



Version 21/04/2016

COST Action FA1403 (Action 11 DEC 2014 – Action 10 Dec 2018)

Inter-individual variation in response to consumption of plant food bioactives and determinants involved - POSITIVE

PROGRESS REPORT AT MONTH 24

This report is submitted by the MC Chair on behalf of the Management Committee.

Confidentiality: This report, other than section II.D, is non-confidential. Section II.D is confidential to the Management Committee and the COST Association (including the Committee of Senior Officials, Scientific Committee and Administration).

Executive summary of the Progress Report:

The COST Action-POSITIVE is organised in 3 WGs with specific objectives, a Focus Group (FG) for dissemination, and a Think-Tank Group of ECIs. To reach the scientific objectives, the Action has hitherto organized 4 WG meetings, 2 COST scientific workshops in connection with International Conferences. To support mobility, strengthening and fostering collaborations, POSITIVE has funded 13 STSMs.

WG1 performed an extensive literature search to evaluate determinants of interindividual variability in ADME after oral intake of plant bioactives. Eight subgroups dealing with relevant compound classes and three methodological subgroups have been formed. The metabolomics subgroup has started activities to improve the analytical coverage of plant bioactives in human samples and facilitate metabolite identification. The current state of the art has been transferred to the scientific community through webinar series and a training school. The microbiome subgroup has selected metabolites for which microbial metabolism is crucial and for which there is information on the crucial metabolic steps. From available knowledge, the distribution of genes encoding enzymes across microorganisms and how their presence may stratify human individuals are now examined. Following a similar approach, the gene variants subgroup will gather information on the variability of genes encoding human biotransformation enzymes and transport proteins.

WG2 aims to assess the inter-individual variability in biological response to plant food bioactives regarding cardiometabolic endpoints and to identify the main factors responsible for such variability. The initial review conducted allowed to conclude that very few studies have investigated this interindividual variability, which seems to be dependent on genetic and non-genetic factors. Several systematic reviews of published clinical studies are currently being conducted to evaluate interindividual variability in response to plant bioactives and identify which factors impact their biological response. Working subgroups also evaluate cellular and molecular targets of bioactives about cardiometabolic health and the interindividual variability in nutri(epi)genomic response. Several publications related to this work are currently under review or in preparation.

For WG3, its main missions are to integrate key findings from WG1 and WG2, and its activities will be more important in the two next years. From now, WG3 has worked to redefine concrete and manageable deliverables aligned with the activities of WG1 and WG2. This year, WG3 focussed on the development and distribution of a SurveyMonkey questionnaire to identify and prioritise deliverables that are most important for the different stakeholders and end-user groups in an extensive range of European countries.

The FG has successfully developed and delivered a range of communication materials for different publics which are of crucial importance to promote the visibility of the Action.

POSITIVE also acts to mentor, provide multidisciplinary training and favour exchanges between ECIs. To this end, a TTG of ECIs has been shaped. First, TTG has put in place an online forum for regular discussion and exchanges. During the second year, TTG proposed to lead a project complementary to WG1 and WG2 activities and focused on the establishment of a quality index to evaluate the interindividual variability reported in scientific papers.



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I. Progress Report

I.A. COST Action Profile

Objective/ Aim

The aim is to create an open European scientific network to tackle the question of the inter-individual variation in response to plant food bioactives consumption in relation to cardiometabolic health. The main aim of this network is to analyse in a systematic/integrated way the available knowledge to evaluate the extent of inter-individual variation for the main families of plant food bioactives and to identify the key factors responsible for the inter-individual variation, regarding both bioavailability and bioactivity related to cardiometabolic health outcomes. Identifying these factors, as well as developing new and innovative methodologies to account for such variability constitute an overarching goal to ultimately ensure that the cardiometabolic health-promoting effects associated with bioactives present in plant foods are applicable for everyone.

Details

MoU: 035/14 Start of Action: 11/12/2014
 CSO approval date: 14/05/2014 End of Action: 10/12/2018

COST Member Countries and Cooperating State having accepted the MoU

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Parties							
Country	Date	Country	Date	Country	Date	Country	Date
Austria	02/02/2015	Belgium	01/07/2014	Bulgaria	19/11/2014	Croatia	04/06/2014
Cyprus	20/04/2015	Czech Republic	15/09/2014	Denmark	23/06/2014	Finland	24/06/2014
France	26/06/2014	Germany	12/06/2014	Greece	01/07/2014	Hungary	15/07/2014
Ireland	19/06/2014	Israel	13/11/2014	Italy	27/08/2014	Latvia	30/01/2015
Lithuania	04/07/2014	Luxembourg	27/08/2014	Netherlands	02/06/2014	Norway	18/12/2014
Poland	18/06/2014	Portugal	03/07/2014	Romania	01/08/2014	Serbia	04/08/2014
Slovenia	21/01/2015	Spain	02/06/2014	Sweden	29/07/2014	Switzerland	20/08/2014
Turkey	07/08/2014	United Kingdom	22/05/2014	fYR Macedonia	16/07/2014		

Total: 31

Intentions to Accept the MoU

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Other participants:

Institution Name	Country
Copy from Action page on COST website	
Technical University of Moldova	Moldova, Republic of

Contacts

Chair/ Vice Chair

Position	Name	Contact details	Country	Date of Ph.D.:	Gender
Chair:	Christine MORAND	Institut National de la Recherche Agronomique INRA Centre Clermont Fd - Theix 63122 Saint Genes Champanelle - France christine.morand@clermont.inra.fr	France	1991	F
Vice Chair:	Francisco TOMAS-BARBERAN	CEBAS-CSIC Campus de Espinardo 2530100 Espinardo (Murcia)Spain fatomas@cebas.csic.es	Spain	1984	M

Working Group Leaders

WG#	WG Title	WG Leader	Country	Date of Ph.D.:	Gender	Number of participants
1	Inter-individual variation in bioavailability	Tom Van de WIELE	Belgium	2004	M	120
2	Inter-individual variation in biological responsiveness regarding cardiometabolic endpoints	Ana RODRIGUEZ-MATEOS	Germany	2006	F	108
3	From emerging science to applications	Baukje de ROOS	UK	2000	F	107

Other positions if applicable (STSM Coordinator, WG Vice Leader, Task Force Leader...)

Position	Name	Country	Date of Ph.D.:	Gender
WG1 co-leader	Rikard LANDBERG	Sweden	2009	M
WG2 co-leader	Eileen GIBNEY	Ireland	2001	F
WG3 co-leader	Marina HEINONEN	Finland	1990	F
FG leader	Maria Teresa GARCIA-CONESA	Spain	2000	F
FG co-leader	Iwona KIEDA	Poland		F
STSMs coordinator	Aleksandra KONIC-RISTIC	Serbia	2013	F
TTG representative - Year 1	Mireia URPI-SARDA	Spain	2008	F
TTG representative - Year 1	Laurent-E MONFOULET	France	2009	M
TTG representative - Year 2	Mar GARCIA ALOY	Spain	2014	F
TTG representative - Year 2	Antonio GONZALEZ-SARRIAS	Spain	2009	M

Action website: <https://www6.inra.fr/cost-positive/>

I.B. Progress with MoU objectives and deliverables and additional outputs

MoU objectives

MoU objective	Achieved Yes/ Partially/ No	Evidence of (partial) achievement including a hyperlink to enable assessment of the achievement ¹ . Justification if full achievement is not foreseen
Copy from e-COST or MoU		For each objective insert evidence of (partial) achievement including hyperlink to enable assessment (by the Action Rapporteur) of the achievement and access by end users
Aim/primary objective:		
1. Create an open European scientific network to tackle the question of the inter-individual variation in response to plant food bioactives consumption in relation to cardiometabolic health	Partially	<p>Over the period, the Action has worked to promote exchanges/interactions between partners and to develop the scientific activities within the WGs:</p> <ul style="list-style-type: none"> ○ Four WG meetings have been organized (including internal scientific sessions with oral presentations and/or posters): http://www6.inra.fr/cost-positive/Events; ○ 13 Grants for STSMs allocated to young scientists. ○ Some specific initiatives have been undertaken to strengthen the link between partners, for instance: <ul style="list-style-type: none"> - At the Opening Meeting (Belgrade, March 2015), the Think-Tank group (TTG) of ECIs has been created. So far, two face to face meetings of TTG have been organized, however, this group exchanges regularly through online meetings organized monthly. Since its 2nd meeting in Bucharest (March 2016), a subgroup of ECIs develops a specific project of high interest for the Action. - The organization of a multi-laboratory analytical coverage test for untargeted metabolomics across European laboratories (n=16), with the ultimate objective of developing a consensus harmonized method with wide coverage of bioactives exposure. <p>Several initiatives have been undertaken to provide visibility of the action, including:</p> <ul style="list-style-type: none"> ○ The development of the POSITIVE website: https://www6.inra.fr/cost-positive ○ The organisation of the 1st scientific COST workshop in Tours (26-27 October 2015) in satellite to the 7th International Conference on Polyphenols and Health; ○ The organisation of the 2nd POSITIVE Scientific Workshop as a part of the International Conference on Food Bioactives and Health (Norwich, 13-15 September 2016); ○ The establishment of concrete links with other European Networks, such as NuGO, ISEKI Food Association (organisation of a round table, Bucharest meeting, March 2016);

¹ The links to the outputs and deliverables will be used by the Action Rapporteur in assessing the progress.

