

Brussels, 24 March 2020

COST 047/20

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action “European Venom Network” (EUVEN) CA19144**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action European Venom Network approved by the Committee of Senior Officials through written procedure on 24 March 2020.



MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA19144 EUROPEAN VENOM NETWORK (EUVEN)

The COST Member Countries and/or the COST Cooperating State, accepting the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action (the Action), referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any new document amending or replacing them:

- a. "Rules for Participation in and Implementation of COST Activities" (COST 132/14 REV2);
- b. "COST Action Proposal Submission, Evaluation, Selection and Approval" (COST 133/14 REV);
- c. "COST Action Management, Monitoring and Final Assessment" (COST 134/14 REV2);
- d. "COST International Cooperation and Specific Organisations Participation" (COST 135/14 REV).

The main aim and objective of the Action is to promote a proactive cooperation among research fields and between academia and other stakeholders, to fully develop the potential of venom research at the European level.. This will be achieved through the specific objectives detailed in the Technical Annex.

The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 28 million in 2019.

The MoU will enter into force once at least seven (7) COST Member Countries and/or COST Cooperating State have accepted it, and the corresponding Management Committee Members have been appointed, as described in the CSO Decision COST 134/14 REV2.

The COST Action will start from the date of the first Management Committee meeting and shall be implemented for a period of four (4) years, unless an extension is approved by the CSO following the procedure described in the CSO Decision COST 134/14 REV2.

OVERVIEW

Summary

Venomous organisms produce complex mixtures of bioactive compounds that have evolved through million years of natural selection in evolutionary arms races. As such, they are extremely efficient, being usually effective at a very low concentration via highly specific interactions with key molecular targets (ion channels, enzymes and membrane components), identifying them as ideal candidates for therapeutic and biotechnological development.

Venom research is an emerging and highly multidisciplinary field that involves studies of the biodiversity, ecology and evolution of venomous organisms, the structure and function of venom deployment systems, the biochemistry and pharmacology of venoms, the pathophysiological effects that venom induces in prey and predators, and the translational development of venom components for biomedical and biotechnological applications. These different research facets tend to be pursued by different research groups that usually are poorly coordinated in Europe, hampering a full development of venom investigation and applications.

The overarching aim of the EVEN COST Action is to foster venom investigation at the European level. The Action will identify priority targets and promising innovative approaches, develop best practice pipelines ensuring consistency across Europe and providing international standards in venom research. Further, it provides a novel platform to promote synergistic interactions between academia, industry and society, and to nurture a new generation of venom researchers with a multidisciplinary expertise. Building a gender, age and geographically balanced network involving all the relevant stakeholders will be the fundamental prerequisite to leverage the extraordinary biochemical warfare enclosed in animal venoms, with an enduring scientific, technological and socioeconomic impact.

Areas of Expertise Relevant for the Action	Keywords
<ul style="list-style-type: none"> ● Biological sciences: Zoology, including animal behaviour ● Biological sciences: Transcriptomics ● Biological sciences: Proteomics ● Basic medicine: Pharmacology, pharmacogenomics, drug discovery and design, drug therapy 	<ul style="list-style-type: none"> ● venomics ● evolution ● ecology ● biodiscovery

Specific Objectives

To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination

- Identify most promising targets at the organismic, biochemical and functional level for venom research, to coordinate and focus the scientific efforts of the European venom community.
- Establish community-accepted best practice principles and methodological pipelines in tackling venom research.
- Promote new methods and technologies for the investigation of venom.
- Develop specialized on-line public resources for the integration, sharing and utilization of relevant information and data.

Capacity Building

- Create a pan-European network of scientists with complementary backgrounds to study animal venoms in order to identify and develop innovative research concepts and ideas and to promote the implementation of optimized and innovative discovery and investigation projects.
- Create a synergistic relationship between scientists, private companies, and experts in intellectual property, patents and benefit sharing across Europe for biotechnological development of venom

compounds.

- Nurture a new generation of venom researchers with interdisciplinary expertise and international collaborative perspectives, able to maintain and improve inter-sectorial synergistic relationships.

TECHNICAL ANNEX

1 S&T EXCELLENCE

1.1 SOUNDNESS OF THE CHALLENGE

1.1.1 DESCRIPTION OF THE STATE-OF-THE-ART

Venomous organisms are ubiquitous, and distributed widely across the animal phyla: more than 220,000 animal species are known to be venomous, corresponding to approximately 15% of all described animal biodiversity on Earth. Venomous animals inhabit virtually all aquatic and terrestrial habitats, ranging from desert to Antarctic sea. Animal venoms are complex mixtures of bioactive compounds that have evolved through million years of natural selection, in a co-evolutionary arms race involving the prey and the predator as major selection agents. As such, they are extremely efficient, being usually effective at a very low concentration via highly specific interactions with key physiological targets of prey and/or predators (e.g. ion channels, enzymes and cellular membrane components).

The specificity, potency, stability, and speed with which venom molecules manipulate their molecular targets make them ideal candidates for therapeutics, biotechnological developments and useful tools in cell biology. Although various classes of organic molecules have been described from venoms, their major constituents are peptides and proteins. Many peptide venom toxins target the neuromuscular system and modulate the generation and propagation of action potentials by acting on central or peripheral neurons, axons, the synapse or the neuromuscular junction, while others possess anticoagulant, cytolytic, anaesthetic and hypotensive activities. These properties make them important biological tools for the study of their target receptors, many of which are associated with specific human pathologies. Very interestingly, some venom toxins with no or low toxicity can also be directly usable for therapeutic purposes.

Seven animal-derived drugs are available on the market at the moment, and a number of others are in various stages of clinical trial to treat a wide array of diseases including cancer, hypertension, acute coronary syndromes and chronic pain. Among them are the FDA-approved drugs exenatide, an antidiabetic peptide from the venomous Gila monster (*Heloderma suspectum*), and ziconotide, an analgesic peptide from the venomous cone snail *Conus magus*. Other promising venom compounds for translational developments, at different stages of progress, include monomeric insulins found in the venom of cone snails; the sea anemone venom peptide ShK for treatment of autoimmune diseases; chlorotoxin from the deathstalker scorpion for imaging brain tumors during surgery. Beside use in medicine, venoms include substances with a potential to be used in other fields. For example, spider toxins as eco-friendly insecticides; ion channel blockers from cone snails and bees for cosmaceutical applications; and pore-forming toxins for new nanopore sequencing and sensing technologies.

Venom investigation is a highly interdisciplinary enterprise that involves studies of the biodiversity, ecology and evolution of venomous organisms, the structure and function of venom deployment systems, the biochemistry and pharmacology of venoms, the pathophysiological effects that venom induces in prey and predators, and the translational development of venom components for biomedical and biotechnological applications (figure 1). These different facets of venom research tend to be pursued by different research groups, especially in EU, with little coordination between each other. It is one of the central goals of this Action to bring these specialist communities closer together.

