



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

Brussels, 22 November 2013

COST 054/13

MEMORANDUM OF UNDERSTANDING

Subject : Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action ES1307: Sewage biomarker analysis for community health assessment

Delegations will find attached the Memorandum of Understanding for COST Action ES1307 as approved by the COST Committee of Senior Officials (CSO) at its 188th meeting on 14 November 2013.

MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as
COST Action ES1307
SEWAGE BIOMARKER ANALYSIS FOR COMMUNITY HEALTH ASSESSMENT

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 provide insights into how sewage biomarker analysis can be used to inform on different aspects of community 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 68 million in 2013 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

Sewage contains the excreted biomarkers of endogenous human metabolism that directly reflects the exposure and stressors placed upon an entire contributing community. The quantitative measurement of these specific biomarkers in sewage from communities allows the averaged patterns of factors related to lifestyle, disease and environment to be used for the assessment of community health. The Action will develop and expand an existing pan-European inter-disciplinary network, bringing together experts from relevant disciplines interested in the application and development of using the quantitative measurement of human biomarkers in sewage to evaluate lifestyle, health and exposure at the community level. In order to achieve its objectives the Action will manage a common Europe-wide testing platform that will develop best practice, provide a significant increase in the comparable spatio-temporal resolution of available data, coordinate the development of new biomarkers in sewage with focus on new psychoactive substances and new biomarkers for the community assessment of factors such as environment, health, lifestyle and diet, and integrate sewage-based approaches with other available metrics. The Action will have a major impact on the development of this emerging field and ensure that the technology is used in a responsible and effective manner and it is potentially fully exploited in collaboration with end-users.

Keywords: Sewage analysis, epidemiology, illicit drugs, biomarkers, health

B. BACKGROUND

B.1 General background

Sewage contains the excreted biomarkers of endogenous human metabolism that directly reflects the exposure and stressors placed upon an entire contributing community. The quantitative measurement of these specific biomarkers in sewage from communities allows the averaged patterns of factors related to lifestyle, disease and environment to be used for the assessment of community health. Thus far, the approach has been successfully used to determine illicit drug use at the community level with the illicit drug habits of communities studied in Europe and worldwide. It has been shown that individual communities present different patterns with respect to levels of various illicit drug residues and it is hypothesized that this will also concur for other biomarkers. Hence, there is the clear potential to develop a wider range of innovative solutions to quantitatively assess patterns of factors related to health and illness within populations, while also providing a

means of collecting data for epidemiological and socio-economic studies.

The analysis of biomarkers in sewage is a novel and innovative approach to study lifestyle, health and pollutant exposure in a community. The main advantage of the approach is to provide evidence-based, objective, and near-real-time information of the human biomarkers investigated. The application of this approach to determine the exposure to any type of health stressor will, therefore, provide direct and objective information on the real state of exposure of a specific population.

Moreover, the application of sewage analysis in different communities can be used to identify any peculiar characteristic of a population and integrate them with other epidemiological data in order to support conventional epidemiological approaches and overcome several of the limitations faced by these approaches, such as the low objectivity of estimates, long study times, and high costs.

The potential of the analysis of sewage for biomarkers was first recognized in the field of illicit drug monitoring, albeit after a significant level of scepticism from the drug epidemiology community at the outset. Some of the key challenges were related to communication between the established drug epidemiology community and the new group of sewage engineers and chemical analysts who were attempting to interpret the results of sewage analysis. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) was however quick to recognize the potential of the methodology and organized the first international workshop on this subject in 2007 in Lisbon (EMCDDA, 2008).

The EMCDDA has also supported a Europe-wide network of 15 partners that was initiated to facilitate the advancements required for sewage biomarker analysis to be successful (i.e. standardization and the evaluation of uncertainties). The Sewage analysis CORE group (SCORE) network has thus far performed international studies involving 25 European cities in 2012 and up to 43 cities covering 25 countries in 2013. The network has also performed inter-calibration exercises for quality control purposes, hosted workshops, innovatively developed the necessary technologies, responsibly communicated results and liaised with both the EMCDDA and United Nations Office on Drugs and Crime (UNODC) as end-users of the data. The SCORE network and the EMCDDA most recently organized the first international multidisciplinary conference on detecting illicit drugs in wastewater in 2013(<http://www.emcdda.europa.eu/events/2013/testing-the-waters>).