		<ul style="list-style-type: none"> ○ The publication of a collaborative position paper addressing the topic of the Action in a scientific journal of high impact.
<p>Secondary Objectives</p>		
<p>2. Identify the relative importance of factors such as age, gender, genetic background, microbiota, lifestyle, in explaining the inter-individual variation in bioavailability of common plant food bioactives.</p>	<p>Partially</p>	<p>WG1. Participants in WG1 soon agreed that the foreseen activities cannot only focus on variability in bioavailability but that all processes of pharmacokinetics (absorption, distribution, metabolism and excretion) need to be considered to further the understanding of why variability in health outcome between individuals is so high upon ingestion of plant food bioactives. A first set of activities focuses on extensive literature searches over different classes of plant bioactives: carotenoids, anthocyanins, lignans, phenolic acids, ellagitannins, flavanones, flavonols, catechins, and phytosterols. WG1 members indicated in which subgroup of chemicals they wanted to participate. To categorize information, a data input template was made available through several dropbox folders in which WG1 participants can indicate which articles cover determinants including age, gender, genetics and microbiota, among others. Over 3200 papers have been searched, from which 700 were selected for their relevance in explaining the interindividual variability. Data extraction using a common template is currently made in each of the chemical subgroups to prepare review papers for bringing knowledge together or position papers to discuss knowledge gaps and needs for further research.</p>
<p>3. Identify the main determinants, beyond variation in bioavailability, of the inter-individual variation in the biological responsiveness to the consumption of plant food bioactives</p>	<p>Partially</p>	<p>WG2: The first step of this objective was to write a review paper on existing knowledge regarding interindividual variability in response and the factors involved. The preparation of the review involved nine partners from 6 different countries, and has been submitted last August to the journal <i>Advances in Nutrition</i>, and is currently under favourable review. This review highlighted the limited existing clinical and prospective studies which have investigated, to some extent, the interindividual variability in the biological response to the consumption of plant food bioactives. These studies suggest that some individuals may benefit more from the health effects of these bioactives than others, and genetic and non-genetic factors may be important ones contributing to the variability in biological effects observed between individuals. Factors identified were: genetic polymorphisms, health status, metabolic status, age, gender.</p> <p>Building on this review, several meta-analyses of published work, examining the effect of individual plant bioactives and markers of cardiometabolic health are underway. A standardised screening, selection and data extraction protocol was developed, and submitted to the journal <i>Systematic Reviews</i> (under review).</p>

		<p>Using this protocol, several meta-analyses are underway including:</p> <ul style="list-style-type: none"> - Flavonol intake & cardiometabolic risk factors - Flavonol intake & lipid profile and BMI - Flavonol intake & BP & FMD - Anthocyanin, ellagitannins & cardiometabolic risk factors - Phytosterols & cardiometabolic risk factors <p>An example of a data extraction sheet of these meta-analyses is available at HYPERLINK1</p> <p>Analyses within each of these meta-analyses are first done at a total population level, and subsequently at population group level (e.g. sex, BMI, age, disease, medication, ethnicity) where population group differences will be identified.</p> <p>All this work is ongoing, and it is expected that at least four scientific papers will be published in 2016/17.</p>
<p>4. Increase understanding of what could be the optimal exposure that will ensure the best benefit from plant food bioactive intake regarding cardiometabolic endpoints</p>	<p>No</p>	<p>WG1. At this stage of WG1 activities, this is not yet tackled. WG1 participants first want to increase their understanding of what determinants contribute to interindividual variation (e.g. microbiome composition, genetic predisposition, age, gender, ...) before making assessments of optimal exposure. Their activities will focus on taking state-of-the-art knowledge one step further by a transition from plant bioactive ADME average data on cohort level to ADME data on an individual level. This will facilitate new insights into the mechanisms that drive interindividual variability in bioavailability and bioactivity from plant bioactives. It can result in a concept of personalized pharmacokinetics in which one's unique microbiome composition and functionality and one's genetic polymorphisms, as well as other possibly relevant factors such as age and gender, need to be taken into account. If such concept becomes more concrete, it creates opportunities for domain-crossing approaches like the pharmaceutical field.</p> <p>WG2: Within the meta-analyses underway and whenever possible, the effect of the intake (dose/time) on the cardiometabolic variables will be examined. The aim is to enhance our understanding of the optimal required amounts of a particular product for a biological impact at the total population level and population group level (e.g. sex, BMI, age, disease, medication, ethnicity).</p> <p>Ultimately, the knowledge accumulated in WG1 and 2 will be shared, and the optimal exposure will be defined in concertation.</p>
<p>5. Develop a paradigm and related methods to stratify individuals into defined metabotypes and responders groups</p>	<p>Partially</p>	<p>WG1 participants are not only affiliated with the different plant chemical subgroups but also distributed over three methodological subgroups. Firstly, we need to get the methods right to make a stratification possible. The metabolomics subgroup focuses on</p>

		<p>analytical coverage of plant bioactives and metabolites in human biological samples. It promotes the expansion of compound databases, metabolomics information, and accessibility of chemical standards and it organizes a multi-laboratory analytical coverage test across European laboratories. A second mean of stratification is according to microbiome composition – at least if microbiome variability plays a role in ADME processes. Queries of microbial gene catalogs for genes of interest (encoding specific metabolizing enzymes) and assessment of their distribution (gene or microbe) across the human population has been demonstrated for enzymes such as rhamnosidase, demethylase and many others that are crucial for bioactivation. Thirdly, the gene variants subgroup will explore variability between human individuals in genes encoding biotransformation enzymes and transport proteins. Given the huge lack of knowledge in this domain, activities are at a very initial stage.</p> <p>WG2: Following the ongoing meta-analyses, study datasets examining the impact of plant bioactives on cardiometabolic risk factors available to COST members will be identified. Data sets will be merged, and analysis will be undertaken to identify responders and non-responders at individual and population group level using analyses such as clustering & PLSDA (partial least square discriminate analysis).</p> <p>Both WGs need to have fully exploited the data from their literature survey to be able to merge their results and define the stratification criteria/ metabolites usable for stratification.</p>
<p>6. Identify subpopulations of consumers that may particularly benefit from plant food bioactives</p>	<p>Partially</p>	<p>WG1: too early in the process</p> <p>WG2: Several meta-analyses of published work, examining the effect of plant bioactives and markers of cardiometabolic health are underway. Using the standardized protocol developed by the WG (see obj 3), several meta-analyses are underway including:</p> <ul style="list-style-type: none"> - flavonol intake & cardiometabolic risk factors - flavanol intake & lipid profile and BMI - flavanol intake & BP & FMD - anthocyanin, ellagitannins & cardiometabolic risk factors - phytosterols & cardiometabolic risk factors <p>Analyses within each of these meta-analyses are first done at a total population level, and subsequently at population group level (e.g. sex, BMI, age, disease, medication, ethnicity) where population group differences will be identified. All work is ongoing, and it is expected that at least four scientific papers will be published in 2016/17.</p>

<p>7. Develop guidelines/best practice for a full consideration of inter-individual variation in future research on the health effects of plant bioactives</p>	<p>Partially</p>	<p>This point will be fully addressed later. However, a subgroup of the TTG of ECIs is currently developing the project about ‘How to Report Interindividual Variability in Publications’ where one of the goals is to propose guidelines / checklist / suggestions / recommendations / opinion paper to cover the requirements necessary for correctly reporting data concerning inter-individual variability in the most accurate possible way in future papers. The information provided by the ongoing meta-analysis and prospective individual data analysis within WG2 will inform this process, outlining what information will need to be captured and how to report this in future publications.</p>
<p>8. Increase knowledge on/develop the potential of omic studies to supply new biomarkers for studying the health effects of plant food bioactives</p>	<p>Partially</p>	<p>WG1: The microbiome subgroup has been active in this respect and set out a strategy for trying to stratify human individuals for their conversion potency based on microbiome composition. One test case on microbial rhamnosidase activity was illustrated: the distribution of the rhamnosidase encoding gene over the microbiome and stratification of human individuals based on microbiome composition was carried out. This approach would primarily provide the group with an indicator of exposure. The metabolomics group has also been very active to compare the different analytical strategies for a wide coverage of compounds of interest with the multiplatform coverage test currently ongoing. From this test, the expected outcome is to develop a consensus metabolomics method of analysis for plant food bioactive exposure. In WG2, 3 subgroups were created to identify and put together molecular targets of plant food bioactives underlying cardiometabolic health. The literature analysis is underway, considering published studies performed in humans, animal models, and cells. This work involved over 30 partners from the WG2. Search criteria and standards for selection of papers have been defined with the aim to be as physiologically relevant as possible. Paper search has been done, and papers were screened for flavanols (working documents available for humans: HYPERLINK2; animals: HYPERLINK3; cells: HYPERLINK4). Bioinformatic analyses will be performed to select a group of genes and test if gene expression profile of these genes could be used as a biomarker of effect.</p>
<p>9. Identify knowledge gaps and methodological needs for future research and provide a consensus roadmap to encourage innovative scientific investigations in the area</p>	<p>Partially</p>	<p>WG1. Each methodology subgroup (metabolomics, microbiome variants, and gene variants) is involved in the identification of knowledge gaps. The metabolomics subgroup has advanced the most, particularly with the elucidation of the analytical coverage of plant bioactives and their metabolites in biological samples. On microbiome and gene variants, there are enormous gaps in knowledge in metabolic</p>