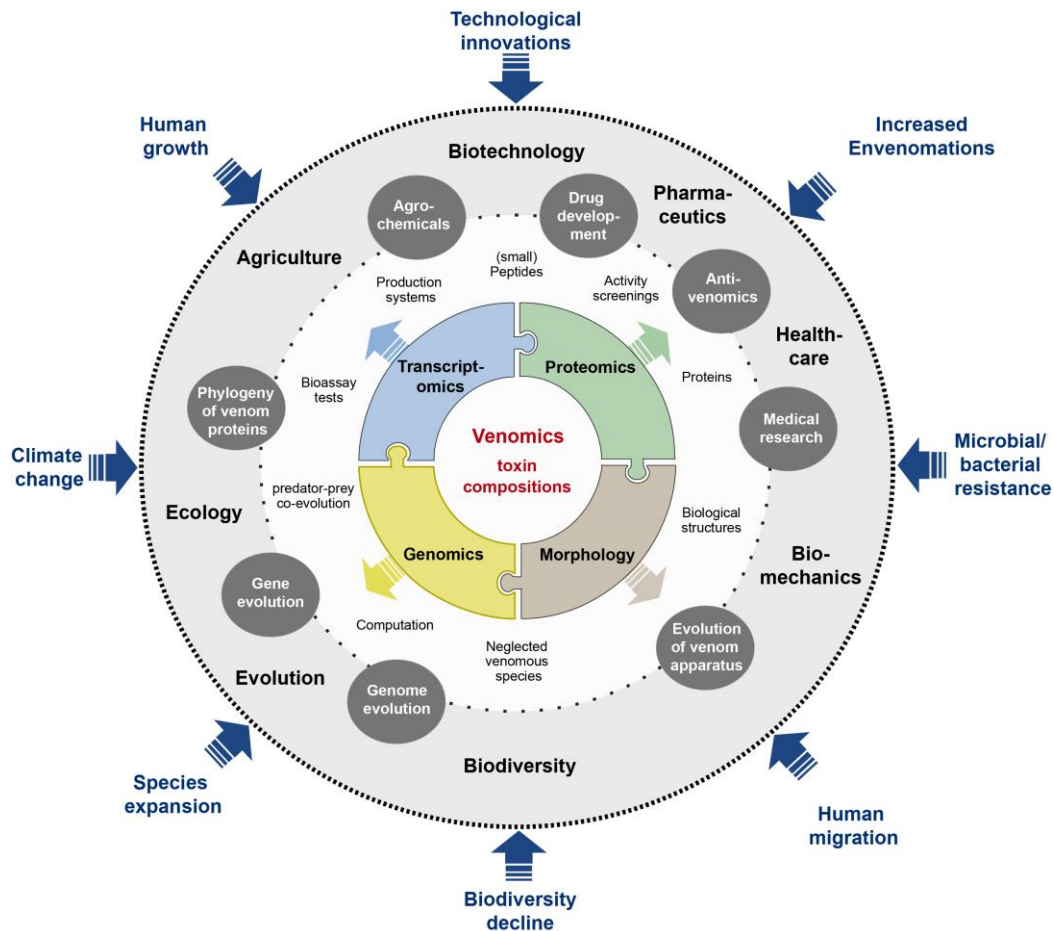


Figure 1. The multidisciplinary nature of venom investigation, including its connection with different research fields, and main drivers affecting it.

In recent years, advances in high-throughput techniques, such as proteomics, transcriptomics and genomics approaches have facilitated the characterisation of venom peptides and proteins in complex mixtures as venoms, even in non model organisms. Currently transcriptomic data obtained through high-throughput sequencing-by-synthesis RNASeq technologies are often integrated with bottom-up proteomics, in which high performance liquid chromatography is coupled with tandem mass spectrometry. Both approaches can be adjusted to provide relative quantification of expressed proteins. While the sensitivity of transcriptomics allows the detection even of scarcely expressed proteins, proteomics allow the identification of post-translational modifications (PTMs) which are extremely common in venom proteins. The integration of genomic data is still uncommon in venomics, especially for non-model organisms, despite its promise for understanding evolutionary and regulatory patterns of venom compounds.

Once venom peptides and proteins have been identified, they are generally produced via solid phase synthesis and regioselective folding, or by recombinant expression systems. These procedures aim at yielding a considerable amount of proteins for subsequent activity testing, that would not be achievable through chemical fractionation of raw venom when the starting amount is very low.

Technologies used for activity screening rely mostly on electrophysiology e.g. on multiple neuro-receptors, ligand-gated and voltage-gated ion channels involved in neurodegenerative and drug-dependency disorders; on ion channels selective for anaesthesia and neuropathic pain; on voltage gated potassium channels for auto-immune diseases; on a wide range of voltage gated sodium channels for chronic pain. Electrophysiology includes also *ex vivo* assays for the neuro-muscular disorders for pain or anaesthesia and multiple electrode bi-dimensional array assays on tissue preparations for neurological disorders and trauma. Other activity screening tests may comprise e.g. binding assays on G-coupled protein receptors involved in hormonal pathways; cell based assays for cancer; enzymatic activity and enzyme inhibitors for cardiovascular or inflammatory disorders; factors involved in the

inflammatory response such as cytokines and glucose metabolic pathways for diabetes and obesity; as well as various anti-microbial, anti-parasitic and anti-viral assays for infectious diseases.

In addition, biophysical approaches such as X-ray crystallography, nuclear magnetic resonance spectroscopy, surface plasmon resonance spectroscopy and isothermal titration calorimetry have become key components of drug discovery platforms. Biophysical technologies are used extensively in hit finding (fragment-based screening and high-throughput screening), hit validation, in depth characterization of compound binding and lead optimization. The efficient use of these methods requires experience in experimental design and data analysis, and a strategic combination of orthogonal methods. In silico approaches such as molecular modeling have also become widely used for studying venom components, providing structural information and theoretical understanding of molecular mechanisms for toxin action which is not easily obtained by the “wet biochemistry”.

No single researcher or research group possesses the complete technical know-how to carry out and control all the steps that are needed for a full development of venom research. This is also mirrored by the long lists of authors with a broad range of different expertises in individual published papers, and constitute a major hindrance to the exploitation of the potential of venom as a bioresource.

During the last World Economic Forum (2019), venomics was indicated as one of the four most promising research fields for its applicative and biotechnological potential <https://www.weforum.org/agenda/2018/11/venomics-deadly-toxins-life-saving-drugs-mande-holford/>. Despite these promises, major hurdles still hamper the characterization and exploitation of most of the chemical diversity encoded within animal venoms. Some obstacles are inherent in the complex nature of animal venoms, and can be eliminated by technological improvements, while others reflect the fragmentation that characterizes venom research on both the interdisciplinary and the intersectorial levels. The European VEnom Network will promote efficient and effective exchanges at all levels, and involving all the relevant stakeholders, to remove both technological and organizational bottlenecks.

