NanoImpact 23 (2021) 100337

Contents lists available at ScienceDirect

NanoImpact

journal homepage: www.elsevier.com/locate/nanoimpact

Research Paper

Blueprint for a self-sustained European Centre for service provision in safe and sustainable innovation for nanotechnology

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ARTICLE INFO

Editor: Dr. Bernd Nowack.

Keywords:
Safe(r)-by-design
Nanomaterial
Nano-enabled product
Nanoprocess
Nanosafety
European Centre
Catalogue of services

ABSTRACT

The coming years are expected to bring rapid changes in the nanotechnology regulatory landscape, with the establishment of a new framework for nano-risk governance, in silico approaches for characterisation and risk assessment of nanomaterials, and novel procedures for the early identification and management of nanomaterial risks. In this context, Safe(r)-by-Design (SbD) emerges as a powerful preventive approach to support the development of safe and sustainable (SSbD) nanotechnology-based products and processes throughout the life cycle. This paper summarises the work undertaken to develop a blueprint for the deployment and operation of a permanent European Centre of collaborating laboratories and research organisations supporting safe innovation in nanotechnologies. The proposed entity, referred to as "the *Centre*", will establish a 'one-stop shop' for nanosafety-related services and a central contact point for addressing stakeholder questions about nanosafety. Its

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https://doi.org/10.1016/j.impact.2021.100337
Received 2 April 2021; Received in revised form 5 June 2021; Accepted 17 June 2021
Available online 2 July 2021

Business plan
Safe innovation
EC4SafeNano project

operation will rely on significant business, legal and market knowledge, as well as other tools developed and acquired through the EU-funded EC4SafeNano project and subsequent ongoing activities. The proposed blueprint adopts a demand-driven service update scheme to allow the necessary vigilance and flexibility to identify opportunities and adjust its activities and services in the rapidly evolving regulatory and nano risk governance landscape.

The proposed *Centre* will play a major role as a conduit to transfer scientific knowledge between the research and commercial laboratories or consultants able to provide high quality nanosafety services, and the end-users of such services (e.g., industry, SMEs, consultancy firms, and regulatory authorities). The *Centre* will harmonise service provision, and bring novel risk assessment and management approaches, e.g. in silico methodologies, closer to practice, notably through SbD/SSbD, and decisively support safe and sustainable innovation of industrial production in the nanotechnology industry according to the European Chemicals Strategy for Sustainability.

1. Introduction

A central challenge to ensuring the sustainable production and use of nanomaterials (NMs) and nanotechnologies is to understand and effectively control the potential risks along the industrial innovation value chain. Prevention through Design (PtD) (NIOSH, 2018), Safety Integration (European Commission, 2006; European Commission, 2019a) or Safe(r)-by-Design (SbD) (NanoREG II, n.d.), are similar concepts that refer to strategies to design out hazards and/or reduce exposure and thereby minimize risks early in the design process. In addition, the European Commission has recently set out ambitious plans towards achieving a sustainable, fair and inclusive economy through its Green Deal (Gottardo et al., 2021). Industrial innovation can be enhanced through further establishment of relevant regulatory principles and additional adaptations/modifications of current regulations. Three currently running EU H2020 risk governance projects (Gov4Nano (Gov4Nano, n.d.), NanoRIGO (NanoRIGO, n.d.) and RiskGONE (RiskGone, n.d.)) propose the development of an authoritative nano risk governance framework and the creation of an intermediating nano risk governance body (council) supporting risk management, regulation of nanotechnology and FAIR data exchange in Europe. Their approach will aim to promote and encourage the transfer and translation of scientific data/knowledge into industrial and product safety, regulation, standardisation and guidance, facilitate reliable knowledge sharing on the risks and benefits from nanotechnologies, and maintain constructive dialogue between the different stakeholders including civil society (Scott-Fordsmand, 2021; Isigonis et al., 2020; Porcari et al., 2019).

The above nano risk governance projects, build upon previous research funded under EU FP6, FP7 and H2020 on various aspects of nanosafety, including tailored standardisation and regulation tools (NanoSTAIR (nanoSTAIR, n.d.), NANoREG (NANoREG, n.d.) & NanoREG2 (NanoREG II, n.d.) projects and the ProSafe White Paper (ProSafe, 2017)); integrated risk management throughout the NM life-cycle (LICARA (van Harmelen et al., 2016), NanoValid (NanoValid, n.d.), MARINA (MARINA, n.d.), NanoMILE (NanoMILE, n.d.), NanoFATE (NanoFATE, n.d.), NanoFASE (NanoFASE, n.d.), SUN (SUN, n.d.)); practices and tools for occupational risk management (SCAFFOLD (SCAFFOLD, n.d.), GUIDEnano (GUIDEnano, n.d.)), a first operational and nano-risk governance framework supported by validated tools (caLIBRAte (caLIBRAte, n.d.)); database building and management (eNanoMapper (eNanoMapper, n.d.)); shared infrastructures (QualityNano (QualityNano, n.d.)) and knowledge (OpenRiskNet (Exner et al., 2018)), and excellence laboratories (EU-NCL (EUNCL, n.d.)) etc.

In recent years, a strong emphasis has been placed on making NMs and Nano-Enabled Products (NEPs) safer by applying a SbD approach (Kraegeloh et al., 2018). In the absence of an accepted and harmonised definition of SbD, the NanoREG2 SbD concept aimed at identifying, estimating and reducing uncertainties and risks for humans and the environment along the entire value chain, ideally starting at the earliest stage of the innovation process. This approach was demonstrated by implementation through a few industrial case studies (Jiménez et al., 2020). Often, in the innovation chain, a decision may have to be made on whether to continue, stop or re-design the NM / NEP and/or the process, sometimes with scarce information on the potential hazards and exposure throughout the entire life cycle of the product. In such conditions, only qualitative risk assessment can be performed at early stages, giving some preliminary insight into the next steps to take. Through these NanoREG2 case studies, it appeared that reliable predictive tools that can forecast hazards, exposure and functionality, enabling more quantitative assessments of risks, costs of products and processes and their societal impacts regarding various intended and accidental industrial scenarios, are urgently needed for a proper implementation of SbD. The design and implementation of new pilot lines and test beds for the manufacture of NEPs, supported by H2020 projects such as PLATFORM (PLATFORM, n.d.) or OASIS (OASIS, n.d.), have led to the development of ad hoc methodologies and tools for SbD of nanomanufacturing processes (López de Ipiña et al., 2017; López de Ipiña et al., 2019), aligned with the relevant regulation (European Commission, 2006). The GoNanoBioMat project elaborated a methodological SbD approach for nanomedicines and in particular polymeric nanocarriers (Schmutz et al., 2020). The REFINE project prepared a white paper to launch a public debate on regulatory needs for nanomedical products and devices (Halamoda Kenzaoui et al., 2019).

Nanosafety risk assessment throughout the development chain is challenging, because of the diversity in the physical and chemical composition of NMs, their surface functionalisation and structural properties; and because it is not always possible to rigorously assess the risks of each alternative configuration of a NM. For this reason, there is an increasing need for informatics tools to manage and process the available data, and extract useful knowledge on the physicochemical, exposure and toxicological properties of novel NMs to enable in silico risk assessment.

In response to this need, the EU is currently funding the establishment of a nanosafety data management research infrastructure (NanoCommons (NanoCommons, n.d.)) and two major research and innovation projects (NanoInformaTIX (NanoInformaTIX, n.d.) and NanoSolveIT (NanoSolveIT, n.d.)) to develop regulatory-relevant informatics tools for predictive SbD, grouping and risk assessment of nanomaterials. The prime joint impetus of these nano e-infrastructure and e-development projects is the improvement of data quality and FAIRness (findable, accessible, interoperable and re-usable data) (Wilkinson et al., 2016) in the nanosafety assessment field, to support SbD and prediction of NM / NEP safety. In this regard, NanoCommons establishes a platform for cross-linking available nanosafety data repositories and offers a suite of openly available in silico tools for experimental workflow design and implementation, data processing and analysis, data visualisation and predictive toxicity, as well as data storage and online accessibility. Additional in silico tools, currently under development by the NanoInformaTIX and NanoSolveIT projects, will be integrated into the NanoCommons e-infrastructure platform, with further distribution and amplification via the education, dissemination, exploitation and sustainability channels of the European NanoSafety Cluster.