		<p>pathways and the involved enzymes as well as in proteins involved in the transport of metabolites across membranes and tissues. This can lead to novel ideas for submitting project proposals within an H2020 framework and it could even result in advising when drafting calls for H2020 proposals.</p> <p>WG2: The review paper on existing knowledge regarding interindividual variability in biological response written by WG2 highlighted the limited existing clinical and prospective studies which have investigated this topic. The meta-analyses that are currently underway will identify specific gaps in knowledge regarding which factors are responsible for variability in response, and will indicate the type of clinical studies that are needed in future research. The work conducted by the cell and molecular targets subgroup will identify the main pathways involved in the biological response and will give directions to researchers for future research in mechanisms of actions. In future work, WG2 will also assess and provide recommendations on the best methods to use for assessing inter-individual variability in biological response.</p>
<p>10. Provide a multidisciplinary training to early stage researchers and develop their leadership skills for future European research</p>	<p>Partially Achieved and Ongoing</p>	<p>The TTG of ECIs was initiated at the Opening Meeting of the Action (March 2015) with as the main objective of promoting an extensive exchange of knowledge and know-how between ECIs: http://www6.inra.fr/cost-positive/Working-Groups2/Think-Tank-Group</p> <p>During the first year, an on-line forum of discussion for ECIs was created, and regular meetings were organized to get to know each other, to ask for new proposals/suggestions within the COST Action POSITIVE, discuss scientific publications relevant to the Action, and present the research they perform related to the COST Action.</p> <p>In the second year, apart from the online meetings, the TTG identified a project whose purpose is to establish a quality index to evaluate the interindividual variability reporting in scientific papers. The main goal of this project is to assess dietary intervention studies dealing with plant food bioactives in reference to the quality of the inter-individual variability data reported, not only regarding cardiometabolic endpoints (WG2) but also regarding bioavailability (WG1). To reach this goal, two main interrelated tasks will be performed: 1/ the establishment of a quality index to express inter-individual variability in response to plant food bioactives; 2/ to propose suggestions/recommendations for how to report data concerning inter-individual variability. This project was suggested by a subgroup of ECIs during the 2nd meeting of the TTG (Bucharest, March 2016) and validated by the SC.</p>

		<p>WG1: Metabolomics webinar series (May 2016) and 4-day practical training school (July 2016) with priority given to ECIs: https://www6.inra.fr/cost-positive/Trainings/2016-Use-of-Metabolomics</p> <p>Details about this TS are provided in the section 'Additional outputs'. Five young scientists received grants from the Action to perform STSMs related to the activities of the WG1, including two that directly contribute to the tasks and deliverables defined for WG1.</p> <p>WG2: Several STSM have been undertaken by young scientists within WG2. Three of them involved work directly related to WG2 tasks. One of them involved a visit of a young scientist from Barcelona to Dublin, with the aim of developing protocols to initiate the conduction of meta-analysis in WG2. This was key for WG2 tasks to start and also gave the opportunity to the young researcher to learn useful new skills and write a first author publication currently under review. Another STMS was undertaken between Portugal, Spain, and the UK to trained 2 ECIs on how to conduct a meta-analysis. These ECIs are now leading several tasks from WG2 and are currently writing several publications related to this. These STSMs have provided invaluable help to progress in WG2 work, and more STSM are planned for this year. Another example of STMS was one performed between a group from Belgium and a group from France giving an opportunity for a young scientist to be trained and work on nutrigenomic effects of plant food bioactives and bioinformatic analyses. The collaboration was also important because it initiated the work on docking structure analyses between cell signaling proteins and bioactives. This work will continue in WG2.</p> <p>Another important multidisciplinary training event: "a training school on nutrigenetics /nutrigenomics" is currently being organized by WG2 and schedule for September 2017. This proposition of TS has been accepted by the SC. It will give opportunities to young scientists to interact with specialists in this field through webinars and 2-day face to face training. Partners involved in the organization of this training school have been identified as well as several potential speakers.</p>
<p>11. Increase the capacity building of the scientific community working on plant food bioactives</p>	<p>Partially Achieved and Ongoing</p>	<p>The main achievements of the Action in this way have been previously listed in the objective 1.</p> <p>The FG carried out some dissemination activities that have contributed to the capacity building and exchanges of the scientific community working in the field of Bioactive Compounds & Health, as well as to enhance the impact of the Action. These activities can be found at the POSITIVE website (http://www6.inra.fr/cost-positive/).</p>

		The specific achievements (together with links to the documents and website locations) are listed in the next section (MoU deliverables) and in the section I.E.
12. Foster exchanges between scientists, industry and regulatory authorities to fuel development of innovative applications from scientific findings	Partially Achieved and Ongoing	The POSITIVE network is a multidisciplinary and multisectoral network gathering scientists, members of regulatory agencies, representatives of the Food sector (national federations of food and drink, food companies) who interact together, especially in WG3 whose activities might grow in the second part of the Action.
13. Support the development of new strategies to increase plant food intake, and pave the way for future dietary recommendations for plant food bioactives	No	Planned for the last year of the Action
14. Identify perspectives for personalised nutrition applications based on inter-individual variation in response to plant food bioactives	No	Planned for the last year of the Action
15. Maximize the usefulness and the impact of POSITIVE on different scales and for different stakeholders/end-users through tailored communication and dissemination activities	Partially Achieved and Ongoing	<p>The dissemination activities carried out by the FG and that have contributed to the capacity building and exchanges of the scientific community working in the field of Bioactive Compounds & Health as well as to enhance the impact of the Action can be found at the POSITIVE website (http://www6.inra.fr/cost-positive/).</p> <p>The specific achievements are listed in the next section (MoU deliverables) together with links to the documents and website locations.</p> <p>FG also works to dissemination about POSITIVE to general public and industry locally, for instance:</p> <ul style="list-style-type: none"> - National/Local presentation of POSITIVE: Murcia (SPAIN) <ul style="list-style-type: none"> * Local radio: ROM Murcia (5th of March 2015) * Local Food Journals: CTC Alimentación (Issue December 2014) * Local Meetings: 1st Europe Direct Meeting in the Region of Murcia (I Encuentro Regional de Puntos de Información Europea, 3rd of March 2015) * Science Public events: The Science Weekend (11-13 November 2016) <p>WG3. Identification and prioritization of the deliverables that are most important for each of the different stakeholders and end-user groups. For that, a survey has been developed and translated (English, French, Spanish, Polish and Portuguese languages) to send out to stakeholders and end-users across Europe. Dissemination of the survey by POSITIVE partners who know and have personal contacts in each of the stakeholder and end-user groups.</p>

MoU deliverables

MoU deliverable	Level of progress ¹	Evidence of (partial) delivery achievement including a hyperlink to enable assessment of the delivery ¹ . Justification if full achievement is not foreseen
Primary deliverables		
1. Database existing knowledge on bioavailability of common plant food bioactives reporting between-subject variation	Finalized	WG1. A literature review has been finalized for eight chemical subgroups: Carotenoids, Anthocyanins, Lignans/Phenolic acids, Tannins, Flavanones, Flavonols, Catechins, and Phytosterols. HYPERLINK4.1
2. New paradigm and related methods to stratify individuals into defined metabolotypes	Partially	WG1. The metabolomics subgroup currently conducts an analytical coverage test across several European laboratories. This is necessary for later detection and quantification of biomarkers of exposure/bioactivity in biological samples and subsequent stratification according to metabolite status or 'metabotype.' HYPERLINK4.2
3. Identify gut microbiota species and activities of importance to explain inter-individual variation in metabolism	No	WG1. Too early stage
4. Identify variants of key genes which may modulate bioavailability of plant bioactives	No	Although currently virtually unknown, common variants in key genes involved in (a) bioactive absorption, metabolism, distribution and elimination (ADME), and (b) in the physiological regulation of health end points, are likely to be important in modulating the response to bioactives intake. A Gene Variant Subgroup gathering members from WG1 and WG2 has recently started to work on this aspect (4th WG meeting, Norwich, September 2016). See Minutes at HYPERLINK5 The analysis of the relevant literature on genotype*plant bioactive interactions would provide biological insight into the metabolism and metabolic impact of plant bioactives, inform future research design and could also contribute to the refinement of dietary recommendations and the targeting of sensitive and responsive population subgroups.
5. Establish the contribution of other factors, such as age, gender, dietary habits to the inter-individual variation in bioavailability	Partially	WG1. This is covered within the different plant chemical subgroups. Literature survey has been finalized. Conclusions regarding importance of determinants will be addressed in review papers
6. Critically review the existing tools and methods to evaluate the biological responses to plant food bioactives in humans regarding cardiometabolic endpoints	Partially	WG2. As part of the tasks that WG2 is currently undertaking, a systematic review of published data related to the impact of plant food bioactives on cell and molecular targets related to cardiometabolic health is currently ongoing. One of the aims of such review is to investigate the methodology used. A review paper on the best methods for evaluation of the biological responsiveness to plant food

		bioactive intake is planned to be written once the task is completed and data extracted from all the papers selected
7. Assess inter-individual variation in selected clinical and molecular biomarkers of cardiometabolic risk in response to plant bioactives consumption	Partially	WG2: Several meta-analyses are currently ongoing which will help us to assess the interindividual variability in clinical biomarkers of cardiometabolic risk. Reviews on molecular biomarkers are also underway to establish interindividual variability in response to plant bioactive consumption. Future work will examine datasets to determine biological responsiveness at an individual level and will build on the ongoing work in meta-analysis and reviews.
8. Determine to what extent variation in bioavailability can explain the variation observed in biological responsiveness	Partially	WG2. The review that has been performed by the WG on known interindividual variability has shown that there are very few studies demonstrating the role of bioavailability in variation in biological response, and such studies are limited to only one bioactive, the isoflavones. Such studies showed that the microbiota profile responsible for the production of equol has an influence on the variability in response to the consumption of soy protein containing isoflavones. Meta-analysis investigating the variability in response to several plant food bioactives are currently ongoing, and the role of bioavailability will also be evaluated. This work will be done in collaboration with WG1.
9. Identify factors beyond bioavailability that can contribute to the inter-individual variation in response to plant food bioactives consumption	Partially	WG2. Currently, five meta-analyses on different plant food bioactives are ongoing in WG2 investigating the factors that may contribute to interindividual variability in clinical biomarkers of cardiometabolic risk: flavanols, flavonols, anthocyanins and ellagitannins, phytosterols and chlorogenic acids. One of them, the flavonol group is the most advanced. Results have been presented (oral communication) in the COST session of the International Conference on Food Bioactives and Health (Norwich, UK, September 2016). Programme available at http://www6.inra.fr/cost-positive/Events/2nd-Scientific-Workshop-Norwich-2016 Also, a draft of a manuscript has been written and will soon be submitted to a peer review scientific journal. Data suggests that factors such as health status, medication, and ethnicity may have a major role in explaining the variability in response to food bioactives.
10. Evaluate the strength of scientific evidence which would allow the stratification of individuals based on their biological responsiveness	No	WG2. The factors affecting inter-individual variation in biological response that will allow stratification of individuals will be established depending on the results of the meta-analyses of different plant food bioactives that are currently ongoing, and based on the analysis of individual data from clinical studies of plant food bioactives that will be carried out within POSITIVE partners.
11. Evaluate how POSITIVE findings may be a lever to enhance the overall consumption of plant foods	No	WG3. Too early in the process