1.1.2 DESCRIPTION OF THE CHALLENGE (MAIN AIM)

The aim of the European Venom Network COST Action is to foster the full development and exploitation of venom research at the European level, promoting synergistic interactions between stakeholders, and nurturing a new generation of venom researchers. This overarching aim can be fulfilled by removing bottlenecks to the development of venom research, which pertain to two main categories: a) organizational issues, linked to the fragmentation and lack of communication between stakeholders; b) technological challenges that are inherent in research on animal venoms

The European Venom Network will focus its activities to remove the following major **bottlenecks at the organizational level**:

- **Lack of interdisciplinary collaboration.** Venom investigation has been tackled from many different angles, and involves researchers working in many different fields, including structural and analytical chemistry, pharmacology, genomics, molecular biology, cell biology, evolutionary biology, ecology, taxonomy, physiology, etc. (see figure 1). Although the collaboration between researchers in different fields has been increasing in recent years, as reflected by the authors' list of the latest publications in venom research, the community has a strong need for a tighter integration. The selection of promising target organisms for venom research relies on data about the phylogenetic relationships of target organisms, their geographic distribution, as well as ecological data such as habitat and prey specificity. Additionally, specialists of the different groups often include non-academic amateurs that possess valuable though anecdotal information on species biology that is not readily available to researchers working in academia. A bottleneck but crucial intersection to screen and to identify toxin candidates on proteome, transcriptome and genome level is the field of bioinformatics, in which venom researchers need more insights and interaction. Often molecules with interesting folds are described, but not tested for their activity. Activity tests are on the other hand limited by the quantity of produced and purified toxins linked to inefficient production systems. Bridging the different expertises would be crucial to build a solid collective knowledge base on which venom research can thrive.
- **Lack of coordination between academia and other stakeholders.** In the past years, intersectorial collaboration has been mostly restricted to the exploitation of research outputs for medical applications by pharmaceutical companies that are no longer internally pursuing research and development (R&D). The Action aims to promote a more effective communication between research and industry, both by jointly exploring the opportunities for financial support in R&D, and by soliciting input from industry in terms e.g. of orphan receptor for which a venom approach

can provide new effector molecules. Additionally, it will be crucial to increase the exploration of other potential fields of application of venom compounds beyond pharmacology, such as diagnostics, cosmetics, agrochemistry and bioengineering, which have been largely overlooked in the past. In particular, environmental-friendly bio-pesticides as a replacement for conventional and extremely harmful pesticides allow to take immediate action in the context of the decline of insects and biodiversity which is currently a prominent public focus. The European Venom Network aims also at ameliorating the communication between researchers, industry and governmental agencies, to increase the knowledge on benefit-sharing issues in the framework of the Nagoya protocol, in an effort to better exploit bioresources.

The European Venom Network will concentrate its efforts to eliminate the following **technological obstacles and challenges**:

- **Knowledge of biodiversity and natural history data.** The global biodiversity known today represents barely 20% of estimated biodiversity, much of which remains unexplored and unknown, particularly in hotspots regions but also in our backyards. Biodiversity loss due to human activities and climate change not only leads to ecosystems that are less resilient to shocks and disturbances, but also decreases the availability of potentially promising bioresources. In venom studies the situation is worsened by the lack of information about natural history, internal anatomy and envenomation physiology that affect particularly neglected venomous species. In this context, it is crucial to identify appealing organismal targets before their loss, and improve the knowledge of their basic biology. The European Venom Network will promote biodiversity and basic biology studies on venomous organisms by integrating experts on zoology, taxonomy and biology as well as institutions such as natural history museums and centers for biodiversity research.
- **Identification of small molecules contained in the venom.** Recent developments in transcriptomics and proteomics have fostered venom research, but allowed the investigation on the peptidic and proteic components of the venom only. Although evidence has been accumulating that small non-peptidic components may play an important role in envenomation, this fraction has generally been ignored. The integration of metabolomics techniques into venom research is one of the major technological challenges that the European Venom Network aims at overcoming to promote venom research and catalyse new discoveries. New mass spectrometry technologies are also very promising for the development of peptidomics, for unravelling the contribution of extremely short peptides to envenomation. These are particularly appealing for exploitation given the relative ease of their production.
- **Production of venom peptides.** While solid-phase synthesis is an effective strategy to produce short venom peptides, longer proteins need to be produced via recombinant approaches. To date, despite the enormous growth in numbers of described potentially bioactive peptides, only a few comprehensive recombinant libraries are accessible for activity screenings aiming to identify novel therapeutics and lead compounds. Fusion venom proteins are also a very promising emerging class of biotechnology products. The development of high-throughput approaches to venom peptide and proteins production is needed to foster the identification of their targets, their biological activity and their applicative potential. Technically promising are approaches that establish cell free expression systems based on different cell lines that guarantee higher quantity and more realistic peptide/protein foldings.
- **Biological activity screening.** High-throughput screening techniques have been developed for pain pathways, however, robust high-throughput assays for determining the molecular targets and activities of a broad spectrum of new compounds are still lacking. Additionally animal models are often extremely expensive and complicated to maintain, calling for the development of novel low-cost models for *in vivo* screenings. Among them, *C.elegans*, in which nervous system, connectome and neuronal dynamics have been largely clarified, zebrafish and *Drosophila* for behavioural experiments may be particularly worth of further exploration for their potential use as effective venom screening models. Also newly emerging biophysical approaches such as cryo-electron microscopy (cryo-EM) or synchrotron based micro-computer tomography for high-resolution determination of biological structures and rapid methods for the characterization of binding kinetics and thermodynamics may greatly improve drug discovery.
- **Computational methods** for extracting relevant information from large databases. Novel toxins and their interactions with molecular targets can be obtained through comprehensive screening of large datasets, which will allow focusing on the most interesting molecules. Identification of novel venom proteins is largely based on the *de novo* assembly of transcriptomic data, and used for reconstructing protein sequences obtained through shotgun proteomic methods. These approaches would greatly benefit from more standardized methods of analysis. Genome data which will be present for many species in few years will help to further understand processes and to give more realistic predictions, but call for a better integration of transcriptomic and genomic data.

1.2 PROGRESS BEYOND THE STATE-OF-THE-ART

1.2.1 APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE-OF-THE-ART

The main rationale underlying the European Venom Network Action is that a single key can open both the technological (intrinsic) and the organisational (extrinsic) locks hampering the full development and translation of venom research at the EU level: **an effective cooperation among the different research fields and between academia and other stakeholders, including mainly industry, natural history museums and amateurs societies**. To date there has not been any other COST Action on venoms, and no EU funding scheme is currently allocated to venom-centered research. Within such an interdisciplinary topic, this COST Action offers an unprecedented opportunity to join researchers tackling venom research from different fields, thus overcoming their relative isolation due to a lack of coordination, tools, and resources. The Action will optimize efforts in venom research by promoting discoveries and innovative research studies through the combination of different expertise and skills, at the same time reducing redundancy by improving communication among researchers. In bringing a large group of experts together European Venom Network will endorse a solid agreement on best practices in venom studies, and identify most promising novel technological tools and animal models to be integrated into current research. The involvement of other stakeholders such as research agencies and policy makers will promote future development of venom research.

The effectiveness of the translation to industry of research products will be dramatically fostered promoting an effective two-way communication approach, under which industry will help researchers to identify most promising targets in terms of chemical structures and function for further investigation (input) and promote medical, diagnostics, agrochemical, cosmaceutical exploitation or nanobiotechnological application of selected compounds (output). This tighter link will be managed with the collaboration of IP (intellectual property) and benefit sharing experts and will be the prerequisite for a joint evaluation of research opportunities. The broader diversity of the industrial sectors that will be involved in this COST Action is another relevant novelty with respect to current interactions mainly focused on pharmacology.