The outcome of these initiatives will depend on the value of the

evidence generated, and its validation and application in managing the emerging NM risks. Ultimately, this investment should lead to safe practices in the production and use of NM and NEP by industry as well as their customers and consumers. Integration of the above-mentioned joint efforts will be further implemented by the recently launched SbD projects SAbyNA (SAbyNA, n.d.), SABYDOMA (SABYDOMA, n.d.), ASINA (ASINA, n.d.) and SbD4Nano (SbD4Nano, n.d.), which endeavour to collaborate closely on this matter. These projects will address the challenges to support the development of SbD products and processes, from an integrated vision and over the whole NM / NEP life cycle. These projects also aim to access the robustness of digital technologies and tools for process and product design. The ultimate goal is to provide the industry with science-based and easy-to-use SbD methods, tools, guidelines and databases, to access accurately and manage efficiently the potential risks associated with nanoproducts and nanoprocesses.

The scientific and expert community needs to compile, harmonise and communicate this accumulated knowledge, and make available its expertise and technical services in a timely way to respond to the developing market for NMs and NEPs. Following the work of the EU-funded EC4SafeNano project (EC4SafeNano, n.d.) (see Section 2), this paper presents a blueprint for the creation of a sustainable European Centre of collaborating reference laboratories and research centres, referred to as "the *Centre*", to establish a 'one-stop shop' for nanosafety related services to support safe use of NMs. These services could also include responding to technical questions about safe practices for and during the manufacture, use, processing, recovery, re-use or disposal of NMs from a variety of stakeholder organisations.

An e-based platform will be used to respond to any specific query, providing access to collaborating national or regional centres of relevant expertise in Europe, and advanced search tools to guide interested parties to the right service provider(s). The future *Centre* will create an open hub connecting all interested parties dealing with the safety of (engineered) NMs during their entire life-cycle. The core of the *Centre's* activities will be risk assessment and risk management for safe innovation, as well as provision of technical services. The Centre will be set up to support competent authorities / national environmental, health and safety laboratories, research centres and academia, industrial stakeholders, government institutions, standardisation bodies, regulatory bodies and the OECD. Important aspects of the *Centre's* activities will include (a) the provision of collaborative technical services (not able to be undertaken by single service providers) to industry and other interested stakeholders; (b) selected activities jointly conducted by the members of the *Centre* to develop novel or technically advanced and harmonised services. These are discussed in more detail in Sections 3 to 5 of this paper.

In addition, we argue that the proposed *Centre* could play a major role within the evolving landscape of nanotechnology risk governance. The three running EU H2020 projects on nano-risk governance (Gov4Nano (Gov4Nano, n.d), NanoRIGO (NanoRIGO, n.d) and RiskGONE (RiskGone, n.d)) currently consider the creation of a European nano risk governance body (or bodies), which may result in a high-level Nano Risk Governance Council (NRGC). While the concept for NRGC is still in development, and uncertainties about its scope and mandate exist, the proposed blueprint was not driven by the presence of governance bodies, and is valid with or without the mandate for a NRGC. Additionally, the main scope of the proposed *Centre* is around service provision, while the governance bodies are not currently foreseen as service providers per se, and the *Centre* can implement key recommendations on service provision of a potential future NRGC.

In view of these uncertainties and aiming to contribute to the current discussions on risk governance, Section 6 demonstrates that the preparatory work behind the development of our blueprint, the governance mechanisms and the service management procedures proposed here, are essential ingredients for an entity which will need to:

- Act as a conduit to transfer scientific knowledge between the research and commercial laboratories or consultants able to provide high quality nanosafety services, and the end-users of such services (e.g. industry, SMEs, consultancy firms, and regulatory authorities).
- Promote the development and implementation of SbD/SSbD approaches in industrial practice, to identify and address uncertainties and potential risks for environmental and human health from the early stages of industrial innovation of NMs, NEPs and nanoprocesses.
- Promote implementation of the recently published EU Chemicals Strategy for Sustainability by supporting the innovation of industrial production towards advanced materials to deliver the green and digital transition, and low-carbon and low environmental impact production processes (European Commission, 2020).
- Support the validation of in silico service provision offered through nanoinformatics (from the NanoInformaTIX (NanoInformaTIX, n.d), NanoSolveIT (NanoSolveIT, n.d) and NanoCommons suites (NanoCommons, n.d), and other governance tools as started in the caLIBRate project (caLIBRAte, n.d)).
- Support further developments within the current risk governance projects, including research to the development of Technical Guidance and Guidance Documents (e.g. through the "MALTA initiative" (MALTA, n.d.)).

Some of the above are already foreseen to be taken into account by the development of the future NRGC. In this case, our work is useful for the discussion regarding the governance of the NRGC, and also provides a list of the possible fields of interaction between a European service provision *Centre* and a high-level risk governance body.

2. Background

The initiative to develop the operating principles and business plan to enable the establishment of a Centre for European Organisations involved in Risk Management and Safe Innovation for NMs and Nanotechnologies began in 2015. The EC4SafeNano project (EC4SafeNano, n.d) was accepted for funding by the EC, and ran between November 2016 and October 2019, led by INERIS and involving a core team of 15 major European risk-assessment institutes from 11 EU Member States, with the support of over 60 associated partners and links to national nanosafety entities across Europe.

The key outcomes of the EU-funded EC4SafeNano project included the following:

- A **mapping of needs and available resources** through analysis of the results of two extensive surveys (2017 and 2019) involving stakeholders from industry and industrial associations, regulatory bodies, EC / Member States, research centres and academia needing or offering nanosafety services (van Duuren-Stuurman et al., 2019a).
- A **Fit-and-Gap Analysis tool** (FGA tool) to match the customer needs with the available resources, analyse and visualise the data obtained from the needs and resources surveys and identify priority topics associated with the non-covered or poorly-covered demand (Lopez de Ipiña et al., 2019).
- An extensive **inventory of existing tools**, methods, training courses, standards and standard operating procedures (SOPs), guidance documents and best practices for nanosafety and risk assessment. Using suitable templates, each entry includes descriptive parameters and quality criteria (e.g. validation, applicability domain) and enables linking the inventory with other EC4SafeNano tools (van Duuren-Stuurman et al., 2019b).
- A **paradigm for a Catalogue of Services (CoS)** with a proposed template of the Service Data Sheet (EC4-SDS). The EC4SafeNano CoS consisted of 100 EC4-SDSs, covering a range of service categories and topics, and was implemented as an online searchable tool available for consultation and download in English, French and Spanish at: htt

p://ec4safenano.eu-vri.eu/Public/index (López de Ipiña et al., 2019).

- A **list of priority questions in the area of nanosafety**, collating and ranking questions from different sources, including NANoREG and the EC4SafeNano surveys of stakeholder needs (Witters et al., 2019).
- **Implemented case studies** to test and demonstrate the partners' capability to jointly deliver services that required collective expertise, benchmarked against the needs of various types of stakeholders. These case studies addressed methodological approaches and implementation of two SbD pillars, i.e. Safe products by design and Safe use of products (Unger et al., 2019). The case study reports and the procedures for building and managing the case study teams were reviewed by groups of external experts (Marcoulaki et al., 2019a).
- An extensive European-wide market survey to investigate the usefulness of various proposed activities of the future Centre and to aid the development of the business plan (Vercauteren, 2019).
- A thorough survey and workshop on the legal issues, involving the legal departments of 12 project consortium partners (and potential members of the future *Centre*, as service providers). The workshop considered multiple dimensions of the definition of legal structure, most importantly intellectual property and competition law/public procurement issues (Puttemans and Bochon, 2019).
- An initiative to create a blueprint for the planning, development and networking of sustainable national nanosafety centres mirroring the activities of the *Centre* at the national levels (Shandilya et al., 2020a).

