 275–286.
[16]Furxi, I. , Health and environmental safety of nanomaterials: O Data, Where Art Thou?, NanoImpact 25 (2022) 100378

approach and require assessing the conditions that maximise each KPI. Indeed, INTEGRANO approach to SSbD is based on the assessment of each KPI level dependence on the Key Decision Factors (KDF) values. KDFs may be discrete or continuous variables representing NMs options, formulations, synthesis and processing parameters recipes, condition of use or end of life options referred to the NFs life cycle. The KPIs dependence on KDFs values is obtained starting from the experimental direct or indirect KPIs measurements of reference design cases associated to specific KDFs values, spanning from lowest to highest KDFs allowed values according to a predefined Design of Experiment approach, which allows minimizing the number of experimental characterizations and toxicity assessments. The obtained KDFs-KPIs relations provide interconnection between the design space, in which decision variables are selected, and the performance space, where safety and sustainability attributes (KPIs) are evaluated. In this framework each design case is associated to a point in the (multi-dimensional) decision space, whose coordinates are given by the KDFs. The performance space coordinates are the safe and sustainability KPIs. The relation between KDFs and KPIs allows selecting KPIs higher levels which are associated to the specific KDF values through the KDFs-KPIs relations.
Given that the SSbD BAT-related, time- and location-bounded-problem is inherently multi-dimensional (as several KPIs needs to be assessed), MCDA is applied. Indeed, INTEGRANO **SSbD evaluation criteria** consists in finding the values of the KDFs that imply the **simultaneous** and **consistent maximisation** of all the **addressed KPIs** in the design case study. This will be attained by the application of the Multi Objective Optimisation Design (MOOD) algorithm, which provides the set of safer and more sustainable design cases. At this stage of the SSbD analysis, the DST provides the decision maker with the KPIs values associated to each multi-optimal design case (identified by the specific set of relative KDFs values). The set of safer and more sustainable design cases provided by DST is obtained prior to the weighting procedure and enables the decision maker to find the right trade off by selecting one of the DST suggested design cases. At this stage weighting, prioritisation and ranking of KPIs is done implicitly by selecting the multi-optimal design case, mostly suitable with the KPI requirements.
The explicit KPIs quantitative values allow **estimating impacts at EU and global level** through the assessment of the impact categories provided by the regionalized sustainability and safety assessments obtained by the integration of SLCA, LCA analyses, and through impact categories values obtained by toxicology and eco-toxicology measurements, as well as by modelling of release and dispersion of NFs in addressed environmental compartments.
INTEGRANO MCDA approach through the use of the DST allows excluding all design cases which do not simultaneously maximise all KPIs for any given KPIs weighting set, this allows dramatically speeding up the decision-making process, providing transparency and supporting informed decisions, and at the same time avoiding exclusion of potential suitable design cases, as it may happen by performing a ranking and weighting procedure according to hierarchical processes. Nevertheless, the SSbD solutions provided by the DST may be also compliant with hierarchical decision processes by prioritizing KPIs while selecting the SSbD case among the set of multi-optimal design cases provided by the DST.
The INTEGRANO quantitative approach to SSbD is also compliant with other SSbD frameworks that provide SSbD ratings whose metric is based on safety discrete acceptance levels or on more qualitative descriptors. This is possible thanks to the discretization of the KPIs INTEGRANO values.

Project ambition and response. INTEGRANO ambition is to set the basis for a new paradigm for integrated sustainability and safety assessment of NMs through their life cycle stages (LCS), by delivering solutions which overcome present SSbD shortcomings and by filling the present gaps emerging from the SoA analysis. In particular, INTEGRANO:

- Develops a **specific** methodology, in compliance with the proposed general integrated approach, and operates the safe and sustainable assessment by referring to the specific design case study primary data, obtained by direct measurement of related performances, thus overcoming the lack of available harmonized data and unavailability of specific design case studies data.
- Addresses all the five safety and sustainability dimensions (**5Ds**), which are relevant for the successful industrial uptake of nano-enabled solutions, by integrated assessment of: safety, environmental, social, economic and functional performance
- Addresses the **whole Life Cycle** by subsequently analysing: synthesis, incorporation, use phase and end-of-life options.
- Is based on an approach funded on **quantitative** assessment **principles** through data generation, obtained from specific experimental measurements, as well as from modelling and computation to overcome lack of harmonised specific data
- Devises an impact assessment method supporting SSbD case studies, which relies on a **minimum and representative set of primary data** sufficient to predict the set of multi-optimal design cases, thus minimising time and costs
- Proposes a defined SSbD robust procedure based on quantitative evidence that facilitates the decision-making process, which is supported by a **Multi Objective Optimisation Design** (MOOD) algorithm, allowing for automatic rejection of the optional design cases not belonging to the multi-optimal set of safe and sustainable design cases.
- Offers a **digitalised Decision Support Toolbox** (DST), which implements the digital based MOOD algorithm allowing dramatic reduction of RTD lead time and costs along with the minimisation of the industrial and investment risks.
- Provides the DST user **transparent data and freedom of choice** of the best design case based on performance evidence.
- Obtain **emission data** from dedicated sampling campaigns according to standardised procedure and scientific based analyses.
- Moves a step forward in safety and sustainability assessment as it will propose **novel nano-related sustainability impact**

categories for the assessment of mid-point impacts, based on suitable effect factors (EEs) related to nano-toxicity and eco-nano-toxicity associated to different environmental compartments: freshwaters, seawater, soil.

INTEGRANO Goals. The project implementation will allow achieving INTEGRANO Goals (Gs), which will be reflected in the safety, environmental, economic, social positive general impacts as well as specific impacts referred to the addressed value chains.

G-1: To offer academia, industry, public authorities, sustainability assessors and regulators an integrated quantitative based approach which implements consistent guidelines and methodologies for integrative social, economic, health and environment impact assessment; this will enable: (1) Steering innovation towards the green industrial transition, (2) Minimizing the impact on health, climate and the environment during sourcing, production, use and end of life of chemicals and materials, (3) Substituting (as far as possible) or minimise the production and use of substances of concern, in line with and beyond regulatory obligations (existing and upcoming). For the addressed NMs group, to substitute: bactieriocides, antibiotics, promote circularity through biobased NMs sourcing, enabling bio based polymers with nano-enabled improved properties .

G-2: To promote design and redesign of materials and products by reducing the design and development lead time as well as cost burden to attain safe and sustainable solutions by the use of NMs: this will contribute to the effective acceptance and implementation of the methodology and addressed solutions also applicable and transferable to other NMs groups, other NMs application case studies as well as other class of chemicals and advance materials.

G-3: To support industry in decreasing the RTD and innovation risk related to safety and sustainability by enabling measured impact-based informed investment decisions. This will allow substituting or minimising the production and use of substances of concern, as well as degradation and removal of substances of emerging concern (CECs) from the environment in line with and beyond regulatory obligations (existing and upcoming)

G-4: To support public authorities, policy and decision makers enabling the safe and sustainable material transition based on quantitative assessed trade-offs. The proposed integrated methodology will: (1) provide an holistic approach to SSbD, (2) simplify and harmonise the impacts assessment practice, (3) support decisions based on quantitative evidence, (4) support regulators in defining a clear framework to offer industrial risk minimisation related to innovation actions.

INTEGRANO Specific objectives. The project targets nine Specific, Measurable, Achievable, Relevant and Time-oriented (SMART) objectives (Os), which are as follows:

O-1 To develop a toolbox that enables easily identifying the set of safe and sustainable solutions (design cases): this will (1) facilitate quantitatively-based and conscious decisions obtained by **simultaneously weighting multiple sustainability criteria** involving all performances belonging to the five reference dimensions: environmental, social, economic, health and functional, (2) enable the implementation of the integrated methodology, supporting the decision process at different levels: NM engineering, NEPs design, speeding up and setting up of a regulatory framework for SSbD with scientific basis,

O-2 To develop and validate new toxicological and eco-toxicological assessment methods: this will allow investigating and defining new effect factors (EEs) accounting for NMs toxicity and eco-toxicity impacts for the definition of new impact categories,

O-3 To devise specific nano-ecotoxicity and nano-toxicity impact indicators: based on the achievement of objective O-2, this will enable obtaining an integrated and complete nanomaterial safety and sustainability performance profile accounting also for nano-specific effect factors for humans and eco-systems, to be integrated in the standard Life Cycle Assessment,

O-4 To gain insights and predict mid-point toxicity and eco-toxicity of selected NMs as a function of their properties and use scenarios. This will be allowed by assessing correlations between NMs measured intrinsic properties and their hazard on humans and eco-systems, also considering NMs extrinsic properties,

O-5 To promote the integration of existing assessment frameworks, standards and practices: assessment of an integrated performance profile of the addressed solutions will be obtained by: (1) the application of LCA standards with the novel integrated nano-toxicity and eco-toxicity impacts indicators, (2) use of most recent SLCA framework and datasets, (3) implementation of dedicated LCC studies, (4) use of cutting edge NMs P-chem characterisation and emission sampling techniques, (5) application of standardised protocols for functional testing and validation. This will also contribute setting the basis for a new paradigm for integrated sustainability and safety assessment of NMs through their life cycle stages (LCS),

O-6 To apply the SSbD integrated approach to a representative set of NMs classes, including their applications and referring to different sectors and implied value chains (VCs). INTEGRANO addresses the three classes of NMs: carbon (carbon dots), organic (polymers and hybrids), inorganic (oxides and metal oxides); comprises (b) several value chains (VCs): textile, biomedical, renewable energy, air filtration, water purification, packaging, automotive, building and construction, cosmetics.

O-7 To provide recommendations and decision support for standards and policies regarding NMs and NEPs, SSbD INTEGRANO will combine information on potential hazard and exposure of emerging NEPs to comply with the regulatory context (REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals and CLP: Classification, Labelling and Packaging,

including specific regulations for biocides[17] and cosmetics[18]). It will keep a close contact with leading standards-setting organizations (OECD/CEN/ISO), regulatory bodies (ECHA/EFSA/EMA/SCCS), innovation drivers (companies/industrial association), civil society policies (policy makers). It will inform regulatory frameworks and evidence requirements regarding: 1) specific hazard profiles of new materials, 2) validated hazards measurements approaches (emerging p-chem characterisation, toxicology technologies and methods), 3) innovative assessment models (the LCIA approach for NEPs). It will disseminate project results in line with the fair open access philosophy, focusing on transfer to the "market" *i.e.,* to routine use in a regulatory, standardized, and innovation context of the project., a Decision Support Tool (DST based a Multi-Criteria Decision Analysis (MCDA) framework will be provided to support regulators and manufacturers in assessing the sustainability of NMs and NEPs via optimisation of their performance in terms of cost, functionality environmental and health impacts.
O-8 To transfer knowledge and valorise project results towards exploitation: this objective will include concrete measures to make project results FAIR and to promote their impact through concrete and efficient dissemination strategy and roadmap (as part of the dissemination and exploitation plan). These will employ scientific publishing, web-based media (both for dissemination and internal knowledge transfer and data management within the consortium), stakeholder outreach platform and events to foster cooperation and follow-ups as well as education, public awareness and open science practices.

INTEGRANO **objectives** are **SMART** as they refer to **SPECIFIC** research outputs, pragmatic tools and concrete recommendations that will **facilitate the implementation of the proposed methodology and will be specifically addressed to products and processes in nanomanufacturing industry** in line with SSbD approach. They are **MEASURABLE** against defined deliverables and milestones as provided in Tables 3.1c and 3.1d using specific indicators and means of verification. They are **ACHIEVABLE & REALISTIC** given the available **expertise, infrastructure and resources** put in place by the INTEGRANO Consortium, necessary to undertake the proposed ambitious work programme. The objectives are also **TIMELY**, with specific and weighed timeframes for INTEGRANO tasks implementation, checkpoint outcomes spanning over the entire project duration, while also providing a sound and structured dissemination strategy targeting **short- and long-term impacts** beyond the project lifetime (e.g., translating results into regulatory policy and continuing validation of the assessment and prediction models and tools).
TRL of address solution and methodology readiness level. Starting TRL of most NMs synthsis groups is below TRL5 and will reach TRL5 within the project development by addressing the compliance of the KPIs referred to the safety, sustainability and functional dimensions. The starting TRL of some of the incorporation processes exceed TRL5, while others are below TRL5 and will reach TRL5 for the addressed applications at the end of the process. With specific reference to the INTEGRANO implementation methodology, the TRL of the multi-optimisation design algorithm MOOD to be implemented into the Decision Support Toolbox will be elevated from (staring) TRL4 to (final) TRL5-6 by integrating computaion modules generating new response functions capturing higher non linearities levels allowing for and extension of the KDFs value range. The DST will also contribute to the TRL elevation by developing dedicated GUI to enable DST user to easily visualise MOOD results for the validation phase.

Objective	KPIs (obj measurement)	Means of verification
O-1 To develop a toolbox that enables easily identifying the set of safe and sustainable solutions (design cases)	KPI1- availability of toolbox (DST) KPI2-Time required for elaboration of the MOOD algorithm KPI3- resolution of the multioptimal set of safe and sustainable design cases KPI4 GUI usability and easy interpretation of DST provided solutions to SSbD cases	Testing the toolbox (DST) with reference design cases which will enable assessing SSbD solutions compliance and measurement of KPIs
O-2 To develop and validate new toxicological and eco-toxicological assessment methods	KPI1 -Definition of new approach methodology protocols (at least one) to assess toxicological hazard.	Testing of the reliability of NAM with selected NMs and generation of datasets for NAM application
O-3 To devise specific nano-ecotoxicity and nano-toxicity impact indicators	KPI1 availability of nano-specific impact category KPI2 indicator representativeness of nano-ecotoxicology effects (mid and end point)	DST predicitions/indications compliance with reference cases whose impacts are known in advance
O-4 To gain insights and predict mid-point toxicity and eco-toxicity of selected	KPI1 availability of Dataset of toxic responses in relation to the NMs p-	Testing the correlation functions and defining the thresholds for p-

[17]. Biocidal products regulation 528/2012.
[18]. Cosmetic products regulation 1223/2009.

NMs as a function of their properties and use scenarios	chem properties and use scenarios	chem/use scenarios vs toxic outcomes.
O-5 To promote the integration of existing assessment frameworks, standards and practices	KPI1 correlation between SSbD outcomes of INTEGRANO benchmark case studies assessment with other frameworks assessments	frameworks assessment responses comparison between existing and INTEGRANO frameworks Possibility of finding conversion of factors or conversion algorithms between INTEGRANO and other frameworks
O- 6 To apply the SSbD integrated approach to a representative set of NMs classes, including their applications and referring to different sectors and implied value chains (VCs).	KPI1 quantification and qualification completeness with respect to the life cycle stages KPI2 flexibiltty of the SSbD approach when applied to difffernet industrial sectors and value chains	Testing the SSbD framework and tool with respect to different NMs design cases, focussing on different applications, in diverse industrial sectors and related value chains
O-7 To provide recommendations and decision support for standards and policies regarding NMs and NEPs, SSbD	KPI1 possibility of generalising case studies to obtain benchmarks and reference studies supporting standardisation KPI2 identify methodology and tools that may be implemented and used by the majority of end users and decision makers	Availabliy of reference case studies; Applicability of policies and recommendations to decision support.
O-8 To transfer knowledge and valorise project results towards exploitation:	KPI1 involvement of more stakeholders KP2 proof of environmental and social sustainability as well as safety levels improvements	Availability of Report accounting for dissemination and communication activities Availability of draft exploitation plan

INTEGRANO concept and objectives are well positioned in line with the general expectation and the scope of activities outlined in the EU Work programme for the specific call, specific links are highlighted in Table 1.1a.

Table 1.1a. INTEGRANO relation to the Work Programme:

Work Programme topic	**INTEGRANO response**
Select group of chemicals/ (advanced) materials […] integrated approach for health, environment, social and economic impact with societal relevance	The project is built around a number of advanced engineered NMs (oxides, polymers hybrids, C-dots), with a variety of applications: Antibacterial/Antiviral coatings on medical textiles, UV protection and antiaging in cosmetics, Photocatalytic and thermocatalytic membranes for air pollutant and CECs removal, photoactive for energy harvesting, and biopolymer foam performance enhancer. This selection is justified with use cases on its wider impacts on the society-Health (Reduction in HAI and skin cancer), environment (Increase in green energy, and reduction in NM-based pollution), Social (Increased access to Safe and clean water), and economic (CAPEX and OPEX optimization through an advanced algorithm) impact assessments.
Development of methodologies […] integrated health, environment, social and economic impact assessments.	A comprehensive methodology and guidelines will be prepared on the 5 dimensions-Health, environment, social, economic and functionality of the nano materials, using Multi Criteria decision analysis. This will serve as a reference for all the stakeholders in decision making process. New nano specific Impact categories will be developed for the existing Life Cycle assessment applied to NMs addressing its nano toxicity and nano eco toxicity.
Identification of data gaps and availability along the value chain as regards all relevant sustainability dimensions […]	Currently there is no comprehensive framework to address the NMs Risk Assessment (RA) and toxicity profiling, creating a data gap in accessing the safety, environmental, social and economic dimensions of NMs using LCA and MCDA. We will be developing a comprehensive framework for this with active stakeholder engagement across the value chain. The negative externalities (bad water quality, bad air

identification and monetization of life cycle externalities	quality, reduced energy efficiency, increased in HAI) avoided due to the implementation of our NMs will be quantified by monetizing it. This will enable the internalization of externalities into market price of NMs, providing incentives for its development, production and use.
Identification and engagement of all relevant stakeholders along the value chain […]Foster a shared support and agreement on developed methodologies	All the relevant stakeholders across the value chain will be engaged continuously through dedicated platforms (websites and portals), in person events (to share the plan and activity update to get the feedback to avoid conflict of interest), and planned training session for relevant stakeholders. An advisory board will be present for the co-creation of the guidelines and definition of the methodology usability in the target sectors. All the data related to characterisation and prototyping of the new NMs and NEPs will be included into the integrated framework. This will be presented with the case studies, allowing its effective acceptance and implementation by stakeholders in real case scenarios. A digitalised DST will be provided, reducing lead time in development and significantly time to market.
Delivery of FAIR data and methodologies including results	Data FAIRification will ensure accessibility and reliability of generated data. The data and methodologies including the results will be FAIR and promote their impact through concrete and efficient dissemination to enhance its acceptance and wider application across various sectors, Construction, Health, Textile, Cosmetics, Environment.
[…] safety and sustainability of a chemical or material are the result of a mix of intrinsic and extrinsic properties	We will acknowledge to the Safety and sustainability of the NMs and NEPs, by accounting for its intrinsic (Molecular design, process design and Product design) and extrinsic (Hazard assessment, Occupational safety, human toxicity and ecotoxicity) properties. The assessment of the intrinsic property will be carried out by a variety of advanced characterization techniques and methodologies to assess the NMs and NEPs chemical identity. The extrinsic properties will be tested by performing simulations and sampling in real-life scenarios. Mixture-toxicities of the multiple transformation products and with other contaminants will be considered, including additive, synergistic or antagonistic (mitigating) effects. Field monitoring will be conducted to measure NPs concentration levels at relevant locations for specific NEPs, discriminating between specific sources (background from the outdoors, process and other indoor sources). The measurement data will assess exposure determinants, e.g., emission rates (mg/min) and factors (mg/kg) of different chemical components, emission control efficacies, NM mass flows to different compartments.
The developed methodologies should support and facilitate decision making when having to weight multiple sustainability criteria against each other.	The methods, models and tools will provide criteria for decision making, including the scientists, engineers, and policy makers (within EU and globally) to estimate the Health & Safety, Environmental, Economic, Social and Functional impact of the NMs and NEPs using a complex algorithm which uses few experimental data to assess the multiple sustainability criterias with infinite possibilities. This decision support tool allows the user to input the KPI values, and the algorithm will provide results with the KDFs, supporting in making informed decision. This holistic approach is developed through MCDA, that will also support standardisation bodies such as ISO.
Demonstrate synergies with the CE-NMBP-42-2020 and topic HE-CL4-2023- RESILIENCE-01-21 projects HORIZON-HLTH-2022-ENVHLTH-04-01.. […] collaboration with the European PARC	INTEGRANO demonstrates close synergies with the EU funded projects, as it also develops robust and operational methodology to assess the Sustainability throughout its life Cycle. Development of a tool assess sustainability is an essential part of the project, supporting the stakeholders in decision making process. INTEGRANO is in synergy with the project, *HORIZON-HLTH-2022-ENVHLTH-04-01* as it is assessing Health impacts of the NMs in the design phase, Production phase and use cases, by validating the hazard measurement through advanced toxicological techniques. Where biological effects relevant to human health will be evaluated under environmentally relevant exposure conditions. This will allow to bridge the epidemiological data achieved in HORIZON-HLTH-2022-ENVHLTH-04-01 with possible NM-induced health effects. A dedicated platform will be created for stakeholder engagement. This can also be used as a platform for common interaction of the partners from other relevant European funded projects, fostering increasing engagement and discussing the issues during the research phase. We will be collaborating with JRC for their support and expertise in the field.
Proposals should indicate to which chapters of the Strategic Research and Innovation Plan for chemicals and materials they will contribute.	INTEGRANO contributes to the chapters-Stakeholder consultation (with continuous stakeholder engagement with dedicated platforms), Enablers cross-cutting aspects (FAIR data and open platforms, and providing training to relevant stakeholders), SSbD (accounting for the intrinsic and extrinsic properties of NM), Safe and Sustainable production process and technologies (Recuperation and recycling, and optimizing the production process), Exposure (Advanced monitoring strategies with complex ML models), Hazard assessment (through the creation of Ecotoxicity models and tests, and decision support guidelines), Risk Assessment (with improved methodologies and tools, and risk communication), Decontamination and remediating pollution (Assessing and minimizing the existing pollution, and decontamination strategies) and Monitoring implementation (with meetings with stakeholders periodically).

