European Cooperation in the field of Scientific and Technical Research
- COST -

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COST 035/14

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action FA1403: Interindividual variation in response to consumption of plant food bioactives and determinants involved (POSITIVe)

Delegations will find attached the Memorandum of Understanding for COST Action FA1403 as approved by the COST Committee of Senior Officials (CSO) at its 190th meeting on 14 May 2014.

MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as

COST Action FA1403
INTERINDIVIDUAL VARIATION IN RESPONSE TO CONSUMPTION OF PLANT FOOD BIOACTIVES AND DETERMINANTS INVOLVED (POSITIVe)

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 4114/13 "COST Action Management" and document COST 4112/13 "Rules for Participation in and Implementation of COST Activities" , or in any new document amending or replacing them, the contents of which the Parties are fully aware of.

2. The main objective of the Action is to create a European multidisciplinary and inter-sectorial network to tackle the question of the inter-individual variation in response to plant food bioactives consumption in relation to cardiometabolic health.

3. 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 64 million in 2014 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of section *2. Changes to a COST Action* in the document COST 4114/13.

A. ABSTRACT AND KEYWORDS

To combat the burden of cardiometabolic disease, which constitutes a major public health issue in Europe, it is of crucial importance to develop efficient strategies that target the dietary behaviours of European consumers and improve the food supply. Plant foods are rich sources of a large range of bioactive compounds that beneficially affect our health, particularly by decreasing the risk of cardiometabolic diseases. However, heterogeneity in individuals' responsiveness to plant food bioactives can obscure associations between dietary intakes and health, hinder the identification of health benefits for specific population groups and limit our understanding of the exact role of the different bioactives.

POSITIVe specifically addresses inter-individual variation in bioavailability and physiological responses to consumption of plant food bioactives in relation to cardiometabolic endpoints. This Action will coordinate a multidisciplinary and multisectorial European network, harness and combine the currently fragmented knowledge and ensure the optimal translation of findings into applications. It will promote the leadership of European research in this active and high-profile research field, provide scientific knowledge to regulatory authorities for a new generation of nutritional recommendations targeted to large population subgroups and foster the competitiveness of the European food industry by underpinning the development of new functional/customized foods.

Keywords: Plant food bioactives, cardiometabolic health, inter-individual variation, bioavailability, nutrigenomics

B. BACKGROUND

B.1 General background

Cardiometabolic disease, which comprises cardiovascular diseases, type 2 diabetes mellitus, and their associated risk factors including metabolic syndrome and obesity, is the leading cause of death worldwide and a significant public health issue. It is estimated that patient care and indirect costs represent more than 192 billion euros a year for the EU economy. Population studies provide convincing evidence that up to 80% of cardiometabolic disease could be avoided through lifestyle changes - hence the urgency to establish effective strategies targeting physical activity and dietary behaviour of European consumers and to stimulate the food industry to produce healthier, sustainable foods. Beneficial effects of increased plant food consumption on cardiometabolic health

have been shown by both large population based studies and randomised controlled trials. Plant foods are rich sources of a range of potential bioactive compounds including polyphenols, carotenoids, glucosinolates, and phytosterols, recognised as promoting health and reducing risk of cardiometabolic disease. The real impact of these bioactives and their mechanisms of action are not totally elucidated. Research in this field is very active in Europe, as illustrated by previous COST Food and Agriculture Actions (916, 926) and eight FP7 projects.

On the other hand, clinical research has shown that individuals respond differently to nutritional interventions and may experience more or less benefits from particular dietary components. This inter-individual variation to plant bioactive intake has been little explored to date, although it undeniably exists (see B2). Its main determinants and their relative contribution have not been studied in any previous international project or COST Action.

Heterogeneity in responsiveness can obscure associations between dietary intakes and health outcomes and hinder the identification of the effects of plant food bioactives in specific subpopulations. The determination of the main factors responsible for inter-individual variation (age, gender, (epi)genotype, microbiota, etc.) and the identification of "susceptibility profiles" in response to plant bioactive consumption may lead to targeted dietary advices and functional foods customised for population subgroups. This COST Action offers a collaborative initiative in which leading European academics from a range of disciplines (e.g. nutritionists, clinicians, geneticists, bioinformaticians, microbiologists, molecular biologists, epidemiologists, biochemists), who do not currently have optimal ways to integrate and communicate together, and experts from regulatory agencies and industry will join efforts to focus on:

1. the evaluation of the magnitude of inter-individual variation in bioavailability and biological responsiveness for the diverse families of common plant food bioactives,
2. the identification of the main determinants of this variation,
3. the definition of the best ways to address these points in future research projects and the potential concrete applications for end-users.

By raising awareness and enabling networking, training and dissemination activities, POSITIVe will do exactly what is required at the present time to place European researchers at the forefront in this emerging field of plant food bioactives and personalised nutrition. The coordinating network of POSITIVe, unique in the European (and world-wide) panorama, will foster collaboration between existing research groups and with different stakeholders, avoid redundancies in research efforts, and allow the emergence of synergies in the highly competitive field of research on the impact of plant food bioactives on human health. Such holistic and collaborative approach will be an ideal

environment for mentoring young scientists in the successful development of future European research projects. This network will certainly lead to the discovery of innovative research areas and submission of joint proposals for Horizon 2020. Through new strong connections established within POSITIVe, the capacity building of the research community is expected to last long after the Action is completed.

B.2 Current state of knowledge

Plant food bioactives are found in a vast range of fruits, vegetables, grains and plant derived beverages such as coffee, tea and wine. Although they are not essential nutrients, there is increasing evidence that many of them may help to promote optimal health and reduce the risk of chronic diseases. In this respect they have been qualified as "lifespan essential" (Holst and Williamson 2008). Major plant food bioactives with anticipated health benefits are polyphenols, carotenoids, plant sterols and glucosinolates. Some of these compounds have a wide distribution whereas others are mainly found in specific foods, e.g. glucosinolates in cruciferous vegetables or lycopene in tomato. Accumulating evidence from cohort studies and randomised controlled trials has shown that increased intake of plant food bioactives may reduce the risk of coronary heart disease, stroke and type 2 diabetes (Soory 2012, van Dam et al., 2013). For example polyphenol-rich foods and beverages can improve endothelial function, platelet function, insulin sensitivity and decrease blood pressure (Habauzit & Morand, 2012). Plant food bioactives exert their biological activities through a large panel of mechanisms, e.g. acting as modulators of enzyme activities, as signaling molecules and modulators of gene expression, DNA methylation or gut microbial functionality. On the other hand, personalised nutrition (which is firmly within the remit of the Horizon 2020 'Personalised Health and Care' focus area in Societal Challenge 1) is a rapidly recognized paradigm in nutrition research which emerged from the observation that substantial between-subject variation exists in response to dietary interventions, due to both genetic and non-genetic factors. Therefore some population subgroups may gain more benefit than others from the consumption of plant foods and their bioactives. However the determinants of this variability are not known and better knowledge is needed to develop efficient strategies to optimise the beneficial effects of plant food consumption for everyone and inform the provision of targeted dietary advice.