Based on the above outcomes, the authors propose herein a sustainable governance and service management scheme and the business plan for a future *Centre*, bringing together providers of nanosafety services to deliver collaborative services, harmonise service provision and create novel service schemes, as described in more detail in Sections 3 to 6. The results of the surveys, the inventory management and analysis tools (e.g. FGA), the CoS and the expertise gained from the case studies will be available to the members of the *Centre* to use and maintain as they see fit. Also note that, due to the limited funding of the EC4SafeNano project the surveys did not consider civil society organisations (e.g. consumer groups), and the focus was on EHS risks while ELSI (ethical, legal, social issues) were not considered at this stage. Likewise, our surveys and analyses had to be limited to EU service providers and the EU market, but we can assume that the proposed governance would be in principle valid for non-EU providers and customers.

3. The Centre, a governance proposal

This paper presents a solid governance proposal for a self-sustainable entity considering the background outlined in Section 2 and expertise from existing successful entities, like the NORMAN network (Dulio et al., 2018). This Section outlines the benefits of establishing a permanent European Centre, and the proposed governance structure and mechanisms. The proposed *Centre* aims to bridge the gap between (a) the rapidly evolving scientific knowledge about the hazards and risks of NMs for human health and for the environment, taking into account all life cycle stages, and (b) the effective use of this knowledge based on 'fit-for-purpose' risk management tools and strategies, suitable for market actors and other stakeholders.

The *Centre* will be addressed to service providers across Europe to offer consistent, inclusive, up-to-date, evidence-based and high-quality services to industry, regulators and the public across Europe. We argue that these can only be achieved through a permanent entity, open to everyone interested to join, and willing to contribute and/or promote their services through a user-friendly and searchable web portal. This permanent entity will act as a robust, reliable and trustable interface between the scientific community and all the market actors, to provide and communicate operational approaches and tools adapted to each type of stakeholder. Our proposal involves laboratories with established track-records in nanosafety research. They include individual research institutes as well as partnerships between institutes, universities, and national centres for nanosafety. Collaborating under the *Centre*, they will provide collective expertise to those who need to conduct safe operations and manage risks for public and for private organisations. Harmonisation is deeply rooted in the proposed approach, and a necessity for data exchange, knowledge sharing, communication and collaboration between the Members and contributors. This is outlined in more detail in the following sections, as it is highly relevant to promoting novel concepts and tools for risk assessment and management of nanotechnology, as well as data and service management. The *Centre* will also provide a trusted environment in which industry, innovators, universities/research organisations, agencies and other authorities can share and exchange knowledge, information and views on nanotechnology and NMs.

The *Centre* should acknowledge the expected diversities in terms of country-specific legislations, service costs, culture, language, communication styles and approaches etc. among different customers and address these appropriately. The *Centre* can also promote national initiatives providing information for the general public (e.g. DaNa) and/or interested companies (e.g. Contact point), and the EUON.

The proposed governance model for the *Centre* comprises four membership categories: (i) Governing Members, (ii) Regular Members, (iii) Contributors and (iv) Associate Members. Governing and Regular Members will pay a membership fee and have the right to vote. Institutional bodies, Governmental and International Organisations, Standardisation bodies and Non-Governmental Organisations can apply to become Contributors, without paying any membership fee (see Section 5). They will be allowed to participate in the General Assembly and other activities of the *Centre*, but they will have no right to vote. Associate Members will only pay a fee to register their services, without the right to participate in the General Assembly. The *Centre* will be managed by the Steering Committee composed of three to nine members, who shall elect an Executive Secretary, the Delegate for Customers' assistance, the Treasurer and the Chairman. For the first three years of the functioning of the *Centre*, the Steering Committee will comprise exclusively all Governing Members. After this start-up phase, the Steering Committee Members shall be elected by the General Assembly with a mandate of three-years. Table 1 summarises the proposed membership features. The fee refers to the fees/subscriptions paid by the members as explained in Section 5. The check marks indicate which features are valid (✓) or not (□) per member category, e.g. only Governing Members participate in the Steering Committee.

The Steering Committee will be responsible for the direction and strategic orientation of the *Centre*, assisted by an Executive Secretariat and a Helpdesk. The General Assembly brings together all Governing/Regular Members and Contributors of the *Centre* and allows each one to express their position. The Steering Committee will also appoint interested Members/Contributors to Expert Groups, for regular meetings and discussions on high-priority topics selected by members. Each year, the General Assembly will collectively agree on a set of organised collaborative activities for the next year, as discussed in Section 4. The *Centre* will regularly promote its activities to provide an overview of its research projects, on harmonisation / certification and other relevant initiatives in the field of nanosafety in Europe and beyond (Dulio, 2019). Fig. 1 illustrates the different interactions of the *Centre* collaboration

Table 1
Summary of the proposed membership features.

Member category	Governing	Regular	Contributor	Associate
Indicative fee (see Section 5)	10,000€	2500€	None	500€
Steering Committee	✓	□	□	□
General Assembly (GA)	✓	✓	✓	□
Right to vote in GA	✓	✓	□	□
Service promotion in CoS	✓	✓	□	✓
Expert groups	✓	✓	✓	✓

Fig. 1. Positioning of the *Centre* and interactions between contributing parties.

with other stakeholders and how it is positioned in the nano regulatory and risk governance landscape. More details will be provided in Sections 4–5.

The proposed model of governance builds on the experience from the NORMAN network on emerging substances. NORMAN came into existence in 2004 following a call by the EU Commission (DG Research) to create "a permanent network of reference laboratories and related organisations dealing with emerging environmental substances". At the end of the contract, the project objectives were pursued via the creation of a non-profit association. Since 2006 and until now, NORMAN is an independent, self-sustaining and highly recognised network of more than 80 members including leading reference laboratories, research centres and environmental agencies across Europe and worldwide (Dulio et al., 2018).

The *Centre* will publish annually a CoS, and will provide a Helpdesk to create an efficient interface with external customers, and to facilitate access to technical resources and the available services. The catalogue will include all services and resources available by the Members of the *Centre* and other service providers paying a fee to promote their resources though the *Centre* (see Section 5). This combined technical expertise will be exploited to provide science-based advice to simple and complex custom questions from stakeholders, including regulatory bodies and competent authorities, and to undertake reviews of external services. The proposed schemes for service provision by the *Centre* were benchmarked with a large collaborative case study on Safe products by design and a review case study on the Safe use of products (see Section 2).

The proposed *Centre* aims to have a permanent EU Nanosafety Reference platform, able to meet the demands of the stakeholders (including competent authorities) on decisions regarding the safety of the NMs and nanotechnologies. This can be ideal to promote the development of Trusted Environment at European level, and enable an active dialogue among different stakeholders (policymakers, regulatory risk assessors, industry, NGOs, experts, academia and the society) for knowledge-sharing and regulatory preparedness (Shandilya et al., 2020b). The *Centre* can also provide a reference for the implementation of a European regulatory framework for risk governance in nanotechnology. Discussions on how the proposed *Centre* could co-exist and complement potential future risk governance bodies or a future high-level NRGC are ongoing in the governance projects. Of note, the blueprint proposed here and the procedures we followed for its development provide valid ideas and insights for designing the governance of other similar entities, and this can be particularly useful in the current phase of the risk governance projects.

The proposal for the legal definition of the structure of the *Centre* is based on the results of a thorough survey and a 2-day workshop on the legal issues (see Section 2). Our analysis considered options which would not create risks in terms of liability or solvency, and that would enable the hiring of personnel, avoid issues with distribution or taxation of revenues etc. After considering various types of legal entities, we herein propose a non-profit type of legal entity (e.g. AISBL) open to all interested stakeholders dealing with nanosafety, as the most preferable option among the workshop participants. Under the AISBL there will be a need for an agreement on how to distribute the services between the partners. Questions on the intellectual property of the services provided by the *Centre* will have to be resolved on a case by case basis. Clearly, other legal structures can be considered, and it is up to the Steering Committee of the future *Centre* to select the most appropriate scheme according to business or other criteria and constraints (Puttemans and Bochon, 2019). The legal survey also considered that the *Centre* could be the owner of an EU Certification Mark, which would distinguish and protect its certification services, as discussed in Section 4.