Knowledge of natural history and ecology of venomous organisms is also instrumental for biodiversity-based discovery of novel compounds. Such a body of knowledge often lies within amateurs societies, and although anecdotal, can provide fundamental information to scientist and industrial for a wise identification of most promising research targets. **The European Venom Network will promote the interaction with amateurs societies through specific outreach activities and active involvement into Action tasks**, including the development of a common citizen science program for venom research. The collaboration with natural history museums will support and mediate this interaction.

We believe that building an effective network involving all the relevant stakeholders in effective reciprocal interactions would be the fundamental prerequisite to leverage the extraordinary biochemical warfare enclosed in animal venoms.

1.2.2 OBJECTIVES

1.2.2.1 Research Coordination Objectives

Through the European Venom Network COST Action, venom research in Europe will be fostered **by developing coordinated research tasks, that will be carried out synergically by the different Working Groups, favouring the creation of a core of shared knowledge**. Main research coordination objectives will be the following.

1) Identify most promising targets at the organismic, biochemical and functional level for venomics research, to coordinate and focus the scientific efforts of the European venom community. This objective is **specific** since it aims at defining a list of priorities in the field, in relation to pathologies, pharmacological targets, evolutionary questions. It is **measurable** through the number of research proposals that will focus on such new targets. It is **achievable** thanks to the broad range of expertises gathered together in this Action, including pharmacological and biotech companies. It is **relevant**, because it will optimize and coordinate research efforts across Europe to discover new potential targets for known toxins, and new toxins acting on orphan though interesting targets. It is **timely**

due to emerging challenges linked to antibiotic resistance, neurodegenerative and autoimmune diseases that call for new drugs, and also because it is now made possible thanks to recent technological improvement. This objective will be specifically tackled by WG1.

2) Establish community-accepted best practice principles and methodological pipelines in tackling venom research. This objective is **specific** given that it will provide a common roadmap for all the steps that are involved in venom research. It is **measurable** through the collaboration between groups and inside the team. It is **achievable** since the required expertise will be present in the Action network, and new methods promoted by the Action will further support the realisation of this goal. It is **relevant** because venomics is greatly fragmented in different specialized subfields both in terms of discipline and targets, with a low level of communication. It is **timely** due the fast growth of venomics thanks to technological improvements in each of the involved research subfields. This objective, along with the following, will be specifically addressed by WG2.

3) Promote and test new methods and technologies for the experimental investigation of venom. This objective is **specific** since it aims to develop new technological approaches, e.g. in the fields of metabolomics, peptidomics, cell biology and combinatorial techniques, that will be tailored to the investigation of venom complexity. It is **measurable** as the number of collaborations with biotech companies, and the frequency at which new technologies are cited in relevant scientific papers. It is **achievable** through the collaboration with leading biotech companies in Europe that will participate in the Action. It is **relevant** since new powerful technologies trigger scientific breakthroughs and discoveries. It is **timely** because it will keep venom research in Europe at the forefront of this fast evolving field. This objective, along with the former, will be specifically addressed by WG2.

4) Develop specialized public resources (e.g. databases and web-based analysis tools) for the integration, sharing and utilization of information data pertaining to toxins and biology and distribution of venomous species. This objective is **specific** since it will produce online analysis tools and searchable databases that will allow an easy retrieval and integration of information on venom protein classification, functional activity, molecular targets. Its use by the scientific community is **measurable** through the number of data entries, connections to the website, citations in scientific papers. It is **achievable** since participant institutions already have experience in developing such platforms, and thanks to the critical mass of knowledge collectively accumulated. It is **relevant** since it will allow a better coordination of research effort without redundancy, and it will fasten comparative analyses. It is **timely**, given the high amount of information is not easily accessible due to its fragmentation across different specialized websites and the lack of common analytical tools for a better integration of data. This objective will be specifically tackled by WG4.

1.2.2.2 Capacity-building Objectives

The European Venom Network will convene researchers and stakeholders from COST countries and International Partner Countries (IPC) to **increase scientific connection, promote intersectorial synergies and provide training** on the different subfields that are involved into the investigation and exploitation of animal venoms. This main objective will be achieved through different types of meetings, involving students and early career investigators (ECI), that will be supported to attend meetings, training schools and short-term scientific meetings (STSM) within the Action. More specifically, capacity building objectives of the Action can be defined as follows.

1) Create a pan-European network of scientists with complementary backgrounds to study animal venoms in order to identify and develop innovative research concepts and ideas and to promote the implementation of optimised and innovative discovery and investigation projects.

This objective is **specific**, since it involves bringing together scientists through the Action network, who otherwise would not have the opportunity to connect and collaborate. It is **measurable**, since the establishment of collaborations will lead to a number of shared grant applications and publications. It is **achievable**, since a significant number of venom research groups are present in Europe and will participate in the Action. It is **relevant**, since strong networks in venomics research already exist in other parts of the world (including the US and Australia), while the lack of coordination might affect competitiveness of European venom community. It is **timely**, as interest in this topic is high, as witnessed by the last Young Global Leaders meeting at the World Economic Forum, where venomics was identified as one of the four priorities for future scientific research. This objective will be achieved through the whole Action, and especially by the Dissemination plan and WG5.

2) Create a synergistic relationship between scientists, private companies, and experts in intellectual property, patents and benefit sharing across Europe for biotechnological development of venom compounds. This objective is **specific**, since it involves bringing together scientists, private companies, and lawyers through the Action network. It is **measurable**, since the

establishment of intersectorial collaborations will accelerate the pace of translation (more patents, more drugs). It is **achievable**, since a significant number of different stakeholders are present in Europe and will participate in the Action, as demonstrated by the already existent patents on venom derived pharmacologically relevant compounds. It is **relevant**, since it will allow the full exploitation of the applicative potential, and there is a demand for more drugs. It is **timely**, given the current lack of intrasectorial interaction and the need to deal with the Nagoya protocol. This objective will be specifically addressed by WG3.

3) Nurture a new generation of venom researchers with interdisciplinary expertise and international collaborative perspectives, able to maintain and improve intersectorial synergistic relationships. This objective corresponds to the **specific** knowledge exchange between scientists from different fields and other stakeholders. It is **measurable**, since it will lead to shared, interdisciplinary publication and research proposals. It is **achievable** through the implementation of the activity of the Action (summer schools, workshops, STSM). It is **relevant**, since it can dramatically improve the efficacy and translational potential of venom research. It is **timely**, given that the growing body of research results would need an integrative approach to be fully investigated. This objective will be specifically tackled by WG5.