1.2Methodology

1.2.1. Overall management strategy and data flow

INTEGRANO adopts an **Integrated Management Methodology** (IMM) to support the SSbD approach applicable to chemicals and materials, in order to promote **twin (green** and **digital) transition**, where digital tools enable the identification of safe and sustainable solutions. Integration of human expertise with digital support offered by dedicated Decision Support Tool will leverage the new generation of data and the exploitation of existing data on NMs features, performance and safety towards the efficient implementation fo the safe and sustainable design process.

The methodology is based on **quantification** (metrological approach) and is inspired by the following international standards ISO 10040-44 for the Life Cycle Assessment (**LCA**), ISO 14075[19] for Social-LCA (**SLCA**) and by Life Cycle Costing (**LCC**) best practices to assess impacts on environmental, social economic dimensions, respectively. In line with the mentioned standards the assessment framework will refer to the four phases: 1) Goal and Scope definition, 2) Inventory, 3) Life Cycle Impact Assessment (LCIA), and 4) Interpretation. This scheme will be applied by integrating, LCA, SLCA, LCC to assess NMs safety and sustainability throughout their life cycle stages: NMs synthesis, their incorporation, NMs and NEPs use, end of life (EoL) options. The IMM will enable a **stage-gate** (see Fig.1) design process to perform subsequent filtering of unsuitable design options. This method may be assimilated to the "***from-funnel-to-tunnel (F2T)***" industrial innovation process, which starts from several potentially feasible solutions and ends up with the selection of the best suitable solutions. Indeed, the F2T will allow selecting NMs which will **simultaneously comply** with functionality, safety, environmental and social sustainability requirements through their Life Cycle Stages: (I) NM synthesis, (II) incorporation, (III) use-phase, (IV) end-of-life options. The stage-gate process allows for a recursive design at each life cycle stage until the best SSbD case is met, in compliance with the continuous improvement goal promoted by ISO 9001 for quality.

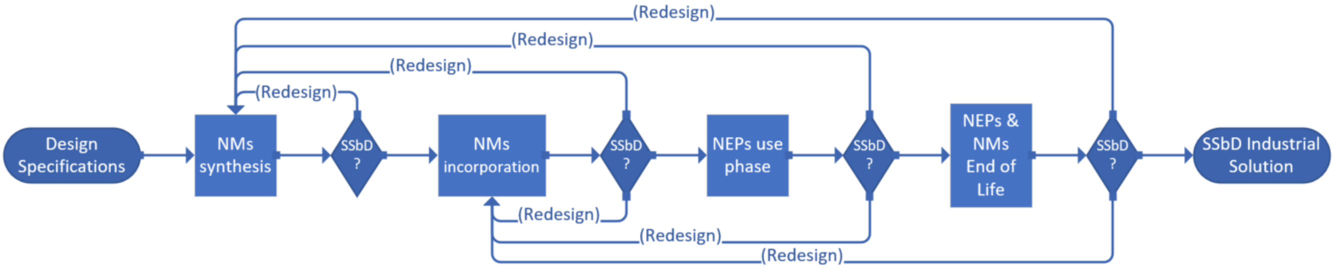


***Figure 1** Stage-gate process throught the NM life cycle stages. A gate check point is set after each LCS to validate the solution. If the solution is not compliant with the safe, sustainable and functional KPIs a re-design session is launched. Thus the F2T selection process is accomplished to achieve the selected best SSbD case.*

The strict conceptual relationship among *sustainability*, *performance* and *quality* suggests to reach a more comprehensive and **industrially-oriented SSbD** approach.

Thus INTEGRANO at each LCS applies **DMADV** design for six-sigma (DFSS) method, which addresses:

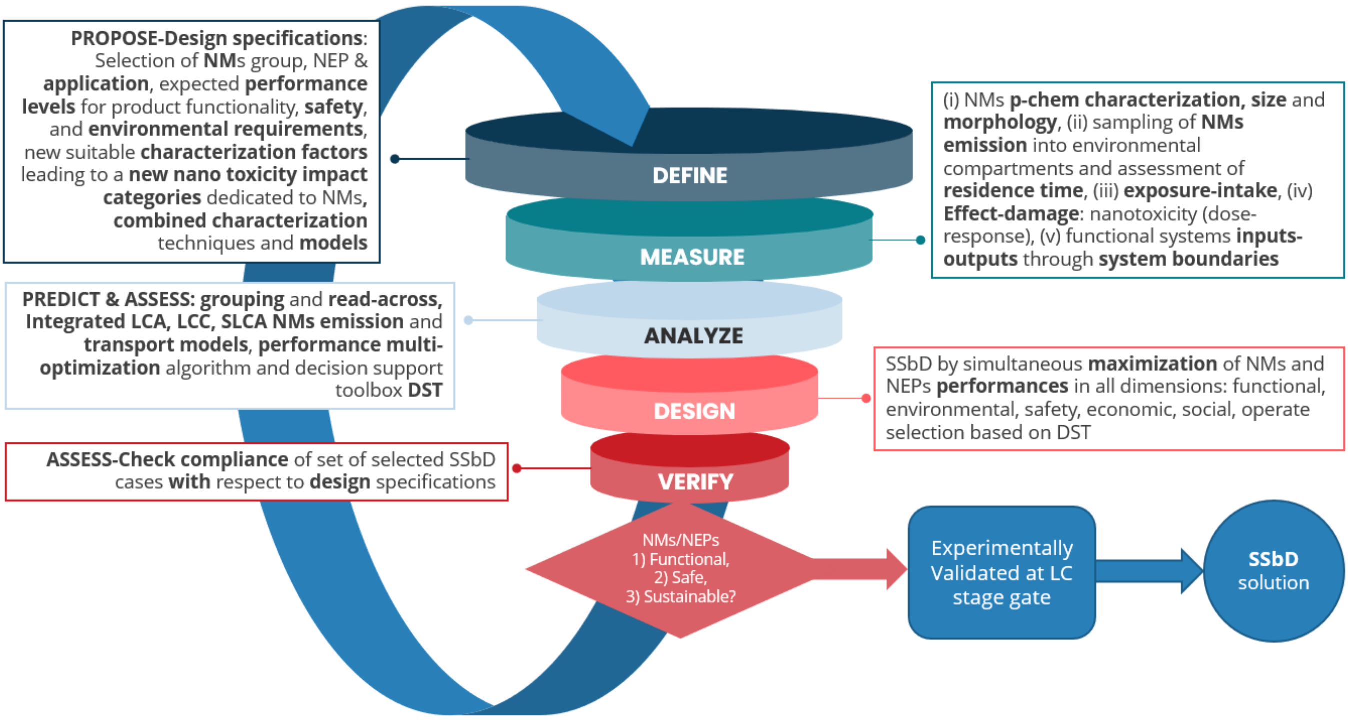
- **D**efinition of: (a) goal and scope, (b) Key Decision Factors (**KDFs**) and (c) Key Performances Indicators (**KPIs**), (d) Design of Experiment (DoE) matrix
- **M**easurement as part of the experimental data generation, p-chem and functional characterisation, emissions sampling, toxicity and eco-toxicity assays, process primary data collection for LCA, LCC and SLCA data inventory,
- **A**nalyse experimental data, process modelling and virtualisation (digital twin), computational data generation by Life Cycle Impact Assessment associated to LCA, LCC, SLCA,
- **D**esign by assessing and evaluating multiple performances supported by digital Decision Support Tool (**DST**) to sort the set of multi-optimal design cases,
- **V**erify by selecting the best SSbD case among the set of multi-optimal design cases and submit it to experimental Validation.

Thus, the SSbD process following the DMADV method is based on the interconnection between the decision space and the related performance space. The decision space is defined by the Key Decision Factors (**KDFs**), whereas the performance space is defined by the Key Performances Indicators (**KPIs**). Each point in the decision space identifies a specific combination of KDFs to which is associated a specific design case. The points in the performance space represent the performance of the design cases associated to safety, sustainability and functionality attributes.

The INTEGRANO workflow, following DMADV method will deal with primary and secondary data. **Primary** (generated) **data** will be obtained by project internal sources: NMs p-Chem and functional characterisation, toxicity and ecotoxicity assays, emission sampling campaigns, processes and systems inventoried data. **Secondary data** will be obtained by Open access NMs databases (e.g. caNanoLab, eNanoMapper, NR, NBIK, NKB, NIL,Nanowerk, and PubVINAS) for p-chem characterisation data, and toxicity data, Eurostat for economic regionalised) as well as licenced databases (Ecoinvent v.3.9.1 Db for LCA, Psilca v.4 DBs) for LCA and SLCA). Primary and secondary data along with data generated by modelling and computation will be subject to **curation**

[19] ISO/CD 14075, Principles and framework for social life cycle assessment, standard under development

and **FAIRification** process before being provided as input to- and elaborated by- the digital decision support tools (DST). The IMM promotes integration of new scientific knowledge and data collection, fostering early-stage technology development, providing innovative data management approaches, and supporting policy work toward NMs and NEPs impact assessment and prediction. The design of safe and sustainable **starting point** is the definition **(D)** of the **goal and scope** of the design case study, associated with the in-depth research of existing and available data related to features of addressed NMs and related functionalities, their toxicology and ecotoxicology profile also considering the environmental fate and Adverse Outcome Pathways (AOPs). The IMM **integrates human** and **digital** contributions to the process of attaining SSbD solutions. Indeed, the Define step of DMADV method implies the involvement of experts, e.g. NMs synthesis process experts. They will allow selecting the relevant (synthesis) **KDFs**, such as reagent concentrations, catalysers, synthesis temperature, which are thought of strongly **affecting** the addressed **KPIs**, as NMs p-chem features (such as Z-potential, NPs size) and functionality (e.g. antibacterial or photocatalytic activity), chemical reactivity (e.g. oxidative power). IMM experts will also define the design of experiment (DoE) matrices which will contribute to obtain primary data specific to the addressed synthesis (and incorporation) processes to achieve a comprehensive knowledge of the KDFs-KPIs relationship. This will integrate the already available NMs datasets from which it will be possible to extract valuable information for the specific SSbD purposes.



With reference to the defined DoE matrixes, dedicated synthesis (and incorporation) campaigns will be performed to obtain a minimum and sufficient number of samples enabling the DMADV measurement phase **(M)**. The synthesis and incorporation processes will be monitored and dedicated near and far field **sampling** campaigns will be performed to measure the size, (mass and number) concentration of NMs emitted to the environment. The synthesized NMs samples will be characterised by **measuring** the p-chem properties and the associated toxicological and eco-toxicological effects through dedicated assaying. The NMs interaction with organisms and environmental compartments along the LCS in varying scenarios will be assessed by applying several interconnected quantitative characterisation techniques, including advanced fluorescence imaging techniques for biological studies. For this purpose, established and reference methods will be employed, including *in-vitro* toxicity tests, as well as *in-silico* modelling approaches to **(A) analyse** the NMs and NEPs potential health risks providing insights on nano-toxicological effects, including AOPs, and eco-toxicology assessment. Ecotoxicological studies will encompass the use of a battery of organisms and the NM effects will be evaluated also in accordance to their capability of bioaccumulating along the trophic chain. This will allow obtaining Effect Factors (EE) for assessing toxicity and eco-toxicity of the addressed NMs along the LC. Assessed models will be employed for evaluating NMs transport and fate through environmental compartments to obtain Fate Factors (FFs), along with exposure and intake models to obtain Exposure and intake Factors (AFs). The obtained FFs, AFs and EFs will be integrated in order to propose NMs-specific toxicity and ecotoxicity mid-point Impact Categories (ICs) referred to the (fresh and marine) water and soil environmental compartments.

The analysis phase will also comprise synthesis (and incorporation) processes **modelling** and virtualisation to carry out dedicated Life Cycle Impact Assessment (LCIA) for **LCA**, **LCC** and **SLCA** dedicated studies in order to link the addressed KDFs with Environmental, Social and Economic KPIs. This will allow achieving a comprehensive profiling of the functional, safety, environmental, social and economic sustainability of the addressed solutions. Thus, LCIA will give an overarching approach to analyse the impacts on safety and sustainability of NMs and NEPs along their LC.

(D) The **design** phase is the central part of the SSbD process addressed by the INTEGRANO approach within the IMM. The DMADV Define, Measure and Analyse phases associated to the specific design case will provide a set of data enabling the correlation between the considered key decision factors (KDFs) and the addressed key performance indicators (KPIs) associated to the five addressed dimensions (5Ds): safety, environmental, social, economic and functional.
The obtained integrated data set will be provided as input to the digital Decision Support Tool (DST), which through a dedicated algorithm will use the limited set of measured and computed data as training set to quantitatively assess the functional non-linear dependence of KPIs on KDFs. Then the **DST** will employ a dedicated algorithm for multi objective optimisation design (**MOOP**), which automatically sorts among all possible design cases associated to specific combinations of KDFs values the ones that are simultaneously complying with the functionality, sustainability and safety requirements. Until this point of the DMADV method no weighting procedure, nor filtering or ranking is necessary to achieve the sorted set of multi-optimal design cases. Thus, the novel INTEGRANO approach preserves all potential suitable safe and sustainable solutions, by discarding only the ones that will certainly not match the requirements. **(V)** The final phase of the DMADV is the Verification and Validation. In this phase the DST user is requested to apply the weighting procedure, which allows him to select the best SSbD case. The weighting procedure may be recursively applied to assess consequences on the obtainable KPIs levels for the selected best design case, thus enabling a critical, informed decision on SSbD. The best safe and sustainable design case will be defined by a specific (selected) combination of KDFs values, which through the KDFs-KPIs functional dependence, will return the expected KPIs values. Once the SSbD case is selected the safety and sustainability experimental testing and validation will be carried out along with the functional performance assessment. The testing and validation in the Verify phase will include compliance to standards and regulations. The DMADV procedure will be sequentially and recursively carried out for performing the SSbD analysis at each stage of the NMs life cycle by applying the a.m. stage-gate process. For each LCS the specific KDFs and (functional) KPIs will be assigned. For instance, durability and service performance may be addressed as functional KPIs in the use phase and maintenance frequency and duty cycle as possible KDFs identifying specific use phase options. KDFs and KPIs may be represented also as discrete variables or by exclusive options (i.e. optional NMs for an addressed functionality within the scope of the design case).

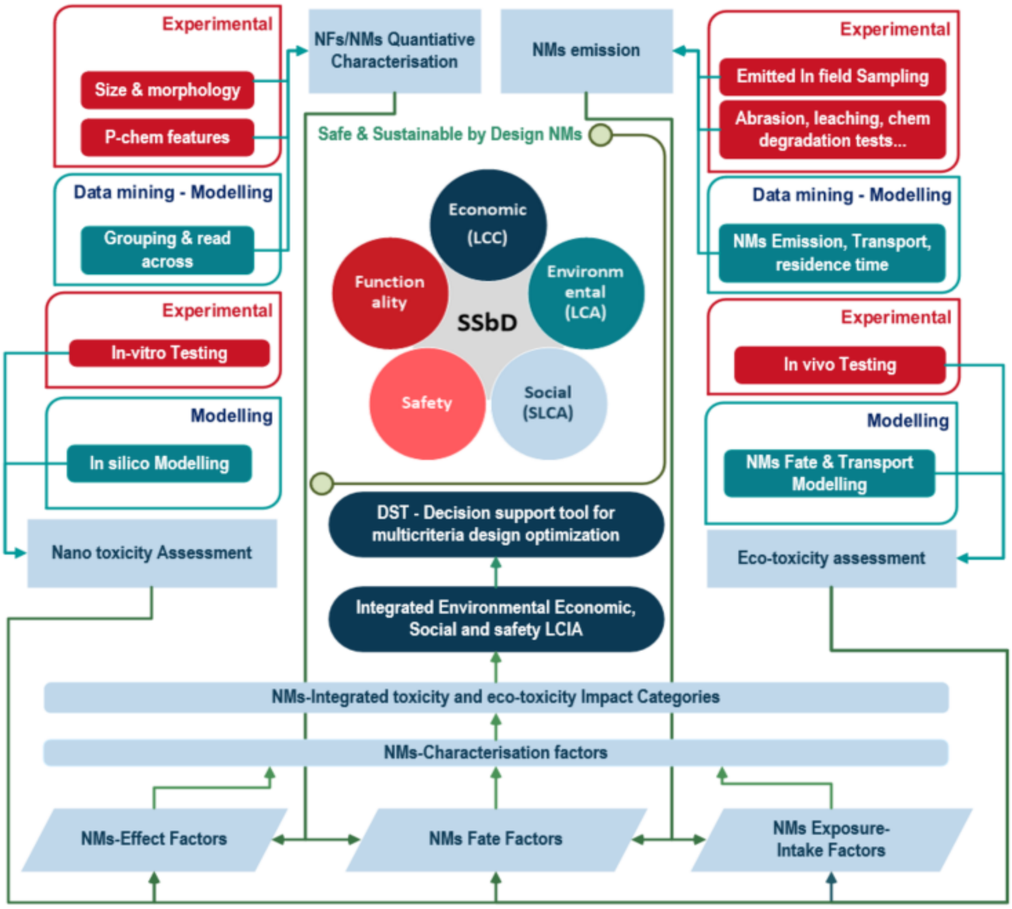


Figure 2 *Data generation and dataflow towards DST elaboration aimed at sorting the multi-optimal SSbD cases*

Compliance with standard and regulations will be applied also to the implied assessment methodologies, which will be in line with the objectives of the EU Taxonomy Regulation and comply with the 'do no significant harm' principle as per Article 17 of Regulation (EU) No 2020/852. Besides, general activities to improve SSbD of NEPs and NMs and the experimental techniques employed are not resource intensive and pose no or little harm to the environment. The project largely employs and aims to deliver digitalized tools and *in-silico* models for data generation and assessment to minimise negative impacts.