4. The service management scheme

The *Centre* will use a set of market-driven mechanisms to ensure that the service provision is kept up-to-date. The ongoing and future needs of customers will be identified via annual surveys and 'fit and gap' analyses, using the tools developed and tested during the EC4SafeNano project (Section 2). Proposed new service products and/or service types will be developed by the *Centre* or its Members and included in the CoS. In particular, implementation of the SbD/SSbD approach in the design of new NMs and NEPs, new manufacturing processes or the modification of existing processes, is expected to lead to short-term demand for novel consulting services, guidelines, tools and databases associated with this trending topic. Close collaboration between the *Centre* and the foreseen governance bodies will also ensure sustainability and regulatory compliance of the SbD products within a Safe(r) Innovation Approach (SIA) (NanoREG II, n.d.; Shandilya et al., 2020b; OECD, 2019). The Centre could also provide tailored services to civil society organisations, such as consumer groups needing guidance on safety of nanomaterials in food and/or other consumer products, though this option was not considered during the development of the business plan (Section 5). These new opportunities should be considered and evaluated to generate the new service offer that feeds and updates the CoS.

New service products and types will be developed through the annual Joint Programme of Activities (JPA). Members taking part in this development will receive a limited remuneration for their work. The objectives of the annual JPA will be selected among currently unmet needs and forecasted needs proposed by the *Centre*'s Expert Groups, and

additional items proposed by the Members. Possible activities could include harmonisation and certification actions, interlaboratory studies to support validation and standardisation, Expert Group meetings on high-priority topics, position papers, and guidance documents, etc. Each proposed item will require an assessment of the required budget and this will be discussed and voted on during the annual General Assembly (GA) meeting of the *Centre*. Each year, the prioritised list of candidate activities will be considered and approved by the Steering Committee, and will form the basis of the next annual JPA. Criteria for final selection will include the interest of the Members, the strategic value of the topic in the field of EU nano risk governance, the balance between different sectors / fields of interest, and the relative value of the proposed in-kind contribution vs. required budget and resources. The Members of the *Centre* will be encouraged to undertake with their own effort and budget the proposed items not selected in the annual JPA (e.g., due to lack of funds). The *Centre* can also support future governance bodies with additional technical expertise to effectively and reliably respond to their questions or demands, by including them in the JPA's or even co-developing the JPA list according to their particular needs (Marcoulaki et al., 2019b).

Regarding new service types, EC4SafeNano had investigated opportunities for the creation and promotion of an EU Certification Mark, which would cover, distinguish and protect the services created by the *Centre* and delivered by its Members. This trademark is available since the 2017 EU trademark reform and can be granted by the EU Intellectual Property Office (EUIPO). An EU Certification Mark "is applied for and is capable of distinguishing goods or services which are certified by the proprietor of the mark in respect of material, mode of manufacture of goods or performance of services, quality, accuracy or other characteristics, with the exception of geographical origin, from goods and services which are not so certified" (see articles 83 to 93 of Regulation 2017/1001).

The originality of the EU Certification Mark is that it could be used by all parties complying with the certification requirements, not just the members of its owner, but it cannot be used by its owner for self-certification purposes. That element is particularly interesting for the *Centre*, as the legal structure will be open to third parties. The legal regime of EU Certification Marks would entail the adoption of certification rules by the *Centre* which, as owner of such trademark, would therefore have to remain neutral and not engage itself in the provision of the services covered by the said EU Certification Mark (Puttemans and Bochon, 2019; EU Certification Marks, n.d; European Parliament, 2017). So far, the rules about the EUIPO do not prevent the owner of the EU Certification Mark from certifying members who are shareholders or are, in another way, controlling the owner of the Certification Mark. Applications for EU trademarks are submitted to EUIPO for examination and registration (if accepted). The *Centre* should also establish procedures for auditing the providers of the EU Certification Marked service(s) by independent organisations, and their training.

Certification activities will further promote service harmonisation, improve service quality and increase profitability of the future *Centre* as discussed in Section 5. Close collaboration with standardisation bodies and the OECD will ensure alignment of activities and will help to avoid unnecessary duplication of effort. Regarding standardisation in SbD, working groups WG 3 (Health, Safety and Environmental Aspects of Nanotechnologies) and TG 2 (Sustainability, consumer and societal dimensions of nanotechnologies) of the technical committee ISO/TC 229 on nanotechnologies, develop and publish Technical Reports and Technical Specifications relevant to SbD approaches (https://www.iso.org/committee/381983.html). CEN/TC 352 – Nanotechnologies has recently decided to establish the project group WG2 / PG3 "Safe by design", for the development of the SbD concept, to provide a working framework for companies dealing with nano-scale materials (MNM) and products containing NMs (https://www.cen.eu/work/areas/nanotech/). In the same vein, the OECD Working Party on manufactured NMs prepared a new document on SbD, as an initial contribution to the field, with definitions, review of available risk assessment tools, experience from case studies, and information on regulatory initiatives. The document proposes the combination of SbD and relevant regulatory strategies for awareness raising and decision making to achieve a SIA (OECD, 2000). All these will be an important guidance to integrate in the strategy of the future *Centre*. In the meantime, since activities in these bodies usually proceed very slowly, an EU Certification Trade Mark (such as proposed above) can cover the time gap between a specific demand for standardisation, or guidance, and the publication of an ISO/CEN standard or OECD test guideline. In addition to forging close interactions with governance and regulatory bodies, inputs from regulatory agencies such as ECHA, EFSA or EMA would be important to identify opportunities and threats for the development of these certificates. Trust in the developed certificates could be further increased by inviting regulatory risk assessors to contribute to their development.

It is worth mentioning that the 'EU Certification Mark of Services for Nanomaterials' and the 'Catalogue of harmonized services' proposed by the *Centre* have been published in the European Commission's Innovation Radar platform. The analysis categorised the market maturity of both innovations as 'business ready', and their market creation potential as 'high' and 'noteworthy', respectively (see European Commission, 2018 for the analysis details).

The future *Centre* will need to address significant organisational and management challenges, both decentralised and networked, where different types of service providers, of different legal statutes, sizes, locations, languages, cultures, services and ways of doing business will converge in the same *Centre*, to work together and provide a global offer of nanosafety services. Information Technologies (IT) are driving the development and growth of new service sectors and new types of services, eliminating geographic borders for their exchange. The *Centre* can benefit from this global trend, to effectively manage the service delivery process of the current/future offer, and to monitor the pipeline of services under development within the annual JPA. The *Centre* will also apply mechanisms to test and validate the service offer, using a suitable set of criteria for the robustness of the technical content and the quality of the reports delivered to the customers, as well as the service cost, speed etc. These mechanisms are important to build its reputation as a reliable and trustworthy actor in nanosafety service provision. The service validation criteria should reflect the expectations of industrial customers, and this can be achieved through interaction with industrial associations, like NIA, which can be invited as Contributors to the *Centre*. Note that, such procedures and criteria were considered under the two case studies of the EC4SafeNano project (see Section 2) and the outcomes of these studies are implemented in the proposed blueprint. EC4SafeNano also developed and validated a set of procedures for building the expert teams (Marcoulaki et al., 2019a). Final decisions on all the governance procedures are up to the members of the future Centre.

The *Centre* should have a strong IT component, integrated at all levels of the *Centre* and in all the processes that make up the provision of the services. The IT provision is particularly needed to manage the integration of services and service components delivered by multiple providers (service integrator status), the storage and processing of the data generated by such services (also see Section 6), and for the communication of information and results to internal and external customers (López de Ipiña et al., 2019).

To manage this IT component as well as the service provision itself, the ISO/IEC 20000–1 standard is proposed as an attractive tool for establishing, implementing, maintaining and continually improving a service management system (SMS), and to meet the service requirements and deliver value for customers, users and the *Centre* delivering the services (). ISO 20000-1 initially focused on IT Service Management (ITSM), but the requirements of the current standard (ISO/IEC 20000–1:2018 (ISO/IEC 20000-1:2018, n.d.)) are generic and intended to be applicable to all organisations, regardless of type or size, or nature of the services delivered. Its application facilitates

management of any type of service, without being limited to IT (López de Ipiña et al., 2019). Fig. 2 shows the service management flowchart. The procedures to collect resources and identify short- and long term needs of stakeholders and customers, the fit-and-gap analysis, the market analysis etc. are designed to be repeated regularly, for continuous updating of the services offered in order to meet emerging needs and the *Centre's* sustainability objectives. The CoS will include the live services, previously incubated in the service pipeline and selected according to the customer needs and the business objectives of the *Centre*. For practical purposes, the CoS is generally divided into two parts: (a) the Business Service Catalogue showing the customer-facing services (customer view), and (b) the Technical Service Catalogue, invisible to customers, including the supporting services required to deliver such services (resources available within the *Centre* and the operating procedures) (provider view). The Business Service Catalogue and all the service provision resources of the future *Centre* will be publicly accessible online (López de Ipiña et al., 2019). Note that the Catalogue will highlight the use of appropriate standards and protocols, and will promote harmonised and certified service offers, when available. This will demonstrate the robustness of the delivered services, and has been proven critical to build trust in the service offer. As was also pointed out, the speed in service distribution and the overall cost are crucial factors for the sustainability and trustworthiness of the future *Centre*, while references to appropriate standards demonstrate the robustness of the output reports especially to industrial clients (Marcoulaki et al., 2019a).