The advantage of COST for this network is that it will allow the focus of the network to expand whilst providing a supportive platform to aid in the communication and trans-disciplinary cooperation that is essential to the success of this technique. COST is the most appropriate mechanism to fund this cooperation since there are 25 countries all advancing the approach, yet there is no platform to coordinate on-going and future activities. Therefore a concerted Action to coordinate this Europe-wide effort is highly required and will be beneficial to both science and the

public.

B.2 Current state of knowledge

Research regarding the objective assessment of community health (e.g. illicit drug, alcohol and tobacco use) by means of sewage analysis is a relatively new scientific topic that started in 2005 when Zuccato and co-workers developed and applied an analytical method to quantitatively analyse biomarkers of illicit drugs, such as cocaine, heroin, cannabis, and amphetamine-like stimulants in sewage influent (Zuccato et al., 2005). Since 2005 other research groups in Europe and elsewhere in the world, embarked on the topic and additional analytical methods were developed to detect and quantify human biomarkers of the aforementioned substances in sewage (van Nuijs et al., 2011). Between 2006 and 2011, individual research groups applied their own methods to assess the use of illicit drugs on local and national scales and demonstrated the potential of the approach in quantifying illicit drugs use at a community level. Unfortunately it is somewhat difficult to compare the results of these early studies because of a lack of a best-practice protocol that would ensure comparable approaches for the sampling of sewage and for the back-calculation of illicit drug use from measured concentrations of drug biomarkers in sewage. Furthermore, no objective indication on the performance of the analytical methods from the different research groups could be provided because of the lack of inter-laboratory data-quality test exercises (van Nuijs et al., 2011). As described in B.1., the creation of the SCORE network in 2010 facilitated these necessary advancements and for the first time brought both practitioners and end-users together. Since 2010 the SCORE network has coordinated and delivered the first ever studies on the regional and temporal differences in illicit drug use in European cities (Thomas et al., 2012). In 2011, this included 19 cities and was followed-up in 2012 with a 30-city study and in 2013 with 43 cities providing the first ever quantitative measurements of illicit drug use in certain European countries and providing important additional and the most actual information on illicit drug use in Europe. The development of this programme has been strategically managed with input from end-users (EMCDDA and UNODC) and policy makers to ensure that the additional countries and drugs included are of value. Additionally the first ever inter-laboratory comparison studies were performed ensuring the quality of the analytical data. Another major step was the involvement of sewer engineers to evaluate the influence of different sewer designs and sampling procedures on the data generated. This has not only allowed the uncertainty associated with sewers and sampling to be evaluated but has also allowed a comprehensive characterization of the major uncertainties of the approach and points for further improvement (Castiglioni et al., 2013).

While most research in this field has been aimed at estimating the use of the ‘classical’ illicit drugs (amphetamine, cannabis, cocaine, ecstasy and methamphetamine), the approach has in recent years also been extended to determine the use of other substances. Reid and coworkers established a method to estimate the consumption of alcohol in large populations by analyzing sewage for ethyl sulfate, a specific metabolite of ethanol (Reid et al., 2011). Most recently, methods have been published to evaluate the use of the so-called new psychoactive substances (Reid et al., 2013; van Nuijs et al., 2013), an issue that poses a current and major challenge for drug policies worldwide (UNODC, 2013). Even though the sewage analysis approach has been restricted to determining the level of community drug use, there is also the clear potential to develop a range of innovative techniques as a solution to quantitatively assess patterns of factors related to lifestyle, health, nutrition, and environmental exposure within populations. In 2011, Thomas and Reid proposed that the analysis of sewage for specific human biomarkers might also reveal other information on the lifestyle, health and pollution exposure of communities. Isoprostanes, for example, have been proposed as potential biomarker to measure the collective and systemic oxidative stress response of an entire community as part of a wider measure of community health (Daughton, 2012). It is hypothesized that individual communities will show different patterns with respect to the levels of various sewage biomarkers in comparison with other communities, and this difference will be related to lifestyle (alcohol, tobacco and drug use), health, nutrition and environment within each community.