1.2.2. Scientific methodologies

The specific scientific methodologies employed by INTEGRANO involving interdisciplinarity links expertise and mobilises partners resources in various thematic fields: chemistry and material science for synthesis and incorporation of NMs and NPs; physics, physical and analytical chemistry for p-chem characterisation; biology, microbiology and toxicology for toxicity assessment; statistics, computational and data science for model development; environmental science for sustainability and RA.

The challenge of assessing NMs safety and sustainability implies both standard analysis of the processes involving mass-energy balance, including raw (bulk) materials and a dedicated assessment of NMs interaction with the environmental compartments involved with NMs emissions and NMs fate. This considers exposure, nano-toxicity, and nano-eco-toxicity effects considering NMs in their (potentially complex) final form at point of intake due to interaction with complex environmental matrices. Another challenge to be considered is the case of low doses intake and prolonged exposure, which provides a more realistic representation of real cases. The proposed LCIA approach to NMs Safety and Sustainability exploits existing environmental sustainability and safety assessment framework.[4,5,14,15,] while benefitting from available data and direct measurements of characterisation and experimental targeted toxicity assessments. A detailed study of addressed NM groups fate will be conducted assessing specific residence time of a NM in a particular environmental compartment, depending on degradation and transport processes e.g., air to soil by rain, water to air by evaporation, soil to water by run-off.
The project will provide a **comprehensive view** including environmental, economic and social sustainability by using appropriate **assessment frameworks** based on common data inventories, and **standard assessment methodologies** (LCA, LCC, and SLCA), considering each stage of the NM life cycle from different perspectives.
Starting from assessed standards[20,21] and guidance[22] INTEGRANO will provide a comprehensive environmental, social, and economic sustainability impacts assessment method to characterise safety and sustainability profile of NMs along their LCS. This will be achieved by integrating safety and environmental impacts in the definition of NMs dedicated impact categories ICs.

LCIA- Harmonised and integrated approach to sustainability: environmental social and economic dimensions: To develop LCIA framework, INTEGRANO will propose a meta-model, leading to a harmonised standardised test method to assess safety and sustainability of NMs. The quantitative method implies specific data acquisition through available data sets, scientific studies, and direct experimental NMs characterisation and assessment of NMs interaction with different environmental compartments. This is based on the concept that specific assessments and characterisations are needed to evaluate the effective sustainability and safety of selected NMs in order to enable concrete nanotechnology industrial uptake and achieve real industrial applications and competitive NEPs commercialization. Given the complexity of this challenge, it has to be faced from a scientific perspective based on a quantitative approach to provide reliable indications for technological applications. INTEGRANO methodology is inspired to the ISO 10040-44, ISO 14075 standards specifying the LCA framework and its assessment phases: 1) Goal and Scope definition, 2) Inventory, 3) LCIA, and 4) Interpretation. This scheme will be applied to all assessments referred to the dimensions considered: LCA integrated with nano-toxicity assessment LCC and SLCA. The data inventory associated to each design case study will be designed in order to enable comprehensive impact assessment and evaluation of the full range of environmental-safety, economic, social and functional key performance indicators (KPIs) assessing the NMs LC sustainability and safety referred to the specified functional unit (connected to the NM functional performance). The LCA and SLCA will be carried out by using standard tools (Open LCA) and acknowledged databases, Ecoinvent 3.8- for LCA and PSILCA for SLCA.
LCIA: Integration safety and sustainability of impact assessment. INTEGRANO challenge for impact assessment integration is twofold. Firstly, the project will enable the integration of the assessment of NMs impact on health (toxicity) with the assessment of the impacts on environment (eco-toxicity) by defining suitable nano-tox and nano-eco-tox Impact Categories. Secondly, by integrating the novel nano-specific ICs to the set of standard ICs for human toxicity and for eco-toxicity (HTTP, FAETP, MAETP, TETP[23]) INTEGRANO will allow a one-step integrated safety and sustainability assessment comprising impacts associated to energy, conventional bulk materials and to NMs at the same time. This will be obtained by taking into consideration nano-specific emissions, exposure, effects on the environment and on human health. The project will propose a dedicated NMs impact method to be associated to the ones currently in use (e.g., CML 2001). Thus, INTEGRANO perspective will allow assessing a comprehensive sustainability and safety impact of NMs by integrating the effects of bulk and NMs implied in the LC of NEPs within the same standardised LCA assessment framework. The LCA will be carried out by using standard tools (e.g., Open LCA) and acknowledged databases (e.g., Ecoinvent 3.8) complemented by the project-generated impact data for the selected NMs.
The proposed novel nano related ICs will be referred to specific nano-toxicology effects correlated to specific features of the involved NMs also based on grouping and read across approach, by identifying benchmark nano-materials providing a reference impact on eco- and human-toxicity referred to specific effect factors (EE). INTEGRANO quantitative approach will be based on a cause-effect mechanism to determine characterisation factors (CFs) of selected NMs groups. Indeed, the nano-toxicity and eco-nano-toxicity ICs will be defined devising suitable CFs that will be obtained by the aggregation of: fate factor (FF), exposure-intake factor (EF) and EE; the latter representing: 1) specific toxic effect of exposure to a given ecosystem in the defined compartment of NM persistence (for eco-toxicity assessment) and 2) hazard accounting for the sensitivity of a specific target (for human toxicity assessment). Specific CFs of similar NMs will be obtained by direct *in-vitro* toxicity assessment which will highlight the specific toxic effect and adverse outcomes, also considering long term effects at low intake or exposure doses. Specific models correlating *in-vitro* toxicity assessment and *in-vivo* toxicity outcomes will be suggested to obtain *in-vitro* – *in-vivo* calibration curves to achieve

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20. ISO standards 14040-14044, Environmental management — Life cycle assessment — Requirements and guidelines
21. ISO/AWI 14075 Principles and framework for social life cycle assessment (under development)
22. UNEP, 2020. Guidelines for Social Life Cycle Assessment of Products and Organizations 2020. Benoît Norris, C et al. (eds.).
23. HTTP- human toxicity potential; FAETP-fresh aquatic toxicity potential; MAETP -marine aquatic toxicity potential, TETP terrestrial eco-toxicity potential

better representativeness and reliability of the effects and potential damages. INTEGRANO will exploit existing models of NMs transfer from source environmental compartment to emission compartments to obtain FF and will carry out specific measurements to obtain transport, diffusion, and solubility coefficients to finally assess the end-point exposure factors.

Toxicology characterisation and assessment of NMs: The NMs and NEPs toxicological profiles will be assessed by exposing *in-vitro* models of lung epithelium, intestine, or skin under realistic exposure scenarios in relation to two NMs exposure pathways for human adverse health outcomes during the NMs LC: inhalation, ingestion, and dermal contact. The *in-vitro*) and nano-specific indicators will be identified following an AOPs-oriented strategy focused on specific diseases (e.g. COPD; lung fibrosis; inflammatory bowel disease). In vitro model of the lung epithelium used in INTEGRANO will be a culture of human bronchial epithelial cells (Calu-3/BEAS-2B), possibly in co-culture with cells of the immune system (THP-1 derived macrophages) and/or fibroblasts, to also mimic responses during pathological conditions (COPD, fibrosis). Advanced complex models with collagen/hydrogels films scaffolds will be developed and used in order to also mimic the contribution of the ECM in the development of fibrosis due to NMs exposure. 3D cell models representative of different target tissues, including human lung and skin cells, and organoids will be selected according to the NP environmental fate and exposure scenarios predicted during NMs life-cycle. When possible, standard OECD or ISO test will be adopted to match the regulatory frameworks. The biological models will be used to investigate AOPs, hazard assessment and the SSbD strategy. Bronchial cells will be cultured at the apical surface of a trans well insert and let to grow for 24h. After this time another cell type (i.e. differentiated THP-1 or fibroblasts) will be seeded and, at least 24 hours prior NMs exposure, the medium in the apical compartment will be removed to promote epithelial cells differentiation at the air-liquid-interface (ALI). After differentiation, the model is stable for some days (from few days up to one month depending on the epithelial cell line used), thus the treatment of the inserts could occur during consecutive days. In the inhalation model, specific pathological conditions will be implemented. The *in-vitro* model of the skin will consist in co-cultures of human keratinocytes (HaCaT) and dermal fibroblast (HDF) on inserts or in already validated reconstructed human epidermis (RhE) *in-vitro* models, composed by fully differentiated keratinocytes (EpiDerm™ by MatTek), eventually cultured with dermal fibroblast constituting a full-thickness model of the epidermis (EpiDerm-FT™). In particular, the inhalation exposure and toxicology studies will be performed at the air liquid interface (ALI) according to the following approaches:

1) At lab scale with the Vitrocell Cloud: this exposure system will be used for the screening of NMs toxicity at the ALI with a more realistic approach. The system consists of a chamber where different inserts can be placed and exposed at the ALI to the NMs, aerosolised by a nebulizer. A separate chamber compartment will include housing for inserts dedicated to control samples. The Vitrocell Cloud exposure chamber come with the option of a quartz crystal microbalance (QCM) that allows for a relatively quick and easy way to evaluate deposition at a resolution of 10 ng/cm^2. This system therefore allows to obtain dose-response relation of toxicological response of interest. The responses will be selected considering the more relevant AOPs already established for NMs, else specific relevant pathways will be defined. Furthermore, data from field monitoring campaigns, associated to MPPD modelling, will allow to estimate the exposure to realistic doses of NMs.
2) Indoor exposure of the lung model directly at elected manufacturing sites: the Cultex-RFS module allows for direct exposure to airborne NMs present in the indoor environment. The system works by sucking the aerosol from the atmosphere via dedicated sampling line connected with the exposure module (Gualtieri et al., 2018). The air is sampled at 1 L/min and diverging, from a well-shaped compensation chamber, 5 mL/min to the surface of the lung epithelium model cultured on the inserts. In parallel, control cells are exposed to filtered clean air always at a flux of 5 mL/min. The cells cultured at the ALI are always in contact with the air/aerosol at the apical level and feed with the maintenance culture medium from the bottom of the insert. Therefore, each exposure test will consist of three inserts exposed to chamber sampled aerosol and three inserts exposed to control air.

After performing ALI exposure with the different systems, toxicological assessment will be performed with an AOPs-oriented strategy. Three relevant nano-specific indicators for NMs hazard assessment have been identified: i) oxidative potential (OP), ii) inflammation and iii) DNA damage. Emphasis will be put on validating key event relationships (KERs) linking the key events (KEs) already identified in AOPs that describe NMs Adverse Outcomes (AOs). oxidative potential (OP): the OP of smart-NMs will be measured with different acellular methods (ascorbic acid, DCFDA, cytochrome c assays) to define the intrinsic reactivity of NMs. The assessment of the reactive oxygen species (ROS) formed in cells will be used to define the potential oxidative reactivity of the particles after the interaction with a relevant biological model. The oxidative potential will be performed according to ALI exposure under controlled laboratory conditions by dedicated apparatus (Vitrocell Cloud α or CULTEX-RFS). These tests will be useful to categorize the NMs in terms of biological reactivity and to obtain dose response curves to extrapolate relevant toxicological parameters (i.e., IC_{10} and IC_{50}). Multiplex and ELISA kit for secretion and gene analysis for expression of inflammatory mediators will be used. After exposure to NMs, media beneath the inserts are recovered and directly frozen for subsequent analysis; the inserts will be recovered from the exposure module and allowed to rest for 24 hours after exposure. Subsequently, recovery cells will be lysate for gene expression analysis. The media will be tested for the release of inflammatory mediators (namely interleukins, IL-6, IL-8, IL-1b …), with ELISA or Multiplex kits. Cell lysate will be analysed by real time PCR to assess differential expression of genes related to biological relevant processes such as oxidative response (e.g. HO-1, NQO1 and SOD1 genes), inflammatory response (e.g. IL-6, IL-8 and NF-kB, IL-1b) and DNA damage and repair (genes characterized

ATM, BRCA1 and PARP1). Differences (increased or decreased gene expression or inflammatory mediators release) between exposed and control cells will be used to discriminate NMs having an effect on the models from those having minimal or no effect. DNA damage including epigenetic modifications will be performed with the genes expression analysis of related to DNA damage and repair (transcriptomics…), genotoxicity assays. Considering the need of bridging the *in-vitro* - *in-vivo* effects of NMs, and to stay in compliance with the 3R principle, zebrafish will be additionally adopted as model organisms to screen the NMs embryotoxic and teratogenic effects potential, based on the OECD 236. In parallel, working at sublethal environmentally relevant concentrations, an AOP-based testing strategy for evaluating endpoints, like neurotoxicity and behavioural changes, will be adopted to measure NM long-term adverse effects. Then, possibility to derive dose-response curves and effective doses (e.g. ED_{50}) will be exploited to obtain reference values to be implemented in the LCA framework. Based on preliminary estimations of the likelihood for humans and environmental organisms to come in contact with the NMs, the following toxicological approaches will be involved:

1) Inhalation toxicity. If relevant exposure will be estimated in working environment, especially during the manufacturing phase of NMs life-cycle, the NPs used during production and/or collected in the environment will be exposed to human *in-vitro* 3D models of the lung and skin in air liquid interface (ALI) conditions in order to assess occupational risks. Since biomolecular composition, stiffness, and signalling molecules of the ECM in cell microenvironment influences cell fates and functionalities the maintenance of cellular homeostasis, the alteration of ECM composition is strongly associated with the onset and the progression of pathological state in lung like tumour progression, fibrosis and inflammation. Furthermore, some ECM components overproduced in pathological states are directly involved in the recruitment and activation of immune system cells (i.e., macrophage) resulting in differential modulation of inflammatory cascades. The coating of polycarbonate membranes of Transwell® with ECM mimetics representative for differential pathological fate allow to emulate *in-vivo*-like functions of lung barrier in both pathological and physiological states. With this aim, hydrogel-based ECM mimetics will be employed to recreate the biochemical and physical composition of the native ECM and to develop double or triple co-cultures of human alveolar epithelium, endothelium and macrophages, to be possibly adapted to ALI exposure systems for more predictive respiratory toxicity endpoints.
2) Skin toxicity. At the use phase, skin exposure is one of the main targets of smart-NMs with antibacterial, photocatalytic and cosmetic purposes. Already validated 3D *in-vitro* reconstructed human skin models, will be used to assess skin corrosion, adsorption, phototoxicity and irritation tests. Furthermore, a panel of genes related to the oxidative stress (HO-1, NQO1 and SOD1), inflammation (IL-6, IL-8, IL-1a, NF-kB) and DNA damage (ATM, PARP1, BRCA1), will be investigated on those models.

Ecotoxicological measurements: Ecotoxicological assessments focus on the ecosafety of innovative materials/products prior to their use, to prevent toxicity effects in the marine (water, sediments) and terrestrial (water, soil) environments by using standard and innovative bioassays. Batteries of bioassays are available at CNR, using model test-species belonging to different trophic levels (Bacteria, Algae, Crustaceans, Rotifers, Echinoderms, Molluscs). Standard (e.g. mortality, immobility, growth inhibition) and innovative (e.g. behaviour) ecotoxicological end-points at different levels of sensitivity can be measured. The proposed ecotoxicological tests can be performed by following standardized protocols (UNI EN ISO, ASTM, UNICHIM etc.) and literature references. They allow performing a complete environmental risk assessment protocol to ensure the safe deployment of innovative materials/products. To measure behavioural (i.e. swimming, frequency of pulsations) responses in crustacean, rotifer, echinoderm and cnidarian species listed in the table above (Table 1.2.2a), CNR has developed a Swimming Behaviour Recorder (SBR, see Fig. 1.2.2a) system to track and analyse movements of aquatic invertebrates.[24] This new automatic system can be used to detect movement alteration in a wide range of model organisms exposed to traditional and emerging compounds (microplastics, NPs) and to environmental matrices (sediment, water), being a suitable tool for environmental monitoring and ecotoxicological surveys. This prototype can be optimized introducing a high-profile innovative solution, developing a new automatically environmental tool to supply the system for the automatic evaluation of both acute (immobility) and behavioural (swimming alteration, frequency of pulsation) responses of aquatic invertebrate organisms. Facilities for invertebrates breeding and culture are available at CNR, as well as a marine station, located in the Genoa Harbour, to perform in field and semi-field experiments (i.e. mesocosms) that belongs to the European Network of Marine Research Institutes and Stations (www.marinestations.org/).

Table 1.2.2a. Ecotoxicological bioassays available at CNR (m.a., marine environment; t.e., terrestrial environment)

Class	Biological models	Endpoint	Exposure	Standard method
Bacteria	*A. fischeri (m.e./t.e)*	Bioluminescence inhibition	Short term exposure (30 min)	UNI EN ISO 11348-3: 2019 DM 173/2016

[24] Faimali M, F. et al. (2006) MARINE BIOLOGY, 149, 87-96

Microalgae	*P. tricornutum (m.e.)* *S. costatum (m.e.)* *S. capricornutum (t.e)*	Growth inhibition	Short term exposure (72 h)	ISO 10253:2006 ISO 8692:2004
	P. subcapitata (m.e)	Growth inhibition	Short term exposure (72 h)	EN-ISO 8692:2012
Crustaceans	*A. amphitrite (m.e.)*	Mortality/Immobility behavior settlement	Short term exposure (24-48 h)	UNICHIM 2245/2012
	A. franciscana (m.e.)	Mortality/Immobility behavior	Short term exposure (24-48 h)	APAT IRSA CNR 2003
	D. magna (t.e.)	Immobility	Short term exposure (24-48 h)	ISO 6341 (1996)
	T. fulvus (m.e.)	Mortality/Immobility behavior	Short term exposure (24-48 h)	ISO14669:1999
Rotifers	*B. plicatilis (m.e)*	Immobility	Short term exposure (24-48 h)	ASTM 2004
Echinoderms	*P. lividus (m.e.)*	Embryotoxicity, fertilization, behavior	Short term exposure (24-48 h)	ASTM 1995 DM 173/2016
Molluscs	*C. gigas (m.e.)*	Larval anomalies	Short term exposure (24 h)	ISO 17244:2015
Cnidarians	*Aurelia* sp. *(m.e.)*	Immobility behavior	Short term exposure (24-48 h)	Costa et al 2015, 2020

The traditional and standardized bioassays will be further implemented using an innovative model organism, the ephyrae stage of Aurelia sp. jellyfish recently proposed as a high value ecotoxicological model thanks to their high ecological relevance and sensitivity to a wide number of traditional and emerging compounds and to their high ecological relevance.[25] Acute and behavioural responses (mobility and frequency of pulsation) on ephyrae jellyfish exposed to NMs will be evaluated. All eco-toxicity studies will be focussed to find suitable quantifier(s) for the toxicity EE to be used in WP5. UNIMIB will assess neurotoxicology using ZF embryos as alternative to *in-vivo* model. The Fish Embryo Acute Toxicity (FET) test with the ZF (Danio rerio) is designed to determine the toxicity of chemicals and is recognized as valuable alternative to *in-vivo* models (OECD TG.236/2013). FET will be used to evaluate NEPs toxicity at multiple levels (mortality, teratogenicity, immunotoxicity, genotoxicity and endocrine disruption capability). Taking advantage from the high number of commercially available ZF mutant strains, the selection of specific mutants will be useful for the identified or presumed AOP of the different NMs. This system will allow to evaluate toxicity and AOPs at whole organism level, using a Vertebrate with very high genetic homology with human. The study of the AOPs for the NMs displaying moderate-strong toxicity will be performed by coupling molecular biology analyses with advanced microscopy techniques, aimed at describing the bio-nano-interactions at subcellular level as relevant initiating event.