5. The business plan

The proposed business plan of the *Centre* is based on demand, resources, market and legal data collected and analysed since 2016, as outlined in Section 2. In particular, the market survey was among over 40 stakeholders (mostly industry, service providers and EU Member States) to investigate the usefulness of the various proposed activities of the future *Centre* and to aid the development of the business plan. Most of the stakeholders liked the idea of having a single point of contact for all their nanosafety related questions. Consequently, they would very much appreciate access to a well-structured, online CoS, regularly updated with reliable information, including the details for service providers in other countries. They also recognised the importance and opportunities of collaborative and multidisciplinary approaches, so that different aspects of hazard, exposure and risk assessment can be covered. Harmonisation of services was seen as crucial and would add value to the *Centre* and underpin the reliability of the services delivered, keeping in mind that, when available, companies prefer standardised methodologies or internationally recognised methodologies. A Certification Mark might be an advantage for service providers, but there are concerns about the extra cost.

In addition, we conducted a SWOT analysis using input from potential members of the centre. The identified strengths included the combined expertise, the one-stop-shop, the strong network via the Expert Groups, and links to European (ECHA, EFSA, CEN etc.) and national bodies. Opportunities were identified in terms of service harmonisation and new service schemes, close links to EU policy-making regarding nanosafety standards/regulations/legislation, and synchronization with other European entities like the foreseen risk governance bodies. There were also potential weaknesses identified which included low flexibility, collaboration problems, disadvantages in location and pricing, and the large volume of promoted services in the CoS. The threats included internal competition, legislation (lagging behind, unclear or heterogeneous), coordination problems and the low demand for harmonised services. External competition presents an important challenge for the *Centre*, since there is a multitude of other/similar initiatives (e.g. common infrastructures, national nanosafety centres etc.), which have the advantage of better pricing (or even free of charge services) and probably also faster response. But in fact, the role of the Centre is not to compete with them, so for simple queries, it is always possible that a customer goes directly to the CoS and choses a single service provider. When questions become much more complex and combined expertise is needed, the *Centre* will have an advantage for addressing these challenges.

The Members of the *Centre* shall have an established record in conducting safe operations and managing risks, for themselves, and for public and private organisations as well as for industry. The *Centre* shall be financed by:

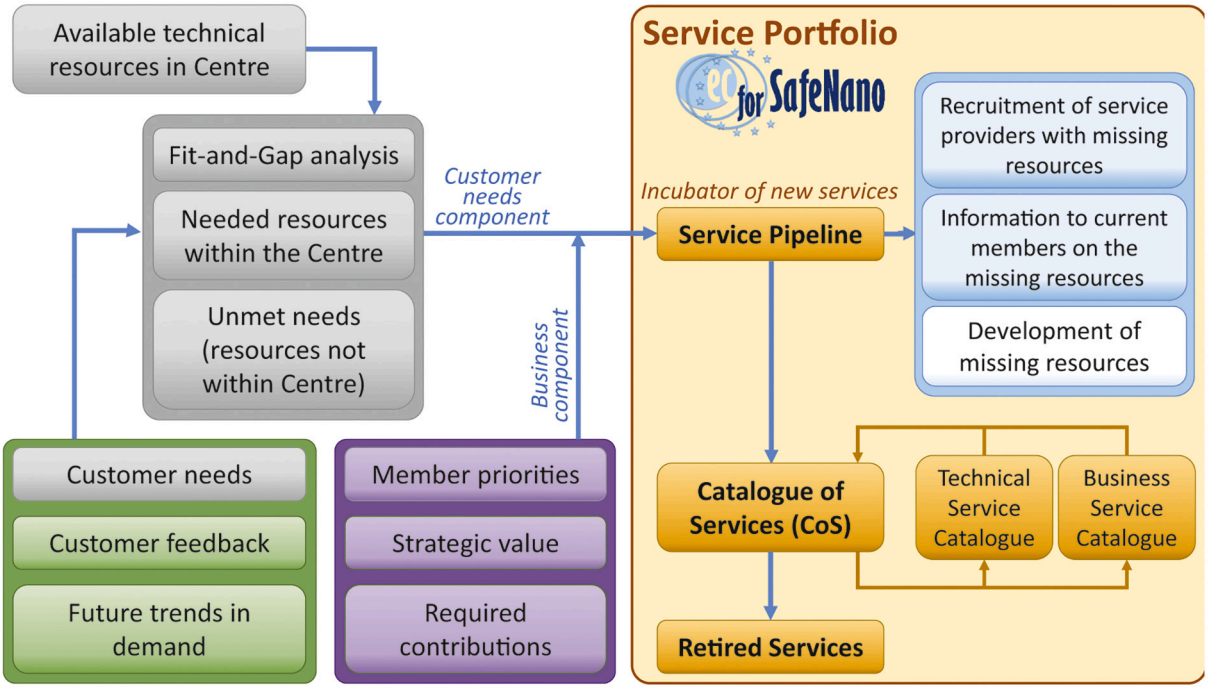

Fig. 2. EC4SafeNano service management flowchart.

- subscriptions or other contributions from the Governing and Regular Members;
- the incomes from the contracts and services delivered to customers (percentage of contract value);
- the fees paid by Associate Members for registration and promotion of their services in the CoS publicly available online;
- funding received from participation of the *Centre* in (EU) funded projects.

Fig. 3 summarises the different building blocks of the business model, which is explained in more detail below.

It is planned to have no employees working directly for the *Centre* during the first years of operation. The necessary tasks and roles will be taken up by the Members of the *Centre* who will receive an annual remuneration (defined as an annual lump sum) to compensate for their work and travel costs. Part of the work will be provided as an in-kind contribution. At this early stage, the Members' commitment will be decisive for the future of the Centre, but there are several examples in the research community of successful schemes emerging after the completion of EU funding (e.g. NORMAN, SAF€RA, EU-NCL etc.). The governance procedures proposed in Section 3 draw ideas from such schemes, their contributor engagement processes, and the benefits of contributing to the *Centre*. For instance, in the NORMAN network, the collaborative activities proposed by the members resulted in win-win situations. Partners who propose to lead new collaborative activities in the *Centre* are already engaged in these activities in their institutes (added value for the leader and for the participants). So, the *Centre* can be instrumental to create synergies, but in principle the time that the partners devote to the collaborative activities of the *Centre* will add to the existing commitment of their respective organisations. Once the *Centre* applies for funded projects, employees will be needed in order to claim costs.

The strategy is to start with limited resources (= lean and mean) and to focus on a few activities (Help Desk, CoS and Collective expertise), in order to test the concept of the *Centre* and confirm the interest expressed by various stakeholders during our market research. The *Centre* will start with a core group of around 5 Governing Members and 10 Regular Members, and end up after five years with a group of about 50 Members. In combination with a sufficient growing number of connected service providers willing to pay a fee to promote their services via the *Centre* and with income from funded projects, the aim is to make the Centre to be financially independent. A large part of these revenues is meant to be invested in the JPAs. Once enough financial resources are available, the *Centre* can grow and develop other activities such as harmonised services and EU certification marked services via its JPA's. Table 2 summarises the advantages of being a Member of the *Centre* for the different organisations foreseen as members during the market and needs surveys of Section 2. Note that, civil society organisations, such as consumer groups, could also become members and/or contributors, so they have to be included in future surveys of the *Centre*.