Inter-individual variation in bioavailability of plant food bioactives

The bioavailability of plant food bioactives is complex and subject to large inter-individual variation. Some compounds can be absorbed in the small intestine, but most of the glycosylated, polymeric or esterified native plant compounds are hydrolysed and metabolised by the gut

microbiota. After absorption, bioactive compounds and their microbial metabolites undergo phase I (oxidation/reduction reactions) and phase II (β-glucuronidation, sulfation, methylation, glutathione conjugation) metabolism. Several metabolising phenotypes, or "metabotypes", exist depending on the concentration and activity of intestinal carriers and of post-absorptive phase I and phase II metabolizing enzymes, or the composition and activities of the gut microbiota of the subject, many of which will be influenced by the genotype of the individual.

Thus, for the same dietary intake, exposure to bioactive metabolites can markedly differ between individuals. As an example, a wide inter-individual variation in blood and tissue concentrations of carotenoids has been consistently observed in healthy subjects, which could not be explained by differences in dietary intakes. This has led researchers to suggest that some subjects were "non-responders" to carotenoids. Several studies recently demonstrated associations between carotenoid status and variants of genes encoding proteins involved in carotenoid absorption and metabolism, such as *SR-BI* and *CD36*, which are involved in carotenoid uptake by intestinal cells, and *BCMO1*, which is involved in carotenoid cleavage into vitamin A (Borel, 2012; Ferrucci et al., 2009). Although it is likely that other factors may contribute to inter-individual variation in carotenoid status, it is now assumed that this is partly due to genetic variations in genes that encode proteins involved in carotenoid absorption and metabolism.

Another well-known example of a marked inter-individual variation in plant bioactive metabolism is the conversion of the soy isoflavones daidzin/daidzein to equol by the gut microbiota. Only 25-35 % of the Western population and 50-70% of the vegetarian and Asian populations possess the ability to produce equol from these precursors, and producers have been reported to gain more health benefit from soy consumption than equol non-producers (Setchell et al., 2013). Bacteria involved in the conversion have been identified, but the determinants that govern the daidzein metabolizing phenotype have not been fully elucidated yet. Identification of these determinants would lead to the development of intervention strategies or food processes to stimulate equol production in non–equol producers. The gut microbiota is also involved in the metabolism of most plant food bioactives, in particular lignans and ellagitannins (Espin et al., 2013; Landete 2012).

Recent advances in metagenomics and knowledge of the intestinal microbiota opened new perspectives for studying the implication of microbiota in inter-individual variation in bioavailability of plant food bioactives. The European MetaHit project (FP7) showed that the microbial communities could be classified into just 3 enterotypes characterised by the predominant bacterial population: Bacteroides (enterotype 1), Prevotella (enterotype 2) and Ruminococcus (enterotype 3) (Arumugam et al, 2011). The association between enterotypes and the individual capacity to metabolise plant food bioactives certainly deserves further investigation (Bolca et al.,

2013).

On the other hand, it is very likely that host genetic and epigenetic variations in metabolising enzymes could be a major determinant of individual metabotypes. Pharmacogenomics studies have long demonstrated that for some drugs, individuals can be categorised into poor, intermediate or extensive absorbers or metabolisers and dosing has to be adapted. The genetic variants involved have been compiled in online databases. Plant food bioactives are absorbed and metabolised through the same polymorphic carriers and enzymatic systems as drugs, thus their pharmacokinetics is also likely to depend on genetic background. Caffeine is a plant bioactive for which the importance of genetic polymorphisms has been demonstrated. Caffeine is mainly metabolised by CYP1A2 in the liver. Subjects with the *CYP1A2*1F* variant associated with a low enzyme inducibility, are considered as slow caffeine metabolisers compared with the rapid caffeine metabolisers carrying the wild-type allele (Sachse et al, 1999). Slow caffeine metabolisers have been shown to be at increased risk of hypertension and myocardial infarction, whereas rapid caffeine metabolisers might safely drink coffee (Palatini et al, 2009). The modulation of the activity of phase II biotransformation enzymes is likely to affect the duration of exposure to bioactive metabolites and consequently the biological response as conjugated metabolites are more rapidly excreted than native compounds. Several variants exist for genes encoding glutathione S-transferases (GSTs), which play a major role in the metabolism of glucosinolates present in cruciferous vegetables. After broccoli consumption, the bioavailability of isothiocyanates was shown to be 20% higher in *GSTM1* null subjects than in GSTM1 positive subjects (Gasper et al, 2005). This is of significance as the prevalence of the null allele for *GSTM1* has been estimated at 40-60% (Riso et al, 2009). Variants for UDP-glucuronosyltranferases could also be of importance for plant food bioactives (Lampe et al., 2009).

Beyond genetic background and enterotypes, other factors such as age, gender and dietary habits may affect the bioavailability of plant food bioactives. For example, a gender difference has recently been found in the glucuronidation of resveratrol, a polyphenol present in grapes and wine, which may be explained by gender specific UDP-glucuronosyltransferase isoenzyme expression profiles regulated by sex hormones (Dellinger et al, 2013). Another important factor could be the dietary habits. Some dietary phytochemicals such as polyphenols and glucosinolates can induce or inhibit the activity of phase I and phase II enzymes. Furthermore diet is known to influence microbiota diversity and activity (Moco et al., 2012).

As illustrated by the examples above, there is a body of evidence that various factors can affect the bioavailability of plant food bioactives through different mechanisms. These factors must now be studied in a more systematic and integrative way to determine their relative importance for each

familly of bioactive compounds. Sharing of knowledge and skills available in all partner laboratories will ensure a more holistic approach to address this question.

Because of the inter-individual variation in bioavailability, the link between dietary intake and internal exposure must be characterised in depth. In the vast majority of epidemiological studies, health outcomes are related to intake data, estimated from dietary questionnaires and tables of food composition without taking into account the bioavailability. Also in intervention studies, the diet or supplementation is usually standardized but this does not guarantee equal exposures among volunteers due to the large inter-individual variation in metabolising capacity. Methods for measuring exposure to bioactive metabolites are crucially needed. Metabolomics has emerged as a very promising tool to analyse in human biofluids a large number of the small metabolites derived from food digestion (Manach et al., 2009; O'Sullivan et al, 2011). With this approach comprehensive profiles of bioactive metabolites present in urine or plasma could be related to health outcomes in intervention and observational studies. Clusters of subjects with distinct biological responses could be identified and the metabolites associated with these responses determined. Another option to assess individual exposure would be to develop *in-silico* models that could take into account dietary intakes as well as determinants of the inter-individual variation in plant food bioactive bioavailability. The usefulness and limitations of metabolomics, modelling and alternative approaches for assessing individual exposure to plant bioactive metabolites need to be evaluated to develop efficient biomarkers and tools.