2 NETWORKING EXCELLENCE

2.1 ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

2.1.1 ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

Investigation of venom and toxins for new drug candidates, cosmetics or agrochemicals is a strong area of research in the US and Australia, yet only two large European programmes, with consortia up to 20 different partners, have been conducted in the past in relation to the exploration and exploitation of venoms, namely the “CONCO” (2007-2012; 6th framework programme) and “VENOMICS” (2011-2015; 7th framework programme) projects. The first project focused on the therapeutic potential of one particular venomous species, the cone snail *Conus consors*, while the second project had a much broader goal, with a survey of 200 venomous species including snakes, spiders, cones, scorpions and hymenopterans. These two projects clearly emphasize the importance of this field in the context of EU Research and confirm the existence of strong European working groups related to our proposal.

While the results of these projects were instrumental to identify major obstacles and roadmap to venom research, their somehow restricted scopes only allowed for the involvement of a reduced number of European researchers

Since 2015 there were no actions related to this category of venom/toxins research at the European level, while medical and agricultural problems such as antibiotic, insecticide and pesticide resistance have become more pressing, and urgently require the development of new approaches. The networking capability offered by the COST Action will allow to build the needed level of excellence to jointly face such challenges at the European level.

In particular, facilitating the communication, exchange of ideas, and feedback between the more established and the newer groups that have recently emerged, the European Venom Network will build on the outcomes of those earlier programmes to foster the application of venom research to emerging challenges. Furthermore, the COST action will also optimize the cooperation in joint grant applications, facilitate the recruitment of skilled early career investigators, and promote the interaction between the academic and industry sectors via the valorisation of novel molecules.

2.2 ADDED VALUE OF NETWORKING IN IMPACT

2.2.1 SECURING THE CRITICAL MASS AND EXPERTISE

The European Venom Network Action will bring together the entirety of EU-based venom researchers, which presently are a small and dispersed community. The network proposing this Action already includes the majority of this community, spanning 10 European countries 5 of which are ITCs, and covers a wide range of expertises ranging from pharmacology to evolutionary biology, from structural chemistry to cell biology, to guarantee the coverage of the broad topics of interest for the European

Venom Network. Among proposers are represented not only established European venom researchers, but also ECIs that will enrich venom research with new perspectives.

Further participants will be gathered through direct contact and taking advantage of forthcoming congresses, including the World Congress of the International Society on Toxinology that will be held in 2021 and the authoritative Gordon Research Conference on Venom Evolution and Biomedical Applications in 2022. Advertising the Action on these occasions will allow us to involve International Partner Countries, including worldwide recognized academic institutions with an established experience in venom research. Several IPCs already expressed their interest into joining the European Venom Network. The involvement of IPCs will be advantageous to the Action both in terms of adding specific scientific expertise, and to enlarge the network among scientists and between scientists and other stakeholders, consolidating European leadership worldwide. At the same time, the IPCs and NNCs will participate in the training activities offered by the Action, contributing to spreading the common knowledge base worldwide. Their contribution will also be instrumental to the development of web resources able to widely respond to users' needs.

The involvement into the Action of European SMEs with a specific interest in the exploitation of animal venoms will assure an effective communication between academia and industry, to focus on common aims and leverage venom applicative potential.

2.2.2 INVOLVEMENT OF STAKEHOLDERS

Stakeholders of the European Venom Network include academic researchers, industry (pharmaceutical, cosmetic, agrochemical, bioengineering), international organizations, policy makers, natural history museums, and amateurs' societies. In order to involve all these different stakeholders, a number of activities will be implemented. 1) To enlarge the network of interested researchers and foster new collaborations, meetings of participants with the broad scientific community will be organized on a regular basis, at the occasion of annual meetings (more than half in ITCs); additionally, two MC members (chosen to maximize the participation of ECIs and women) will participate as Action emissaries to key conferences in venomics and related fields. 2) The connection with industry will be promoted through the participation in WG1 and the activities of the dedicated WG3. 3) International organizations will be involved as partners in training activities through inviting them to share their expertise during specific workshops. 4) Natural history museums will be involved in the organization of outreach activities, such as "Meet the Scientist" event, and activities in schools. 5) Amateurs will be involved by inviting societies' representatives to open meetings, and through the collaboration for the development of a citizen science interface on the Action website. 6) Policy makers and research agencies will be addressed by publishing whitepapers detailing suggestions for incentives to intensify research in key areas for the European Venom Network. Governmental and regulatory authorities will be informed about potentially paradigm-changing discoveries that might call for adaptation of regulatory processes.

2.2.3 MUTUAL BENEFITS OF THE INVOLVEMENT OF SECONDARY PROPOSERS FROM NEAR NEIGHBOUR OR INTERNATIONAL PARTNER COUNTRIES OR INTERNATIONAL ORGANISATIONS

Among secondary proposers the European Venom Network includes two NNCs: Russia and Morocco.

Russia has a long-standing tradition in toxinology, and among the NNC countries could be ranked among the leading countries in the field. The Russian Shemyakyn-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Science (IBCh-RAS) is the country's largest scientific research center in the area of physicochemical biology and biotechnology. The IBCh-RAS includes more than 80 research laboratories, covering both multipurpose fundamental research and applications in medicine and agriculture, and including a renowned Laboratory of Molecular Toxinology. IBCh-RAS has also a strong commitment towards education through a dedicated Educational and Scientific Center. Morocco is an emerging country in venom research, which is mostly pursued at the Institut Pasteur of Casablanca, the first public research institution in biomedical science in the country, within a dedicated Venoms and Toxins Laboratory. In 2017 the Institut Pasteur hosted an international and highly interdisciplinary workshop on Translational Venomics Medicine covering a wide range of venom-related topics.

These NNCs will bring to the European Venom Network specific high-level expertises, contributing to enlarge the coverage of scientific topics related to venom research, but also sharing their experience in education and dissemination issues. Additionally, due to their position and previously established collaborations, these NNCs could contribute to attract scientists also from North Africa, Middle East, Ukraine, Georgia, Belarus, enlarging international participation in the Action and reinforcing the network.

Participation in the European Venom Network would positively affect competitiveness of NNCs in several ways, including scientific, technological and socio-economical impact outlined below. In particular, the acquisition of a shared body of knowledge and the multidisciplinary training of ECIs will boost research in the field with long term effects on the scientific competitiveness of these countries. Moreover, the possibility to put in place coordinate research efforts with EU countries will foster research in the field. Participation in the European Venom Network will increase the discovery and exploitation of novel bioactive molecules, leading to potential breakthroughs in health, agriculture, and bioengineering issues which would greatly advantage NNCs.

3 IMPACT

3.1 IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAK-THROUGHS

3.1.1 SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

Scientific impact: In the **short term** the European Venom Network will foster the development of research synergies between academic groups of quite disparate research fields and the definition of research priorities in venom research. It will also promote the transfer of knowledge between established and emerging countries and research groups in the field. The newly established collaborations will generate high profile interdisciplinary publications and stimulate research activity through coordinate grant applications in European and local funding bodies, and promote early career investigators (ECIs). In the **long term**, the Action will advance a holistic view of venom research and establish new paradigms for basic and translational research on animal venoms. The best practices, technologies and database tools that will be developed through the course of the Action will be valuable resources for the research community for many years to come. Furthermore, through the cross-disciplinary training of ECIs, the Action will nurture a new generation of researchers which will transmit their integrative perspective to the next generation and drive the field of venomics research into the future. In particular, STSMs will open career perspectives and opportunities for ECIs. Eventually, the Action will promote diversity in the leadership ranks of European research by promoting target groups, especially women and researchers from ITCs. These activities will contribute to break down barriers between research fields and advance interdisciplinary cooperation, representing a remarkable scientific breakthrough at the European level.