12. Establish among POSITIVE findings those of major interest for the development of novel foods by the Agro-Food Industry	Partially	WG3 designed and distributed a questionnaire to relevant stakeholders and end-users (such as the food and drink industry, business to business, public health bodies, retailers and consumer organisations) using SurveyMonkey; https://www.surveymonkey.co.uk/r/BF5S5FD The results will be collated and analysed for presentation at the next meeting in February 2017
13. A dissemination and communication plan targeting different categories of end-users	Partially achieved and Ongoing	<p>The presentation of goals and activities of the FG and the discussions carried out at meetings are summarized in the corresponding minutes, available at HYPERLINK6, HYPERLINK7; HYPERLINK8.</p> <p>The key achievements of the FG are listed in section IE. They include the development of the website and its regular update, the channels of the Action in social medias, the production of a range of dissemination products (bi-annual newsletter, flyer, poster).</p> <p>Other documents produced:</p> <ul style="list-style-type: none"> *Slides presenting POSITIVE: Slides introducing the project objectives and its expected impact were prepared by the FG. These slides may be used by the partners to present the Action during conferences and other meetings (sent to partners on request). * Questionnaire addressed to Food Industry and R+D leaders: (in collaboration with WG3) The questionnaire prepared has been translated into several languages, and disseminated through SurveyMonkey or by direct emailing to Food and Drink Industries and related Federations. The results will be used to produce an informative booklet designated to Food and Drink Industry. Then, the booklet will be translated into as many languages as possible to disseminate the information throughout Europe and other countries. * Questionnaire for general consumers: A questionnaire directed to general consumers has been prepared and will be disseminated initially in Spain through Science Public events. The questionnaire will be extended to other languages and countries. The results of these questionnaires will be used to design and release a booklet/card directed to the general public. Equally, the booklet will be translated into as many languages as possible for wide dissemination.
14. Development of a roadmap for future research projects and innovative initiatives in Europe	No	WG3. Too early in the process. This will be done based on the results obtained in WG1 and WG2. (Year 4)
*Secondary Deliverables		<i>*will be developed to varying extent depending on results from primary deliverables and on the commitment of partners</i>
15. Explore the feasibility of modelling inter-individual variation in bioavailability of bioactives using existing or	No	WG1. Too early stage. The conceptual idea is that human genome or microbiome databases can be queried for genes and metabolizing or transport proteins of interest.

new tools, for predictive purpose		This should feed into prediction tools that can assess variation in bioactive bioavailability and bioactivity.
16. Evaluate the usefulness of metabolomics to comprehensively assess individuals' exposure to plant food bioactives	Partially	WG1. Untargeted metabolomics is clearly relevant for assessing individual's exposure to plant food bioactive metabolites in a comprehensive way. The metabolomics subgroup explores the analytical coverage across several analytical platforms (GC-MS, LC-MS, NMR) to detect and quantify metabolites of interest as biomarkers of exposure. From this work a harmonized method will be proposed in a publication.
<p>**17. Evaluate the feasibility of developing phenotypic and/or (epi)genotypic tests to stratify individuals into defined metabolotypes and responder groups</p> <p>**18. Evaluate the feasibility of developing in-silico models correlating measurements of intake, exposure, and effects to predict the physiological relevance of plant food bioactives for each metabolotype</p> <p>**19. Provide the rationale to refine dietary recommendations regarding plant foods rich in specific bioactives, for population subgroups stratified on identified determinants</p> <p>** 20. Visualise what a personalised nutrition business based on inter-individual variation in response to plant bioactives would look like</p>	<p>No</p> <p><i>**Redefined during the first WG3 meeting</i></p>	<p>The 1st meeting of WG3 was organized in Murcia (September 2015) and it gathered academic and non-academic partners, including partners from different backgrounds and with different expertise, namely food scientists, nutritionists, experts in food regulation, representatives of the food and food supplement/ingredient industry, members of non-profit research companies, members of the food and drink federation. Minutes available at HYPERLINK9</p> <p>During this meeting, WG3 evaluated and assessed the feasibility of the tasks and deliverables proposed in the MoU, leading to the reformulation of concrete and manageable outcomes for the Action that are aligned with the activities in WG1 and WG2 and that are of direct benefit to stakeholders and end-users. Indeed, due to the limited amount of information that is currently available in the research area and considering the lack of funding to develop specific research, some of the deliverables initially planned seemed overambitious/unrealistic. Therefore, the overall consensus was to modify the tasks that are necessary to deliver as follows:</p> <ul style="list-style-type: none"> ○ Development of a computational on-line decision-tree-like tool that allows stakeholders and end-users to select from a large range of foods moving to the bioactives available in these foods, to the physiological health outcomes these bioactives can modulate, to the factors that determine the variability in response. The information required to set up this tool will be coming from the reviews published as part of WG1 and WG2 reviews/position papers. (Year 3-4) ○ Development of short movies/webinars to highlight success stories of fruitful academic-industrial partnerships of our POSITIVE members that are currently taking place or have already taken place. This could either be in the area of personalised or other related areas. The aim is to inspire stakeholders and end-users working in the field. These videos will be performed in close collaboration with the FG, and they will be made available on our website and through other (national) websites of interest to the food industry. (on-going) ○ Make accessible the main findings of POSITIVE for stakeholders and end-users: Extraction of relevant

		<p>information from the position paper of the Action and reviews published by WG1 and WG2 and make this information available under different forms: ppt presentations to be presented at meetings for industry partners, development of a technical white paper aimed at stakeholders and end-users which will be available from our website or as a booklet. This work will be done in close collaboration with FG. (Year 3-4)</p> <p>These deliverables will replace the previous ones (n° 17-20).</p>
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Co-authored publications and FP7/ H2020 proposals

The co-authored publications and FP7/ H2020 proposals/ projects resulting from the Action are listed on the page following the “Additional outputs and achievements” section

Additional outputs and achievements

<p>Please describe any other outputs and achievements that have resulted or are in progress, focusing in particular on those that contribute to the COST mission of “COST enables break-through scientific developments leading to new concepts and products and thereby contributes to strengthening Europe’s research and innovation capacities.”</p>
<p>Please describe any additional outputs and achievements from the Action</p>
<p>Outreach activities</p> <ul style="list-style-type: none"> • Organisation of the 1st scientific Workshop dedicated to Interindividual variation in response to plant food bioactives intake (26-27 October 2015, Tours, France) in the satellite to the 7th International Conference on Polyphenols and Health (ICPH, www.icph2015.com). <p>This workshop included eight invited conferences (6 given by COST partners and two by external guest speakers) and a round table between the speakers and the attendees that led to very fruitful discussions (http://www6.inra.fr/cost-positive/Events/1st-Scientific-Workshop-Tours-2015). Over 90 attendees participated in the workshop, 60% of them were ICPH attendees not members of the POSITIVE network. Most of the presentations (pdf) have been made available for POSITIVE partners on the private part of the website of the Action.</p> <ul style="list-style-type: none"> • Organisation of the 2nd POSITIVE Scientific Workshop as a part of the International Conference on Food Bioactives and Health (FBH, Norwich, 13-15 September 2016 (http://www.fbhc2016.com/)). <p>The FBH conference has attracted more than 250 participants from all over the world. A full plenary session (1/2 day) of this International Conference has been organised by the Action on the topic of POSITIVE (http://www6.inra.fr/cost-positive/Events/2nd-Scientific-Workshop-Norwich-2016). During this session two international experts in genetic polymorphisms and interindividual variation were invited (one from the Action and an external one), the leaders of WG1 and WG2 have presented the progress of the scientific activities of the network to the whole attendees (HYPERLINK9.1 ; HYPERLINK9.2) and 6 POSITIVE partners have presented original research related to the topic of POSITIVE</p> <ul style="list-style-type: none"> • Invitations to present the COST Action POSITIVE - Objectives/challenges and activities at several events and places in Europe (see details in I.E.) • Dissemination to industrial partners: Presentation of an overview of the remit of POSITIVE at the ILSI Europe - Obesity and Diabetes Task Force meeting (Brussels, Dec 2015) by the Prof AM Minihanne (MC member of the Action and academic advisor of ILSI Europe).
<p>Other Outputs</p>

- Organisation of a Training School on the “Use of Metabolomics in Nutrition Research”
<https://www6.inra.fr/cost-positive/Trainings/2016-Use-of-Metabolomics>

This TS has combined a series of theoretical courses, open to all through webinars (24, 26, 30 May, 2016), and a 4-day practical training for a limited number of participants (Barcelona, 5-8 July, 2016).