Inter-individual variation in biological responsiveness to plant food bioactives

Compared to the inter-individual variation in bioavailability, between-subject variation in biological responses to the consumption of plant food bioactives has been less studied and the aetiological basis for this variability has rarely been considered. Individual data are rarely published. It is important to emphasize that a biological effect occurring only for a subgroup of subjects can be overlooked when data are averaged for all subjects without any appropriate stratification.

For example, in post-menopausal women, consumption of soy isoflavones resulted in decreased blood pressure and improvement in endothelial function for only 30% of volunteers. The effects would not have been seen with averaged values. The volunteers who benefitted from soy isoflavones intake were found to be equol producers (Kreijkamp-Kaspers et al, 2005), suggesting that the inter-individual difference in the metabolism of bioactives may play a major role in the variation in biological responsiveness. On the other hand, a recent study showed that consumption of flavan-3-ol-enriched dark chocolate resulted in decreased platelet aggregation in a subgroup of volunteers, while this effect could not be correlated with plasma or urine concentrations of flavan-3-ols metabolites (Ostertag et al, 2013). Further analysis of the results with a stratification based on

gender revealed a significant beneficial effect for flavan-3-ols in men but not in women. These observations suggest that inter-individual variation in biological responses is not solely due to variation in the bioavailability of plant food bioactives but can depend on other factors, such as gender. Several clinical studies investigated the variations, according to age and gender, in vascular response to consumption of a flavanol-rich drink in the recently completed European project FLAVIOLA (FP7). Age-dependent differences were observed in response to flavanols at the level of blood pressure whereas only low variations were observed with age and gender at the level of endothelial function (Heiss, Rodriguez-Mateos et al., unpublished data). A significant inter-individual variation has also been described for LDL-cholesterol lowering response to plant sterol consumption, which was associated with the polymorphism of *ABCG8* gene (Rideout et al, 2012). The subjects carrying the A allele of the gene were reported to get a greater benefit from plant sterol intake. Taken together, these studies suggest that inter-individual variation in biological responsiveness to plant food bioactives exists and may be controled by several factors including bioavailability, genetic background, age or gender.

The development of high-throughput "omics" technologies (epigenomics, transcriptomics, proteomics, metabolomics) and bioinformatics has enabled researchers to go deeper in the analysis of the complex mechanisms that are involved in the way the organism responds to plant food bioactives and thus, ultimately impact human health and well-being. For example, the consumption of hesperidin from orange juice has been shown to change leukocyte gene expression towards an anti-inflammatory and anti-atherogenic profile in healthy men (Milenkovic et al, 2011). Nevertheless, the inter-individual variation in the expression profiles of genes involved in the regulation of cardiometabolic health in response to plant food bioactives has never been evaluated in humans. Nutrigenomic studies should reveal genes and expression profiles which could be used as new biomarkers of susceptibility to plant food bioactives.

In conclusion, research in the field of inter-individual variation in the response to plant food bioactive consumption and the determinants involved is presently highly fragmented and many research gaps remain. There is an urgent need to gather and compare existing data for a comprehensive and integrative view of this issue. The strength of the POSITIVe network will be to bring together top-level experts in cutting-edge technologies (metagenomics, nutrigenetics, nutrigenomics, metabolomics) and in forefront research fields such as human gut microbiota or personalised nutrition.

B.3 Reasons for the Action

Reasons for launching, benefits

The central scientific question of POSITIVe is multi-disciplinary. Identification of the main determinants of inter-individual variation in response to plant bioactive consumption requires sharing of up-to-date knowledge in various disciplines, e.g. nutrition, metabolism, molecular biology, cardiometabolic health, (epi)genetics, epidemiology and microbiology. Furthermore, research communities working on the diverse families of bioactive coumpounds (polyphenols, carotenoids, phytosterols, glucosinolates) do not sufficiently exchange so far. Combining this diverse expertise will result in cross-fertilization of ideas and approaches which will ensure that the determinants of inter-individual variation will be considered in a truly integrative way and ensure that the "whole" is greater than "the sum of its parts". This will not happen without a COST Action to structure a large collaborative network of scientists.

POSITIVe is a timely initiative, essential to better coordinate and integrate previously fragmented research efforts across Europe and it coincides with several European research priorities. In particular, the topic of POSITIVe is in line with priorities of H2020 regarding "Agro-food sector for a safe and Healthy diet", with the expectations of the European JPI "Healthy Diet for Healthy Life" in the area of food, nutrition and health, as well as with the Strategic Research and Innovation Agenda of the ETP Food For Life (2013-2020 and beyond) particularly with the challenge 2 "Improve Health, Well-being and Longevity". By providing a structured European research network in the area of plant food bioactives and personalised nutrition, POSITIVe will give Europe a head start, allowing it to strengthen its world-wide leadership role in this promising scientific field. POSITIVe will enhance the potential of on-going nationally funded projects, identify research gaps and hence define pertinent research priorities for Europe. It will also provide an ideal environment for mentoring young scientists for successful development of future European research projects.

Scientific/technological advancement & economical/societal needs

There is strong evidence for a direct link between diet and health. Consumers have embraced this message resulting in an increasing demand for food with health benefits beyond its normal nutritive value. On the other side, it is attractive for Agro-Food companies to try to gain a share in a global functional food market estimated at a value of €25 billion in the European market. Industry is particularly interested in functional foods and personalised nutrition in a context of commercial markets with large consumer segments. However, scientists need to understand the objectives, expectations and constraints of Agro-Food companies and conversely the latter need to understand the difficulties researchers face in translating ideas and findings into economically or societally relevant concepts. This COST Action will foster a better mutual understanding.

The consumption of plant foods is largely encouraged in all European countries through national public health policies. However, there is an urgent need to refine the current advice and provide targeted recommendations towards particular foods rich in specific bioactives or through more focused public health messages. An increased knowledge of the factors that control whether bioactives are effective or not in individuals for the preservation of cardiometabolic health will be invaluable to promote a new generation of more refined nutritional recommendations. Thereby, POSITIVe aims both at scientific/technological advancement and at answering economical/societal needs.

Outcomes, means

This COST Action will produce concrete outcomes:

- Knowledge resources (databases, guidelines & best practices, lists of determinants/targets/variants of major interest, review and position papers, …)
- Research priorities and roadmap for future research based on consensus
- Transfer of knowledge and skills to the next generation of scientists
- Connecting dispersed research communities
- Transferable scientific findings and initiation of spin-off projects with industry.