Technological impact: in the **short term** the European Venom Network will promote the optimisation and standardization of venom research tools, the integration of novel technologies into venom research, and the development of novel ad hoc technological approaches. The translation of novel findings in venom research will be facilitated by establishing two-way interactions between academia and industry, with input from industry to academia in terms of new biotechnological tools to investigate venom diversity (as for activity, targets... etc), and input from academia to industry in the form of new bioactive compounds to be further developed. In the **long term**, the new bioactive compounds identified by the network members, on the basis of the shared body of knowledge developed through the Action, will serve as leads for the development of new drugs, insecticides, cosmaceuticals, diagnostic and bioengineering tools. By increasing the potential for the discovery of lead compounds, this COST Action may convey technological breakthroughs in different fields.

Socio-economic impact: in the **short term** the European Venom Network will increase public awareness on venom research, at the same time using the appeal of venomous organisms to contribute to the education of European citizens in valuing the biodiversity. The direct involvement of amateurs and the outreach activities addressed toward the lay public will increase positive feedback between research and civil society. In the **long term** the potential for discovery of novel drugs, diagnostic tools and eco-friendly insecticides would convey important socio-economic advantages and breakthroughs, by improving human health and protecting the environment

3.2 MEASURES TO MAXIMISE IMPACT

3.2.1 KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

The building of a collectively shared body of knowledge will be carried out with several instruments through the Action. 1) The organization of regular scientific meetings for sharing of information (>half in ITCs), planned well in advance, will foster a reliable network of collaborations. 2) The participation of up to two MC members as emissaries of the European Venom Network to key conferences in the fields of interest will attract researchers and companies, and promote the visibility of ECIs. 3) The organization of training schools and courses aimed at educating Action members with established and novel methodologies and technologies, and with transversal issues such as patenting, IP issues and benefits-sharing will increase transfer of knowledge and foster career development especially for ECIs. 4) The implementation of STSMs will promote the transfer of knowledge and skills between research groups participating in the Action, and between academia and industry. 5) The establishment of connections with funding agencies through the publication of whitepapers detailing suggestions for incentives to intensify research in key fields of the European Venom Network will increase the availability of research opportunities. 6) The use of a dynamic website as hub for data sharing and the implementation of a common online database with analytical tools (linked in the European Venom Network website) will ensure that the transfer of knowledge will proceed beyond the completion of the Action.

3.2.2 PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICY

The European Venom Network Action will disseminate its scientific output mainly through publications, in the form of whitepapers and review articles in peer-reviewed journals, and scientific presentations. Whitepapers will be shared among the participants and with non-scientific stakeholders (funding agencies, policy makers) where appropriate. For publication in peer-reviewed journals, open access will be privileged through the allocation of specific financial support. Action members will also advertise results through presentation at other international meetings (attended with their own funding), leading to the recruitment of new members and partners to the Action. STSMs will play an essential role in crossdisciplinary and intersectoral exchange and dissemination of scientific knowledge and technical know-how.

Since the European Venom Network Action has a great potential to discover new compounds that can be exploited commercially, participants will be kept informed on potentially exploitable results and educated through information and links posted on the Action website and specific workshops on patentability and protection of intellectual property issues. These workshops will be carried out by experts both from academia (e.g. university technology transfer offices) and from industry (e.g. financial and technology officers). Since venomous organisms are often collected in developing countries, the Action will also recruit experts to inform participants on benefits-sharing issues related to the Nagoya protocol.

The general public and non-expert stakeholders will be reached through the internet and social media platforms (e.g. LinkedIn, Twitter, Facebook). Country-specific popular science forums and press releases will be used to communicate the research focus and key findings of the Action to the lay public in their native language. Natural history museums from different countries will be involved into the organization of "Meet the Scientist" events and outreach activities in schools, to exploit the appeal of venomous organisms to the public for conveying information on the applicative potential of basic research, and raising awareness on the need of biodiversity conservation. The Action will also link with amateurs and specialists of specific groups of venomous animals, e.g. through online forums and the participation to Societies meetings, to disseminate scientific results. Amateurs will be involved into the preparation of a program to develop a common citizen-science interface for venomous organisms. During Action meetings, an open session will be organized and advertised well in advance to meet with local communities, including lay public and amateurs. Action members will perform short skits in non-technical language for the lay public (i.e. Science-slam), and will be encouraged to participate in community outreach activities in their countries (e.g. university open days, EU Researchers' night, science fairs and orientation days at schools).

The **Action website** will serve as a hub for all dissemination channels, and will include the following key features: a list of all Action members (including affiliation, link to homepage, discipline and methodological expertise), to catalyse collaborations; a comprehensive list of publications emanating from the Action, including whitepapers; a list of upcoming events (e.g. annual meetings, training schools, community outreach activities), to foster participation; summaries of each meeting organized by the Action; advertisements of open positions in research groups and companies of Action members, to stimulate intersectorial, interdisciplinary and international mobility; links to databases and tools developed in the Action; video recordings of educational materials, including skits and workshops.

4 IMPLEMENTATION

4.1 COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1 DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

The European Venom Network Action will be implemented through five Working Groups (WGs) which together will foster research on venom and translation to industry through the creation of a tight European network. While WG1 and WG2 will identify major gaps in venom research, respectively in terms of targets and in terms of methods, WG3 will promote connections with industry. These three WGs together will ensure the development of a shared research agenda, that will constitute the basis of research breakthroughs and their effective exploitation. The development of a web-based resource for both data sharing and data analyses (WG4) and the implementation of multiple training activities at different career levels (WG5) will ensure the formation and nurturing of a generation of researchers with a holistic view, well beyond the completion of the Action. The objectives and tasks of each Working Group combine the different skills and expertises of the participants, promoting interdisciplinarity and taking advantage of the diverse contributions to maximize the advancement of venom research. The whole network will meet once a year to monitor progress, where WGs will provide reports evaluating the development of activities and results achieved, while continuing communication will be ensured through teleconferences in-between. The European Venom Network website will serve as a hub to communicate and share information, particularly regarding events and trainings.

WG1 – Novel targets in venom research

The pharmacological potential of the optimized molecules found in venoms has been recognized and used to treat human ailments for centuries (e.g. in the Chinese pharmacopeia). Current research efforts mainly focus on just a handful of diseases and molecular targets (pain and dysregulation of hemostasis being the most prominent). However, venom molecules have shown promising effects in many other diseases, such as cancer, neurodegenerative diseases, auto-immune diseases, epilepsy, which have been overlooked. Furthermore, these molecules can also have pharmacological properties compatible with the needs in cosmetics and agrochemical industries, and physical properties appealing for bioengineering developments. For these new and emerging areas, novel targets need to be established and validated to unleash the true potential of venom molecules. The study of basic biology of organismal targets should also be fostered, and the collaboration with amateurs societies will help in defining best strategies to leverage citizen knowledge for research and development.