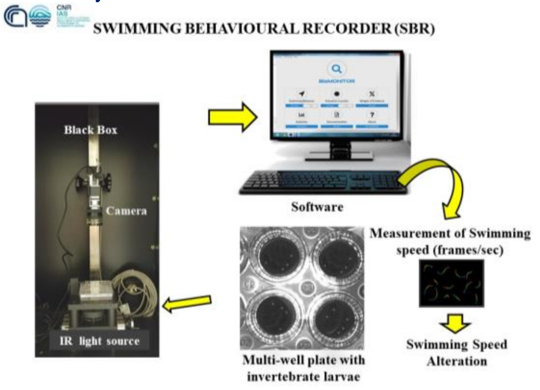


Fig. 1.2.2a. CNR SBR system to record movements of marine invertebrates

Predictive models for (eco-)toxicology and exposure: Air monitoring field campaign will be associated to dosimetry and *in-vitro* exposure with exposure system at the ALI (Vitrocell Cloud and Cultex-RFS), thanks to modelling NMs exposure and impact with MPPD, and to results from airborne NP monitoring campaigns at production sites. ALI exposure, coupled with verified/modelled dosimetry, will allow realistic measuring of biological effective doses and generate more robust toxicity curves. Oxidative potential (OP) assessment of NPs, as intrinsic properties for their reactivity to be validated/confirmed with *in-vitro* models of the lung/skin exposed at the ALI, and intestine exposed in submerged conditions after in vitro digestion of NMs, taking into account the possible association with cell antioxidant response, inflammatory and genotoxic effects at environmentally relevant concentrations. Dose response correlation among p-chem properties and toxicological outcomes by principal component analysis (PCA) or multivariate analyses will be used for predicting the NMs behaviour, reactivity and toxicity, also considering AOPs. A novel *in-vitro* model representative of the alveolar-blood barrier will be proposed for the ALI exposure systems. The ABB will be developed basing on the properties of epithelial and endothelial cells co-cultures grown onto specifically designed mimetic ECMs representative for physiological or differential pathological states. Mechanistic mass balance models are used to quantify the safe Conditions of Use (CoU) according to methods developed in ASINA[26] project for occupational exposure assessment. These will be developed for setting CoU of consumer products. Emission source is a point-of-departure for exposure and health effects. Well-established emission measurement and documentation standards underpin efficient risk communication and management. Mass flow analysis will evaluate which fraction of material is released under different LC stages. The release is described with the help of

25. Faimali, M. et al. (2014). MARINE ENVIRONMENTAL RESEARCH, vol. 93, p. 93-101; Costa, A. et al. (2015), HYDROBIOLOGIA, 759 (1) 75-84.
26 https://www.asina-project.eu/

emission factors, such as NM-mg/kg-of-product, in all relevant environmental compartments, e.g., air, water and solid waste. Product waste generation is minimized by optimising risk. Risk optimisation is based on minimising hazard weighted emission factors with relevant exposure determinants.

Data gathered and augmented in quality by capturing meta-data associated with protocols and experimental conditions will be used for the selected NMs. The data will capture the extensive p-chem properties in combination with hazard potential expressed continuous outcomes. ML algorithms will be trained to generate response functions, describing the change of dependence on variables of interest i.e., a metric of a NM or NEP, due to numerous perturbations of the materials, conditions, or choices in production. For the eco-toxicology modelling, the same principle as the toxicological predictions used in human in vitro derived cultures and the application of machine learning (ML) tools will be adopted and eco-toxicological specific properties of interest will be defined by altering the target species used to generate the hazard related outcomes. In this manner, a distinction of important features depending on thew target organism will be derived.

NMs synthesis and incorporation processes, their dimensional, morphological, p-chem characterisation: INTEGRANO proposes specific groups of composite NMs covering the NM classes of inorganic (oxides and metal oxides), carbon (C-dots) and organic (polymer-hybrid) NMs for selected value chains and related industrial applications. (Table 1.2.2b). In order to analyse performance and stability of selected NMs and their fate and transformation at different LC stages. Several representative use cases addressing n.10 value chains (VCs) with relevant impact on society will be studied in the scope of INTEGRANO. The selected NMs synthesis and incorporation processes as well addressed applications and VCs are reported in Table 1.2.2.b.

Table 1.2.2b. The NMs, NEPs and related properties and applications for industrial exploitation, with associated starting and final TRL

NM class	NMs group	Synth / Extraction Technology	TRL	Incorporation	TRL	Value chain (VC) - Application	Functionality
Inorganic	TiO2	Chemical Synthesis	4->5	Ultrasound/ spraycoating	4->5	Medical Textiles woven/non woven	Antibacterial
	N-TiO2	Chemical Synthesis	6	Ultrasound/ spraycoating	6	air filters, water mambranes, cosmetics	Photocatalytic / UV shielding
	TiO2/SiO2	Chemical Synthesis	4->5	Spraycoating / turbemulsification	6	Medical Textiles woven/ non woven, cosmetics	Antibacterial
	SiO2	Extraction from rice husk	3->5	fillers incorporation in polymerspolymers , Foaming injection moulding	7	Automotive / building and construction) and consumer goods Elastomers and polymers	bio-polymer matrix reinforcement
	CuO/ZnO	Sonochemical synthesis	5	Ultrasound, spraycoating	4->5	Medical Textiles woven/non woven	antibacterial, antiviral
	CoMn2O4 nano-powders	Hot Barrel	4->5	Ultrasound	4->5	water mambranes for CECs abatement	Thermocatalitic for CECs abatement
	nano CaCuSi4O10 / CaOCuO(SiO2)4)	Silica extraction from rice husk + chemical syntheis	3->5	dip / spraycoating, turbomixing and turboemulsification	3->5	HVAC-air filtration, water membranes, cosmetics, Renewable energy-PV, biomedical imaging	photoluminescence energy harvesting and in depth imaging, antibacterial-antiviral
Carbon	C-dots	Chemical Synthesis	4->5	Ultarsound	4->5	Food pakaging	shelf life extension
Polymer-hybrid	Ag-HEC	Ch-Synth	4->5	Spraycoating / turboemulsification	5, 7	Medical Textiles woven/non woven	Antibacterial/Antiviral, enhanced cosmetics shelf life
	Polymers nanofibers	polymerisation	4->5	electrospinning	4->5	non woven Medical Textiles, stents, dental implants, scaffolds, patches	Filters / Scaffolds coating for dental implants

Conventional, industrially established surface functionalisation techniques, such as dip coating, spray coating, and ultrasonic spray techniques, and bulk techniques such as injection moulding, foaming, turbo-emulsification will be identified and selected depending on the type of substrate and the NM/formulation characteristics and on the base of former projects experiences[27]. Synthesis and incorporation processes will provide relevant data for the optimization of SSbD approaches. Produced NCMs and NEPs samples will also be tested in use phase simulated conditions (where possible) according to standardised tests. Settings of field monitoring campaigns directed to handling release scenarios and exposure measurements will be considered.

Physic-chemical (p-chem) NMs characterisation

INTEGRANO will employ of a variety of imaging and p-chem characterisation techniques to various types of NMs and NEPs, for obtaining new specific information relating NMs functionality, safety and sustainability.

Chemical substance information: chemical composition, known impurities, and crystallinity using spectroscopy (Atomic Absorption Spectroscopy (AAS), confocal Raman, UV-Vis, FTIR) and diffraction (X-ray and scanning electron microscopy (SEM)), available at CENTI

1. Particle properties: Dynamic Light Scattering for (i) particle mean hydrodynamic diameter; (ii) particle size distribution; (iii) polydispersity index ; (iv) aggregation state; Electrophoretic Light Scattering (ELS);[28] Inductively coupled plasma-mass spectrometry (ICP), specifically ICP-OES and single particle (SP)-ICP-mass spectrometry (MS) can be employed in field detection and sampling campaigns for elemental analysis and particles/ions distribution; zetasier to assess dispersion state

[27] SONO, Protect, Reinvent, Biomat, Nanoperwater, Nanothecaba, ASINA
[28]. ISO 22412:2017, ISO 22412:2008(E)

and stability of suspensions by zeta potential measurement; SEM and scanning TEM (STEM) for particle size distribution, aspect ratio, aggregation and morphology, available at CENTI, UNITO and CNR

2. Surface properties: specific surface area (BET)[29] and information on surface chemistry (general composition and intentional surface functional groups), surface ionisation capacity and residual acid or base content.
3. the Solid-State NMR (SSNMR) available in UNITO will be used to study chemical modification, molecular packing, distance determination and solvent-matrix interactions is essential for controlling the final product properties and interaction with biological systems. Integrated methods such as the combination of SSNMR with microscopic analysis and computational approaches will be explored.
4. differential scanning calorimetry, electron spin resonance (ESR) and, thermogravimetric analysis and dynamic vapor sorption (DVS) for characterising thermal transitions, superparamagnetic and hygroscopic properties (UNITO, CENTI).
5. Visible-light Induced Luminescence imaging (VIL) to identify and map the presence of NPs on the surface of objects, including biological tissues allowing quick and direct identification of NMs in a completely non-destructive and non-invasive way avoiding the need of sampling and the use of any dangerous radiation or material.
6. Absolute photoluminescence quantum yield (A-PLQY) for the standardization of new light-emitting NMs. Absolute detection method, available in UNITO is the only option for the measurement of samples absorbing or emitting in wavelength regions for which no reliable standards are available, as is the case for IR emitters, and is mandatory for the measurements of all scattering samples like NPs, bioconjugates, films or powders used as converter materials.

NMs and NEP functional assessment, use-maintenance and EoL phase simulation & stressing. Selected techniques and methodologies developed and adapted to the purpose, will be utilized for the detection of NPs in various matrices and measuring their performance in the field conditions. For example, the antibacterial activity for fabrics will be measured by AATCC100-2012 (Test Method for Antibacterial Finishes on Textile Materials), and ASTM E2149-13 (Standard Test Method for Determining the Antimicrobial Activity of Antimicrobial Agents Under Dynamic Contact Conditions) will be used for porous materials (CNR). Photocatalytic efficiency of NMs (e.g., coated TiO_2, N-doped TiO_2, TiO_2@SiO_2) for pollutants degradation under irradiation by UV/VIS fluorescent lamps /LESs will be tested by standard chemical analytic techniques for destruction of NOx and VOCs (at concentrations of 20-200 pbbv) and organic dye Rhodamine B (RhB); (CNR).
Incorporation of NMs in NCMs and in NEPs. NMs and NEP solutions will be subjected to functional performance assessment to better define the functional unit and to assess their performance for intended use. NCMs and NEPs samples will be generated by different techniques: sol-gel; dip coating; spray-coating, spray-drying, turbo-emulsification, polymer blending prior to foaming and injection moulding.

NCMs and NEPs use-maintenance and EoL phase simulation & stressing. NCMs and NEPS use-maintenance and EoL simulation will be considered for assessing functional performance as well as potential NM emissions to the environment. In order to evaluate the stability of the NM on the NEP solutions, adequate performance tests will be conducted. Relevant tests will be selected considering the NEP application and functionality, and product quality tests currently applied in industrial settings. In the case of textiles, for example, the fastness to washing is carried out in accordance with the ISO 6330 standard; for coatings on rigid and flexible substrates (with a thickness of about 125 µm), the tape test can be used, following the ISO 2409:2007 and D3339-09 norms, respectively. These performance tests will allow the establishment of a relation of NMs emission/release with NEPs stress at the use phase. Other addressed functional tests will be:
- Abrasion: ISO 12947-2:2016- Textiles — Determination of the abrasion resistance of fabrics by the Martindale method —ISO 5470-1:2016, Rubber- or plastics-coated fabrics — Taber abrader (CNR)
- Weathering: ISO 4892:2013 Plastics – Methods of exposure to lab light sources – Part 2: Xenon-arc lamps (CNR)
- Fabric maintenance- washing- ISO 105-C06:2010 Textiles -- Tests for colour fastness (domestic and commercial laundering) (AITEX)

Detection of NMs emitted to the environmental compartments in LCS. Dedicated field campaigns will be set up to obtain the NMs emissions into the environment by sampling process at synthesis and incorporation stage as well as during use phase and EoL physical simulations.
- *Airborne NMs detection*. Various direct-reading instruments (DRIs), such as Scanning Mobility Particle Sizer (SMPS), Optical Particle Counter (OPC), Condensation particle Counter (CPC), and personal monitors, as well as personal samplers for off-site analysis, will be used to monitor process airborne emissions and occupational exposure. Specific effort will tackle uncertainties and different instrumentation responses to drive to a better interpretation of experimental data and a correct interpretation to derive exposure scenarios: this will be achieved by the intercomparison and integration of the characterisation methodologies employing the various instruments/techniques. Particle number concentrations and size distributions in the size range 0.01-30 µm will be measured by means of an SPMS combined with an OPC. Mass particle concentrations and LDSA (Lung-Deposited Surface Area) will be obtained by means of aerosol photometers and diffusion charge sensors. On-line and off-line measurements will be carried out simultaneously at near field (NRF) and far field (FRF) positions.

[29]. BET method: ISO 9277:2010

- *Waterborne NMs detection* Leaching tests referred to different stages of the LC will be performed (i.e., leaching of NPs from coated water filtration membranes in use phase, leaching of NPs in coated fabric washing cycles during maintenance phase). Standard procedures will be applied such as Leaching - Toxicity Characteristic Leaching Procedure (TCLP) test (EPA standard Method 1311;167) (CNR)

In association to the functional tests sampling procedures for airborne and waterborne NMs emission will be applied to test leaching, dissolving, diffusion and transport processes due to combustion, handling, disassembly, cutting, grinding, drilling etc.

Data integration towards SSbD solutions. The SSbD challenge is to obtain the suitable combination of the KDFs values (which specify the targeted SSbD case), which simultaneously determine highest attainable performances referred to the addressed KPIs. This requires harmonising human and digital resources and the application of the **DMADV** steps. **D**efine: definition of dedicated DoE matrix specifying reference KDF values will allow performing rationalised minimum and sufficient set of experiments (synthesis, incorporation, characterisation, toxicity assays, emission sampling campaigns) and modelling sessions to generate data from measurements and computation (**M**easure step).

The DST by running the dedicated algorithm will generate the response functions, which allow determining the correspondence between points in the design space (each point in the design case represents a specific design case) to the points in the performance space (which quantify the design case addressed performances) (as part of **A**nalise step).

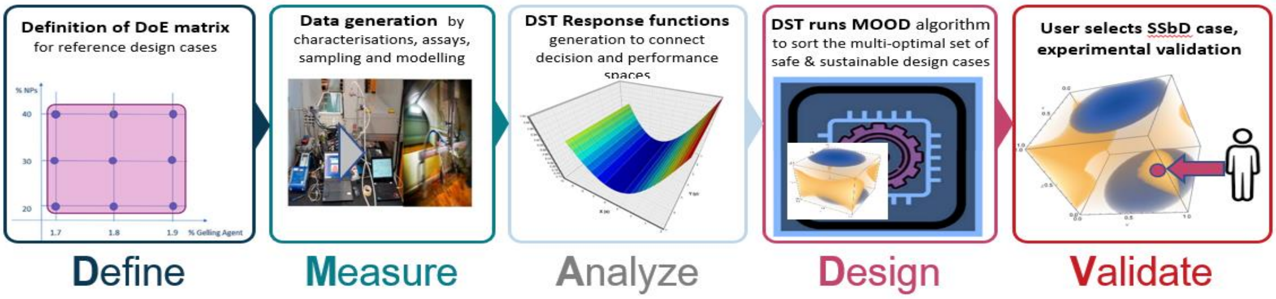


Figure 3 DMADV steps and associated data flow: from DoE definition, through data generation, analysis to SSBD solutions

The values of the Key decision factors (**KDFs**) in design space represent the quantities and selection options that characterise a specific (synthesis or incorporation) process such as type and quantity of reagents, processing parameters or a specific use protocol/condition, (e.g. maintenance frequency, duty cycle) or end-of life options, according to the addressed Life cycle stage. The Key Performance Indicators (**KPIs**) in performance space represent: (1) hazard, environmental, social and economic impact related categories (e.g. exposure and toxicity potentials, carbon emissions, eco-toxicity impact categories, costs), and (2) NMs, NCMs and NEPs specific features and functionalities (e.g. antibacterial or photocatalytic activity, photo-luminescence, quantum yield).

***D**esign: Multi Objective Optimisation Design (MOOD) and Decision Support Toolbox (DST) for SSbD*. The delivery of a quantitatively based decision support toolbox is an integral part of the INTEGRANO IMM. The DST will run the Multi Objective Optimisation Design (MOOD) dedicated algorithm to sort multi-optimal design cases, simultaneously complying with the safety, environmental, social, economic, and functional addressed Key Performance Indicators (KPIs) referring to each LCS. The DST will support the designer in the selection process of the optimal performing solutions complying with minimum attainable costs, environmental and social (negative) impacts as well as by selecting the safer design options guaranteeing the targeted functionalities. Within the sub-set of safe and sustainable optimal design cases provided by the DST the designer will be enabled to freely operate the final selection based on specific KPIs performance requirements. The DST may be applied at different stages of the NMs and NEPs LCS, by selecting suitable synthesis recipes, better raw materials and more sustainable energy sources for synthesizing better NMs. The DST will also support in the selection of safer options for NMs incorporation as well as performing design for use (DfU) by assuring NEPs safe use and maintenance as well as for selecting the best sustainable EoL options, including circularity. This is contextualised in a hierarchical stage-gate process which allows for design and redesign of the safe

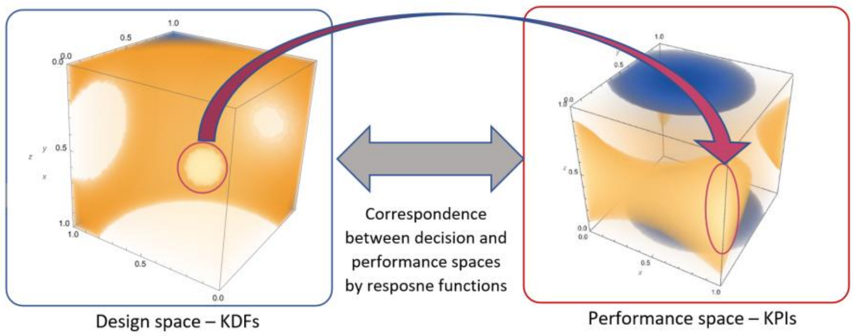


Figure 4 Multi Objective Optimisation Design (MOOD): the Decision Support Toolbox by running the MOOD allows sorting the set of multioptimal deisgn cases represented by the points within the red bubble in the left diagram, representing decision space. The selected multioptimal deisgn cases are associated to specific KPI values represented by the points within the red oval in the rights diatram, representing performance space.

and sustainable solutions in a continuous improvement process through the different LCS. The DST operation will be based on the input of experimental data and data obtained by modelling associated to a restricted number of design cases, each identified by specified design. This enables design and development cost savings, reduction of the industrial implementation risk and a shorter time to market of the nano-enabled solutions.
The DST will be implemented on an IT platform with user-friendly interface to enable the optimal user experience for data input as well as for interpretation represented output results. The User-DST interaction will be facilitated by a dedicated GUI, which will support the User in the final selection of the best SSbD case. The final step is the **V**alidation one, in which the decision maker (DST user) operates the selection of the best SSbD case. Finally, the KDFs value associated to the selected best SSbD case will allow realising NMs physical samples, which will be subject to all characterisations, measurements and assays through the NM LCS for quantitative testing and validation of functionality and hazard profiles (**V**erification and **V**alidation step).
The quantitative safety, sustainability and performance assessment data will also allow for scoring by output data discretisation. Comparison of INTEGRANO SSbD case study scoring with other SSbD design case studies performed with other SSbD tools will be possible.
Data related to the validated SSbD solutions will be stored as in the DST database as reference success case studies.