In addition, the *Centre* should aim for participation in (EU) funded projects starting with focus on SbD and advanced (nano)materials (see Section 6) in order to have more budget available. In the long term, the *Centre* should aim for strong links with the EU in terms of standards / regulations / legislation. The *Centre* can identify needs from service providers and service end-users and communicate them to regulators and regulatory agencies, promote the use of new standards and facilitate the implementation of new regulations and legislations in practice. These procedures will be facilitated under the foreseen risk governance framework, and collaboration of the Centre with (potential) risk governance bodies. Fig. 4 provides the timeline of projected annual operating costs and revenues over the first five years of operation. Note that, the fourfold increase in annual revenues will allow the estimated budget for JPAs to increase annually from about 30 k€ (27% of total) to 230 k€ (56% of total). All assumptions behind these cost/revenue calculations were determined according to market analyses conducted during the EC4SafeNano project (see Section 2). The estimated annual fees per membership type (see Table 1) are based on a qualitative and a quantitative market survey on the amounts that service providers would be willing to pay (Vercauteren, 2019).

It is also important to stress out that the main income of the *Centre* (at least during the first years of operation) will come from the membership fees and only a small fraction may come from other sources. Membership fees account for 90% of the revenues in the first year and drop to 50% in year five (see Fig. 4). Therefore, the main financial backers of the *Centre* are the providers of nanosafety services, and they are also the engine of the *Centre* in terms of developing novel services and novel service schemes as described in the next section.

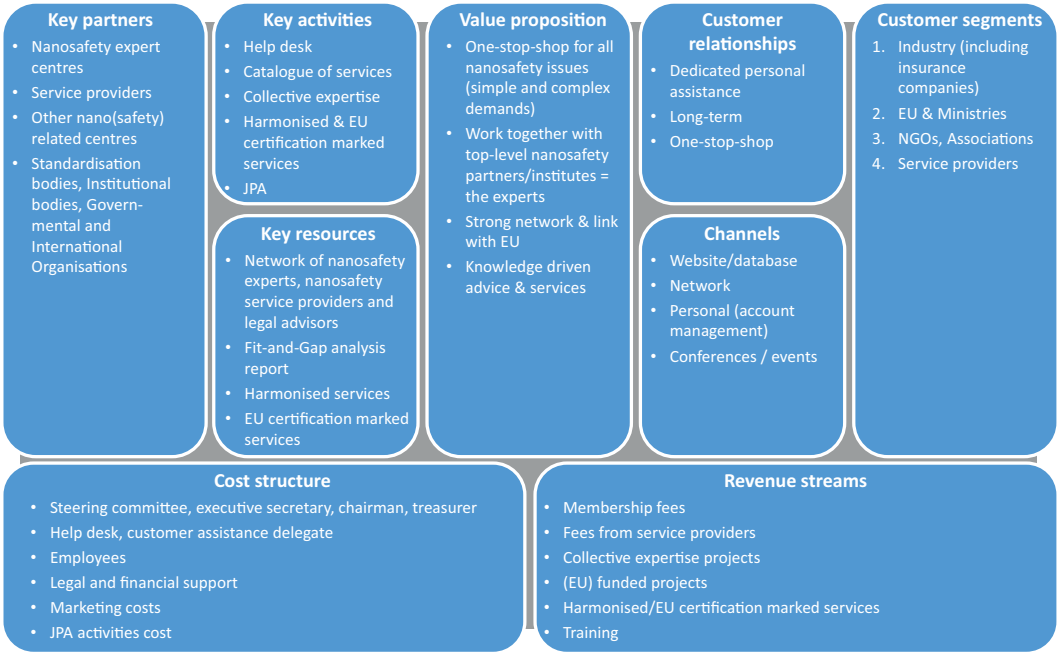

Fig. 3. Proposed Business Model Canvas for the *Centre*.

Table 2
Main benefits of being a Member of the *Centre*, per type of stakeholder.

Stakeholder	Membership benefits
Service providers	• Visibility of their services. • A higher guarantee of the quality of the services provided thanks to a collective review of services by the *Centre*. • Opportunities to promote and participate in initiatives for harmonisation of methods and services. • Active involvement at an early stage in the debate on highly strategic topics.
Competent authorities/National environmental health and safety laboratories	• Fast and easy access to the available information on institutes, current projects and experts in the field of nanosafety and nanotechnologies in Europe and beyond. • Opportunities to promote and participate in initiatives for harmonisation of methods and services.
Research centres/Academia	• Enhanced opportunities to establish quicker contact with other partners and put together a sufficient number of organisations interested in working on a given priority topic. • Active involvement at an early stage in the debate on highly strategic topics. • Gain a bigger voice in speaking to the EC and other public institutions. • Participation in expert group meetings and position papers which will contribute to boost the promotion of new research projects in priority fields. • Opportunities to promote initiatives for harmonisation of methods and services.
Industrial stakeholders	• A higher guarantee of the quality of the services provided thanks to a collective review of services, harmonised services and EU certification marked services. • Fast and easy access to the available information on institutes, current projects and experts in the field of nanosafety and nanotechnologies in Europe and beyond.
Government institutions and standardisation bodies	• Opportunities to promote initiatives for harmonisation of methods and services. • Routes for harmonisation of risk assessment and risk management tools and approaches (including in silico) at the European level, thereby reducing the effort and cost of development by single laboratories at the national level. • A higher guarantee of the quality of the services provided. • Access to a network of highly qualified service providers.

A strong and well-developed marketing and communication plan will be defined once the *Centre* is created. Besides a periodic newsletter to communicate the *Centre*'s achievements, information about Members, and to highlight new and emerging risks etc. The *Centre* will participate at workshops, conferences and trade fairs to promote its activities, disseminate the outcome of projects and to recruit new members. This promotion will be done by all Members, since they will attend such workshops and conferences in the course of their day-to-day activities. The recruitment of service providers will also be crucial to ensure a sufficiently large and wide-range offer of services in the catalogue, paying due attention to the quality and timely delivery of these services. Vercauteren (Vercauteren, 2019) provides more information on the proposed business plan.

In the long term, the *Centre* can adopt Corporate Social Responsibility (CSR) programs in its business models, since strategic CSR can enhance cultural diversity, which is a major characteristic of a cross-national entity and has been shown to have a positive impact on technological innovation aspects (Bocquet et al., 2019). In addition, as a European entity aiming to apply for European funding, the *Centre* will embrace the obligation to align with the Gender Equality Strategy towards a gender-equal Europe by 2025 (European Parliament, 2020).

6. An incubator for novel services supporting SbD

As mentioned in Section 1, the NanoREG2 case studies indicated the need for robust predictive and quantitative risk assessment tools for successful implementation of SbD for NMs, ENPs and nanoprocesses (Jiménez et al., 2020), and predictive tools are inextricably linked to reliable and FAIR data. There is currently a lot of research in these fields, and also on the field of sustainability. The *Centre* will play a significant role as an incubator for these novel tools and approaches, to promote and support further their validation, standardisation / harmonisation, benchmarking, and facilitate their regulatory acceptance and market penetration. Note that, as we move towards multi-component and advanced materials the need to join forces in terms of expertise and resources will increase. The idea here is to establish an open hub of service providers able to offer collaborative and extended expertise and science-based advice on the evolving spectrum of advanced materials.

The preparatory work conducted during the completed EC4SafeNano project (outlined in Section 2) will provide useful insights for the proposed *Centre* and its activities. The EC4SafeNano inventory of published tools includes a variety of software, web-based tools, spreadsheet-based applications and published methodologies. These include tools for human health risk assessment (e.g. Precautionary Matrix, Stoffenmanager Nano, MetaEASE, SprayExpo) and management (e.g. Control Banding Nanotool, Licara NanoScan, SCAFFOLD CB-tool, EGRET, NanoSafer), and environmental risk assessment (e.g. RedNano simulation tool). Additionally, tools for human exposure estimation by inhalation (e.g. ANSES, Consexpo Spray Model, SprayExpo) or dermally (e.g. DREAM, EASE, RISKOFDERM), and for calculation of internal dose by inhalation in the lungs (e.g. MPPD, RETRAC) or other organs for humans and animals. The inventory also reports advanced computational fluid-particle dynamics (CFD) numerical methodologies and software for the prediction of particle transport and deposition within the respiratory system (Pilou et al., 2011) or simulation of NM dispersion within indoor spaces (Pilou et al., 2016), and also models for calculation of key physicochemical properties of NMs based on their toxicity (e.g. nano-QSAR, NanoBRIDGES). For detailed information see (van Duuren-Stuurman et al., 2019b). Many of these tools were performance tested in the caLIBRAte project (caLIBRAte, n.d), and those passed acceptance criteria are part of the tools-supported nano-risk governance framework accessible in their nano-risk governance portal (http://www.nanoriskgov-portal.org/Public/Index).