The webinar sessions have involved as trainers eight members of the Action (from 6 countries) and have been organized thanks to the provision of the license for webinars by the Grant Holder and with the technical support of a partner from Romania. The three webinar sessions gathered 42 to 54 attendees who were from 22 COST Countries. The videos of these webinar series have been put available for COST partners on the private part of the website of POSITIVE: serie1: [HYPERLINK10](#); serie2: [HYPERLINK11](#); Serie3: [HYPERLINK12](#). Twelve POSITIVE ECIs (from 10 COST countries), already familiar with metabolomics or interested to develop rapidly this approach in their lab, have received a grant from the Action to participate in the practical part of the TS organized at the University of Barcelona. This 4-days TS was coordinated by the Biomarkers & Nutrimetabolomic Research Group of the Pharmacy School-University of Barcelona (Prof C. Andres-Lacueva, Dr. R. Llorach) that is a leading group in the field of metabolomics in Europe and that has put his lecturers and cutting-edge equipment at the disposal of the training.

- Since the beginning of the POSITIVE, the COST Action has been acknowledged in 30 Articles published by POSITIVE partners (List available at: <http://www6.inra.fr/cost-positive/Dissemination/Publications>)

Research Projects related to POSITIVE

- Projects submitted by partners to obtain national support for scientific research within frame of the COST Action FA1403

- « Chemoenzymatic preparation of the metabolites of food bioactive quercetin for bioavailability studies » (Jan 2015-Dec 2017), Project Number LD15082
 Investigator: Dr. Kateřina Valentová (MC member, member of WG1)
 Institute of Microbiology, Czech Academy of Sciences; Czech Republic
 Funders: Ministry of Education, Youth, and Sports
- « Interindividual variation in response to plant food bioactives consumption » National grant "N DKOST01/10 (August 2016 – August 2018)
 Investigator: Dr. Elena Kistanova (MC member, member of WG2)
 Institute of Biology and Immunology of Reproduction, BAS, Sofia, Bulgaria
 Funders: NSF, Ministry of Education and Science of Bulgaria

- Projects spinning off from Action and including in the proposing consortium at least 2 Action participants from at least 2 different countries participating in the Action.

- “Prevention with Health-Food Education for Children and Elderly using Medicinal - Aromatic Plants (M.A.P) and nutraceuticals” (Under evaluation)

EU project for cross-border Cooperation, IPA program Greece – The former Yugoslav Republic of Macedonia

Project involving: Dr. Tatjana RUSKOVSKA (Faculty of Medical Sciences Goce Delcev University, Republic of Macedonia, MC member, WG2 member) and Dr. Christos KONTOGIORGIS (Democritus University of Thrace, Greece, MC member, WG2 member)

This submission directly results from the link established between partners in POSITIVE.

- « Lignin for the intestinal health of pigs and chickens » (submitted Sept 2016, under evaluation)

Main proposer: Anna-Marja Aura (VTT, Finland) (MC Member, WG1 member)

Action participants involved as international collaborators: Marion Leclerc (INRA, France, WG1 member) ; Ana Matias, Claudia Santos (Univ Nova de Lisboa, Portugal, MC member, WG1 member)

Funding Agency: Academy of Finland



The Action has helped in identifying and connecting with international collaborators who will broaden the expertise and know-how within the project.

Co-authored publications and FP7/ H2020 proposals

Co-authored publications

Enter in the table below only publications on the topic of the Action, co-authored by at least two Action participants from two different countries participating in the Action and for which the Action networking added value. A maximum of ten publications may be entered. If the Action has more than ten such publications the Core Group should select the ten most significant ones to include in the table below.

NO.	Bibliographic data (including Title, Authors, Title of the periodical or the series, Issue number or volume, Publisher, Year of publication, Relevant pages)	Main author	Number of authors	Action participants listed among the authors (Name, country and role ²)	WGs involved in publication	Date of submission (must be after Action start date)	Expected date of publication (if not already published)	Persistent link to publicly available version of the paper (if available) or the abstract	Is/Will open access ³ be provided to this publication?	Is/ will COST be cited/ acknowledged in the publication?	Are/ will COST funds (be) implicated in this publication	Relevance to H2020 Societal Challenges ⁴ ?	Is it peer-reviewed?	Was the added value of the Action Networking necessary for the publication	Impact Factor (if applicable)
1	<p>Addressing the inter-individual variation in response to consumption of plant food bioactives – towards a better understanding of their role in healthy ageing and cardiometabolic risk reduction.</p> <p>¹Claudine Manach*, ¹Dragan Milenkovic*, ²Tom Van de Wiele, ³Ana Rodriguez-Mateos, ⁴Baukje de Roos, ⁵María Teresa Garcia-Conesa, ⁶Rikard Landberg, ⁷Eileen R Gibney, ⁸Marina Heinonen, ⁹Francisco Tomás-Barberán, ¹Christine Morand (Position Paper accepted for publication in <i>Molecular Nutrition and Food Research</i>)</p>	<p>Manach and Milenkovic</p> <p>Corresponding author: Morand</p>	11	<p>Manach (MC subst, WG1 member, FR); Milenkovic (MC subst, WG2 member, FR); Van de Wiele (MC member, WG1 leader, BE); Rodriguez-Mateos (MC member, WG2 leader, DE); De Roos (MC member, WG3 leader, UK); Garcia-Conesa (MC subst, FG leader, WG2 member, ES); Landberg (MC member, co-leader WG1, EC, SE); Gibney (MC member, co-leader WG2, IE); Heinonen (MC member, co-leader WG3, Finland); Tomas-Barberan (vice chair, ES); Morand (Chair, FR)</p>	WG1, WG2, WG3	June 2016	<p>Mol Nutr Food Res. 2016 Sep 30. doi:10.1002/mnfr.201600557 [Epub ahead of print] Review. PMID: 27687784</p> <p>Issue published in January, 2017</p>	<p>Publication: HYPERLINK13</p>	Yes (in process)	yes	yes	yes	yes	yes	4.55
2	<p>Host Factors Influencing Aspects of Carotenoid Bioavailability in Humans.</p> <p>Torsten Bohn¹, Patrick Borel², Charles Desmarchelier², Lars O. Dragsted³, Charlotte S. Nielsen³, Wilhelm Stahl⁴ (Under favourable revision in <i>Molecular Nutrition and Food Research</i>)</p>	<p>Bohn</p> <p>Corresponding author: Stahl</p>	8	<p>Bohn (MC member, LU); Borel (MC member, FR); Desmarchelier (WG member, FR); Dragsted (MC member, DK); Nielsen (WG member, DK); Stahl (MC member, DE)</p>	WG1	July 2016	Early 2017	<p>Abstract : HYPERLINK13.1</p>	To be determined according to Action budget	yes	yes	yes	yes	yes	4.55

² MC Member/ MC Substitute/ MC Observer/ WG Member/ Training School Trainee/ STSM Recipient/ Other Action Participant

³ Open Access is defined as free of charge access for anyone via Internet. Please answer "yes" if the open access to the publication is already established and also if the embargo period for open access is not yet over but you intend to establish open access afterwards.

⁴ H2020 Societal Challenges are "Health, demographic change and wellbeing"; "Food security, sustainable agriculture and forestry, marine and maritime and inland water research, and the Bioeconomy"; "Secure, clean and efficient energy"; "Smart, green and integrated transport"; "Climate action, environment, resource efficiency and raw materials"; "Europe in a changing world - inclusive, innovative and reflective societies"; "Secure societies - protecting freedom and security of Europe and its citizens"

3		Milenkovic Corresponding author: Rodriguez-Mateos	9	Milenkovic (MC subst, FR) ; Morand (chair, FR) ; Cassidy (WG member, UK) ; Konic-Ristic (MC member, RS) ; Tomás-Barberán (vice-chair, ES) ; Ordovas (MC Subst, ES) ; Kroon (MC subst, UK) ; De Caterina (MC member, IT) ; Rodriguez-Mateos (MC member, WG2 leader, DE)	WG2	August 2016	Early 2017	Abstract: HYPERLINK13.2	To be determined according to Action budget	yes	yes	yes	yes	yes	5,20
		Interindividual variability in biomarkers of cardiometabolic health after consumption of plant food bioactives and the determinants involved: review Milenkovic D ¹ , Morand C ¹ , Cassidy A ² , Konic-Ristic A ³ , Tomás-Barberán FA ⁴ , Ordovas JM ⁵ , Kroon P ⁶ , De Caterina R ⁷ , Rodriguez-Mateos A ⁸ . (Accepted for publication in <i>Advances in Nutrition</i>)													
4		Garcia Aloy Corresponding author: Gibney	22	Garcia-Aloy (WG member, ECI, STSM recipient, ES) ; Andres-Lacueva (MC member, ES) ; Rodriguez-Mateos (MC member, WG2 leader, DE) ; Milenkovic (MC subst, FR) ; Heiss MC subst, DE) ; Istas (WG member, ECI, DE) ; Urpi-Sarda (WG member, ECI, ES) ; Morand (chair, FR) ; Monfoulet (WG member, ECI, FR) ; Kaltsatou (WG member, ECI, EL) ; Sakkas (MC member, EL) ; Konic-Ristic (MC member, RS) ; Kroon (MC subst, UK) ; Dumont (WG member, ECI, FR) ; Massaro (MC subst, ECI, IT) ; Curtis (WG member, ECI, UK), van Schothorst (MC member, NL) ; Gonzalez-Sarrias (WG member, ECI, STSM recipient, ES) ; Garcia-Conesa (MC subst, FG	WG2	September 2016	Early 2017	Abstract: HYPERLINK13.3	no	yes	yes	yes	yes	yes	2.75
		Inter-individual variability in response to the impact of plant bioactives on cardiometabolic biomarkers: a systematic review protocol Mar Garcia-Aloy ¹ , Cristina Andres-Lacueva ¹ , Ana Rodriguez-Mateos ² , Dragan Milenkovic ³ , Christian Heiss ² , Geoffrey Istas ² , Mireia Urpi-Sarda ¹ , Christine Morand ³ , Laurent-Emmanuel Monfoulet ³ , Antonia Kaltsatou ⁵ , Giorgos Sakkas ⁵ , Aleksandra Konic-Ristic ⁶ , Paul Kroon ⁷ , Julie Dumont ⁸ , Marika Massaro ⁹ , Peter Curtis ¹⁰ , Evert M. van Schothorst ¹¹ , Antonio Gonzalez Sarrias ¹² , Maria-Teresa Garcia-Conesa ¹² , Pedro Mena ¹³ , Margherita Dall'Asta ¹³ , Eileen R. Gibney ¹⁴ (submitted to <i>Systematic Reviews</i>)													