1.2.3 Relation with R&I projects

The high-end competences of the INTEGRANO consortium in the aforementioned research fields and methodologies are proved by the longstanding research and Partners' previous and current participation in a number of international initiatives, where often more INTEGRANO partners have collaborated, as the following table shows.

Table 1.2.2c. Major past and present initiatives of Partners within the INTEGRANO fields of expertise

ASINA (H2020 2020-2023) *CNR: ASINA Coordinator. SSbD strategies applied to materials synthesis and incorporation. Material samples identification, and characterisation in terms of p-chem and functional (antibacterial/photocatalytic) properties; emission in situ monitoring; CENTI: Spray coating test bed implementation and validation for the production of textile NEPs, identification of the safety hotspots during the production stages and the evaluation of the performance of the end product. ROV: nano enabled cosmetics. UNIMIB: Material safety design criteria, performing risk assessment of NEPs, in-vitro nano-toxicology studies. PRJ: LCA /LCC analysis and development of the SSbD platform*
PROTECT (H2020 2017-2020) *CENTI: Spray R2R coating. Optimization and scale up of spray coating process. CNR: Safety by process design of the up-scaled pilots. Production of polymer NPs. UNIMIB: Standardised biological tests. Environment safety assessment of nano-coating technologies and end products. Assessment of human nano-toxicity due to exposure to functional NMs and end products. PRJ: LCA and LCC studies of the up-scaled processes and products. Sustainability and economic impact. Business development models and plans.*
NanoTheC-Aba (ERA-NET Cofund Aquatic Pollutants 2021-2024). *CENTI: Synthesis of antimicrobial metal oxide NPs and functionalization of microfiltration membranes for wastewater treatment. CNR: Fabrication of nanoperovskite with thermocatalytic properties. B4C: Fabrication of nanofiltration membrane made by NPs of SiC and prototype development of a thermocatalytic reactor for water reuse. UNITO: Characterisation of the fabricated NPs. PRJ: Design and management*
REINVENT (H2020 2018-2022) *CENTI: Extraction of silica NPs from agro-industrial residues and further functionalization of the biogenic silica NPs. CNR: Investigation of p-chem and mechanical properties of nanocomposite polyurethane foams, identification of upgrade route for sustainable production of foam based on greener polyols. PRJ: Sustainability assessment design and implementation to produce the end-products through LCA and LCC methodology. Business plans.*
BIOMAT (H2020 2021-2024) *CENTI: Scale-up of of biogenic silica extraction and functionalization of silica NPs. CNR: Characterisation of nano-enabled and advanced PUR foams for Building, Construction, Automotive, Furniture & Bedding UNIMIB: WP Leader recycling tech., regulatory issue, responsible of the nanosafety and nanotoxicology assessment PRJ: sustainability assessment of the end products through LCA and LCC methodology*
BIONANOPOLYS (H2020 2021-2024). *CENTI: Production of bionanocapsules with antimicrobial and antioxidant properties (cosmetic and packaging applications), and preparation of bio-based coating formulations for functional NMs and bioinks*

1.2.4 Interdisciplinary Approach.

The specific scientific methodologies employed by INTEGRANO involving interdisciplinarity links expertise and mobilises partners resources in various thematic fields: chemistry and material science for synthesis and incorporation of NMs and NPs; physics, physical and analytical chemistry for p-chem characterisation; biology, microbiology and toxicology for toxicity assessment; statistics, computational and data science for model development; environmental science for sustainability and RA.
The consortium is made up of 12 partners of 8 countries coming from private and public sector, industry, academia, research centres and consultancy services. Each partner were selected in order to ensure the achievement of the project objectives on the basis of interdisciplinary competences addressing all the five safety and sustainability dimensions: Safety, Environmental, Economic, Social and Functional. The different expertise involve: nanotoxicology, Human toxicology, in vitro and in vivo testing and eco-toxicity assessment, NMs synthesis and p-chem characterization, testing related to human and eco-toxicity of a selected numbers of NMs, using advanced P-chem analytic techniques. Risk Assessment and modelling of emission. Social and economic

modelling, social assessment applied social science and humanities, communication and exploitation expertise, environmental and sustainability impact assessment as well as ESG strategy and implementation, manufacturing and assessment for skin care, textile and water treatment membranes.

1.2.5 Expertise in Social Sciences and Humanities (SSH)

INTEGRANO expertise SSH will allow us to successfully implement the framework, by implementing our comprehensive understanding of the social and economic impact of the NMs and NEPs, while accounting for the involvement of the relevant stakeholder. Implementation of the sociology aspect will help us understand the social and ethical implications of the NMs and NEPs, as well as the needs and expectations of the stakeholders and the public. This will foster a responsible and inclusive innovation process. Co-creation methodology will be applied by the involvement of stakeholders in the open It platform and following coaching and design thinking criteria.

Social LCA of the NMs and NEPs will be conducted by PRJ using the PSILCA database with a top-down approach, and with a bottom-up approach by collecting information, which will involve continuous interaction (and interviews) with stakeholders and the preparation of comprehensive questionnaires for the stakeholders to input both qualitative and quantitative information asked. This will allow us to assess the social impact of INTEGRANO with high granularity, using sociological methodologies

The group of SSH experts from BIU will identify and quantify the negative externalities that can be prevented through the implementation of NMs and NEPs. This will involve a comprehensive framework for NMs risk assessment and toxicity profiling, which will be used as input for the MCDA using mathematical models. The mathematical model will support the decision-making process of an organisation, as it will be integrating environmental, health and safety criteria into the model. The incorporation of multiple sustainability criteria will improve the credibility of the tool, as the recommendations provided by the tools are based on a holistic approach towards sustainability. The SSH expert group would be to monetize the positive externalities, which will be done by assigning a monetary value to the avoided impacts. This will enable the internalization of externalities into the market price of NMs, providing incentives for their development, production, and use.

1.2.6. Gender aspects

The research will account for how biological characteristics (sex) and socio-cultural factors (gender) influence the research questions, methods, results and impacts of R&I. This activity will be carried out at each stage of the project. The impact assessment at socio-economic and human health levels will take into consideration the gender issues. In particular, in the S-LCA framework will address specific impact categories related to gender discrimination (e.g. gender wage gap, female-male literacy, female-male child labour)[30] .As regards the gender-related responses in humans toward environmental stressors, since INTEGRANO only involves nano-animal experimentation, according to the 3R principle (EU directive 2010/6), and since it is recognized that NM adverse effects involve oxidative stress and inflammation, which have been recently recognized as biological responses influenced by gender[31], special efforts will be put in considering the biological markers showing different modulation in the two sexes. The quantitative measurements coming from these markers might be then computed for RA and LCA impact categories by taking into account the gender-related variability

A continuous analysis will be conducted to assess the needs, preferences, behaviour and impact of men and women as end users and stakeholders with regard to the project's outcome. Women and men will be equally involved in the co-creation and co-evaluation of the activities of the project, as well as the solutions. Gender-related indicators will be monitored and reported, like the sex ratio of the participants during events, workshops, and surveys conducted (both online and offline). The benefits and challenges of addressing gender issues in R&I will be highlighted during the dissemination and communication of the project results and impacts. Allowing INTEGRANO to enhance the quality, relevance and social acceptability of the R&I content, by supporting gender equality and social inclusion.

1.2.7. Data management and management of other research outputs

Data management will be the project success enabling factor and will be ruled by FAIR principles. A common repository of structured and referenced data will be set up as the first step in the project development (INTEGRANO Database) in order to assure data traceability and availability. Referenced data will be essential and enabling factor to allow grouping, read across, correlation of KDFs and KPIs in specific assessment and characterisation campaigns referred to specified DoEs.

INTEGRANO considers the whole LC of selected of emerging NMs and NEPs to identify data and links/knowledge gaps in terms of their p-chem/system dependent p-chem/hazard-related properties and have insight into related environmental transfer, fate, and AOP based on exposure pathway scenarios and routes. High quality data will be merged for safety and mostly sustainable purposes while capturing the functionality/performance of the products in combination with economic cost-related features (LCC). The data FAIRification, a timely procedure towards scientific excellence, will ensure observability and quantifiability of inputs, e.g., p-chem properties and toxicological responses, together with their alterations, reflecting realistic cases. The application of ML tools will consider the entire NMs LC, merging the criteria generated, the dimensions, and outcomes of interest, for a quantifiable methodology that drives innovation towards safety and sustainability. CNR will be responsible for data management, including

[30] PSILCA database v.3 documentation

[31] De Toda et al 2023. Sex differences in markers of oxidation and inflammation. Implications for ageing. Mechanisms of Ageing and Development 211 (2023) 111797

accumulation, curation and FAIRification processes, in order to capture the attributes of importance and outcomes of interest, in terms of safety and sustainability, in a systematic manner. The FAIR principles provide compelling guidelines on how to achieve reusability of NMs data. This process will also provide quantitative associations of all process' determinants and the outcomes of interest. This will be the result of applying ML models that enable *in-silico* reproduction and extension of experiments leading to valuable insights and accurate functions for the optimisation tasks, as described in WP3. This work will include managing all data streams and quality generated from experiments and related case studies of data generating packages (WP1 and WP2), to achieve the following project specific data management goals: (1) Data management planning and execution, (2) Data integration of data sources across NMs LC, (3) Data pre-processing and generation of tailored response functions using ML algorithms, (4) Exposing the relationship between variables of interest identified in the WPs with specific safe and sustainable assessment categories and (5) Extending experimental limited data to a continuous space of value ranges

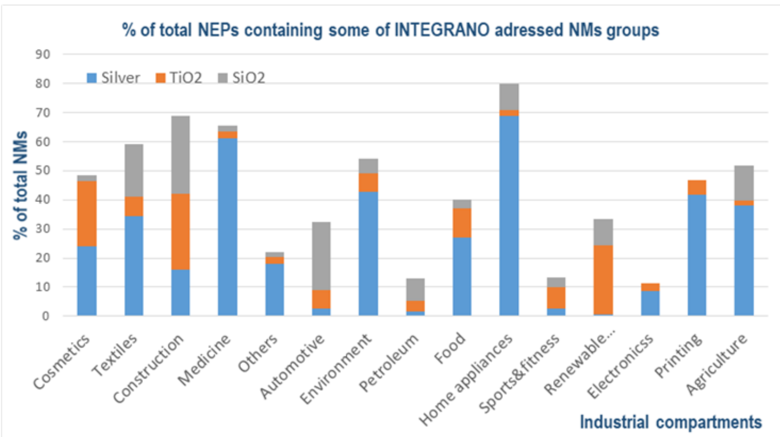
1.2.8. Open science practices

INTEGRANO will employ Opens Science practices in selected processes of data collection, revision and publishing process. Firstly, regular meetings of the consortium and the workshops involving the partners and Advisory Board members and selected external participants shall be instrumental for establishing sharing data practices within the Consortium and establishing links for sourcing new data, supported by the INTEGRANO Think Tank. INTEGRANO open science strategy workflow will consider different actions, practices and tools for various research stages. The European Open Science Cloud (EOSC) and the Open Research Europe (ORE) will represent crucial platforms to allow easier replicability of INTEGRANO results providing findability, interoperability and open access to research outputs. Open Access Infrastructure for Research in Europe (OpenAIRE), the Registry of Open Access Repositories (ROAR) and the Directory of Open Access Repositories (OpenDOAR) will be used for storing scientific and technical data. Where applicable, the data collected for the INTEGRANO purpose and being analysed or reviewed are going to be made available to all Consortium partners for their inputs, revision or comment. This will guarantee transparency and credibility of data collection. All partners would be encouraged to contribute to data revision and validation. Another layer of transparency will be introduced with the practice of inter-consortium open review process for any content to be published in open access using the dedicated INTEGRANO dissemination channels. The open review process will assign on a voluntary basis the referees from the consortium or make all partners be able to participate in the review. Similar practice will be made for the production of major project deliverables, such as the reports submitted to the commission. Moreover, the consortium will promote a special issue in a high impact journal to publish the project results under creative commons conditions. The community involvement will also be stimulated on a dedicated feedback section of the INTEGRANO IT platform, where such feedback will be instrumental to establish the efficiency of the communication strategy, research goals and strategy, and lastly help materializing specific advices in terms of needs, concerns and opportunities wish are sources from a broad scientific community and general public. EC portals and tools (OpenAIRE), Horizon the EU Research and Innovation Magazine, research*EU magazine, research*EU focus will also be considered to make the INTEGRANO research outcomes publicly available to citizens and civil society, also involving of ISO Committees (particularly Spanish AENOR) and OECD, SETAC / UNEP. Periodical surveys will be conducted (yearly) with key stakeholder groups to identify improvements in real time for project implementation and to plan follow-ups. They will also aim at needs assessment in the general context of SSbD and future developments or intensification of dissemination measures specifically related to INTEGRANO outcomes.

2. Impact

2.1Project's pathways towards impact

INTEGRANO main aim is to develop **an integrated moltiobjective methodology to assess simultaneously environmental, social and economic sustainability, health and functionality of new develop chemicals and materials.** The development a new reference framework for the assessment and prediction of health and environmental effects of NMs together with the provision of better decision criteria will support the **rapid development and market intake** on novel NEPs, proving to EU countries the leadership in a sectors which can affect positively several industry and support the European policies to reach carbon neutrality by 2050. Focusing on several p-chem characterisation techniques, toxicological tests, modelling and prediction methods, and assessment/decision frameworks, INTEGRANO aim is to make notable improvements in functionality, expand the scope of applicability, develop new protocols and procedures, and produce related recommendations for providing guidelines and



standards to decision-maker at industrial and policy level. These benefits altogether translate into the **wider societal and economic impact dimensions** of INTEGRANO: a wider safe and sustainable application of NMs and NEPs in the EU market. Indeed, the project enjoys involves key actors in several industrial groups which will promote the development of the SSbD methodology to develop advances materials. Based on the different applications of the NMs and NEPs researched and assessed during the project, INTEGRANO impacts are expected to involve different sectors, maximising positive societal, environmental, human health and economic impacts. The paramount and ultimate goal of INTEGRANO, is to enable the SSbD of which translates into a **faster commercialisation of valuable end-products**, having numerous applications and impacts on our life. INTEGRANO framework will be applied to a selected group of advanced NMs, involving Silver, silica and titania, which potentially address on average 43% of the total (>9600) registered NEPs, manufactured by more than 3000 companies in 64 countries. The major industrial compartment involved are Automotive, Construction, Health, Textile, Cosmetics, Energy, Water treatment, which account more than 50% of the NEPs in the reference industrial compartment. Only some of the commercialized products are certified and no integrated safety and sustainability NMs degree is reported. INTEGRANO will leverage current applications and enable new applications benefitting from the selected NMs groups, furthermore INTEGRANO framework is conceived to develop and on framework and database to be extended to a wider set of chemicals and advance material classes.

In INTEGRANO negative environmental outcomes are intrinsically quantified on a single case study basis through the NFs life cycle impact assessment, by addressing standard impact categories in a “cradle to grave” or “cradle to cradle” assessment, according to the NMs end-of life options. Nevertheless, specifically addressed assessments for nano-eco-toxicity will complement the standard eco-toxicity categories through the development of dedicated datasets and suitable nano-related impact categories.

INTEGRANO management of environmental impacts is carried out intrinsically in each SSbD case study analysis, in which the use of the INTEGRANO DST will support decision maker in minimising impacts by the proper selection of the suitable key decision factors (KDFs) including: more sustainable reagents sourcing options, different NMs formulations along with selection of BATs and related optimal processing recipes allowing for minimisation of emissions and workers exposure.

2.1.1 Expected Outcomes and Wider Impacts

In specific INTEGRANO will results in the following Expected Outcomes (EO) related to the work programme, whose barriers are reported (Barriers to Expected Outcomes - BEOs), Specific Outcomes (SO) linked to the societal benefit of selected class of NMs Wider Impacts (WI) and the Key Strategic Orientations (KSO), related to the Destination.

EO1: The stakeholder community including academia, industry, public authorities and NGOs will have access to more robust and consistent guidelines and methodologies for integrative social, economic, health and environment impact assessment. In the past decades, European policies have increasingly mentioned Life Cycle approaches (LCA, LCC, LCT, etc.) as crucial concepts and methods in support of sustainable twin transition. INTEGRANO will contribute to the development of an integrated impact assessment framework, which is robust and consistent, as it will be developed on Multicriteria Decision Analysis and accounts for all the 5 dimensions (human safety, environmental, social, economic and functional performance) proposing a holistic approach to SSbD. By applying this framework to a range of real-life case studies, the project will generate evidence-based recommendations and best practices for the stakeholders. The community will be provided with: (1) a robust evidence-based **methodology**, (2) an **IT platform** for sharing and engagement (3) an open and living **database** and a **new entity** for DB management and service provision (4) general and specific **guidelines.**

(1) Methodology: the framework will combine quantitative and qualitative methods, data sources and indicators, and will account for the interactions and trade-offs between social, economic, health and environmental outcomes. The developed methodology will be shared among all relevant stakeholders, such as industry associations, scientific community, innovation hub (incubators, accelerators), standardization organizations, facilitating informed decisions by **weighing multiple sustainability criteria simultaneously.** **(2) IT platform:** INTEGRANO will contribute to the integration and interaction of different stakeholder groups, such as scientists, innovators, industry and policy makers, through the set up and the continuous feeding of a ***Think Tank* dedicated to sharing data for integrated sustainability assessment and SSbD methodology co-creation.** The *Think Tank* will be supported by an IT platform for organizing webinar, f2f meetings, data repository and sharing, matchmaking among different stakeholders. Through its research and innovation activities, outreach and dissemination and the Think Tank platform, the project will stimulate adhesion of new parties and produce long-terms partnerships and follow-ups, supported by the availability of the database, the DST the also after the project completion. This will strengthen the already existing good cooperation within the scientific community, and better engage decision makers and public due to its orientation to the provision of open and general user-oriented frameworks. **(3) Open database and new entity:** INTEGRANO SSbD framework will be based on DST support by an open data database, collecting experimental data from novel chemical and materials developers, connected and integrated results from other EU funded projects and initiatives, to wider the usability and applications of the SSbD methodology among users in different sector. In order to feed the database and keep it active partners UNIMIB, PRJ, CNR, CENTI and AITEX will create an organization at the end of the project that can guarantee the further development, data accessibility and interoperability, as well as providing services for safety assessment, characterization, open innovation. The specific outcome will be a **living database for creating connections and collecting expertise.** **(4) Guidelines:** in form of open access publication for application of integrated impact assessment of chemical and material, based on SSbD framework. Specific guidelines dedicated to the development on NMs and NEPs, including the new NMs impact categories developed in the project.