To achieve the objectives and obtain the outcomes, a range of specific means will be used:

- Networking through WG meetings, Action workshops, sharing of resources via website (see D2, E1/2, F)
- Dissemination through the POSITIVe website, e-newsletter, publications, communications in international conferences, professional/technical journals, press releases (see H)
- Training through thematic Training Schools, exchange of know-how and skills (STSMs) (see E1).

POSITIVe will aim for maximally productive outcomes by:

- Performance management of working groups
- Bringing together key scientists and relevant stakeholders whose role will be decisive for future applications of the Action findings
- Inviting external experts in specific research area on an ad hoc basis.

- Creation of a Think-Tank group providing a stimulating environment and fostering commitment and shared leadership within the community of Early-Stage Researchers (ESRs)
- Maintaining the framework of the Action flexible.

B.4 Complementarity with other research programmes

The outputs of this Action will be complementarily tied to already existing national and European research projects within the FP7 and COST programmes. This will avoid duplication of efforts and facilitate the exchange of information. POSITIVe will have many interactions with:

- FP7-Food4Me project, which analyses challenges and opportunities for personalised nutrition in the field of essential nutrients and micronutrients, but which does not include plant food bioactives. Food4Me will produce scientific outcomes, tools and resources that will be precious for POSITIVe,
- FP7-BIOCLAIMS, aiming at developing nutrigenomic-based early predictive biomarkers for applications in human nutrition
- other ongoing FP7-KBBE projects that are concerned with better understanding of the health effects of food bioactives, but without addressing the question of inter-individual variation: i) BACCHUS, aiming at developing tools and resources to facilitate the generation of scientific evidences to support claims for consumption of bioactive peptides and polyphenols to maintain cardiovascular health; ii) PATHWAY-27, addressing the role and mechanisms of action of selected bioactives, known for their efficiency in reducing some cardiometabolic risk factors
- COST Actions: i) FA1005-INFOGEST, in which food digestion models are developed that may be useful for POSITIVe and ii) FA1001-FOODSTRUCTUREDESIGN aiming at developing intelligent food structures to ensure optimal delivery of bioactives to targeted physiological sites.

POSITIVe will also have link with NuGO, the international Nutrigenomic Organization that evolved from an EU Framework Network of Excellence. NuGO aims at stimulating developments in nutrigenomics, nutrigenetics and nutritional systems biology, and incorporating these aspects in nutrition and health research.

C. OBJECTIVES AND BENEFITS

C.1 Aim

The main objective of this Action is to create an open European scientific network to tackle the question of the inter-individual variation in response to plant food bioactives consumption, and work with industry and regulatory authorities to translate the findings in terms of innovation and refined dietary recommendations. The major expected benefits will be to strengthen the international leadership of the European scientific community in the field of plant food bioactives and cardiometabolic health, to foster competitiveness of the European Agro-Food industry and to help policy makers in refining public health strategies to improve the health and well-being of European populations.

C.2 Objectives

The overall aim of this multidisciplinary and inter-sectorial network will be achieved through the following secondary objectives:

Scientific objectives:

1. 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.
2. Identify the main determinants, beyond variation in bioavailability, of the inter-individual variation in the biological responsiveness to the consumption of plant food bioactives
3. Increase understanding of what could be the optimal exposure that will ensure the best benefit from plant food bioactive intake regarding cardiometabolic endpoints
4. Develop a paradigm and related methods to stratify individuals into defined metabotypes and responder groups
5. Identify subpopulations of consumers that may particularly benefit from plant food bioactives whilst also examining subgroups who may be at risk following high intakes
6. Develop guidelines/best practice for a full consideration of inter-individual variation in future research on the health effects of plant bioactives

7. Elucidate the potential of "omic" studies to supply new biomarkers for studying the health effects of plant food bioactives: biomarkers of exposure, susceptibility biomarkers (related to metabotypes/responder groups), biomarkers of effect
8. Identify knowledge gaps and methodological needs for future research and provide a consensus roadmap to encourage innovative scientific investigations in the area.

Operational/translational objectives:

1. Provide a multidisciplinary training for Early Stage Researchers (ESR) and develop their leadership skills for future European research
2. Strengthen the capacity building of the scientific community working on plant food bioactives
3. Foster exchanges between scientists, industry and regulatory authorities to fuel development of innovative applications from scientific findings
4. Support the development of new strategies to increase plant food intake, and pave the way for future dietary recommendations for plant food bioactives
5. Identify perspectives for personalised nutrition applications based on inter-individual variation in response to plant food bioactives
6. Maximize the usefulness and the impact of POSITIVe on different scales and for different end-users through tailored communication and dissemination activities.

C.3 How networking within the Action will yield the objectives?

The interest in POSITIVe was overwhelming; more than 50 researchers from 36 academic and 2 private institutions as well as 7 national federations of the Agro-Food sector representing Small to Medium Enterprises (SMEs), so far expressed their interest to join this Action and actively contributed to the MoU.

No equipment or specific infrastructure will be required to achieve the objectives listed in C1 and C2. A range of specific means including networking, dissemination and training activities will be developed:

Networking will be achieved through WG meetings, Think-Tank meetings for ESRs, Action workshops, joint publications, databasing and sharing of resources via the secured part of the POSITIVe website. **Dissemination** activities include the POSITIVe website, an e-newsletter,

publications in peer reviewed or professional/technical journals, position papers, communications in international conferences, booklets, press releases. Dissemination activities will be supported by experienced partners in the field of providing to targeted audiences easily understandable science-based information in nutrition. **Training measures** are based on thematic Training Schools and STSMs to exchange know-how and skills.

C.4 Potential impact of the Action

POSITIVe will:

1. Set up an interdisciplinary network bringing advances in the global understanding of the inter-individual variation in the response to plant food bioactives
2. Improve harmonisation and standardisation of methods to more accurately assess inter-individual variation
3. Improve evaluation of the benefits induced by plant bioactives on cardiometabolic health by considering different “susceptibility profiles” in response to consumption
4. Foster harmonisation of national research efforts to avoid overlaps and help concerted actions at the European level
5. Promote the establishment of new collaborations, interdisciplinary cross-fertilisation, exchange of know-how and expertise between partner institutions and strengthen existing collaborations
6. Develop capacity building of the research community on plant bioactives and health, which will last long after the COST Action will be completed
7. Improve training and education of young European researchers in this key research field for the future
8. Strengthen dialogue with end-users and ensure research activities are in line with their needs
9. Provide the scientific basis for future innovative spin-off projects
10. Disseminate cutting-edge results to support the development of new functional/customized foods and increase the European Agro-food industry competitiveness

11. Provide more targeted dietary advices, thereby reducing the social and economic burden resulting from cardiometabolic diseases
12. Contribute, with other European initiatives, to improve lifelong health and well-being of EU populations through improved nutrition and reduce health care costs.