				leader, ES); Mena (WG member, ECI, IT); Dall'Asta (WG member, ECI, IT); Gibney (MC member, co-leader WG2, IE											
5		Menezes Corresponding author: Pinto	17	Menezes (WG member, PT); Rodriguez-Mateos (MC member, WG2 leader, DE); Kaltsatou (WG member, ECI, EL); González-Sarrías (WG member, ECI, STSM recipient, ES); Greyling (WG member, NL); Giannaki (MC member, CY); Andres-Lacueva (MC member, ES); Gibney (MC member, co-leader WG2, IE); Dumont (WG member, ECI, FR); Schär (WG member, UK); Garcia-Aloy (WG member, ECI, STSM recipient, ES); Milenkovic MC subst, FR); Durán; Ruskovska (MC member, MK); Maksimova (WG member, MK); Combet (WG member, UK); Pinto (MC member, PT)	WG2	Autumn 2016	2017	Abstract: HYPERLINK13.4	To be determined according to Action budget	Yes	yes	yes	yes	yes	
<p>Inter-individual variability in response to the intake of flavonols on biomarkers of cardiometabolic risk: a meta-analysis of randomized controlled human trials Regina Menezes¹, Ana Rodriguez-Mateos², Antonia Kaltsatou³, Antonio González-Sarrías⁵, Arno Greyling⁶, Christoforos Giannaki⁷, Cristina Andres-Lacueva⁸, Eileen Gibney⁹, Julie Dumont¹⁰, Manuel Schär¹¹, Mar Garcia-Aloy⁸, Dragan Milenkovic¹², Susana Durán, Tatjana Ruskovska¹³, Viktorija Maksimova¹³, *Emilie Combet¹⁴, *Paula Pinto¹ <i>(ready for submission)</i></p>															

FP7/ H2020 Proposals and projects

This table contains FP7/ H2020 proposals/ projects spinning off from Action activities and including in the proposing consortium at least three Action participants from at least three different countries participating in the Action.

NO.	Title	Name and country of main proposer	Number of proposers	Action participants listed among the proposers (Name, country, role ³ in the Action)	Funding agency submitted to	Date submitted	Date results expected	Result	Call identifier	Relevance to H2020 Societal Challenges ⁴ ?	Was the added value of the Action Networking necessary for the proposal / project?
Projects											
1	List FP7/ H2020 projects resulting from the Action in this section of the table										
2	« Food quality and food innovative strategies to prevent reproductive and eating disorders — REP-EAT »	University degli Studi di Teramo, Italy (Supervisory board member: Prof. Paola Pittia (Substitute MC, WG3 member)		COST Action identified as non-academic partner Contribution of POSITIVE to REP-EAT Action: Internal and external	H2020-MSCA-COFUND-2015			Accepted the call for the 12 PhD positions is	H2020-MSCA-COFUND-2015		It helped but was not crucial

				seminars, workshops, webinars, meetings				currently running			
Proposals											
List FP7/ H2020 proposals submitted as a result of the Action in this section of the table											
	" NUTritional Ageing and Extracellular Vesicles – NUTRAGEV"	R.Andriantsitohaina INSERM Angers, France	5	- INRA, France: D. Milenkovic (WG2 member), C. Morand (chair), LE Monfoulet (ECI, WG2 member) - Univ Duesseldorf, Germany; C. Heiss (Subs MC, WG2 member) ; A Rodriguez-Mateos (MC member, WG2 leader) - G d'Annunzio University of Chieti, Italy: R. de Caterina (MC member, WG2 member) - CNR Lecce, Italy: M. Massaro (WG2 member)	HDHL-JPI	April 2016		Unsuccessful	Call for Joint Translational Research proposals on "Biomarkers for Nutrition and Health" - JPI HDHL		yes
	« Modulation of arterio-ventricular coupling by berry polyphenols to prevent and improve heart failure with preserved ejection fraction »	Christian Heiss (Univ Duesseldorf, Germany, WG2 member)	5	Claudia dos Santos (Univ Nova de Lisboa, Portugal, MC member, WG1 member), Wim Van den Berghe (Univ Antwerp, Belgium, MC member, WG2 member), Christian Heiss and Ana Rodriguez-Mateos (Univ Duesseldorf, Germany, WG2 leader, WG2 members)	ERA CVD Joint Translational call	March 2016		Unsuccessful	ERA CVD Joint Translational call		Yes
	« Effects of polyphenol supplementation on cardiovascular disease prevention and progression	Ana Rodriguez-Mateos (Univ Dusseldorf, Germany, WG2 leader,)	8	Wim Van den Berghe (Univ Antwerp, Belgium, MC member, WG2 member), Antonia Kaltsatou, (Univ Thessaly, Greece, WG2 member), Daniele del Rio (Univ Parma, Italy, MC member, WG2 member), Ana Rodriguez-Mateos (Univ Duesseldorf, Germany, WG2 leader, WG2 members)	EU RISE (Research and Innovation Staff Exchange)	April 2016		Unsuccessful	Marie Skłodowska-Curie Research and Innovation Staff Exchange (RISE)		Yes
	The relevance of interindividual variability in plant food bioactives has been presented in a document to the H2020 representatives in order to be aware of the relevance of this topic in future calls of the European program. In this direction during October 2016, a topic on « Inter-individual variation and personalized foods » has been provided to some H2020 regional representatives in several participating countries to include them in the next calls 2018-2020 (Societal Challenge 2, domain of food security and food production).										

I.C. Networking

Added value of the Networking

Please describe here the added value of the networking, highlighting in particular anything that would not have happened without the Action networking.

- The network includes renowned expert scientists from different disciplines from all around Europe, representatives of the food and food supplement/ingredient industry, members of the food and drink federation, experts in food regulation (<http://www6.inra.fr/cost-positive/Organisation/All-Partners>). This composition provides us with a broad range of interdisciplinary expertises that will help to fulfill the deliverables of the Action.
- The writing of a collaborative position paper addressing the questions addressed in the Action and related challenges which are now accepted for publication in a special review issue of the high impact journal Molecular Nutrition and Food Research
- The first collaborative reviews resulting from the activities of the WGs are submitted (1 for WG1, 2 for WG2) or in preparation (1 for WG1, 1 for WG2); Half a dozen of other papers are foreseen before the end of GP3.
- The Initiation of concrete scientific collaborations between research groups partners of POSITIVE with (1) the funding of 13 STSMs since the beginning of the Action, (2) the establishment of several consortiums involving POSITIVE partners to apply to research calls.
- Creation of a Think Tank Group of ECIs (TTG) promoting a great exchange of knowledge and know-how among the European community of young scientists working in the field of plant food bioactives and health. This is done through monthly online meetings and by the organisation by the Action of an annual face to face meeting of the TTG. These meetings are providing a forum for discussion of specific scientific techniques, know-how, and approaches related to the inter-individual variation responses.
- Identification and Development by the TTG of a specific project aiming to establish best practices on “How to report interindividual variability in publications.” This project constitutes a perfect complement to WG1 and WG2 activities and provides add-value to the COST Action. The outcomes of this project will be of great interest to the scientific community aiming to understand the role of plant bioactive in human health. In particular, they will include the requirements necessary for correctly reporting data concerning inter-individual variability in the most accurate possible way in future papers.
- Thanks to the interest and willingness of some active members of WG1 who are also top-level experts in Metabolomics, the Action has organised its 1st Training School on the “Use of Metabolomics in Nutrition Research” (coordination Univ Barcelona). The programme of the webinars series of this TS has involved eight partners of the Action from six countries (<https://www6.inra.fr/cost-positive/Trainings/2016-Use-of-Metabolomics>). These webinar series on metabolomics were for European junior and senior scientists partners in the Action.
- The possibility of STSMs, particularly for applicants from ITCs, constitutes a unique opportunity for mobility, to realise and unlock their research potential by working with world-class food scientists and leaders in the field and deeper integration into ERA.
- Beyond developing and broadening their research competences, STSM grantees used their missions to gain training or experience in transferable skills that will support the outreach activities related to both their research and general POSITIVE aims and outcomes. These activities so far included : writing articles for the POSITIVE newsletter, posts and discussions at the POSITIVE Facebook site and other social media, lectures for undergraduate students, articles for the general public in national magazines, talks at national TV shows (an example is the successful participation of Dr. Nevena Kardum (ECIs, STSM recipient) to a national television show on public health 02/10/16 (<https://www.youtube.com/watch?v=gyy0YuGtNPo> , min 22:22, 43:55).
- Importantly, knowledge acquired during STSM is often transferred further to the POSITIVE scientific community, through coordination of activities within the Action. For example, two ECIs trained in meta-analyses during their STSMs are now the coordinators of meta-analyses works in WG2.
- In-depth discussion of the pharmacokinetic steps to which plant bioactives are subjected upon oral intake.
- Concerted efforts to have scientists from diverse expertise and disciplines go through an extensive literature search and check publications for their relevance in assessing interindividual variability in the absorption, distribution, metabolism and excretion of ingested plant bioactives, as well as in their bioactivity related to cardiometabolic endpoints.