BEO1: *a) lack of environmental sustainability framework and methodology acceptance due to missing benchmarks which simplify analyses outcomes interpretation, b) lack of sufficient available primary data to feed databases, c) potential limitation to the open access policy of data generated within specific industrial case studies due processes development confidential information.*

EO2: Industry will be enabled to make impact-based informed investment decisions for future chemicals and materials. Impact-based informed investment decisions are those that take into account not only the technical and economic aspects of a project, but also the social and environmental impacts that can provide a global risk assessment and, through the risk minimization and compensation, guarantee the business continuity. INTEGRANO major outcome will be a comprehensive and integrated SSbD framework based on a Decision Support Tool that can provide relevant and reliable data and indicators on the impacts of chemicals and materials, allowing the industry to make impact-based informed investment decisions. This framework will be based on sound scientific methods and standards, incorporate stakeholder perspectives and values, and address the uncertainties and complexities related to development of new advanced materials. The framework will be based on an open database, as it will support continuous learning and improvement. INTEGRANO DST is an eco-design and predictive tool to support the development and the commercialization novel materials allowing companies in different sector to assess and demonstrate the sustainability of their business and their products. The SSbD framework can support competitiveness in the EU market where the demand of sustainable products is increased of 10% in the last 3 years and earned 59% of its sales from sustainable products in 2019[32]. **The tool will contribute to reduce time to market up to 80% and development cost up to 60%**. **Eco-design potential benefits** include: encouraging innovation, lower production and labour costs and greater efficiency; reduced material and resource costs, lower waste disposal costs, improved functionality and quality of products, improved environmental performance, improved customer and supplier relationships, easier and lower cost of compliance with legislation, easier disassembly and increased potential for recycling, most suitable product design life, a better working environment and business culture for the staff, provide marketing tool. As indicated by the KPMG Survey of Sustainability Reporting 2020[33] 80% of N100 companies worldwide report on sustainability and there is growing trend to link corporate targets to SDGs and international climate goals, in particular SDGs linked to responsible consumption is one of the most frequently prioritized by businesses. LCA, LCC and SLCA are widely used in Sustainability reporting, being key to analysis and quantify the 3 aspects of sustainability: Environment, Social and Governance-ESG**. The INTEGRANO framework will further support the monitoring and targeting of economic and sustainability KPIs, by its integrated multi-objective methodology and tool**. Based on extensive research by Oxford University and others, it is confirmed that sustainability and ESG practices are linked to lower operating costs, more profitable businesses, and improved share prices. According to research by Deutsche Bank, which evaluated 56 academic studies, companies with high ratings for environmental, social, and governance (ESG) factors have a lower cost of debt and equity; 89 percent of the studies they reviewed show that companies with high ESG ratings outperform the market in the medium (three to five years) and long (five to ten years) term.

BEO2*: a) lack of available primary data limit the possibility of conducing specific design cases; b) difficulty in selecting the relevant KDFs to devise a proper and treatable Design of Experiment campaigns turns into an excessive number of experiments to be carried out, implying longer than expected time to market and excessive R&D costs, c) acceptable multi-optimal solution cannot be identified due to excessively strict KPIs constraints (set thresholds)*

EO3: Public authorities and policy makers at EU and national level will be supported in the implementation of policies, including the transition to safe and sustainable chemicals and materials through improved understanding of potential sustainability trade-offs. INTEGRANO framework will provide a holistic view to impact assessment, by quantifying the 5D (Safety, Environment, Economical, Cost and Functionality), allowing the policy makers to make informed decision taking in account integrated impacts for the transitions towards SSbD chemicals and materials. This will support regulators and policy makers in defining a clear framework to offering industrial risk minimization related to all new Innovative actions. The DST that will be provided, is based on MCDA, which will support complex decision-making process and provide quantitative results for optimised scenarios for the policy makers to choose from, allowing increased flexibility. The DST will be based on live data base and open to the public, allowing growing of the database with increased experimental data. The policy makers can utilize the DST to assess the product/process based on the KPIs they choose and select one of the optimized cases. This tool supports human interaction and allows the decision-maker to choose from the list of optimized cases based on their

[32] The European Union Market For Sustainable Products - International Trade Centre, European Commission, 2019
[33] https://home.kpmg/xx/en/home/insights/2020/11/the-time-has-come-survey-of-sustainability-reporting.html

preference. For each case, the trade-offs can be assessed easily, as each factor will be quantified (Environmental impact, Societal impact, Economical impact, Impact on Health&Safety, Functionality performance), ensuring a faster decision-making process.
***BEO3**: a) although the SSbD framework is properly defined, specific application to a larger number of NMs may be hampered by insufficient data and available options supporting the transition to safe and sustainable chemicals and materials, b) higher sustainability level of innovative (expected) environmental friendly chemicals and materials lack of sufficient quantitative proofs due to lack of representative benchmarks; c) technological development and material science provides innovative solutions to a faster pace with respect to the definition of policies and provision of reference case studies.*

SO1: Enabling the faster, safer and more effective commercialization of NEPs- reducing time-to-market.
Innovation in nanotechnology and NMs can support an effective development and efficiency improvement in several industrial sectors with novel commercial applications. New products based on nanotechnology with novel characteristics are continued to grow and benefit the society. Being nonspecific technology, NMs and NEPs can contribute to the wellbeing and the development of the society and of the economic systems, positively affecting fields like energy, environmental remediation, health, manufacturing, commerce, space exploration. In some of the application sector these commercialization barriers are even stronger, as for instance in packaged food products[34] where the presumed toxicity and risk of migration of NPs to food items is a matter of concern. In a market, such as NMs, valued roughly 8,0 billion USD in 2020, with a CAGR of 19% to 2028, removing important barriers link to environmental and safety assessment means creating opportunity for companies and employments. In EU countries NM market employs more than 400K people[35], with a perspective to reach roughly 500K in 2027[36] and the market is expected to reach USD 4.5 billion by 2028, owing to support from the national governments and investment in the respective domestic markets in the region.
SO2: Unlocking the potential of NMs and NEPs. The developed of the integrated impact assessment applied to specific case of SSbD NMs and NEPs will which translates into a faster commercialisation of valuable end-products, with numerous applications and impacts on our life. In particular the use cases involved in the project will contribute notably to the improvement of health and wellbeing (through antimicrobial applications), to the reduction environmental impacts (through improved water treatment technologies). As demonstrate in the H2020 project Protect (CNR, PRJ, UNIMIB, CeNTI) the use of antimicrobial (AM) products can have wider impact on society, economy and wellbeing. According to the World Health Organization (WHO), Antibiotic resistance is a growing threat to global health and for the attainment of the Sustainable Development Goals (SDGs). AMR can compromise the achievement of the SDGs, affecting health security, poverty, economic growth and food security. As a result of infection with drug-resistant bacteria an estimated 700000 people die each year worldwide including 230000 deaths from multidrug-resistant tuberculosis, a figure that could increase to 10 million deaths globally per year by 2050 under the most alarming scenario if no action is taken[37] Within this scenario Health Care-Associated Infection (HAI) represent the most frequent adverse event during care delivery. Avoiding the occurrence of HAIs by the implementation of AM textile (functionalised through NPc coatings) corresponds to a huge saving for health care systems valued between USD35 billion and USD45 billion for acute-care hospitals annually. The total direct, indirect and nonmedical social costs of HAIs are estimated at around USD96 billion to USD1 47 billion annually, including loss of work, legal costs and other patient factors. In parallel the application of NPs coating to water membranes can support solutions linked to water scarcity challenge which affect every aspect of life. Access to safe water and sanitation can quickly turn problems into potential – empowering people with time for school and work, and contributing to improved health for women, children, and families around the world. Today, 1 in 9 people in the world lack access to safe water

Table 2.1. Impacts of NMs and NEPs addressed in INTEGRANO safe and sustainable by design case studies

NM/NEP & applications	Scientific	Economic/Technological	Societal	Scale & Significance
Anti-microbial nano-enabled spray coatings **NM:** N-TiO_2, Egyptian Blue **Applications:** Nano-coating spray technology on other covering substrates	*Multi-method approach implemented to measure the particle size of N-TiO_2 and Ag-HEC in atomic scale.*	*5% decrease in national sanitary costs*	*Reduced occurrence of respiratory diseases due to cleaner indoor air (10% hospitalization reduction)*	***Scale**: 307,000 premature death due to exposure to polluted air* ***Significance**: Reduction in premature death by at least 21%*[38]

[34] Neha Chausali a, Jyoti Saxena a,**, Ram Prasad Recent trends in nanotechnology applications of bio-based packaging Journal of Agriculture and Food Research 7 (2022)
Recent trends in nanotechnology applications of bio-based packaging
[35] https://ec.europa.eu/growth/sectors/chemicals/reach/nanomaterials_en
[36] Considering current market growth rate
[37] World Health Organization, No time to wait: securing the future from drug-resistant infections, Report to the secretary-general of the United Nations ,April 2019
[38] Health impacts of air pollution in Europe, 2021 — European Environment Agency (europa.eu

Anti-virucidal/Anti-bacterial nano-enabled spray coatings **NM**: ZnO, CuO, TiO2, Ag-HEC **Applications**: spray coating technologies on medical textile	*An easily scalable and ecofriendly synthetic process at room temperature to embed Ag NP.*	*New high value Anti-bacterial virucidal medical textile: viruses deactivated after 30' exposure.*	*33% reduction in the virucidal activity on Ag-HEC loaded fabrics.*	***Scale**: externalities up to $147B due to HAI globally.* ***Significance**: Saving 10% of the externality cost due to safer medical textile.*
"Anti-bacterial and photocatalytic **NM:** TiO2, n-perovskite, Egyptian blue and TiO2@SiO2 nano-enhanced membranes **Applications**: hospital wastewater treatment	*Novel methodology to abate >99% of CECs and AMR pathogens from water*	*5% decrease in national sanitary costs*	*15% water use reduction in hospitals and other relevant sectors thanks to efficient nano-enhanced water treatment systems;*	***Scale**: AMR regarded as one of the top 10 public health threats by WHO* ***Significance**: Increased access to safe sanitation water and food for. 1% of global population;*
UV Protection and Antiaging (Oxidative Stress Reduction) **NM:** Ag-HEC, TiO2/SiO2, Egyptian Blue and N-TiO2 **Application**: Cosmetics	*Highly stable and resistant under UV light, moisture and oxygen. Does not degrade or lose its functionality*		*Reduce 10% of skin cancer cases and deaths per year due to skin cancer.*	***Scale**: Skin cancer accounts for 4% of all new cancer diagnosis in EU[39]* ***Significance**: Reduction in mortality rate by 10% caused due to skin cancer*
Filler for biopolymers foam performance enhancer **NM:** SiO2 **Application:** Automotive and Building sector	*Increased heat insulation of the biopolymer*	*With 3wt% of nano SiO2, an increase in flexural strength of 61%.*	*Decreasing CO2 emission in building life cycle*	***Scale**: with 12M cars/year produced in the EU, this can be employed in at least 10% of the cars during scale up* ***Significance**: Increasing light weight material and recyclability to reduce energy in different LCS[40]*
Photoactive for Energy harvesting **NM** Egyptian blue **Application:** Solar Photovoltaic panels	*50% increase in photoluminence intensity of solar concentrator*	*Higher efficiency of solar concentrator*	*Decreased CO2 emission, with increased green energy*	***Scale:** Solar Concentrator capacity of EU at 2.3 GW[41]* ***Significance:** An overall increase in 10% in the performance of the Solar concentrator[42]*

WI1 Industrial leadership and increased autonomy in key strategic value chains with security of supply in raw materials Innovation in nanotechnology and NM can support an effective development and efficiency improvement in several industrial sectors with novel commercial applications. New products based on nanotechnology with novel characteristics are continued to grow and benefit the society. NMs and NEPs can contribute to the wellbeing and the development of the society and of the economic systems, positively affecting fields like energy, environmental remediation, health, manufacturing, commerce. One of the most common commercialization challenge and constraint for NEPs is represented by: (1) the absence of proper information about the environmental effects of NMs and its impact on human life, (2) the fear of health-related side effects due to NEPs usage; (3) ecological impacts of the release of nano-wastes into the environment and effect of nano-waste on animal and plant cells are unknown[43]. These commercialization challenges can be overcome by implementing the framework and DST provided in INTEGRANO. Although the DST provided, along with the methodology and guidelines are based on the NM and NEP, it can be used for optimizing any product or process in every industry. This will enable the user to get the best results in each criteria (technical, environmental, social, health and regulatory concerns), with just a few experimental data. Allowing the EU industry to be autonomous and leading in the development of process at every stage in the value chain with reduced lead time

WI2 Raw Materials for EU open strategic autonomy and successful transition to a climate-neutral and circular

[39] Skin melanoma burden in EU-27 | European Commission (europa.eu)
[40] Biopolymers in Automotive Industry | SpringerLink]
[41] www.statista.com
[42] Zondag, S.D.A., Masson, T.M., Debije, M.G. et al. ,. Photochem Photobiol Sci 21, 705–717 (2022)
[43] Aithal, Sreeramana and Aithal, Shubhrajyotsna, Nanotechnology Innovations and Commercialization – Opportunities, Challenges Reasons for Delay, MPRA, 2016

economy. INTEGRANO DST is an eco-design and predictive tool, that allows the product/process designer to assess the sustainability of the product in 5Ds (human safety, environmental, social, economic and functional performance). This will support the designer in the development of sustainable product/processes in a shorter time, facilitating an accelerated transition to climate neutral economy. The DST will support the safe and sustainable design of the materials (advanced material, raw material, rare earth metals, etc.,) used in the product/process, allowing the designer to choose the most sustainable alternative. INTEGRANO will play a key role in the strategic autonomy and green transformation of the EUs key industrial ecosystem by providing the Decision Support to properly select raw materials based on their safety, environmental, economic, social and functional attribute.

WI3 Safe and Sustainable by Design (SSbD) chemicals and materials INTEGRANO will acknowledge the Safe and Sustainable by Design guidelines for the NMs by accounting for both its intrinsic (Molecular design, process design and Product design) and extrinsic (Hazard assessment, Occupational safety, human toxicity and ecotoxicity) properties. INTEGRANO will propose a defined SSbD robust procedure based on quantitative evidence that facilitated the decision-making process, which is supported by Multi Objective Optimisation Design algorithm. The decision makers could be the scientists, innovators, designers, technicians, and policy makers. INTEGRANO will put the basis to create an integrated and living database of use cases that can be fed and developed during and after the project duration. While during the development of the project the use cases are limited to the NPs developed and assessed by partners, the database will be a living repository for collecting data and expertise from all the other European projects, enriching the database with new data. The DST will only need the experimental data to be inserted into the database once, and the experiment need not be repeated again by another user, allowing time and cost saving. In order to carry out the above activity, a common platform will be created promoting the inclusion of Safe and Sustainable by design strategy and methodology. INTEGRANO will act as a reference for SSbD in chemicals and advanced materials, which can be used as a source for extending scientific knowledge base for regulators and policy makers

WI4 Strategic Innovation Markets driven by Advanced Materials. INTEGRANO will be contributing to the strategic innovation markets driven by advanced materials in the EU, by providing a comprehensive and reliable framework for evaluating and optimizing nano materials. Strategic innovation markets that will be directly disrupted by INTEGRANO are-Nanoenvironment, Nanoagriculture, Nanomedicine and Nanoenergy. In a market, such as NMs, valued roughly 8,0 billion USD in 2020, with a CAGR of 19% to 2028, removing important barriers link to environmental and safety assessment means creating opportunity for companies and employments. The DST provided will assess all the dimensions of sustainability, allowing stakeholders such as researchers, developers, manufacturers, regulators, and consumers can make informed decisions about the benefits and risks of nano materials, and identify the best practices and solutions for their specific needs and contexts. The usage of the tool is not limited to nanomaterials, as it can be extended to all the advanced materials. This way, our tool fosters the development and innovation of the advanced materials in the EU, increasing their competitiveness and sustainability in the market (EU and globally).

WI5 Improving the resilience of EU businesses, especially SMEs and Startups. Nearly 91% of SMEs are taking action to become environmentally and socially sustainable. The DST can enable the startups and SMEs to measure the environmental and social sustainability of the action (developing sustainable product/services, Impact on society), based on the priority set by the user. SMEs represent 99% of the EU businesses and play a key role in bringing innovative solutions on sustainability and climate change into EU businesses. The DST will allow SMEs and startups to be resilient in the continuously changing landscape and quantify all the sustainability criteria. SMEs and Startups in EU can also benefit with the DST by subscribing it as a service instead of buying it, making it more economical and affordable. NM can improve the resilience of EU businesses, by offering new opportunities for innovation, competitiveness and sustainability, as the NEPs will have enhanced performance, durability and functionality while reducing the cost, environmental impact, and resource consumption. The optimized NM is achieved using the DST, which using the MOOD INTEGRANO focusses on the application of the selected NMs in select sectors depending on its functionality. But the framework is not limited to the select sectors, and can be implemented into every sector, and every organization, allowing SMEs and startups to be more resilient. Their full-scale development will be accelerated with the Multi Optimal Optimized solutions, created based on the few experimental data provided.

KSO C, Making Europe the first digitally led circular, Climate neutral and sustainable economy, through the transformation of its mobility, energy, construction and production systems

INTEGRANO enable the EU mission to be the first digitally-led circular, climate-neutral and sustainable economy through its digital innovation of creating a Decision Support System based on Safe and Sustainable by Design framework. The Decision Support System will allow to develop a product or a process which is sustainable by Design by accounting for the 5 dimensions of Sustainability (Safety, Environmental, Economic, Social and Functional). The DSS and Multi-Objective Optimization Design (MOOD) system will foster the development of safer options in the incorporation of NMs, and ensure safe use and maintenance as well best sustainable End of Life (EOL) options including circularity. While embracing circular economy principles is crucial for reducing resource consumption and minimizing waste, this tool will incorporate circular economy principles into the designing of the NEPs allowing the transformation of the NEP's production systems to being circular, climate-neutral and sustainable.

KSO A, 'Promoting an open strategic autonomy by leading the development of key digital, enabling and emerging technologies, sectors and value chains to accelerate and steer the digital and green transitions through human-centred technologies and innovations.'

The NEPs developed in the INTEGRANO project are based on its human-centric application, by prioritizing the well-being and interests of individuals. The antimicrobial textiles are designed for individuals to be worn at hospitals and public places, which deactivates the viruses on it after 30 minutes of exposure. These products are designed in accordance with the SSbD framework to reduce the Health Care Associated Infections (HAI), using the DSS. This allows the Nano Materials sector to be digitally enabled and be at the forefront of the EU's mission for a sustainable transition.

KSO D, 'Creating a more resilient, inclusive and democratic European society, prepared and responsive to threats and disasters, addressing inequalities and providing high-quality health care, and empowering all citizens to act in the green and digital transitions.'