C.5 Target groups/end users

The target groups and end users are the following:

- Scientists researching/teaching in the areas of food, nutrition and health, metabolism, cardiometabolic health, nutrigenetics, nutrigenomics
- Policy makers from national and international bodies
- SMEs, spin-outs and industries involved in functional food production, human nutrition or health management
- Public health and regulatory authorities
- Health care professionals and dieticians
- The ultimate end user shall be the consumer.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The understanding of the importance of plant food bioactives in human nutrition, particularly regarding the prevention of cardiometabolic diseases, could be dramatically improved by in depth knowledge of the factors contributing to inter-individual variation in response to their consumption. This requires integration, assembly and critical analysis of the current fragmented knowledge to identify the main determinants affecting the bioavailability and physiological responses in relation to cardiometabolic endpoints for the main families of plant food bioactives. Based on the findings that will emerge, an integrative and prospective view of possible implications for the different end-users will be developed. To reach these goals, the following main research tasks have been envisaged:

Main Research Tasks of the Action

1. Database (for the first time) existing knowledge on bioavailability of common plant food bioactives, including pharmacokinetics data, mechanisms, molecular players and reported between-subject variation*
2. Evaluate the strength of scientific evidence which would allow the stratification of individuals based on their metabotype, i.e. their relative ability to absorb/metabolise common plant food bioactives*
3. Identify the functional properties of specific microbial groups or even gut microbiota species of importance to explain inter-individual variation in metabolism and try to correlate metabotypes with identified human enterotypes§
4. Identify variants of key genes which may modulate bioavailability of plant bioactives§
5. Assess the contribution of other factors, such as age, gender, dietary habits to the inter-individual variation in bioavailability*
6. Explore the feasibility of modeling inter-individual variation in bioavailability of bioactives using existing or new tools, for predictive purpose§
7. Evaluate the usefulness of metabolomics for the comprehensively assessment of individuals' exposure to plant food bioactive metabolites§
8. Critically review the existing tools and methods to evaluate the biological responses to plant food bioactives in humans regarding cardiometabolic endpoints*****
9. Assess inter-individual variation in selected clinical and molecular biomarkers of cardiometabolic risk in response to plant bioactives consumption.*****
10. Determine to what extent variation in bioavailability can explain the variation observed in biological responsiveness*
11. Assess the contribution of other factors, such as age, gender, life-style to the inter-individual variation in clinical biomarkers and molecular responsiveness in response to plant food bioactives consumption*
12. Evaluate the strength of scientific evidence which would allow the stratification of individuals based on their biological responsiveness*
13. Evaluate the feasibility of developing phenotypic and/or (epi)genotypic tests to stratify individuals into defined metabotypes and responder groups§

14. 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 metabotype§
15. Evaluate how POSITIVe findings may be a lever to enhance the overall consumption of plant foods, at least in populations with increased cardiometabolic risk*
16. Provide the rationale to refine dietary recommendations regarding plant foods rich in specific bioactives, for population subgroups stratified on identified determinants§
17. Establish among POSITIVe findings those of major interest for the development of novel foods by the Agro-Food industry*
18. Visualise what a personalised nutrition business based on inter-individual variation in response to plant bioactives would look like§
19. Prepare a communication plan that i) defines key messages; ii) establishes target audiences; iii) selects the appropriate modes of communication and communication tools; and iv) tailors information to the intended outlets and deliver*
20. Determine research priorities in the areas of scientific research, industry and public health*

**: priority tasks; §: will be developed to varying extents depending on results from priority tasks and commitment of POSITIVe partners for the task.*

Structure and flexibility of the plan: The frame of the work plan will be sufficiently flexible to permit, if needed, the inclusion, all along the Action, of new disciplinary perspectives and activities not included in the MoU. Consequently, the Action will be open access to new partners during the whole course of the Action.

Achieving the plan: The objectives of POSITIVe will be achieved by stimulating and organising collaborative work on concrete outcomes between scientists from different disciplines, representatives of regulatory agencies and industry, and experts in scientific dissemination. Young scientists will play an essential role in the activities. Effective communication tools and a robust protocol to monitor and evaluate the achievement of the objectives will be implemented (See E1).

D.2 Scientific work plan methods and means

To reach its scientific goals, the Action will be structured into three interacting Working Groups

(WG) with specific objectives, and one Focus Group (FG) in charge of the Dissemination plan of POSITIVe:

- WG1: Inter-individual variation in bioavailability
- WG2: Inter-individual variation in the biological responsiveness regarding cardiometabolic endpoints
- WG3: From emerging science to applications
- FG: Communication and Dissemination of scientific information

To minimise fragmentation, a limited number of WGs has been envisaged. However, it might be necessary to form subgroups (SGs) within each WG to address more specific questions. In this case, a SG Leader will be nominated and will report to the WG Leader.

WG1- Inter-individual variation in bioavailability

This WG will bring together scientists from various specialties: nutritionist experts in the bioavailability of different classes of bioactives, microbiologists, geneticists, epidemiologists, food technologists, experts in metabolomics and mathematical modelling. The aim of the WG will be to identify the main factors which modulate the bioavailability of plant food bioactives and to improve methods and tools to assess individual exposure. WG1 will respond to the objectives 1, 3-8 (see C2) by developing the research tasks 1-7 and 13 (see D1).

Expected concrete outcomes:

- Drawing of metabolic pathways for the various bioactives including carriers, enzymes and bacteria involved and integration of the validated pathways in online open-source databases such as HMDB, KEGG, FooDB, PhytoHub
- Determination of the range of plasma metabolite concentrations observed after dietary doses of bioactives of each family
- List of factors among sex, age, genetic background, physiological/health status, as well as habitual dietary intakes and food processing/preparation practices which substantially affect bioavailability for each family of bioactives
- List of genes likely to affect bioavailability, their SNPs and structural variants with associated frequencies

- List of microbiota families/microbial enzymes associated with inter-individual variation in the metabolism of the different bioactives as well as factors affecting their presence and activities
- Consensus opinion on the usefulness of in vitro models (digestion models, genetically–defined human liver microsomes, etc.) and of *in silico* tools (metabolism prediction, pharmacokinetic modeling) to study inter-individual variation in metabolism and provide data for modeling. List of technological needs.
- Consensus opinion on the usefulness of metabolomics to measure individual exposure to bioactives and their metabolites. List of research gaps and technological needs.

Methods: Systematic reviews and non-systematic literature surveys, additional analyses and interpretations of published data and possibly new data made available by the partners during the Action. Knowledge databases with standardized operating procedures for data selection and data entry.
Means: WG meetings, invitation of external experts to discuss specific points in depth, STSMs, Action workshops and seminars, networking with other ongoing European initiatives.
Deliverables: Online database; WG reports; scientific review papers; communications in international conferences.