WG1 Objectives: 1) Discuss and identify the potential new targets, both at the organismic and at the functional level, in each area of the therapeutics, cosmetics, and agrochemicals fields. 2) Determine gaps requiring specific efforts to bring these new targets to the bench. 3) Establish a strategy to develop common citizen-science approaches for venom research. 4) Promote ongoing and future research to validate these targets

WG1 Tasks: 1) Review the current knowledge on existing and putative new targets. 2) Establish links with amateur societies 3) Incentivize venom research through its promotion at relevant agencies

WG1 Milestones: MS1.1 Whitepaper on future directions for venom research. MS1.2 Report on common citizen-science approaches

WG1 Deliverables: D1.1. Report on current status and future directions for venom research. D1.2 Report on feasibility and implementation strategies for a common citizen-science approach D1.3 Organization of specific workshops with amateurs D1.4 Publications in high profile journals to disseminate the potential of these new targets relative to therapeutics, cosmetics and agrochemicals

WG2 – Best practices and innovative tools

Comparison of protocols and data from different laboratories is necessary to facilitate the comprehension of results and advance knowledge in venom research. In order to compare results, generated data must meet newly developed high standards, which apply from the collection of samples to the generation and analysis of data, so that variations are minimized and results are accurate, reproducible and comparable. Protocols, technologies, and procedures will be assessed in a document that will be shared and discussed among participants. Standard strategies will be delineated for better quality control and study comparison, tackling all the fields contributing to the process of venom investigation. Additionally WG2 experts will identify best innovative tools to remove technical and organism based locks which hamper a full exploitation of venom potential. The European Venom Network members with unique knowledge will share their expertise through meetings, STSMs, and training schools.

WG2 Objectives: 1) Review current pipelines used in the different steps of venom research. 2) Identify critical steps in venom research, including uneven coverage of research fields and fields where accuracy and reproducibility can be improved, along with amelioration and unification strategies. 3) Identify innovative tools that may scale up the pace of venom research, and evaluate the feasibility of their application in the field.

WG2 Tasks: 1) Devise best practice and guidelines for venom characterization, selection of most interesting compounds, production and functional assessment of specific small molecular weight compounds, peptides and proteins. 2) Provide an evaluation of most promising novel tools to foster venom research. 3) Define standard protocols in each of the experimental steps of the various venomous disciplines. 4) Provide methodological guidelines for the publication of results. 5) Contribute to the organization of meetings, STSM, and training activities.

WG2 Milestones: MS2 Guidelines for the development of best research and technology strategies.

WG2 Deliverables: D2.1 Report on current approaches in venom research D2.2 Report on novel tools to be integrated in venom research D2.3 Handbook of protocols and best practices in venom research

WG3 – Connection with industry

One of the WG3's main missions is to promote the work of the researchers within the network of the COST Action, by accelerating their transition from the laboratory to the market. This will be achieved by bringing the academic approach into line with industrial strategies and needs. The ultimate goal being to increase the interplay between academic researchers and industrial partners to transform discoveries, inventions or know-how of researchers into innovations for society. Traditionally, securing industry support for very early stage projects is difficult, mostly because industrials usually look for much advanced technologies to support and invest in. Therefore, WG3 will take several initiatives to encourage the early participation of industry representatives to our meetings and discussions, and to bring promising projects to the point that they could be considered for collaborations.

WG3 Objectives: 1) Promote interactions and collaborations between academic laboratories and industries for exploitation of venom bioactive components (i.e. pharmaceutical, cosmetic and agrochemical). 2) Identify specific opportunities already existing in EU to initiate and support the development of new academic-industry collaborations. 3) Sensibilize academic researchers, postdocs and students to access and benefit sharing, intellectual property and patent issues through workshops with professional lawyers.

WG3 Tasks: 1) Solicit and invite industrial representatives to participate to the European Venom Network meetings and workshops 2) Define the needs of the industry, which will help academic laboratories tailor their discovery efforts towards the relevant targets. 3) Coordinate ongoing research on novel targets and encourage joined research efforts with industrial partners.

WG3 Milestones: MS3 Calendar of dedicated academic-industry meetings and workshops.

WG3 Deliverables: D3.1 Report on priority areas in the industry (diseases, molecular targets, unmet needs...). D3.2 Workshops and meetings for connecting with industrial stakeholders D3.3 Workshop on patentability, intellectual property and benefit sharing.

WG4 – Web resources

Despite some comprehensive databases being already available for venom toxins, including the Uniprot Toxin Database and the VenomZone website of the Swiss Institute of Bioinformatics, the information there available is often not completely overlapping with specific databases, such as Conoserver or Arachnoserver, calling for a better integration of web resources. It would be optimal to include in the same web resource not only the venom components database, but also their structure, their molecular targets, and their biological activities. Additionally, the availability in the same web resource of analytical tools e.g. for protein modelling (both model based and *ex novo*), *in silico* docking to potential targets, reconstruction of molecular evolution patterns (e.g. positive/negative selection), will greatly facilitate the identification of new toxins, at the same time fostering the recognition of folds/activities of potential applicative interest. Specific features to be included will be indicated by the Action participants

WG4 Objectives: 1) Create a unified web resource for venom research. This aim will be accomplished merging and unifying available venom toxins databases in a novel format 2) Identify and implement in the web resource most useful analytical tools for modelling 3D structure, molecular interactions and evolutionary patterns.

WG4 Tasks: 1) Identify major issues in the available databases and online tools, along with best improvement strategies. 2) Identify most desirable features that should be included into the web resource. 3) Implement the web resource

WG4 Milestones: MS4 Release of the first version of the web platform.

WG4 Deliverables: D4.1 Report on available databases and online analytical tools. D4.2 Survey to be given to the Action participants to identify major features that should be included into a web resource. D4.3 Web platform to serve as databases repository and analytical tools provider.

WG5 – Training

This WG is a transversal platform for the Action, aiming at organizing and coordinating training initiatives within the European Venom Network. Given the multidisciplinary nature of venom research it is crucial to offer extensive training opportunities in all the fields contributing to venom research, to build a solid core of shared knowledge in the European research community and foster the development of a holistic view of venom research across researchers from different fields. Training will be one of the main activities implemented by the Action to strengthen venom research in Europe, and as such deserves a dedicated Working Group, which would nevertheless implement its activities in tight collaboration with the other WGs. All the deliverables of this WG will be made available through the Action website.

WG5 Objectives: 1) Offer highly qualified training on all the experimental and analytical steps of venom research 2) Support individual inter-disciplinary mobility 3) Guarantee access to cutting-edge infrastructures 4) Educate young generations on venom research,

WG5 Tasks: 1) Organization of training schools on experimental approaches and data analysis for the study of venom. 2) Coordination of Short Term Scientific Missions (STSMs). 3) Preparation of syllabus and materials of a Master level course on animal venoms

WG5 Milestones: MS5 Launch of the advanced courses program and STSMs calls

WG5 Deliverables: D5.1 Training School programme on experimental methods and data analysis in transcriptomics and proteomics for venom research. D5.2 STSMs calls and awards. D5.3 Syllabus and materials for Master level course.