The EC4SafeNano registry of resources is representative of the resources generally available in Europe. The registry included expertise in software development for risk assessment, risk prevention and exposure simulation using computational fluid-particle dynamics; and in model development, including grouping and read-across models, models for hazard/toxicokinetics assessment (health effects, physical hazards, ecosystem effects), modelling of NM concentrations and characteristics (physical / chemical properties), exposure assessment (workers, environmental organisms), efficacy of Personal Protection Equipment (PPEs), and Life Cycle Assessment (LCA). We also see contributions on shared databases, including data sharing on NM concentrations and characteristics (physical/chemical properties), fate (bioavailability, bioaccumulation, degradation, leaching, environmental distribution), hazard / toxicokinetics assessment, exposure assessment and efficacy of PPEs. These emerging approaches still represent a minority of the 2019 registered resources (in total $< 15\%$), and this portion is in line with the 2017 survey results (van Duuren-Stuurman et al., 2019a).

The EC4SafeNano list of priority questions indicated demand for services and information related to SbD in high priority topics. Knowledge can be advanced with the use of nanoinformatics tools, about toxicity related to physico-chemical properties, and surface chemistry and reactivity of engineered NMs to be related to the behaviour and

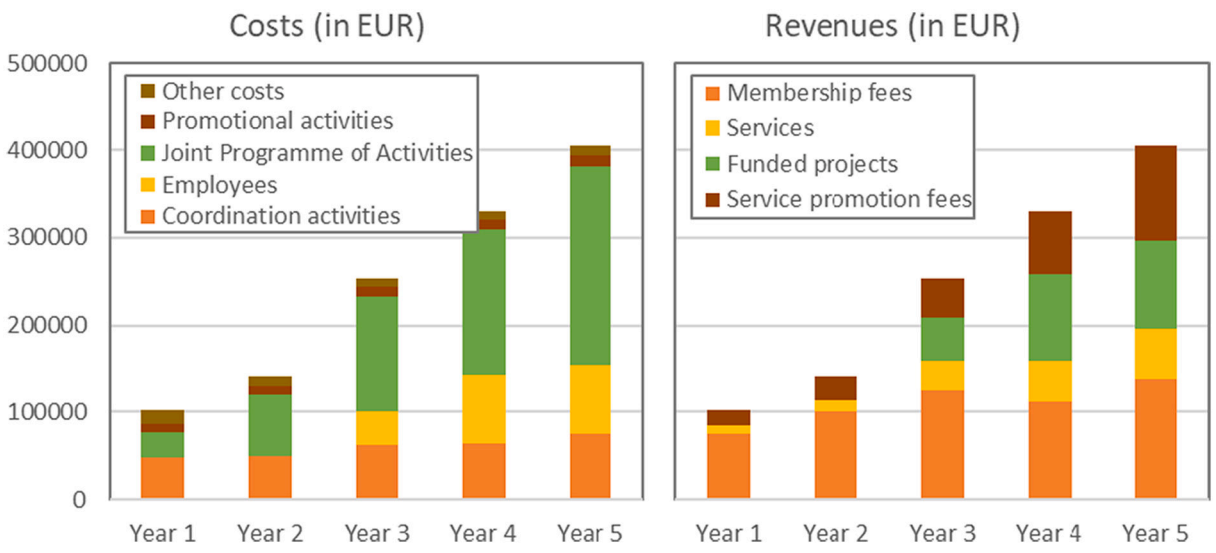

Fig. 4. Expected timeline of operating costs and revenues over the first five years of operation.

transformation in environmental media, which were the two top ranked questions. These could be in the form of QSAR models exploring mechanistic information to provide a prediction of the relationship between descriptors (structural, physico-chemical, biological) and the investigated endpoint (environmental fate, transformation, reactivity, toxicity). In this context, various chemoinformatic methods using artificial neural networks, machine learning, multivariate statistical modelling etc. have demonstrated added value e.g. in predicting activity of nanostructured fullerenes (Fjodorova et al., 2020), assessing the environmental fate of TiO2 nanoparticles (Brunelli et al., 2018) or modelling nanotoxicity (Furxhi et al., 2020; Afantitis et al., 2018), or for SbD functionalisation of carbon nanotubes (Varsou et al., 2019).

The use of computational models for predicting biokinetics, environmental fate, exposure levels and toxicological effects of manufactured NMs would also bring significant benefits e.g. to prioritise extended experimental studies requiring dedicated infrastructure; to reduce experimental effort and costs regarding the need for experiments; to anticipate 3R principles for reducing animal testing as a major priority for the EC (European Commission, 2019). In silico tools can be extremely demanding in terms of data (e.g. for regression or machine/deep learning models) and computational resources (e.g. molecular modelling tools, or CFD simulators of material dispersion in workplaces or the human body). Taking advantage of the exponential advances in computer hardware and the increasing number of properly curated and organised datasets, we should expect further evolution in nanoinformatics tools in the near future. For example, determination of physicochemical descriptors of NMs from TEM images and utilisation of those descriptors directly to predict physicochemical properties of new materials has recently been reported (Varsou et al., 2020). The first ecotoxicology machine learning model utilising images of *Daphnia magna* exposed over 4 generations to a panel of silver and titanium dioxide, and prediction of toxicity based on a number of phenotypic changes (e.g. changes in eye tail length, lipid deposits) is also available, and rapid further progress is expected in the near future (Karatzas et al., 2020).

On the other hand, computational models are not yet described in a consistent manner in the scientific literature, which might be a barrier to their broader use and acceptance, especially for regulatory purposes (Lamon et al., 2019). Moreover, work in the caLIBRAte project (caLIBRAte, n.d) showed that stakeholders are interested, but often not prepared to use such tools and need instruction and guidance to implement safe work with NMs (Porcari et al., 2019; Kirkegaard et al., 2020). Hence, substantial effort was made to identify and align existing tools with both R&D and service provider competences and needs to enable nano-risk innovation governance (Isigonis et al., 2019; Sørensen et al., 2019; Franken et al., 2020). With a critical mass of relevant expertise among the Members of the future *Centre*, it will be possible to promote collaboration and knowledge transfer about the development and use of in silico tools, so that they become more and more widely applicable across the innovation chain from the early stages of material and process design. Collaboration of the *Centre* with regulatory risk assessors (see Sections 3 and 4), will ensure the acceptance of these in silico tools. The Members could also promote the use of uniform data formats, and the development and use of common interfaces for nanoinformatics software components, to increase their potential for integration in future nanoinformatics tools suites (like the NanoInformaTIX SNF (NanoInformaTIX, n.d) and the NanoSolveIT IATA (NanoSolveIT, n.d)).

Within its annual JPAs, the *Centre* can design experiments for systematic data gap filling of NM databases, and conduct them with the budget of the *Centre* and/or by in-kind contribution of Members and Contributors (see Sections 3–5). Clearly, a permanent and sustainable entity promoting harmonised and (possibly) certified services, has increased potential for such activities that improve the quality and coherence of the data available for regulatory use. The JPA can also include the development of nanoscale certified reference materials for accurate physico-chemical characterisation (including standardised biomolecule corona formation and cellular uptake), the building and maintenance of NM libraries, and the development of harmonised protocols for the synthesis of safe and environmentally benign materials. Note that, there are a number of organisations already selling reference NMs, including the JRC and NIST.