WG2 - Inter-individual variation in the biological responsiveness regarding cardiometabolic endpoints

WG2 will bring together scientists from various specialties, such as clinicians, nutritionists, geneticists, epigeneticists, molecular biologists, bioinformaticians. The aims of WG2 are to assess the biomarkers related to cardiometabolic disorders, the inter-individual variation of these biomarkers in response to the consumption of plant food bioactives and to identify the underlying determinants. WG2 will respond to the objectives 2-7 (see C2) by developing the research tasks 8-13 (see D1).
Expected concrete outcomes:

- Consensus on physiological processes (e.g. vascular function, lipid metabolism), associated clinical biomarkers and molecular targets to be covered, as well as methods and tools, including "omics", for their assessment
- Determination of the plasma concentrations of bioactive metabolites presenting beneficial/potentially detrimental effects

- List of cellular pathways involved in between-subject variation in biological responses
- List of factors among sex, age, physiological/health status, bioavailability, dietary patterns, life-style, etc. which affect biological responsiveness
- List of candidate genes likely to affect biological responsiveness, their SNPs and structural variants with associated frequencies
- Consensus opinion regarding translatability of mechanistic and physiological data, including biomarkers, from animal studies to humans.

Methods: Systematic reviews and non-systematic literature surveys, additional analyses and interpretations of published data and possibly new data made available by the partners during the Action, integrative bioinformatics analyses of the different 'omics datasets, knowledge databases with standardized operating procedures for data selection and data entry.
Means: WG meetings, invitation of external experts to discuss specific points in depth, STSMs, Action workshops and seminars, networking with other ongoing European initiatives.
Deliverables: WG reports; scientific review papers; communications in international conferences.

WG3 - From emerging science to applications

A large community of European experts including scientists from different disciplines also involved in WG1 or WG2, as well as representatives from the regulatory agencies and Agro-food industry will constitute this WG. This WG will ensure continuous exchange between WGs for integrating outcomes from WG1 and WG2 and will identify the findings that will have the greatest impact. WG3 will work in close connection with the Focus Group in charge of translating scientific findings into key messages for the different end-users (see C5). The aim of WG3 will be to compare and align the objectives, as well as to integrate the constraints of academic scientists with those i) of the agro-food industry to boost innovation and product development, and ii) of public authorities responsible for the derivation and refinement of dietary recommendations. To achieve this aim, WG3 will respond to the objectives 4-6, 8, and 11-13 (see C2) by developing the research tasks 14-18, and 20 (see D1).

Expected concrete outcomes:

- New paradigm for the stratification of individuals based on their ability to absorb and metabolise plant bioactives (metabotype) and to respond to their consumption
- Bases for the development of predictive bioinformatic tools for modelling inter-individual variation in bioavailability and biological responsiveness to bioactives

- Guidelines for ensuring inclusion of inter-individual variation in future research on the health effects of plant bioactives
- Scientific basis for dietary recommendations regarding plant foods rich in specific bioactives for stratified population subgroups
- Scientific basis for the development of innovative and healthy foods targeted at large population subgroups, e.g gender, age, low metabolisers/responders, taking into consideration also the health claim regulation
- Scientific basis for the development of innovative tools (interactive devices, websites, mobile applications…) for individual counselling along personal profiles of determinants affecting the bioavailability and responsiveness to bioactives
- Initiation of spin-off projects with industry
- Prospective vision of a future personalised nutrition business based on inter-individual variation in response to plant bioactives (driving forces, players, opportunities and threats)
- Roadmap for future innovative initiatives in Europe.

Methods: Integration of the Action findings and partners' experiences; Exchanges between experts.
Means: WG meetings, Action workshops, Invitation of external experts (such as international experts in personalised nutrition, policy makers…) to discuss specific points in depth; networking with other ongoing European initiatives.
Deliverables: WG reports; position papers; communications in international conferences, booklets.

FG - Communication and Dissemination of scientific information

Successful dissemination of the POSITIVe results is considered essential for the long-term impact of the Action and for the benefit of academics and other end-users. The focus group will support the Steering Committee in the dissemination activities of the Action. Among its members will be partners highly experienced in communicating science-based information for diverse publics, who will work in tight connection with Steering Committee members, including WG Leaders, Training coordinator and the Website coordinator responsible for the conception and updating of the POSITIVe website. The FG will be led by a Dissemination Coordinator who will also be a member of the Steering Committee. To reach its main objectives 9, 10, 14 (see C2), the FG group will have to fulfil the task 19 (see D1), divided in the following subtasks:

- Continuously review and update the communication plan, as well as the processes and procedures of dissemination;
- Develop and deliver with partners different communication material;
- Communicate and disseminate the findings of POSITIVe to key target audiences, including the scientific community and relevant stakeholders and end-users
- Liaise & communicate with all relevant communication experts to maximise information exchange, and share resources and experiences.
- Contribute to the organisation of Training Schools, workshops including one addressing industry and the final conference.

***Expected concrete outcomes*:**

- A well-defined and regularly updated communication plan for an effective dissemination
- Production of communication materials (see H) for different targeted audiences
- Creation of privileged ties and communication with SMEs networks and links with current projects and networks or future European initiatives.

***Means*:** Discussions with WG Leaders and other SC members; participation to WG meetings and Action workshops.

***Deliverables*:** Project website, project leaflets, e-newsletters, publications in professional/technical journals, podcasts, Web-based seminars, booklets, press releases.

E. ORGANISATION

E.1 Coordination and organisation

POSITIVe has attracted interest from at least 16 COST countries at its start, reflecting a wide European dimension.

The Action will be carried out according to "Rules and Procedures for Implementing COST Actions". In a kick-off meeting, the Management Committee (MC) will elect the Action Chair, Vice-Chair, WG Leaders, a Dissemination Coordinator, a Training Coordinator and a Website Coordinator. All these elected persons will form the core of the Steering Committee (SC). After the kick-off meeting, **the Management Committee** (MC) will meet once a year (see F) to evaluate the Action progress. The MC will be responsible for coordination and management of the Action

activities by:

- Validating the establishment of the WGs, and other management groups outlined in the MoU
- Approving the proposals of Training Schools and workshops, with respect to the budget
- Reviewing and approving applications for STSMs
- Coordinating financial activities within the Action
- Managing reporting obligations, including revision of annual and final reports
- Approving the introduction of new participants to the Action
- Validating the recommendations of the Steering Committee on the strategic direction of the Action

The Steering Committee (SC) will include, in addition to the members elected by the MC, the Leader and Vice Leader of the WGs (appointed within each group), and two Early-Stage Researchers (ESRs) representatives of the "Think-Tank" Group. The SC will meet face to face annually and will regularly communicate through conference calls and e-mails.
The SC will be in charge of monitoring all activities towards the objectives of the project in order to deliver the scheduled outcomes in due time and within the budget. The following actions will be performed to monitor and evaluate the achievement of the objectives:

- A monitoring protocol, approved by MC, will be defined at the start of the Action. It will describe the assessment of a set of monitoring indicators on a six-monthly or annual basis, generally shortly before reporting to the COST Office.
- Monitoring indicators include the number of meetings organised, the amount of communication material produced, the quantity of items uploaded to the website, the number of scientific publications in international and national journals produced and the observance of the timeline for any activity.