INTEGRANO is positioned to play a pivotal role in creating a more resilient, inclusive and democratic European Society. With a specific focus on antibacterial and medical applications, and through experience in research funded projects such as PROTECT and NanoTheC-Aba, we are enabling the transition to high-quality health care and wellbeing in Europe. Due to the increased HAIs, there are multiple negative social impacts such as loss of work, legal costs, and other patient factors. The NEPs designed using digital tools built on SSbD will reduce HAIs and waterborne diseases, allowing access to safe water and sanitation. This way, INTEGRANO plays a pivotal role in empowering people and contributing to improved health for women, children and families.

2.1.2 Scale and Significance

EC describes advanced materials as leading both to new reduced cost substitutes to existing materials and to new higher added-value products and services. Advanced Materials offer major improvements in a wide variety of different fields, e.g. in aerospace, transport, building and health care. They facilitate recycling, lowering the carbon footprint and energy demand as well as limiting the need for raw materials that are scarce in Europe[44]. The Energy Materials Industrial Research Initiative, an industry-driven clean energy association, estimates that 70% of technical innovations across all sectors are directly or indirectly attributed to advanced materials. Advanced Materials have the probability to contribute to the Sustainable Development Goals in different ways and substitute the critical raw materials (CRM) making EU economy more resource independent, so it is of paramount importance to apply SSbD framework in their development to accelerate their uptake. The INTEGRANO methodology can contribute to boost the marketability of new advanced materials and chemical support the global advanced materials market size that was estimated at USD 61.35 billion in 2022 and it is expected to hit around USD 112.7 billion by 2032, poised to grow at a CAGR of 6.27% from 2023 to 2032[45]. R&I in the spending in the advanced materials and chemical industry globally was forecast at roughly 12.9 billion USD in 2022, slightly up from 12.4 billion dollars a year earlier. The DST will contribute to reduce time to market up to 80% and development cost up to 60%.
For reaching this industrial target the project will involve in its Think Tank platform at least:200 representatives from industry, 50 representatives from international bodies and agencies, 50 representatives form academy and research, 2.000 students. The living database will support the assessment of 100 design cases in the first year after the project completion and at least 200 companies in the development of SSbD material in the first three year after the project end.

2.1.3 Requirement and potential barriers

INTEGRANO requirements are availability of a complementary pool of experts to generate a common open task force to consult different stakeholders within and beyond the project accomplishment in order to set the basis for a structured, standardised and accepted approach to the SSbD of chemicals and materials, including NMs. Preparedness to bridge the industrial R&I needs and timing with the availability of academic, research and scientific servicing resources is also required. The current pool of experts covers the requirements. Nevertheless, the present situation may evolve into possible missing of any of the pillars that enable the proposed SSbD methodology. The INTEGRANO contingency plan provides risk mitigation by implementing an open approach by linking to other networks and allowing for other group of experts to be integrated into the pool and to be harmonised with internal standards and procedures. This will also allow to replicate and to propagate the implementation of INTEGRANO approach and methodology in compliance with standards and developed best practices.

2.2Measures to maximise impact Dissemination, exploitation and communication

2.2.1 Dissemination and exploitation of results

The main objective of dissemination and exploitation activities is to give great visibility to INTEGRANO results in identified sectoral communities (national and European regulation institutions, standardization bodies, EC agencies and initiatives) and specific target groups in the international industrial context (i.e., manufacturers implementing NMs, chemicals, advanced materials industrial associations, incubators).
In order to enhance direct and rapid dissemination and effective exploitation of project results to relevant identified stakeholders, the dissemination and exploitation (D&E) strategy will have three key features: (1) to identify key users and cluster mapped

[44] https://ati.ec.europa.eu/technologies/advanced-materials
[45] https://www.precedenceresearch.com/advanced-materials-market

stakeholders according to relevance of reach for each result, associating the most appropriate method for directly reaching and engage each stakeholder group (see graph on the right); (2) periodic **reviews** throughout the project duration in order to assess effectiveness of implemented dissemination activities, allowing for ongoing adjustment of the strategy, (3) to identify **key "multipliers"** among the mapped stakeholders e.g., National Contact Points (NCPs), scientific academies and industry associations, Responsible Research and Innovation (RRI) networks, incubators and accelerators, EC partnerships and Initiatives platforms etc. The identified key multipliers will be directly contacted and engaged in INTEGRANO *Think Tank*, and a selected group will be involved to participate to an International Advisory Board to promote co-creation of the novel methodology and enhance impact of D&E activities. A group of experts from different organisations, who would provide advice and guidance to INTEGRANO in every stage of the project will be set as an advisory board. Their advice and guidance will ensure the project meets the ethical standards and requirements of the European Commission (EC) and relevant legislation. The advisory board (JRC, PARC) will also play a crucial role in project's activities like-methodology, work plan, deliverables and dissemination. Facilitating the projects networking and collaboration with other relevant initiative and actors by the advisory board (EIT) as part of the dissemination will allow INTEGRANO to achieve wider effect.

Table 2.2a. Preliminary stakeholders mapping and analysis (enabler, multiplier, leader)

Sub-set	Stakeholders' categories	Key role	Preliminary mapping
I	International standardization bodies, regulatory agencies, EC agencies, platform and Initiatives	Leader	European Chemical Agency (ECHA), European Partnership on Assessment of Risks from Chemicals (PARC) EFSA, International Standard Organization (ISO), Organisation for Economic Co-operation and Development (OECD), European co-operation for Accreditation (EA), Joint Research Centre (JRC), European Institute of Innovation & Technology (EIT)
II	National authorities and public agencies for health and safety research	Multiplier	National Institutes of Health, European Agency for Safety and Health at Work (EU-OSHA) national focal points
III	National and International authorities on regulation for chemical and advanced materials	Leader	EC, Observatory on Nanomaterials (EUON), European Agency for Safety and health at Work (EU-OSHA), National standard organizations, International Association of Advanced materials (IAAM), European Network of the Heads of Environment Protection Agencies (EPA Network)
IV	Cross-sectoral associations, incubators, other EU-funded projects	Multiplier	Global Coalition for Regulatory Science Research (GCRSR), Italian Association for Industrial Research (AIRI), RRI Practice, European Business and Innovation Centre Network (EBN)
V	Relevant industrial sectors and associations	Enabler	European Chemical Industry Council (Cefic), Cosmetic Europe, European Apparel and Textile Confederation (EURATEX), Water Europe
VI	Sustainability impact assessment associations	Enabler	Life Cycle Initiative, Global Compact, Rete Italiana LCA, EU Environment Agency (EEA), European Platform on LCA, EPD international
VII	Scientific communities and committees, RTO	Multiplier	Universities, Scientific Committee on Consumers Safety (SCCS), NanoSafety Cluster (NSC), European Federation of Academies of Sciences

The stakeholder engagement activities will be supported by the development of the IT platform serving as the INTEGRANO and trough the following activities, including Dissemination channels and means addressing the Target Audience in a specific way according to what described above and, in the table, below.

Table 2.2b. Stakeholders clustering by expected outcomes and correlated dissemination & exploitation strategy

Activity	Description	Output
Training activities	Didactive initiatives will be carried out implementing seminars and courses on impact assessment and SSbD criteria and framework for University Bachelor, Masters and PhD students, young research and representative form industrial sectors, with seminar, webinar and realization of didactic videos.	**At least 10 training activities**
Academic publications	Peer-reviewed publications in scientific journals covering areas and journals such as: Chemistry journal (MDPI), Materials journal, Chemical Engineering Journal, Societal Impact Journal,	**At least 20 Open Access**

	International journal of cosmetic science, Journal of Nanomaterials, Journal of Ecology and Toxicology, , Journal of Environmental Hazards, Journal of Analytical & Bioanalytical Techniques	**publications**
Events targeting Industrial sectors and end-users	The project will be presented in public local events, national expos and TV shows and other thematic business fairs. Internationally important events are: Cosmoprof, international cosmetic industry fair (annual, Bologna) -International Conference and Expo on Nanosciences and Nanotechnology - 3rd Global Summit and Expo on Nanotechnology and Nanomaterials	**At least 3 public presentation**
National international scientific conferences	Active participation international scientific conferences including: Tribology International Conference - Plasma Processing and Technology International Conference - Material Science And Nanotechnology Conference - International Conference on Nano Research and Development - International Conference on Polymer Science and Nanotechnology - Global Experts Conference on Nanotechnology and Nanoscience - World Conference on Materials Science and Nanotechnology	**At least 3 contributions delivered**
Workshops and Events	The INTEGRANO Think Tank IT platform will be employed in order to allow the attendance to virtual meetings such as e-learning courses, webinars, workshops and training events with the main objective is to allow a better understanding of SSbD framework and on the INTEGRANO methodology, sustainability assessment along the value chain, MCDA application to complex decision, LCA, S-LCA, regulatory framework and policy at EU level. The seminars and events will be directed to professionals from involved value chain: at least one event for each sector (cosmetics, textile, energy and water treatment) at least 2 events for involving all transversal stakeholder such as standardization bodies	**At least 3 workshops, 8 webinar and 2 open events**
Synergy with other EU projects	Annual meeting/event on line or f2f, during relevant conference or other international events to exchange results, best practises and approaches with other EU funded project	**At least 4 events**

2.2.2 Communication activities

INTEGRANO consortium will analyse the communication-needs of the target audiences and fit them into the three layers of the PDER. The communication plan will be discussed at the kick-off meeting to be then further refined with all partners. It will be updated continuously based on project evolution as new findings may require adding new relevant communication activities.

Table 2.2c shows how target audiences will be reached, as well as the messages conveyed by the communication and dissemination strategy.

Audiences	Messages /objective	Channels
Scientific community	Raise awareness of project results. Ensure that project results are peer reviewed, published in a timely manner and accepted by the scientific community as robust. Ensure links are made between INTEGRANO and related projects, networks and clusters. Participation in further education and training.	Project website; Presentations at conferences, seminars, workshops; Scientific peer reviewed publications, reviews, opinion and perspective pieces; Special Issues in selected journals and dedicated workshops; Training schools and supporting materials; Online scientific communities (e.g., LinkedIn, ResearchGate, twitter), datasets and software under open licenses.
Industry	Demonstrate use of the INTEGRANO framework for chemicals and advance materials impact assessment. Illustrate the potential integrated assessment and DST for reducing cost and time-to-market.	Project web site, Social pages (LinkedIn) Stakeholder workshops; Presentations at conferences, trade exhibitions; Newsletters; Scientific/technical publications; Technical reports; Special interest magazines; Media releases; INTEGRANO guidelines
Policy makers, regulators, standardization bodies and NGOs	Demonstrate the use of the INTEGRANO framework to support regulation and standards development for SSbD materials	Dedicated brochure. Project website. Presentations at conferences, seminars and workshops. Multipliers (personal network) and f2f meetings. Stakeholder workshops; social media; Newsletters; Scientific publications; Reports.
Public, including media	Demonstrate proactive approaches to assess risks of impact of materials and chemicals application in order to protect workers, consumers and environment.	Social media; Project website; Communication flyer; video; Media releases.

2.2.3 Knowledge management and IPR

Access rights and intellectual property will be managed according to the grant agreement and the Consortium Agreement (CA). The CA will regulate all legal matters related to knowledge management and -protection. It will be based on the widely accepted best-practice document of the DESCA group. Before the start of the project, it will be ensured that the partners have access rights to necessary background, and they will grant each other access rights to needed background royalty-free and free of any administrative transfer costs. Partners must inform each other as soon as possible of any restriction that might affect the access to needed Background. Ownership of results rests with the partners who contributed to its generation. INTEGRANO will set clear procedures to ensure that partners cannot publish results of other partners without their written approval. The WP leaders will ensure that no rights of other partners are jeopardized on WP level and will inform the Coordinator in case of joint claims to intellectual property or in case of conflicts. The background will be defined in detail for all contractors and remains the property of the contractors bringing this background to the project. Particular interest will be paid to the background, the generation of which has started before the project and will end during the project. Dissemination will be controlled to protect the interests of the partners. Beneficiaries will inform the consortium of their intention to publish their results that may be relevant IP. Dissemination of results is granted with the approval of the consortium, making sure that the period of secrecy needed for a successful patent application is respected. The knowledge acquired during the project shall be considered as a property of the contractor generating it, and the originator is entitled to use and to license such right without any financial compensation to the other contributors. If the features of a joint invention are such that it is not possible to separate them, the contributors may jointly apply to obtain and/or maintain the relevant rights and make effort to reach appropriate agreements. D&E manager will organize a session to ensure awareness about the PEDR, legal conditions and basic procedures. The Consortium will establish a common understanding of PEDR and procedures (e.g. obligation to inform all other partners about planned dissemination prior to publication). During each WP meeting there will be a fixed spot to identify results relevant for the PEDR. The owners will keep lead, control and responsibility at all times strongly supported by the coordinator and the combined expertise of the consortium

2.3 Summary

KEY ELEMENT OF THE IMPACT SECTION

SPECIFIC NEEDS	EXPECTED RESULTS	D & E & C MEASURES
To have robust and consistent guidelines for SSbD of advanced materials (nano materials) by targeted and simplified characterisation methodologies: End-users have to be offered a trustable basis for the assessment of health, environmental, economic and societal risks of NEPs to promote a more robust commercialization of NEPs. This requires specific validated methodologies and knowledge base to be available. **To strongly reduce the industrial risk in nanotechnology uptake:** Many companies are sceptical or tend to avoid the use of NMs because of concerns on possible safety and environmental impact and risk of related restrictions to be imposed by new regulations **To improve the NMs & NEP design:** NMs and NEPs designers cannot cover all domains of expertise involved with technical performance & cost assessment, environmental sustainability, social impact and nano-toxicology. **To reduce the NMs and NEPs time-to-market & development costs:** Given a growing number of NMs-hosting matrices and related AOPs, the extensive R&D work required to confirm safety and sustainability can be delaying the product commercialisation. **To have a tool to improve policy makers and regulator's understanding of potential sustainability trade-offs and risks of chemicals and materials:** Policy makers cannot assess all the aspects of sustainability and need a tool to estimate the impact by varying the KPIs according to the need.	➡**New generated NMs-related data sets, new** proposed **nano-toxicity and nano-eco-toxicity impact categories** as well as NMs-specific **characterisation factors** will enable application of the LCA standardised impact assessment methodology by integrating conventional materials and NMs Life Cycle Impact Assessment (LCIA). ➡**An integrated assessment framework** enabling a comprehensive assessment safe and sustainability by combining LCA (integrating safety and sustainability), SLCA, LCC and functional performance. Sustainability assessment including novel nano-specific Impact Categories (ICs) will enable attaining a comprehensive toxicity and eco-toxicity mid-point impact indicators. The application of the general integrated methodology to specific case studies will be based on experimental data and modelling results to generate new open data applicable to other assessment frameworks based on scoring metrics. ➡ **Reliable data** will be obtained through: (1) direct experimental measurements, (2) use of open access databases (2) data FAIRification, (3) toxicity predictive models calibration (4) sampling emissions to environmental compartments, comprehensive LCA, SLCA, LCC computations. ➡ **Digital DST for multi-optimization to assess safety, sustainability commercial viability and functionality of NMs and NEPs:** A dedicated digital toolbox supported by quantitative experimental measurements and modelling data will be provided to assess functionality, cost effectiveness, environmental sustainability and health&safety on NMs and support decision makers in identifying multi-optimal design options.➡**An integrated RA model with probabilistic exposure** parametrised with reasonable worst-case parametrization to quantify exposure determinants and safe Conditions of Use (CoUs) for processes and products involving NMs.	**Exploitation:** (1) Patenting the multicriteria decision algorithmic model for obtaining SSbD NMs solutions. (2) request of trademark for the digital optimisation tool for. (3) designing an extended European advanced characterisation servicing infrastructure operated on-demand for sector-targeted applications to enrich the tool NMs safety & sustainable database **Dissemination towards stakeholders**: after carrying out a materiality analysis specific stakeholders' values will be identified by determining the specific dissemination contents directed to the target audience: scientific community, project designers, regulatory experts, consumers, and large public. Open house sessions will be organised **Communication towards citizens:** Open house event and video to show the genesis of SSbD NMs will be organised and produced, respectively, to reassure industrials and end-users on the protocols that lead to SSbD of NMs.

TARGET GROUPS

Manufacturing companies and product designers: Companies will benefit from a robust and well-defined method supported by digital tool for the use of NMs to manufacture competitive NEPs. Product designers will be strongly supported by the multi-sectorial knowledge embedded in the digital tool to conceive sustainable, safe and competitive NEPs.

Regulators: Policy and standards setting bodies will benefit from a deployed methodology supported by digital tools to assess safety and sustainability of NMs intended for industrial applications and NEPs commercialisation.

Scientific community will have a central part in the NMs LC characterisation enabling the NMs sustainability and safety assessment. Research labs, models developers will take an active part in building the NMs safety and sustainability knowledge embedded in the digital tool DB, implying their continuous involvement in contributing with measurements and characterisation through advanced means

Society at large: Consumer goods end users will be provided with a clearer view and with higher guarantees on the innovation process for ensuring safe and sustainable use of NMs based on advanced characterisation methodologies supported by digital tools to obtain NEPs.

OUTCOMES

Reduced industrial innovation associated risk, better and faster nanotechnology uptake: with a clearer approach to the safety and sustainability assessment of NMs use manufacturing companies will remove their concerns towards the risk of use of NMs taking the opportunity to achieve enhanced NEP functionalities and a better competitive advantage along with the implementation of responsible innovation guidelines.

Extended use of open access data: Integration of available databases on safety and sustainability of NMs for targeted applications will increase the scientific knowledge and will leverage research and development of new NMs and their incorporation into NEPs with a better perspective on their toxicity referred to specific exposure scenarios and the related AOPs.

Enhancement of advanced characterisation methodologies: The challenge of providing broader information related to different knowledge domains on NPs and their interaction with complex environmental matrices and biological media, will foster and give more impulse to the design and development of integrated characterisation methodologies providing NMs full profile related to their p-chem features, their toxicology and eco-toxicology, along with the midpoint environmental impact.

Broader use of modelling and design tools: Given the complex dynamics and interaction between NMs and environmental matrices as well as the dynamics underlying the AOPs, will promote the extended use of models and design tools for addressing the challenges of multifactorial decision modelling supported by digital tools. Chemical safety concepts for rapid process safety decision making and dissemination of consumer products safety. Extending the tool's usage to other advanced materials and assessing their health&Safety, societal, environmental and economic impact.

IMPACTS

Scientific: (a) New LCIA approach to the assessment of safety and sustainability of NMs, along with the implementation of a MCDA tool for selection of the best design options at NMs synthesis and incorporation stage along with the definition of the use safety protocols and the best EoL options. **(b)** Provision of a fertile ground for the definition on new standards for detection, quantification and characterisation of NMs in connection with their p-chem properties and intended application within their whole LC also in connection to the safety and sustainability requirements.

Economic: (a) 50% increase in NMs commercialisation and incorporation into NEPs is expected, starting from the field of the targeted applications. **(b)** 15% servicing turnover increase by material characterisation laboratories. **(c)** 20% turnover increase for servicing and consultancy on processing and products improvement services in connection to the NMs and NEP design

Economic/Technological: Enabling designing commercialising new competitive nano enabled solutions with 20% cost reduction during their LC, better and safer NEPs due to the selection of the suitable NMs and processing options.

Societal: (a) 10% increase in the job creation potential related to the NMs p-chem characterisation, nano-toxicology and environmental impact assessment; **(b)** 20% reduction in climate change and use of non-renewable resources, 50% reduction of wastes in products manufacturing due to the extended use of the digital tool for the implementation of the SSbD methodology.