- Exploit new microbiome gene catalogs for assessing the microbial diversity in specific metabolic and their distribution across the human population and stratification according to health status, age or gender.
- Organise a multiplatform metabolomics test across European laboratories to develop a consensus harmonized method for analysis of bioactives exposure in biofluids.

Extent of the networking

Describe the scope of the networking among the participants in the Action. Were all participants integrated into the networking equally? Were those targeted by COST policies on Inclusiveness Target Countries (ITCs), Early Career Investigators (ECIs)/ Young Researchers, and gender balance fully integrated into the Action networking?

Status of the network

Since the acceptance of the Action (16 countries involved) the network has grown quickly and substantially (27 countries at the kick-off meeting in Brussels, Dec 2014) reflecting the interested of the European scientific community for the question tackled in POSITIVE. At present (see: slides chair at the 3rd MC meeting_FA1403_ Norwich September 2016 at: [HYPERLINK14](#))

More than 75 research institutions from 32 countries are involved in the network (see booklet of participants at <http://www6.inra.fr/cost-positive/Download>), together with representatives from industry (8 National Federations of Food & Drink, and some large companies and SMEs) and regulatory authorities (EFSA). The network had over 270 participants providing multiple disciplines including nutritionists, clinicians, geneticists, epidemiologists, microbiologists, experts in nutrigenomics, bioinformatics, molecular biologists, biochemists and food scientists.

Regarding geographic distribution, the network involves: 15 CC countries with 56 research groups represented (176 partners); 15 ITC Countries with 28 research groups represented (92 partners); 1 CS state with three research groups (6 partners) and 1 NNC country with one research group (1 partner). There is a right balance between the number of participants per participating COST member state and that of the research groups involved. In POSITIVE, 27% of the members are ECIs and the Male/Female ratio is 40/60.

Promotion of target inclusiveness countries

In POSITIVE, 32% of the research groups involved and 33% of the total partners are from ITCs.

- Regarding invitations and attendance to meetings, over the Grant Periods 1&2 (Dec 2014 to April 2016) and including the 1st meeting of the GP3 (September 2016), a total of 394 invitations have been sent by the GH and 31.3% of them were for ITC, 311 partners attended these meetings (33% from ITC), including 244 who were refunded by the Action (33% from ITC). There is a right balance between these rates for ITC (31-33%) and the level of representation of ITC countries in the network.

- Regarding the organization of meetings, on the 3 WG meetings organized over the GPs 1 &2, two were organized in ITC countries (Serbia and Romania).

- Regarding the allocation of STSMs, on the 13 STSMs funded since the beginning of the Action, 6 benefited to ITC.

- In term of budget, on the period covering GP 1&2, 35% and 53% of the Action budget spent for meetings and STSMs respectively benefited to ITC countries. Thus, in total, ITC countries benefited from 37% of the total amount of the Action. This rate is well balanced with the representation of partners from ITC countries in the network (33%).

Gender Balance

The Gender balance for the invitations to meetings fits with that in the network (40% males, 60% females in both cases). Regarding STSMs, the gender distribution of researchers successfully granted in the first part of the Action was as follows: 9 female and 4 male scientists, reflecting their respective level of application. More balanced gender distribution will be addressed in the selection process during the next period. However, at the same time, the need for education and career development of experienced female scientists must be considered, knowing that gender balance in senior scientist population is still a relevant issue.

Promotion of ECIs

In POSITIVE a special attention is paid to the advancement of Early Career Investigators and for that several measures have been taken:

- The creation of the TTG of ECIs. The Action organize each year a face to face meeting of the TTG (joint to WG meetings) and the TTG organizes monthly online meetings. The TTG is coordinated by two young researchers who are nominated by its members and renewed each year to provide several ECIs an opportunity to lead a group. With the creation of this TTG, the objective of the Action was to favour the establishment of privileged relationships within the community of young scientists and foster their capacity building.
- Priority is given to ECIs for STSMs (until now, all grantees were ECIs and Ph.D. students). The full reports of accomplished missions are available on the website (<https://www6.inra.fr/cost-positive/STSMs/STSMs-2015>), (<https://www6.inra.fr/cost-positive/STSMs/STSMs-2016>) and successful stories from completed missions of ECIs regularly published in the POSITIVE newsletters. The extent of the networks established during all STSMs was supported by complementarities of home and host institutions, ensuring the long-term impact on candidates' career, beyond the duration of the Action.
- 2 ECIs are full members of the Steering Committee, one as WG co-leader and the second as STSMs coordinator. The ECIs who coordinate of the TTG are invited to sit at the SC of the Action.
- From the beginning of the Action, there is a right balance between the rate of participation of ECIs to meetings (30%) and their representation in the whole POSITIVE network (30%).

I.D. Impacts

The impacts that have resulted, or might result from the Action are described in the following table.

Description of the impact	Type of impact ⁵	Timing of impact ⁶
The position paper addressing the topic of the COST Action has been received with interest and expectation from the scientific community and will be used to sensitize stakeholders at different levels	Scientific	Achieved
Increased knowledge/skills of the POSITIVE community in Metabolomics thanks to the Training school, with a special impact on young scientists	Scientific	Achieved
Networking resulting from the COST has promoted the establishment of new collaborations between several research groups and already led to the submission of collaborative projects and topics for future research proposals at the European level	Scientific	Achieved
Scientific sessions organized by the action as a satellite to International meetings have been received with high interest and participation by scientists from different institutions that are not involved in the COST action and that show their willingness to collaborate in the present project and to be informed of future developments of the action.	Scientific	Achieved
A community of young scientists with high capacity building	Scientific/ technological	Foreseen in 2-5 years
Provide the scientific basis for future innovative spin-off projects	Scientific/ technological	Foreseen in 2-5 years
Foster exchanges between scientists, industry and regulatory authorities to fuel development of innovative applications from scientific findings	Scientific/ technological	Foreseen in 2-5 years
Identify subpopulations of consumers that may particularly benefit from plant food bioactives	Scientific/ Technological/ Societal	Foreseen in 5-10 years
Boost innovation and product development based on inter-individual variation in response to plant food bioactives	Scientific/ Technological/ Societal/ Economic	Foreseen in 5-10 years

⁵ Scientific/ technological, Economic, Societal

⁶ Achieved/ Foreseen within 2 years/ Foreseen 2-5 years/ Foreseen 5-10 years/ Foreseen 10+ years

Refinement of dietary recommendations for plant food bioactives	Scientific/ Technological/ Societal	Foreseen in 5-10 years
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I.E Dissemination and exploitation of Action results

Describe the Action's dissemination and exploitation approach as well as all activities undertaken to ensure dissemination and exploitation of Action results and the effectiveness of these activities.			
Add description here			
Item/ activity	Target audience	Result	Hyperlink
Active website	General scientific audience	Regularly updated with all POSITIVE events, links with other European initiatives and networks, promotion of POSITIVE workshops, minutes of MC meetings, etc.	http://www6.inra.fr/cost-positive/
Restricted area of website active	POSITIVE partners	Minutes of WG meetings, other working documents	http://www6.inra.fr/cost-positive/
POSITIVE COST Action summaries for dissemination	Scientific community	-Available in all languages of countries involved in the Action - Published at the website of Research Institutions/ organisations of POSITIVE partners - Introduce and expand the Action amongst the Scientific community and beyond	http://www6.inra.fr/cost-positive/Dissemination http://cebas.csic.es/Positive_Cost/positive_cost_eng.html http://www.ictan.csic.es/en/1240/ictan-participates-in-positive-cost-action-fa1403/ http://www.alimh.inra.fr/Toutes-les-actualites/COST-POSITIVE http://www.eufic.org/article/en/show/eu-initiatives/rid/Positive_COST_Action_Initiative/ https://www.iseki-food.net/webfm_send/2341
Facebook	Open for everyone	- POSITIVE in Facebook has promoted and shared different types of information: scientific articles of interest to the POSITIVE community, POSITIVE newsletters, announcements of scientific events of interest to POSITIVE partners, pics of different POSITIVE meetings and social events	https://www.facebook.com/costpositive/
Twitter	Open for everyone	- POSITIVE in Twitter has promoted and shared different types	https://twitter.com/Cost_POSITIVE

		of information: scientific articles of interest to the POSITIVE community, POSITIVE newsletters, announcements of scientific events of interest to POSITIVE partners, pics of different POSITIVE meetings and social events	
Booklet of research groups member of the network	Open for everyone	- Favour the mutual knowledge of partner group - Help in the identification of hosting groups for STSMs	http://www6.inra.fr/cost-positive/Organisation/All-Partners
Poster	Scientific community	- Summarizing the organization and objectives of the Action - Aim to introduce and expand the Action amongst the Scientific community	http://www6.inra.fr/cost-positive/Dissemination/Posters
COST Action Flyer	Scientific community	The printed version of this flyer is available upon request for dissemination at international workshops, conferences attended by partners	http://www6.inra.fr/cost-positive/Dissemination
Bi-annual POSITIVE newsletter	General scientific	-Issue 1, June 2015 -Special Issue, September 2015 (1st Scientific Workshop announcement) - Issue 2, December 2015 - Issue 3, June 2016 Aims to Introduce and expand the Action amongst the Scientific community	http://www6.inra.fr/cost-positive/Dissemination/Newsletter
11th NuGOweek nutrigenomics of foods (November 08-11th, 2014) Castellammare di Stabia, Italia	Scientific audience	Introduction of the Action (poster)	http://www6.inra.fr/cost-positive/Dissemination/Posters