Only one reported study has to date tried to evaluate sewage analysis alongside traditional epidemiological techniques (Reid et al., 2012). Even though this is very complicated and fraught with difficulties it is clear that the approaches are very much complementary and are very powerful when used together. More importantly, when applied tandem there is clear synergy and this will be a major area of focus over the coming years.

Looking forward there is the clear potential to increase the spatio-temporal resolution of the sewage analysis approach, bringing together additional research groups from across Europe and worldwide. Application on a broader scale will require further optimization, standardization and validation of the sewage approach. There are numerous future research needs; developing new biomarkers, both for new psychoactive substances and health and lifestyle factors, tools for the better estimation of population, optimization of sampling frequencies, non-target/retrospective analysis of new drugs, in-sewer stability of biomarkers, pharmacokinetics during poly drug use and triangulation with other epidemiological measurement. In this light, this Action is highly relevant.

B.3 Reasons for the Action

The primary reason for the Action is to facilitate the advancement of sewage analysis through providing an expert network for the application of a harmonized approach at the European level and as such serves as a point of contact between the practicing community and end-users

The scientific challenge of the network will focus on the robustness and uncertainties of the proposed methodologies, thus developing new analytical methods, and identifying and filling gaps in existing knowledge. The societal benefits of sewage analysis lie in providing reliable and objective data on lifestyle, health, nutrition and environmental exposure, providing for example data on exposure, as well as spatial and temporal trends across Europe. A key benefit of the work performed on illicit drug use will be data on the prevalence of new psychoactive substances on the European market. The analysis of biomarkers in sewage will provide information complementary to existing inventories and, because of its inherent short response time, has the potential for signalling and early warning of changes in the lifestyle, health and nutrition factors across Europe. The network has obvious and relevant links with the COST Domain “Individuals, Societies, Cultures and Health”. Two more Domains are clearly relevant for this network, viz. “Biomedicine and Molecular Biosciences” (in particular the transformation of drugs consumed in the human body, and resulting biomarkers occurring in urine), and “Chemistry and Molecular Sciences and Technologies” (since reliable sampling and ultra-sensitive chemical detection methodologies including non-target high resolution mass spectrometric methods will be developed). This again highlights the trans-disciplinary character of this Action.

B.4 Complementarity with other research programmes

Due to the emerging and very specific nature of this area of research, there is only one European research project: Marie Curie SEWPROF ITN (www.sewprof-itn.eu) that started in October 2012 and includes 16 institutions from across Europe. The SEWPROF ITN is a training programme that aims to advance the knowledge of the epidemiology of illicit drug use through sewage analysis with the ultimate goal of applying this cutting edge interdisciplinary approach in epidemiological studies of community-wide health. SEWPROF, although truly interdisciplinary, has already identified many gaps in the expertise and knowledge available and has also emphasised the critical need for trans-disciplinary and cross-sectorial research. The Action will therefore be highly complementary to the current training activity within SEWPROF. The Action will provide a platform for researchers from different disciplines and sectors to exchange ideas, and will go significantly

beyond the objectives of SEWPROF in researching new avenues in human epidemiology utilizing sewage biomarker analysis. Nationally there are a large number of on-going and new projects in this area, and a goal of the Action is to avoid duplication in the development of new methods within these projects.

C. OBJECTIVES AND BENEFITS

C.1 Aim

To develop and expand the existing pan-European inter-disciplinary SCORE network to provide insights into how sewage biomarker analysis can be used to inform on different aspects of community health. The Action aims to (i) deliver best practice advice for performing sewage biomarker studies, (ii) consolidate developments with respect to developing new approaches and techniques, (iii) facilitate greater interaction between different disciplines, (iv) identifies research needs, (v) facilitate the exchange of ideas and (vi) generate projects at the forefront of research, (vii) serve as forum for Early Stage Researchers to network and present results and (viii) develop new transdisciplinary partnerships.