3. Quality and efficiency of the implementation

3.1Work plan and resources

The work proposed in INTEGRANO is organized in a logical framework described in Fig. 3.1.1 which reflecting the main data flows among the WPs. On the other hand, the WPs are also positioned along the key elements described in the IMM for the SSbD process (1.2.1) according to the circular scheme shown in Fig 3.1.2.

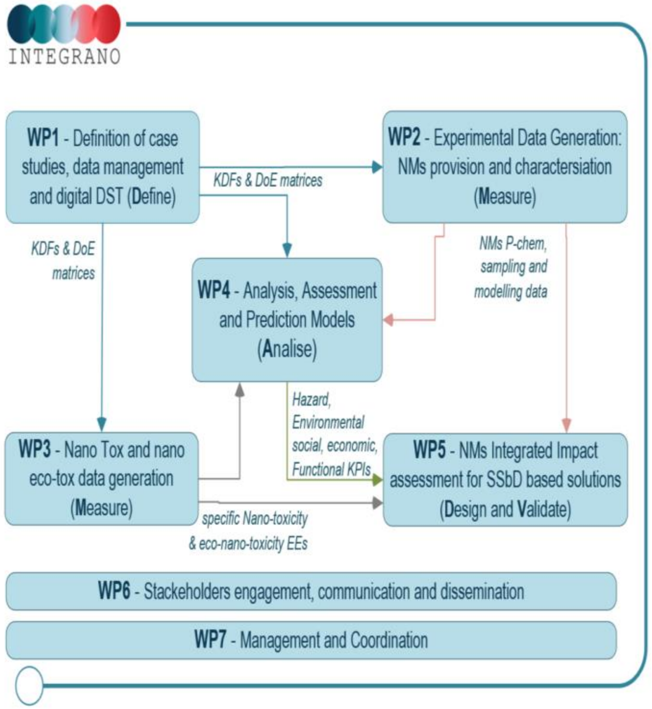


Figure 5 INTEGRANO Pert Diagram with WPs interconnections and associated flows. (EE=effect factors, DoE=design of experiment matrices; KDFs=Key decision Factors, KPIs=key performance indicators

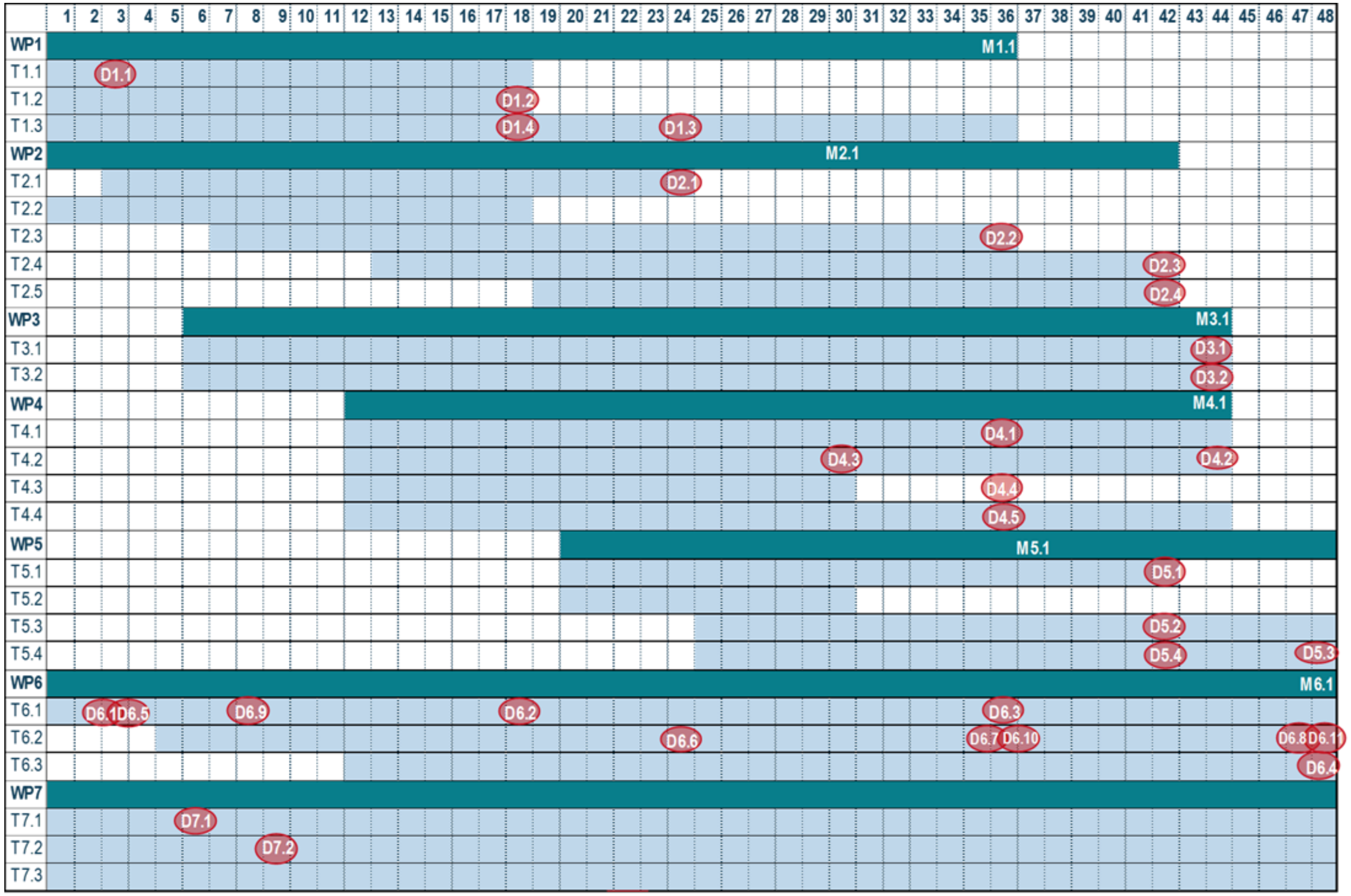


Table 3.1.1. INTEGRANO Gantt diagram

Risk management
In order to ensure a smooth project proceeding, a risk register will be created and periodically reviewed by the Steering Board at its scheduled meetings. The board will have ad-hoc consultations to address any urgent or unforested risk mitigation action or new discovered risks.

Table 3.1h: 'Purchase costs' items (travel and subsistence, equipment and other goods, works and services)

No. 1 / UNIMIB	**Cost (€)**	**Justification**
Equipment	30,000	Cell exposure and imaging systems.
Other goods and services	30,000	molecular probes and kits
Other goods and services	12,000	labware: plastics, glass, small lab equipment, chemicals and reagents
Remaining purchase costs > 15%	42,000	
Total	114,000	
No. 3 / CENTI	**Cost (€)**	**Justification**
Other goods, works and services	16,075	Solvents, Reagents, Nanoparticles, Laboratory Consumables, Small characterization services (SEM, TEM, Antimicrobial activity), Equipment Spare parts
Remaining purchase costs > 15%	29,925	
Total	46,000	
No. 4 / CNR	**Cost (€)**	**Justification**
Other goods, works and services	14,297	Chemical reagents, Materials and consumables for the synthesis of materials and for equipment.
Remaining purchase costs > 15%	71,325	
Total	85,622	
No. 5 / AITEX	**Cost (€)**	**Justification**
Other goods, works and services	20,000	Polymers, solvents and chemical auxiliaries for developing nanomaterials,
Other goods, works and services	20,000	stakeholder events organization
Other goods, works and services	8,000	Laboratory consumables (gloves, glass, electrospinning needles, protective material)
Other goods, works and services	400	Organization of project meeting
Remaining purchase costs > 15%	30,600	
Total	79,000	
No. 8 / UNITO	**Cost (€)**	**Justification**
Equipment	25,000	Solid state NMR probe
Other goods and services	8,527	Consumables: raw materials, chemicals, gases.
Remaining purchase costs > 15%	27,973	
Total	61,500	
No. 9 / PRJ	**Cost (€)**	**Justification**
Other goods and services	8,400	Events organization.
Remaining purchase costs > 15%	40,200	
Total	48,600	
No. 11 / B4C	**Cost (€)**	**Justification**
Other goods and services	3,0000	Service provider from Aalborg university and university of Seville
Other goods and services	10,000	Membranes substrates for Nanoparticle deposition .
Travel	1,160	International conferences
Remaining purchase costs > 15%	15,840	

Total	57,000

Table 3.1i: 'Other costs categories' items (e.g. internally invoiced goods and services)

No. 1 / UNIMIB		
	Cost (€)	**Justification**
Internally invoiced goods and services	10.000	Microscopy, spectroscopy and zebrafish facilities services.
No. 6 / BIU		
	Cost (€)	**Justification**
Internally invoiced goods and services	10.000	Laboratory analysis and data collection facility

3.2Capacity of participants and consortium as a whole

INTEGRANO is an interdisciplinary and multipolar initiative whose objectives spread over a number of specific technical fields, such as p-chem characterisation and toxicology, and integrated and crosscutting areas, such as modelling and assessment studies. The areas of disciplinary expertise are mapped as clusters in the scheme on the right which also shows partners' positioning in one, or more clusters, according to the role they undertake in the project. There is certainly a critical mass of expertise in the field of **characterisation** technology, where CENTI, CNR, UNITO and BIU contribute with a pool of p-chem analytic techniques and longstanding expertise of their application in the field of NMs (also ref Table 1.2.2b). These techniques also referred to in the methodology description (1.2.2) include the majority of main characterisation methods recommended for NMs including advanced imaging techniques. On the other (**toxicology**) side, the same materials as such, related NMs or transformation products will be subject of human and eco-toxicity tests, where the main partners are UNIMIB and CNR for *in-vitro* and *in-vivo* measurements. These measurements are supported by the expertise of RoV and DRT in AOPs. CNRs contribution will be widespread across some of its multidisciplinary institutes. CNR responsibilities within INTEGRANO are (but are not limited to) - NM synthesis (Ag-HEC, SiO2, n-perovskite), Ecotoxicology measurements (air & water), synthesis of nanofillers for biopolymers, and characterization of NMs, which are carried out in different institutes of CNR who are specializing in the activity. The CNR Departments involved in the project are: **ISSMC** Istituto di Scienza, Tecnologia e Sostenibilità per lo Sviluppo dei Materiali Ceramici, **IPCB** Istituto per i Polimeri, Compositi e Biomateriali, **ISAC** Istituto di Scienze dell'Atmosfera e del Clima, **SCITEC** Istituto di Scienze e Tecnologie Chimiche "Giulio Natta", **IAS**-Istituto. impatti Antropici e Sostenibilità in ambiente marino, **ISMN** Istituto per lo Studio dei Materiali Nanostrutturati. The p-chem characterisation partners possess the infrastructure for industrial scale-up and advanced testing of materials. Some among this partner cluster are also providing NMs synthesis and incorporation pilot processing and are well connected to end-users and industrial partners (LARGE enterprises and SMEs) targeted to industrialisation and future commercialisation of NMs and NEPs. The role of the **manufacturing** cluster partners (B4C, VERL, CENTI) in INTEGRANO is instrumental because they provide the opportunity to exploit incorporation of emerging NMs in NEPs for measurements and offer facilities for testing (e.g., detection of airborne NPs during the production phase or testing specific functional properties). It is expected that they closely cooperate with the partners in charge of **p-chem characterisatio**n, **toxicological studies** (for provision of materials), **modelling and assessment** (for provision of data on specific NMs hazard and sustainability). Indeed, the work of some groups from the assessment domain, such as PRJ, and ARCHE, also strongly rely on the results of the **detection tests** (leaching, airborne NPs sampling in incorporation and abrasion tests, etc.) to perform RA, or collecting data for performing **LCA, LCC and SLCA**. PRJ has a long-assessed experience in the sustaibility evaluation methodology, in particular being involved in the sustainability assessment though LCA and LCC of nanotechnologies and nanomaterials since more than 20 years. PRJ experts and founders participated in several EU project (since FP4) with the role of LCA and LCC experts and WP leader of the sustainability assessment WPs. PRJ also provides consultancy on LCA, LCC and SLCA to industries, ranging from SMEs to major multinational groups. UNIMIB also will contribute with its expertise in LCA. UNIMIB and PRJ had already collaborated in other projects focused on the sustainability assessment of nano-enabled solutions. P-chem characterisation and toxicology data will be complemented by development of grouping and read across models. PRJ helped by CNR, CENTI, BIU, AITEX, UniTO, and UniMIB in data collection and other tasks related to LCA will be the main data recipient for the development of the overarching assessment models also in social aspect. Social and economic modelling will be performed by BIU SSH experts in sociological and economic disciplines, though the identification and quantification of the economic and social externalities of the developed solutions. Though the MCDA approach all the different aspect (including social and economic) will be considered in the SSbD framework, allowing the full integration of SSH in the Key decision parameters. UNIMIB will play a key role in managing the day-to-day project activities, along with the support from PRJ. The partner AITEX will ensure **engagement amongst all the stakeholders** to address the conflict of interest (if any) during the execution of the project and carry out the dissemination activity as planned.

Involvement of JRC. The involvement of JRC in the Advisory Board will contribute at the project success at different levels: (1) overseeing that the applied methodologies willl be compliant with the developed framework for SSbD chemicals and materials guidelines, (2) to support and validate the INTEGRANO New Approach Methodologies (NAMs), (3) to maximise the impact on the regualtory side by invovling experts and by supporting the proposal of new integrated assessment standards, (4) to support the European policymaking process (5) to integrate the NMs database with new samples and assessed NMs case studies, (6) to extend the application of the proposed integrated methodology to a wider class of chemicals and materials resulting in high positive social impact, (7) to further investigate a comprehensive and integrated application of LCA and assessment on human hazard and eco-toxicity (8) to leverage INTEGRANO results for significantly contribute to the chemical strategy for sustainability by addressing safe ans sustainable use of chemicals and materials
The following table (3.2) also list specific expertise description of partners.

Table 3.2. Partners role, specialisation and contributions to the project

Partner	Expertise and contributions to INTEGRANO
UNIMIB	Human toxicology, specific expertise on nanotoxicology, *in-vitro* and *in-vivo* testing, eco-toxicity assessment
ARCHE	Risk assessment, mass transfer models (in-silico) for determination of emission and transfer coefficients to determine fate and exposure factors; assessment of Safe CoU
CENTI	P-chem characterisation: differential light scattering and zeta potential, UV-Vis, differential scanning calorimetry, etc. NPs synthesis and incorporation by spray coating, dipping and bar coating
CNR	Ecotoxicology (full range of aquatic toxicity measurements, including bioaccumulation), NMs synthesis and p-chem characterisation, in field airborne NPs sampling, functional testing (antibacterial activity photocatalytic efficiency, leaching tests…)
AITEX	Ensuring effective communication amongst the stakeholder during the project, and project dissemination by establishing a dedicated platform to foster active engagement
BIU	P-chem characterisation, NM detection and sampling, NM synthesis and supply to partner, SSH contribution, modelling and externalities monetization
VERL	Development verification and validation of NEP (cosmeceutical devices).
UNITO	P-chem characterisation: SSNMR, VIL, luminescence techniques; NMs provider: nano-EB
PRJ	LCA, SLCA, LCC, DST, dissemination and communication
ROV	NEP manufacturer (cosmetics), Verification and validation
B4C	NEP manufacturer: water filtration (catalytic) membranes, leaching tests for NMs detection, NEPs stress tests
DRT	NEP testing, sampling and certification (cosmetic)

4. Ethics self-assessment

General

The consortium ensures that all ethics issues related to activities in the grant are addressed in compliance with ethical principles, the applicable international and national law, and the provisions set out in the Grant Agreement. This includes the ethics issues identified in this report and any additional ethics issues that may emerge in the course of the grant. In case any substantial new ethics issues arise, the coordinator should inform the granting authority.

Personal data

The objectives of the activities involve the **Generation and sharing of data through the scientific and dissemination actions. T**he scientific activity, including the generation of data by each participant will proceed according to the guidelines of good scientific practice of national and European regulations. In particular, Open Science principles, including Open Access publications, Open Data and possible access to Open Infrastrures will be followed, also in line with the institutional policy adopted by each partner.
The **Involvement of stakeholders, students, aurhorities which requires personal data collection will be perfomed by** procedures and criteria shared by the consortium, useful to identify/recruit research participants and stakeholder engagement. All the data will be treated according to the General Data Protection Regulation (GDPR), Regulation EU 2016/679. The informed consent procedures, as well as all the procedures to guarantee the highest ethical standard for safeguarding the personal data, here including the appointment of a data protection officer (DPO), will be specified in the Data Management Plan (DMP).

Non-EU Countries

The only partner in the consortium belonging to non-EU Countries (Israel) is BIU. BIU will implement research activities related to NMs synthesis and characterisation as well as to SSH studies. All BIU activities will be managed in compliance with ethical principles and applicable EU regulations as detailed in the previous and following paragraphs.

Environment health and safety

The activities will involve **the synthesis and testing of new and already marketed nanomaterials:** all experimental work with the nanomaterials as well as reference test materials will be performed under proper working safety conditions, according to the safe, security and prevention rules in place in each institutions and the national legislation in compliance with the Directive 98/24/EEC. Only competent and trained staff will be authorized to handle hazardous or potentially hazardous chemicals and materials and precautions will be taken to ensure protection of staff and environment.

In particular, regarding the health safety issues related to the use of nanomaterials, the following EC reccomendations will be considered:

- European Commission, Directorate-General for Employment, Social Affairs and Inclusion, Working safely with manufactured nanomaterials – Non-binding guide for employers and health and safety practitioners, Publications Office, 2019
- European Commission, Directorate-General for Employment, Social Affairs and Inclusion, Working safely with manufactured nanomaterials – Non-binding guide for workers, Publications Office, 2019

All the efforts to minimize the wastes cointaining nanomaterials and/or other hazardous compounds will be performed and the solid/acqueous wastes will be treated as hazardous waste, according to the national rules, to guarantee environmental protection. A precautionary principle will be adopted to prevent exposure and hazard to the newly synthesized nanomaterials.

Laboratory experiments will be performed to assess the environmental and human toxicity of the new materials. In this context, no experimental work with animals, as specified in the Directive 2010/63/EU on the protection of animals used for scientific purposes. The human toxicology experiments will be limited to in vitro testing, according to the 3R principles and for implementing the application of New Approach Methodologies (NAMs). Commercial cells and tissues will be used under the ethical and safety reccomendations from the providing repository and/or company. The invertebrate species and the zebrafish embryos used until 96-120h post-fertilization for the ecotoxicological assays do not fall into the Directive 2010/63/EU.

Artificial Intelligence

In INTEGRANO Artifical Intelligence will be used for data mining and data analysis, and it will be used mainly to support human autonomy in decision making through the DSS.

The AI systems will be used in the full respect of privacy and data protection, while the quality, integrity and security of data will be rigorously checked and adequately managed. All the data sets that will be analysed through AI will be declared and documented in the Data Management Plan (DMP), transparency and traceability will be the core principle of the data collection.

The impact on individuals, society and environment of the AI techniques that will be used, will be carefully evaluated and any type of risk will be avoided. AI system will be, indeed, applied to build a SSbD system and approach and, therefore, will bring positive transformative changes to the society, environment, or the economy. In order to take in account accountability all the users that will interact with the DSS, will be informed on the AI system employed for the data collection and mining.