4th International Conference of Food Digestion. Naples, 17-19 March 2015, Italy	Scientific audience	Invitation of the COST Action Infogest (FA1005) to present POSITIVE at its annual International Conference	https://colloque.inra.fr/cost_infogest_icfd2015
Research meeting of the FP7-REGPOT REFRESH Project, July 3-4, 2014, Olsztyn, Poland	Scientific audience	Presentation of objectives/challenges of the COST Action POSITIVE (chair)	
Scientific Seminar University of Belgrade, October 2014, Serbia	Scientific audience	Presentation of objectives/challenges of the COST Action POSITIVE (chair)	
1st COST-POSITIVE Scientific Workshop (in satellite to ICPH), October 25-26, 2015, Tours, France	Scientific audience	This workshop included an introduction of the Action, plenary lectures and a Round Table on "The future for plant food bioactives in personalized nutrition" involving speakers and the audience	https://colloque.inra.fr/workshop-cost-positive-2015 http://www6.inra.fr/cost-positive/Events/1st-Scientific-Workshop-Tours-2015
2nd COST-POSITIVE Scientific Workshop at the 1st International Conference on Food Bioactives & Health (September 13-15, 2016, Norwich, UK)	Attendees of the FBH Conference	POSITIVE workshop organized as a full session of the FBH Conference	http://www.fbhc2016.com/programme/
Metabolomic webinar series	POSITIVE partners	Videos available on the website of the private of the Action - Introduction to Metabolomics	serie1: HYPERLINK10 ; serie2: HYPERLINK11 ; serie3: HYPERLINK12

		<ul style="list-style-type: none"> - Data analysis and metabolites identification - Nutrimetabolomics in discovery markers studies 	
<p>Interview in the newsletter of ANIA (French National Federation of Food & Drink) – February 2016</p>	<p>Food Industry</p>	<p>Presentation of the COST Action POSITIVE</p>	<p>http://www.ania.net/recherche-innovation/cost-positive</p>



I.F. Action success(es)

COST regularly communicates the successes of Actions. At this point what aspect(s) (outcomes and/ or impacts, rather than activities) of this Action is/ are the most suitable for communication?

Description of the success story	Dimension of the success <ul style="list-style-type: none"> ■ Breakthrough: scientific, technological or socioeconomic ■ Policy implementation (specify which policy) ■ Capacity building
N/A	N/A

II. Management Report

II.A. Overview of expenditure

Insert below in the yellow cells the summary of figures from the Yearly Financial Reports (YFRs) of completed Grant Periods and an IFR of any incomplete Grant Period – the Totals (non-yellow cells) will automatically sum.

	Grant Period 1	Grant Period 2	Grant Period 3	TOTAL
GP start and end dates	(01/02/2015-31/08/2015)	(01/09/2015-30/04/2016)	(dd/mm/yyyy-dd/mm/yyyy)	
Grant Holder institution	INRA (FR)	INRA (FR)	INRA (FR)	
Meetings	EUR 49 093,16	EUR 94 574,97	EUR 40 187,82	EUR 183 855,95
Training Schools	EUR -	EUR -	EUR 8 776,48	EUR 8 776,48
STSMs	EUR 2 500,00	EUR 17 330,00	EUR 6 000,00	EUR 25 830,00
Dissemination	EUR -	EUR -	EUR -	EUR -
OERSA ¹	EUR -	EUR -	EUR -	EUR -
Total Scientific Expenditure	EUR 51 593,16	EUR 111 904,97	EUR 54 964,30	EUR 218 462,43
FSAC ²	EUR 7 738,97	EUR 16 785,75	EUR 8 242,45	EUR 32 767,17
TOTAL	EUR 59 332,13	EUR 128 690,72	EUR 63 206,75	EUR 251 229,60

¹ OERSA = Other Expenses Related to Scientific Expenditure (e.g. bank charges)

² FSAC = Amount received by Grant Holder for Financial Scientific and Administrative Coordination

II.B. Budget and Participation management

II.B.1 Budget spent in relation to individuals/ institutions outside participating COST countries			
<i>STSMs from or to institutions from countries other than Participating COST countries</i>			
The table below describes the added value STSMs to approved institutions in IPC or NNC or Specific Organisations and any STSMs from an approved institution in an NNC to a participating COST country.			
Grantee	Host	Date	Topic and value added to the Action

Institution	Country	Institution	Country	Date	Describe topic of the STSM and the added value to the Action
Add home institution and country		Add host institution and country		Date	Describe topic of the STSM and the added value to the Action
Add home institution and country		Add host institution and country		Date	Describe topic of the STSM and the added value to the Action
Add home institution and country		Add host institution and country		Date	Describe topic of the STSM and the added value to the Action

Invited Speakers

The table below highlights the added value of Invited Speakers from COST countries that have not accepted the MoU and/ or non-participating NNC, IPC or Specific Organisations whose participation at a meeting or Training School was reimbursed by the Action.

Participant name	Institution	Country	Event date	Topic and added value to the Action
Johanna LAMPE	Fred Hutchinson Cancer Research Center, Seattle	USA	25-26 October 2015	Topic: Interindividual differences in metabolism of plant food bioactives: impact on dietary recommendations Added value: this outstanding American expert in the domain addressed in POSITIVE shared her knowledge and contributed to fruitful exchanges with experts from POSITIVE and the audience at the roundtable organized concomitantly by the Action on "The future for plant food bioactives in personalized nutrition."
Peter JONES	Richardson Centre for Functional Foods and Nutraceuticals, Winnipeg	Canada	2nd COST Workshop, September 2016	Topic: Interindividual variation to lipid-lowering sterol esters and PUFAs: probing the reasons why Added value: This leading expert presented his original research on interindividual variation in response to plant sterols intake. Participation of Dr. Jones to the plenary session of the 4th WG meeting to share with POSITIVE partners his view of how to consider genetic factors and plant food bioactives response
Add	Add	Add	Add	Describe the speaker's topic and the added value to the Action

Dissemination meetings

The table below highlights the added value of Dissemination Meetings financed from Action funds.

Participant name	Role	Country	Date	Location	Topic and added value to the Action
Add	Add	Add	Add	Add	Describe the speaker's topic and the added value to the Action

II.C. Participants

Management Committee		
Name	Country	Email address
Copy MC Member name, country and email address from e-COST into the relevant columns		
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Annex 1

Definitions:

COST Action Challenge (main aim)	“The research question addressed by the COST Action targeting scientific, technological, and / or socioeconomic problems.”
COST Action Innovation	“The creation and / or development of new or improved concepts, products, processes, services, and / or technologies that are made available to markets, governments, and society.”
COST Action objectives	“COST Action objectives are the results that an Action needs to achieve to respond to meet its challenge. These are SMART (Specific, Measurable, Achievable, Relevant, Timely) and twofold: research coordination objectives and capacity building objectives.”
COST Action research coordination objectives	“Achieving these objectives turns COST Actions from initially scattered teams into one transnational team and leverages the existing funded research. These objectives entail the distribution of tasks, sharing of knowledge and know-how, and the creation of synergies among Action participants to achieve specific outputs.”
COST Action capacity building objectives	“Achieving these objectives entail building critical mass to drive scientific progress, thereby strengthening the European Research Area. They can be reached by the delivery of specific outputs and / or through network features or types and levels of participation.”
COST Action networking activities	“any activities organised by the COST Action (whether or not directly funded by COST) to achieve research coordination and capacity building objectives.”
COST Action networking tools	“instruments through which eligible activities can be funded.”
COST Action outputs	“direct results from the COST Action activities. These can be codified knowledge, tacit knowledge, technology, and societal applications.”
COST Action Impact	“the short- to long-term scientific, technological, and / or socioeconomic changes produced by a COST Action, directly or indirectly, intended or unintended.”
COST Action deliverable	“a distinct, expected and tangible output of the Action, meaningful regarding the Action’s overall objectives such as a report, a document, a technical diagram, software, etc. Action deliverables are used to measure its progress and success.”
COST Action milestones	“Control points in the Action that helps to chart progress. They are also needed at intermediary points so that, if problems have arisen, corrective measures can be taken. A milestone may be a critical decision point in the Action where, for example, the MC must decide which of several technologies to adopt for further development (e.g. core group and MC meetings, mid-term reviews)”
Inclusiveness Target Country (ITC):	Current COST Member Countries targeted by the COST inclusiveness Policy (“Inclusiveness Target Countries” (ITC)): EU 13 (Bulgaria, Cyprus, Czech Republic, Estonia, Croatia, Hungary, Lithuania, Latvia, Malta, Poland, Romania, Slovenia, Slovakia), EU candidate countries (the former Yugoslav Republic of Macedonia, Montenegro, Republic of Serbia, Turkey) and potential EU candidate countries (Bosnia and Herzegovina). Also, to comply with the EC criteria for ‘Spreading Excellence and Widening Participation,’ Portugal and Luxemburg are included.