C.2 Objectives

The Action will focus on the following **secondary objectives**:

1. Deliver best practice advice for performing sewage biomarker studies in view of an already agreed common protocol currently used within the established Europe-wide network. The Action will allow continuous exchange of knowledge that will be used to constantly update the best practice protocol.
2. Consolidate developments with respect to refining the existing approaches used to determine illicit drug use in a population. The Action will enhance the production of comparable data among different community that will be used to study different patterns of drug use.
3. Share scientific background with respect to developing new approaches and techniques to provide information related to lifestyle, health, nutrition and pollutant exposure within populations
4. Facilitate and promote greater interaction between different disciplines such as analytical chemistry, criminology, pharmacology, biochemistry, sewage engineering, sociology, spatial epidemiology, statistics, toxicology and conventional drug epidemiology
5. Identify research needs through a transdisciplinary network that will be essential to understand complexities and uncertainties related to the different disciplines involved

6. Facilitate the exchange of ideas and generate projects at the forefront of research.
7. Serve as forum for Early Stage Researchers to network, present results and receive advanced knowledge through an interdisciplinary and cross-sectorial programme.
8. Develop new interdisciplinary partnerships to cover knowledge gaps and improve scientific results in a novel field of investigation as sewage biomarker analysis
9. Provide end-users (national health, illicit drugs and crime agencies) and stakeholders (public authorities) with objective and updated information about lifestyle and health status of communities to integrate with existing metrics

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

To achieve the above objectives requires trans-, inter- and multidisciplinary collaboration and a strong and integrated network has been created with (sewage) engineers, chemists, environmental scientists, biologists, toxicologists, epidemiologists, medical doctors, industry representatives and public servants, plus end-users (national health, illicit drug and crime agencies as well as EMCDDA and UNODC) and stakeholders (public authorities). The Action will provide the perfect platform to unify research efforts on the European level and add value in terms of knowledge exchange for both scientific and non-scientific communities. This is possible since (i) the basic funding, necessary state of the art instrumentation, methods and manpower are already available within each Working Group (WG); (ii) most of the participants are experienced in project management on an international level; (iii) the scientific and public status is well known by the SCORE network that will enable an immediate start.

The networking activities listed below will play a key role in accomplishing the Action's objectives:

- Trans-disciplinary discussions, exchange of data, ideas and proposals through WG meetings, an open web-forum and formal questionnaires. This will identify already available experience, assess present and future needs and prepare for the initial conference.
- An initial conference with thematic and cross-disciplinary sections to assess the current situation and establish targets and strategies to achieve the objectives.
- Cross-disciplinary workshops on scientific advances, awareness raising and risk-management for end-user groups.

- Web-based discussion platform to facilitate communication.
- In-person and virtual meetings for the continuous exchange of ideas, experience and solutions.
- Short-term scientific missions for the diffusion and harmonization of methods and approaches.
- Interlaboratory comparisons to evaluate and validate analytical methods for detection, identification and quantification of different biomarkers as they are developed.
- The creation of a Europe-wide (and beyond) testing platform allowing participants to test their technologies across Europe.
- Organization of an observatory that, in collaboration with the Early Warning System of EMCDDA, will survey the appearance new psychoactive substances.
- Liaison with end-users such as public servants, politicians and other decision makers involved in the broader scope of illicit drugs, crime and health, globally (UNODC; World Health Organisation), across Europe (EMCDDA, European Centre for Disease Prevention and Control, The Executive Agency for Health and Consumers) nationally and locally.
- Use of the Action's website to enhance communication and dissemination of outputs, including outreach to the general public, social and health authorities and end-users.
- A closing conference to present the results of the Action and to propose further collaborations.