4.1.2 DESCRIPTION OF DELIVERABLES AND TIMEFRAME

The Action will commence with the kick-off meeting (KoM) of the Management Committee (MC), at which the European Venom Network Annual Conference (AC) will be organized, and the WGs will be established. In the organization of WGs, particular care will be given to ensure the involvement of early career and ITC investigators; gender balance; balanced participation of participants from different countries. Over the four years the Action will hold yearly WG meetings (1-1.5 days), to discuss required strategies for achievement of WG DLs & MSs, identify specific needs, define priorities and organize activities. Communication within WGs will be maintained by regular teleconferences. Reports will be prepared and disseminated within the Action network

Four Annual Conferences (AC; 2-3 days) will be held in conjunction with MC (in order to minimize travel costs), including plenary sessions on specific topics as proposed by MC and WGs, reflecting WG activities, and open to the broad scientific community. A session or roundtable will be specifically dedicated to the communication of the European Venom Network activities to the lay public and to steer the interaction with amateurs societies.

At least 3 Workshops (WS; 1-2 days) will be organized by WG3 in conjunction with ACs, to promote interaction between academia and industry, and to train participants on patentability, intellectual property and benefit sharing issues. A further workshop will be organized by WG1 together with the Dissemination Group to gather together amateurs and academics. Reports will be prepared and disseminated within the European Venom Network .

At least 4 Training Schools (TS; 4-5 days) will be organized by WG5 to promote homogenisation of knowledge across and beyond Europe. Foreseen topics cover the main steps of the venom research pipeline, including -omic approaches and data analysis, bioassays, in silico methods and novel technologies. Other topics will be identified in case resources for more TS will be available. Reports and teaching material will be disseminated within the Action network.

Teaching materials for a master course on venom research will be prepared by WG5 with the collaboration of the other WGs, including slides, videos, a shared corpus of review papers, and other features to be disseminated within the European Venom Network to attract students into this research field.

Short Term Scientific Missions (STSM) will be selected by MC based on applications by single CC/NCC members, with the aim to provide: training on specific topics, techniques and activities in best qualified groups; equal access to cutting-edge infrastructures distributed across Europe; transfer of knowledge from “pockets of excellence” in European science and technology to less research-intensive countries; support to individual inter-group and inter-disciplinary mobility; reinforcement of existing networks and promotion of new collaborations. Special prioritising considerations will be made by the MC to support COST policies by promoting gender balance, ECI, new applicants and geographical inclusiveness.

After completion of the activities described above, WGs will collaborate to the preparation of Reports that will be disseminated within the European Venom Network. Further Dissemination Activities and Outreach Activities to communicate Action outcomes to the civil society will be implemented as detailed in 3.2.2

4.1.3 RISK ANALYSIS AND CONTINGENCY PLANS

Capacity building and management risks

1. The risk of **not attaining and maintaining a critical mass of excellent academic researchers** is low. Venom research in Europe is carried out by a small yet scientifically excellent community, that is already almost completely included in the Network of Proposers given the common interest to develop a more collaborative network. To mitigate the risk of waning interest and declining participation during the implementation of the Action, the MC will proactively recruit participants by announcing the European Venom Network COST Action at European and international meetings and contacting directly principal investigators of the most recent and significant publications in the field. Initial interest and enthusiasm will be also maintained during the lifetime of the Action by having a detailed and well-planned meeting schedule that benefits all participants with learning and networking opportunities.

2. The risk of **not attracting industry and pharmaceutical company involvement** is low. Europe hosts many well-established companies as well as smaller start-up ventures, a few of them explicitly focused on venom compounds as pharmacological or research tools, that are keen to collaborate with academic scientists. Representatives from several pharmaceutical or biotech companies have already expressed interest in participating in the Action. The previous EU-funded projects (CONCO and VENOMICS) already established successful cooperation between academia and industry, although restricted to the pharmaceutical field, that this Action will further enlarge to agrochemical, cosmetical and bioengineering. Any eventual lack of representation of industry will be mitigated by proactive recruitment, as described above.

3. The risk of an **unstable management** is considered medium. The network of proposers is well balanced since it includes both experienced researchers with established management skills and ECIs that will bring novel energies and enthusiasm. This risk that MC members will no longer serve in their capacities due to e.g. appointments outside COST countries will be mitigated by maintaining a diverse and fully involved MC so that substitutions can be readily made without harming Action progress. In addition, there will be expertise-overlap in WG leaderships, so that the burden of management can be shared if necessary.

Research coordination risks

1. The risk that **key results corresponding to Action deliverables are published by competitors outside the network** is medium, considering the strength of venom research outside Europe. This risk will be minimized by the involvement of the IPC where venom research is more developed into the network. However, this possibility does not undermine the overall goal of the Action: findings published from outside the network will be incorporated into the Action’s knowledge base.

2. The risk of failing to **deliver reports on promising targets, best practice and innovative tools** is low. Expertise for input at all levels will be present, and WG Leaders will ensure that information is integrated in a useful way. Regular meetings where WGs will present their results will allow a timely detection of any lack of progress and facilitate the identification of causes and the implementation of appropriate corrective actions.

3. The risk of failing to **develop web based resources** is low. Databases and analysis tools are already available in most cases, and need to be integrated in a single resource. The optimization of the web

resource according to the users needs will be optimized thanks to the survey that will be given to participants at an earlier stage and the regular meetings to present WG progress.

4. The risk that **necessary technologies and techniques are not available** within the Action is low. The importance of advanced methodologies and technologies in pushing research forward is why the Action has a WG devoted to this topic. WG2 will promote cutting-edge technologies available within the Action network and thereby spur internal collaborations that will mitigate lack of progress due to technical limitations of individual partners. WG2 will also identify methodological deficiencies in the network and mitigate this problem by recruiting academic/industry experts from COST countries as well as non-COST countries who may follow different strategies.

4.1.4 GANTT DIAGRAM

Year-Trimester	Y1-I	Y1-II	Y1-III	Y1-IV	Y2-I	Y2-II	Y2-III	Y2-IV	Y3-I	Y3-II	Y3-III	Y3-IV	Y4-I	Y4-II	Y4-III	Y4-IV
MC	KoM			M1				M2				M3				M4
CG	KoM	TC	TC	M1	TC	TC	TC	M2	TC	TC	TC	M3	TC	TC	TC	M4
WG1-5		TC	TC	M1	TC	TC	TC	M2	TC	TC	TC	M3	TC	TC	TC	M4
ANNUAL CONFERENCE				1				2				3				4
WORKSHOPS				D1.3			D3.2					D3.3			D3.2	
TRAINING SCHOOLS					D5.1			D5.1			D5.1			D5.1		
WG1						D1.1			MS1.1		D1.2			MS1.2		
WG2				D2.1				D2.2		MS2						D2.3
WG3			MS3								D3.1					
WG4				D4.1				D4.2					MS4			D4.3
WG5		D5.2	MS5							D5.3						
Dissemination & Outreach	Website								Other activities							
STSM																

KoM: Kick-off Meeting, TC: Teleconference, M: Meeting