The *Centre* will additionally consider best practices for reporting and data management, propose new operating procedures where needed and adaptation of FAIR principles to NMs and nanosafety. This again can be aligned with the activities of future risk governance bodies or the foreseen NRGC (RiskGone, n.d; Gov4Nano, n.d.; NanoRIGO, n.d.), and with ongoing work in NanoInformaTIX and NanoSolveIT to integrate and curate data from different sources (NanoSolveIT, n.d; NanoInformaTIX, n.d.). It will also build on the nanospecific guidelines emerging from the community (such as the MIRIBEL guidelines for bionano studies (Faria et al., 2018) and the MINBE guidelines for NMs protein corona studies (Chetwynd et al., 2019)). The above can be applied to the experimental and computational data generated through the JPA and the services provided through the *Centre*, at all stages of the service life cycle (see Section 4). Proper consideration of IPR and data security issues will be crucial to lift concerns of the service customers over sharing their data. A

key aspect of the proposed approach to data management (Lynch, 2019) is alignment with, and utilisation of the resources developed in the NanoCommons (NanoCommons, n.d) and OpenRiskNet (Exner et al., 2018) e-infrastructures. The goal is thus to minimize unnecessary duplication of data by enabling access to the data from their original source and using the interoperability layer (added by NanoCommons) to harmonise the data services. NanoCommons has developed workflows for annotation and upload of small or large datasets to the NanoCommons KnowledgeBase (NanoCommons, n.d), as well as Electronic laboratory notebooks to support the transition of data management to the earliest point in the data lifecycle, i.e., experimental design and data capture. Similarly, the NanoCommons tools for text mining will be utilised to support the literature mining and dataset gap-filling activities noted above, all leveraging the existing data management infrastructures provided by NanoCommons and OpenRiskNet (including extension and operationalisation of model reporting templates such as QMRF (European Commission and JointCentre, 2020) and MODA (European Materials Modelling Council (EMMC), n.d.)) which are also embedded into the European Open Science Cloud (European Open Science Cloud (EOSC), n.d.).

7. Conclusions and perspectives

There are multiple tools and data to support safe innovation of nanotechnologies and NMs, developed through projects supported by the EU and other funding schemes. These should be made widely available as practical and reliable services that address the needs of industry, public authorities, regulators and civil society to protect the investment and maximise the utility of the tools. This paper presents a blueprint for the operation of a sustainable and permanent European Centre of collaborating reference laboratories and research centres to provide and maintain such tools and services. This *Centre* aims to meet the needs of industry and other parties concerned with the safe and responsible innovation of nanotechnology, by establishing a one-stop shop for a wide variety of nanosafety related services, and providing a central contact point for questions about nanosafety in Europe and beyond.

The paper presents a solid governance blueprint for a self-sustainable entity for service provision in safe innovation for nanotechnology. We expect this to serve as a working document for the top management of parties interested in establishing this Centre (mainly research labs and SMEs offering nanosafety services). All the governance features (including the legal status and operational procedures) and the proposed business plan have been developed systematically using input from workshops and surveys with service providers, market actors, national centres, regulators and other stakeholders. The proposed blueprint is by-design (a) vigilant to respond to external opportunities and changes, and (b) flexible to interact with other European or national entities, so the proposed *Centre* can easily be adjusted to benefit from the presence of risk governance bodies or a high-level NRGC, as collaborators, advisors and/or end-users. Also, the blueprint and the procedures we followed for its development provide valid ideas and insights for developing the governance of other similar entities, and this can be particularly useful in the current phase of the risk governance projects.

The key pillars of the *Centre* include a one-stop-shop offer of expertise and science-based advice from established service providers; the organization of activities as part of a voluntary annual joint programme of activities (JPA) and the development and promotion of harmonised and EU certification marked services. The significant innovation and market creation potential of harmonised and certificated services for nanomaterials as proposed here is now acknowledged by the European Commission's Innovation Radar. A strong IT vision for these services will be important, with the provision of customizable services, to help ensure continuous improvement of service innovation. The proposed governance for the *Centre* foresees a demand-driven evolution of the service offer, so that the annual CoS remains relevant to the short and long-term trends in customer needs. Future versions of the catalogue will list integrated, harmonised and certified services, reflecting the activities jointly selected and undertaken by the Members and Contributors of the *Centre*. Advanced IT tools will be used to monitor the development of new services; integrate service components delivered by different providers; manage data generated by these services; and communicate the results to internal and external customers of the *Centre*.

For successful implementation of SbD/SSbD strategies we need robust predictive and quantitative risk assessment tools for NMs, ENPs and nanoprocesses. Predictive in silico modelling, using accessible knowledge base-deposited data (including relevant metadata) on the properties of NMs, can be used to support risk assessment and risk prevention in the early stages of industrial innovation. Such applications will be greatly accelerated through the development and proper use of FAIR data management systems using nanoinformatics. Recent scientific developments, lessons learned from past and ongoing projects, and the increasing number and complexity of engineered NMs, presents an opportunity for service providers to benefit from the growing field of in silico modelling and data science. These include the development of diverse nanoinformatics tools for data management, predictive in silico modelling needed for exposure simulation, nano(*eco*)toxicology prediction, environmental fate assessment for intended and accidental scenarios and beyond, with due regard also to socio economic impacts. The proposed blueprint provides a suitable environment for the incubation of these and other novel technologies, as well as the framework to promote and further support their validation, standardisation, harmonisation and benchmarking, and to facilitate their regulatory acceptance and penetration into service provision practices.

Author contributions

Valeria Dulio, Jacques Bouillard and Oliver Aguerre-Chariol proposed the governance mechanisms, with additional contribution from Sven Vercauteren, Anthony Bochon and Effie Marcoulaki (Section 3). Effie Marcoulaki, Valeria Dulio, Marika Pilou and Maria Gini developed and implemented procedures for service validation and proof of operational functioning of the Centre (Sections 3 and 4). Sven Vercauteren conducted the market analyses and developed the business plan, with additional contribution from Valeria Dulio, Anthony Bochon and Effie Marcoulaki (Section 5).

Jesus M Lopez de Ipina and Alfonso Arevalillo compiled the Catalogue of Services, proposed the service provision framework and developed the FGA tool. Vasile-Dan Hodoroaba, Valentin Kunz, Wolfgang E. S. Unger and Neeraj Shandilya coordinated the two case studies. Karin Persson, Ian Cotgreave, Petru Niga, Iseult Lynch, Maria Gini, Konstantinos Eleftheriadis, Martin Himly, Albert Duschl and Mark Geppert contributed to the SbD case study. Effie Marcoulaki, Marika Pilou and Maria Gini developed service update mechanisms and tools, with additional contribution from Jesus M Lopez de Ipina. Anthony Bochon conducted the legal survey and workshop, proposed the legal status and elaborated the proposal for EU certificates (Section 4).

Effie Marcoulaki, Jesus M Lopez de Ipina, Jacques Bouillard, Martin Himly, Iseult Lynch and Valeria Dulio comprised the team for SbD/SSbD, together with Vasile-Dan Hodoroaba, Neeraj Shandilya, Keld Alstrup Jensen, Marika Pilou, Hilda Witters, Delphine Bard, Gareth Evans and Simona Scalbi. Iseult Lynch developed the proposed data management approach (Sections 1 and 6). Birgit van Duuren-Stuurman, Hilda Witters and Anna-Kaisa Viitanen were responsible for the needs and resources surveys. Witters Hilda and Vercauteren Sven were responsible for compiling the list of priority questions (Sections 2 and 6).

Emeric Frejafon coordinated the writing of the EC4SafeNano H2020 proposal, and was the first project coordinator followed by Valeria Dulio. Bastien Caillard was the project administrator, he also implemented the online Catalogue of Services and various online survey tools.

Effie Marcoulaki coordinated the writing of this manuscript.

Together with Martin Himly, Iseult Lynch, Keld Alstrup Jensen, Vasile-Dan Hodoroaba and Anna-Kaisa Viitanen they updated the manuscript with the latest developments on nano risk governance. All authors contributed to the preparatory work during the EC4SafeNano project and the Catalogue of Services (Section 2), as well as to the general discussions regarding the manuscript, the introduction, conclusions, review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors acknowledge funding from the European Union's Horizon 2020 research and innovation programme under the project EC4SafeNano, grant agreement N° 723623. This paper reflects only the authors' views, and the Commission is not responsible for any use that may be made of the information contained therein.

The authors are grateful to the members of the EC4SafeNano International Advisory Board for their strategic advice and the Associated Partners for their support to the project. They also thank Mr. Olivier Salvi for his contribution in developing the first concept of the *Centre*. The experts evaluating the case studies and all the respondents to the Section 2 surveys on needs/demand and resources for nanosafety services are kindly acknowledged for their valuable input.

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