C.4 Potential impact of the Action

The Action will enable new research groups in European countries, without research expertise and practical experience in biomarker measurements in sewage, to mutually benefit from others with this expertise. It is expected that the awareness raising, training and technology transfer via networking will disseminate more than 5 years' worth of relevant research expertise and risk

management experience, of currently limited geographical spread, to the whole of Europe. Specific impacts of the Action include:

- Public health protection through the transfer of knowledge and best-practices to end-users (public authorities, waste water utilities, recreational water managers, health authorities, other sectors).
- Development of a transnational approach in the preparation of guidelines, standards and regulations for harmonized risk assessment and management of illicit drugs.
- Development and dissemination of better, innovative monitoring tools (early warning; real-time; macro- and micro-scale).
- Development of novel proactive strategies and control measures for illicit drugs via sewage analysis.
- Optimization of available research resources (man-hours, equipment, facilities) and funds and avoidance of duplicate work.
- Better use of the data for reasonable risk assessment and decision-making.
- Improvement of public and authorities' awareness and risk management capabilities on health issues.
- Increase the best practice in the analytical chemistry of markers of on lifestyle, health, nutrition and environment in sewage.
- Dissemination of new unbiased perspectives of scientific knowledge to health authorities, decision makers and the general public.
- Extensive exchange of information and know-how that will foster increased scientific discovery and innovation at a European dimension.

These developments will be performed in the frame of their economic feasibility, reliability, and impact, thus resulting in effective benefits for society (less impact), economy (lower operational costs) and society (improved use of resources).

From a long-term perspective the horizontal networking between experts in illicit drugs, who are

individually involved in different national and EU projects will therefore gain great momentum. Duplication of efforts will be reduced, developments accelerated, and scientific and technological gaps will be identified much faster. Hence, this Action will counteract the vertical fragmentation of European scientists, decision-makers and other societal groups and will deliver a surplus by producing a better understanding of the illicit drug problem throughout Europe.

The Action will communicate scientific knowledge about illicit drugs in the urban water cycle to key public groups in an accessible manner. One powerful tool available for the expert groups is the publication of freely accessible position papers. A further main task is the collaboration with public servants and politicians during decision-making processes related to this topic. Most of all, Early Stage Researchers will directly benefit from the COST instrument support. Additionally, intensified exchange between the Action partners will enable an increase in scientific innovation.

The economic impact of the Action is very difficult to predict but is potentially very significant. Better understanding of how communities respond to various stressors and the impact and effectiveness of intervention measures will lead to the better and more effective use of valuable resources.

C.5 Target groups/end users

The interest of this Action for end users will be demonstrated by the inclusion of crime, illicit drug and health organizations within the Action's networking activities. It is a main aim of this Action to foster the transfer of innovative technologies to full-scale applications. National health, illicit drug and crime agencies and public authorities will exploit the results, nationally and internationally. As side-benefit water companies will obtain information on the communities that they serve (their customers).

The following target groups and end users will be addressed/ reached by this Action:

- Scientists involved in the analytical and technological research of human biomarkers in sewage.
- Scientists with an interest in health, drug and environmental epidemiology at the community level.
- Public servants, politicians and other decision makers involved in the broader scope of illicit drugs, crime and health, globally (UNODC; World Health Organisation), across

Europe (EMCDDA, European Centre for Disease Prevention and Control, The Executive Agency for Health and Consumers) nationally and locally.

- The non-scientific community (interested public and non-governmental organisations).
- Representatives from local authorities, public, social and clinical sectors involved in the drug prevention.
- Law enforcement (police) authorities, customs officials and criminologists.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The Action will bring together experts from relevant disciplines interested in the application and development of using the quantitative measurement of human biomarkers in sewage to evaluate lifestyle, health and exposure at the community level. The collaboration is already established for illicit drugs, in the form of the SCORE network that will be enhanced and expanded to include a wider area of expertise based upon the COST Action tools presented in sections E and F. The aims and objectives of the Action will be achieved by 3 interlinked research tasks.