In addition, the SC will:

- Propose adjustments of the Action framework and scientific work plan to the MC for approval, when necessary
- Ensure the establishment and maintenance of the POSITIVe Action website for both internal communication and external dissemination

- Propose the annual program of activities (workshops, trainings schools, group meetings, STSMs) an present it to the MC for approval
- Decide the publication policies and dissemination actions according to the plan described in section H
- Present the annual provisional budget of the Action to the MC for approval
- Implement links to other related programmes and bodies at a European and international levels for scientific exchange and potential collaboration
- Elaborate annual and final reports and submit them to the MC.

Within the SC, three delegates will be in charge of particular tasks:

- The Dissemination Coordinator, who will also be the leader of the Focus Group, will coordinate all the dissemination activities of the Action, as detailed in D2.
- The Website Coordinator will be responsible for the conception and updating of the POSITIVe website, which is the primary communication and dissemination channel of the Action. He/She will work closely to the Dissemination Coordinator and will be assisted by ESRs involved in the Action.
- The Training Coordinator will be responsible for handling the applications for STSM, developing and regularly updating a Training Opportunities Database referencing all relevant events inside and outside the Action, and organizing the Training Schools. He/She will be assisted by ESRs.

Two specialized committees will be formed:

A Workshop Organizing Committee (WOC) renewed every year, will be responsible for the organisation of the annual workshops and final conference that will take place in various COST countries. The WOC will consist of local organisers and representatives of each WG. It will be chaired by the local organiser, elected by the MC. The WOC will set the scientific programme and be in charge of the practical organisation of the event. The WOC chair will report progress in the organisation to the SC and write a report including financial features for the MC after closure of the event. At the closure of each annual workshop, the topic and the location of the next event, as well as the WOC composition will be proposed by the SC for approval by the MC.

The Think-Tank Group: gathering the ESRs from the participating countries, it will promote an extensive exchange of knowledge and know-how at their level. Innovative ideas, concepts or strategies to address the Action issues are also expected from the Think-Tank. The launching and

maintaining of interactions within this group of young scientists will be ensured using the Open Space Technology. This self-organizing practice releases the inherent creativity and leadership in people within a group. Two representatives of the Think-Tank will be appointed as members of the SC, giving them the opportunity to regularly communicate on the ideas and suggestions raised by the group. Beyond the regular meetings of the Think-Tank group, members will also have the opportunity to continuously exchange through the forum on the website of the Action. The Think-Tank will be an excellent mean of promoting the establishment of privileged relationships within the community of young European researchers involved in the Action. These tight connections will be a major advantage for the construction of future collaborative projects.
Whenever possible, the SC and MC meetings will be held respectively on the first and the last day of each major annual event of the Action (workshops, final conference) (see F). In addition, web-based or videoconferences will be scheduled by the SC on an ad-hoc basis for a smooth progression of the Action workplan. As far as possible, issues will be solved by e-mail and conference calls. All electronic communicating tools will be also highly encouraged for the exchanges within the different committees and Working Groups. The decision-making process in the SC and MC will be the result of a collegial discussion and if the board fails to agree, decision will be done by majority voting.

E.2 Working Groups

As presented in the section D, the scientific programme of POSITIVe will be developed by three Working Groups (WG) and the dissemination activities of the Action will be assigned to a Focus Group (FG).
Each WG will be coordinated by a Leader and a Vice Leader. They will be responsible for the management of their WG and the achievement of deliverables scheduled and validated by the SC and MC. They will ensure good communication between all partners of the WG and best use of the partner skills to deal with the different WG tasks. To monitor straight progress of the scientific programme, an excel file “proforma” will be written for each task, available on the protected, internal POSITIVe website. It will describe all individual activities to be conducted in order to achieve each deliverable, with persons in charge and deadlines agreed by the WG. The proforma will have to be regularly updated by WG Leaders, at least every 3 months, and before and after each WG meeting. WGs will have their own email list, and a shared working space in the Action’s website. At each WG meeting, the members will decide the priority tasks, distribute the tasks among them depending on their expertise and skills, and report on work made in subgroups between

the meetings. Each WG Leader will report to the SC and MC on the progress of the WG in relation to the deliverables achieved and on any issues causing delays. They will propose contingency plans if deliverables are delayed or not achieved.
All participants in the network, according to their expertise and interest, will be invited to join at least one WG. Members will be free to move between WGs and cross-WG-memberships will be encouraged to have different disciplines represented in all WGs. The active involvement of the ESRs in all WGs especially the multi-sectorial WG3 will be stimulated.

E.3 Liaison and interaction with other research programmes

The Action will be an open platform for discussion and active collaborations with other related European research projects and ongoing COST Actions (as detailed in B4). Several experts who already expressed their interest in participating in POSITIVe also coordinate or participate in these projects or networks. They will serve as the primary contact point, which should greatly facilitate interactions.
To promote exchange of information and synergies, the SC will:

- invite Leaders of research programmes or networks related to the present Action to participate to POSITIVe workshops and final conference, to link their web pages to the Action's web site and to join forces for the organization of meetings and Training Schools
- offer the possibility for ESRs involved in these projects to join the Training Schools organised by this Action, and conversely. In particular, we will foster active contacts with the European Nutrigenomic Organization (NuGO) which organises many training events in the field of nutrigenomics, nutrigenetics and nutritional systems biology.

The connecting activities will secure proper alignment and synergy with related projects, thereby helping to further consolidate the fragmented research pattern of this particular scientific area within the ERA.

E.4 Gender balance and involvement of early-stage researchers

The coordinator of this COST Action is female and 46% of the participants who so far expressed their interest in POSITIVe are female. At the moment of the election or nomination of persons in responsibilities, special attention will be devoted to the gender balance.