1. The Action will manage a common Europe-wide testing platform

Coordinated action is required on a number of levels in order to advance the current state-of-the-art. There is a fundamental need to develop best practice so that there is a significant increase in the comparable spatio-temporal resolution of available data. Through working on a common platform and generating data in a common format, it will allow large scale epidemiological studies to be performed and bring synergy and added value to studies that would otherwise be performed in isolation, as well as avoiding duplication. This research task will also promote the uptake of the approach across Europe as there is a requirement for the continued increase in the rate of uptake of the approach across Europe that needs to be performed in a coordinated and comparable manner. This will not only provide data on, for example, illicit drug use, over the whole of Europe, including regions where no data are currently available, but will also provide the basic data required to triangulate with traditional epidemiological survey data as well as performing higher level correlations with other Europe-wide data sets (e.g. Eurostat).

2. The Action will coordinate the development of new biomarkers

The number of potential biomarkers requiring development is vast and their development needs

coordination if the challenge is to be met. The proliferation of new psychoactive substances onto the drug market is a major challenge facing Europe with the EMCDDA's Early Warning System reporting 73 new drugs in 2012 alone. This clearly illustrates the scale of the challenge, with many hundreds of new substances available on the market. The task to develop biomarkers for their detection in sewage requires a multidisciplinary and coordinated action to avoid replication of what is a major effort. In addition to new psychoactive substances there is the clear potential to develop new biomarkers for the community assessment of factors such as *environment, health, lifestyle and diet*. Examples include potential biomarkers of general community health (F2-isoprostanes), cancer (specific antigens), nutrition (isoflavonoids and lignans) and lifestyle (e.g. alcohol, caffeine and nicotine). Through a coordinated effort it is clear that the potential of the approach to inform on the lifestyle, health and environmental exposure of a community will significantly advance our ability to monitor and evaluate the impacts of different stressors on a community scale.

3. The Action will integrate sewage-based approaches with other metrics

Sewage based approaches provide community level data, for example, on the amount of a substance used by a particular community. The technique has the potential to provide information on the exposure of a community to a particular stressor, both in the level of exposure and over time. It is therefore possible to use the approach alongside intervention measures such as monitoring the effectiveness of health campaigns or even the regulation of particular drug. There is enormous potential to create synergy through using sewage-based metrics with other data sources. The benefit of such an approach would be to better inform on the health status of a community and thereby use the, often-scarce, resources available to deal with health related issues. At the most basic level this could be the comparison of different complementary techniques in estimating community drug use and patterns. This in itself is a very difficult task since different survey techniques and data sources have their different strengths and limitations. The EU already collect a large amount of data through Eurostat and this itself could be correlated with sewage based measurements at the European level. The Action aims to link sewage analyses to the defined populations, specific health outcomes, and general socioeconomic data at the community level.

D.2 Scientific work plan methods and means

The most important research tasks to be coordinated by the Action are based around the three themes that will be coordinated by three respective working groups (WG):

WG1. Sewage biomarkers analysis: methods and technology

WG2. Innovative techniques for community health assessment

WG3. Integration with epidemiology and social sciences

WG1. Sewage biomarkers analysis: methods and technology

The first working group will focus on the methods and technology required to deliver high quality quantitative data. This is pivotal to obtain accurate data at the community level. One of the first tasks of WG1 will be to develop and distribute a best-practice guide for performing sewage studies based upon a common protocol that is already being used within the SCORE network. This will cover all types and scales of sewage studies and ensure comparable and high level data at all levels of application, no matter how experienced the practitioner. The protocol will cover all aspects of the approach, including how to characterize sewer networks, evaluate the type of sampling being performed and how it should be performed, sample storage, the best way to estimate the population under investigation, the most appropriate analytical methods to be used and the correct back-calculation methods to be used.

The Action will coordinate the development of new analytical for the screening of sewage samples for new psychoactive substances. High-resolution mass spectrometry (HRMS) offers the potential to screen sewage for the presence of residues of, yet unidentified, new psychoactive substances. Samples from across Europe will be screened using HRMS techniques and when a substance is detected this information will be circulated among Action members as well as the EMCDDA (Early warning system) and UNODC. This will facilitate the rapid involvement in establishing the extent of the drug use across Europe.

Annual inter-laboratory studies (ILS) will be organized as part of WG1 in order to maintain the quality assurance of the analysis. This will involve providing all interested participants with sewage spiked at two concentrations with a broad suite of biomarkers. The ILS will allow the evaluation of the analytical methods applied by all participants, with the goal to improve and guarantee an adequate level of performance. The ILS will develop from the biomarkers of illicit drugs already routinely measured to include biomarkers of new psychoactive drugs (following input from the EMCDDA Early Warning System and UNODC), health, nutrition and lifestyle over the period of the Action.

WG1 will coordinate investigations into the stability of biomarkers in sewers between the point of excretion and sample collection as well as in samples once they have been collected. The stability of new biomarkers in sewage will be evaluated using short-term stability experiments in the laboratory that replicate sewer conditions across Europe and will allow the suitability of biomarkers to be evaluated as well as assessing whether any stability corrections should be made to any

quantitative estimation. The Action will provide a common platform for stability studies and coordinate the testing of the large number of potential biomarkers to avoid duplication. A guidance document will be prepared for the use of appropriate modelling tools to evaluate the effects of in-sewer transformation on biomarker concentrations.

A key aspect of sewage-based approaches is the accurate estimation of the population under investigation. A key role of the WG will be to find the best suite of population metrics for the normalization of biomarker data. This will involve a range of metrics based upon census data and the presence of specific markers in sewage (e.g. nitrogen, biological oxygen demand, creatinine, pharmaceuticals such as ibuprofen, hydroxycotinine and the neurotransmitter metabolite vanillylmandelic acid).

WG1 will develop quality guidelines for the analysis of human biomarkers in sewage. The guidelines will include e.g. STP performance questionnaire, storage requirements, analytical method performance criteria, reporting protocol, and criteria for intra and inter laboratory variability. A platform will be created where inexperienced researchers will be able to get advice and expert opinion.

The WG will perform an internal annual review of the state of the technology. Depending on the novelty of the analytical developments these reviews may result in a peer-reviewed manuscript and serve as a basis for improving the best practice guidelines.

WG2. Innovative techniques for community health assessment

The main aim of WG2 is to verify the potential of sewage analysis for (i) the assessment of community health and health risk prediction through the analysis of health biomarkers (e.g. protein and DNA biomarkers of cancer) (ii) nutritional biomarkers and (iii) the assessment of collective exposure to environmental stressors such as environmental and food toxicants. WG2 will also manage the Europe-wide application of the biomarker technology based on the best-practice identified in WG1 and the needs of WG3.

This highly exploratory WG will focus on the identification of new specific biomarkers for environment, health, lifestyle and dietary factors drawing from current knowledge in the area of molecular epidemiology and clinical studies. The emphasis will be put on identification of both biomarkers of exposure (e.g. carcinogens and their metabolites) and biomarkers of effects (e.g. DNA adducts, proteins) in order to provide comprehensive information on community-wide health and improved risk assessment with the ultimate goal of disease prevention. Such an approach can lead to: an increase in the accuracy of exposure estimation; prediction of disease outcome and identification of susceptibility factors.

For a biomarker to be suitable for use in sewage it needs the following attributes:

- Be a specific marker of the factor under investigation (i.e. be produced exclusively by the drug, disease or stress) and not formed exogenously by, for example, microorganisms in the sewer system.
- Must be stable within the sewer system.
- Be present in sewage at sufficiently high concentrations to be accurately measured.
- Excreted at sufficiently high levels to observe significant differences between 'normal' and 'stressed' communities.
- Excreted in urine and do not extensively partition onto solids

The above attributes will be taken into account in scrutinizing existing and new specific biomarkers for environment, health, lifestyle and dietary factors. WG2 will also verify existing and new methodological approaches for biomarker identification and quantification including hyphenated techniques (chromatography coupled with mass spectrometry), bioanalytical techniques (microarray or quantitative reverse transcription polymerase chain reaction (qRT-PCR) and OMICS approaches (genomics, proteomics and metabolomics) as well as real-time sensing with the aim of providing an integrated tool for comprehensive and real-time community wide health assessment.