Training and promoting employability of a new generation of creative and entrepreneurial young researchers in line with the key drivers of future innovative research in Europe is a crucial objective of POSITIVe. The Action will be committed to considerably involve ESRs and foster their capacity building. ESRs will be given priority for STSM and will be encouraged to present their work in Training Schools and workshops organised in the Action. These activities will contribute to the mobility of the ESRs, and will help them expand their contact networks. ESRs will play an active role in the Action. The organising committees of each workshop will systematically include at least two ESRs. A network of ESRs will be created to function as a Think-Tank and to promote an extensive exchange of knowledge at this level. Two representatives of this Think-Tank will be members of the SC, with a regular renewal of the representatives to provide many ESRs an opportunity to sit on it. An ESR will assist the Training Coordinator and he/she will be in charge of the Training Opportunities Database. ESRs will also be invited to participate to MC and SC meetings as auditors. Active involvement of ESRs in the WGs, especially in the inter-sectorial WG3 and the Focus Group, and in preparation of their annual reports will be strongly stimulated. All these activities will give the ESRs an exceptional exposure to project management, to interdisciplinary and inter-sectorial sharing of ideas and they will be inclined towards public engagement.

F. TIMETABLE

The POSITIVe Action will have a total duration of four years. The Action will start with the Kick-Off meeting of the MC. The core of the SC will be set up. Three months later, a first meeting gathering all Action participants will be organised. The Action framework, the COST instruments and the main lines of the scientific programme will be presented. The composition of the WGs will be defined and first WGs meetings will be held. A concerted effort will be made to identify potential new Action members to build a network as wide as possible.
Following this meeting the first version of the Action's website will be launched and it will be updated regularly throughout the 4 years. A total of five MC meetings, five SC meetings, three Workshops, four Think-Tank meetings and two Training Schools. The Action will finish with a final conference where all the partners involved will present their most striking findings. A satellite workshop, especially for industry, will be organised with the final conference. For maximum time and cost efficiency, efforts will be made to hold the MC and SC meetings as well as Training Schools concurrently with annual workshops. The tentative schedule of these events (« X »), continuous activities (---) and of the deliverables (« * ») of the Action are summarized in the Table

below:

	Year1		Year2		Year3		Year4	
	Sem1	*Sem2*	*Sem3*	*Sem4*	*Sem5*	*Sem6*	*Sem7*	*Sem8*
Management Coordination								
Positions Appointment	*							
MC meeting	X	X		X		X		X
SC meeting	X	X		X		X		X
Website Launch and Update	------	------	------	------	------	------	------	------
STSM Approval	------	------	------	------	------	------	------	------
Election of WOC	*	*		*		*		
WG progress reports		*		*		*		*
Annual Report		*		*		*		*
Final Report								*
Major Events of the Action								
Kick-off meeting	X							
Scientific Workshops		X		X		X		
Industry Workshop								X
Closing								X

Conference								
Networking								
WG/FG meetings	X	X	X	X	X	X	X	X
Think-Tank meetings		X		X		X		X
WG1 Activities	------	------	------	------	------	------	------	------
WG2 Activities	------	------	------	------	------	------	------	------
WG3 Activities				------	------	------	------	------
FG Activities	------	------	------	------	------	------	------	------
Training								
Training Schools			X		X			
STSMS	------	------	------	------	------	------	------	------

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: BE, CH, DE, DK, ES, FI, FR, HU, IE, IT, NL, PL, RS, SE, TR, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 64 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

POSITIVe identifies the following **target audiences** for its dissemination activities:

- All participants of the POSITIVe COST Action, from both academia and industry

- Other scientists researching/teaching in the areas of food, nutrition and health, metabolism, nutrigenetics, nutrigenomics.
- ESRs active in the areas of food, nutrition and health, metabolism, nutrigenetics, nutrigenomics (those participating in POSITIVe and others active in the field)
- Policy makers from national and international bodies.
- SMEs, spin-outs and industries involved in functional food production, human nutrition or health management
- Public health and regulatory agencies
- Health care professionals and dieticians
- The ultimate target shall be the consumer, thus the public at large.

H.2 What?

To address its target audiences, the POSITIVe Action will use the following **dissemination channels**:

- A public website
- A secured part of the website for POSITIVe-internal communication
- A POSITIVe e-newsletter
- Scientific publications and position papers in peer-reviewed journals
- Publications in professional/technical journals
- Communications in international conferences, lectures, poster presentations and round tables
- Popular scientific leaflets
- Press releases
- A final popular scientific booklet.

Moreover, the following **training activities** will complete the communication with the targeted groups:

- Thematic Training Schools
- Exchange of know-how and skills (STSMs).

H.3 How?

Public website: The public part of the POSITIVe website will be the main source of dissemination, addressing all different target groups with tailored information. It will provide information of general interest such as the project objectives, work plan overview and participants. A news channel will inform about the current activities of the Action and invite for participation and contributions when appropriate. For ESR, it will also announce job, fellowships and training opportunities. Links to other relevant organisations will help the target communities to complete their information about on-going developments in the field. For ESR, it will also announce job, fellowships and training opportunities.

Secured part of the website for POSITIVe-internal communication: Participants of the POSITIVe Action will moreover benefit from the access to an internal platform of exchange, which will offer a repository of internal documents and an exchange platform for documents in preparation, an online forum of discussion, a timeline of the Action, detailed contact information, practical information about internal meetings, reporting instructions, COST requirements etc. Furthermore, participants will be invited to use this secured part of the website for data-basing and the sharing of resources.

E-newsletter: The FG, based on findings from the three WGs will publish regular newsletters on the Action's website. Online subscription to the newsletter will allow to constantly expand the recipients list of this newsletter.

Peer-reviewed articles will mainly address the scientific community in the areas of food, nutrition and health, metabolism, nutrigenetics, nutrigenomics, informing about recent findings of the Action participants. **Review articles** will focus on the combination, comparison and critical review of literature data and recent results, aiming at a broader understanding and cross-fertilisation of findings. **Communications in international conferences, lectures, poster presentations and round tables** will complete the exchange with the scientific community.

Position papers: will aim at diffusing consensus opinions arising from discussions between POSITIVe partners and possibly external experts on specific points of wide relevance.

Publications in professional/technical journals and popular scientific booklets: Recent findings of relevance to industry, public health and regulatory agencies as well as health care professionals and dieticians will additionally be presented in an easier accessible manner in professional or technical journals as well as in popular scientific booklets.

Press releases & podcasts: Press releases and podcasts will be launched at the Action's start and

end and at any time highlights have been achieved by the Action. These activities shall inform the general public how to improve lifelong health and well-being through improved nutrition, contribute to targeted dietary recommendations and ultimately reduce health care costs.

Thematic Training Schools and exchange of know-how and skills (STSMs): These training activities, in complement to their in site formation and research project, will provide a multidisciplinary training to Early Stage Researchers to develop their leadership skills for future European research. The training courses will be recorded and made publically available via the POSITIVe website. STSMs beyond ESR training may serve to lay the foundations of new collaborations or research projects.