A substantive contribution from clinicians and health epidemiologists as well as analytical scientists is envisaged in WG2 in order to get a full understanding of the applicability and usefulness of chosen biomarkers and associated analytical techniques. WG2 will gather existing data, identify gaps in knowledge and will provide recommendations for further work.

The objectives of WG2 will be met via: regular meetings, workshops, training events and short proof-of-concept projects (Short-term scientific missions) offered to early stage career researchers by participating institutions. Several partners within this Action have state-of-the-art analytical facilities and the required expertise, which will be utilized in this project and will provide a unique opportunity for early stage career researchers to get hands-on experience and exposure to cutting edge analytical instrumentation and innovative research approaches. The projects will aim to develop new approaches towards the identification and quantification of selected biomarkers in

wastewater with chemical and bioanalytical methods including mass spectrometry, hyphenated techniques, PCR and electrochemical and biosensors.

WG3. Integration with epidemiology and social sciences

WG3 will integrate sewage data with other available metrics. There is huge potential for sewage to provide the answers to many as yet unanswered questions and a key objective of this WG will be to bring the necessary scientists together. This highly transdisciplinary and ambitious WG will for the first-time bring together experts in the analysis of human biomarkers in sewage with medical doctors, epidemiologist, statisticians, toxicologists, health workers and social scientists with the sole goal of exploiting the potential of sewage based measurements on a wider-scale.

The first task of WG3 will evaluate and identify the most appropriate statistical data available from sewage-based measurements under the different epidemiological scenarios. This is a key step in fully utilizing the potential of the approach. Focus will be placed on the required data resolution and the frequency of sampling for determining weekly trends, annual estimates and for monitor the effectiveness of interventions. Statistics associated with the spatial distribution of target populations will also be investigated to ensure accurate national and international data.

WG3 will also evaluate the utility of the illicit drug data from sewage measurements that have been gathered over the past eight years alongside conventional drug prevalence data sources. WG3 will pose major challenges because the available epidemiological data will vary between the different studies and study populations. A key task will be to identify which population is missing from the each of the data sets, and what drug patterns this population may represent in the total population. Important steps will also be taken to use multiple data sources for comparison, correctly report and interpret data and adequately describe scale and/or direction of biases.

Social, economic, and general health outcomes at the community level can be assessed in the context of the sewage biomarkers, using relevant statistical methods, e.g., logistic regression, without going to individual or personally identifiable information. Multi-biomarker interactions (i.e. cocaine + alcohol =different biomarker pattern) and differences between locations will be evaluated using a range of multivariate statistical approaches (e.g. principle components analysis, multivariate linear analysis, multidimensional scaling and clustering systems). The processed biomarker data will be compared with publicly available health and socio-economic data in order to see how this and conventional approaches compare. A first attempt at this for a single biomarker of drug use has shown that this approach is feasible and is an excellent means of checking the quality and accuracy of different measurement techniques because they each approach a problem from a different viewpoint. Together complimentary approaches provide a well-balanced assessment of a

community related factor and identify areas where further research is required.

The WG will also develop study scenarios that exploit the potential of sewage analysis in addressing gaps in our understanding of the impact of various stressors on communities. This may be as simple as monitoring the effect of an intervention through measuring a single biomarker, or to performing multiple biomarker measurements on a population while simultaneously gathering other types of data. These scenarios will feed into WG2 and the Europe-wide platform, offering the potential to develop hypotheses at the European level.

E. ORGANISATION

E.1 Coordination and organisation

The Action will bring together experts from specific disciplines with their own funding to work within a transdisciplinary environment within the three WGs. Using organisational features common to COST Actions the skills and knowledge of these experts will be successfully unified and national barriers will be overcome to provide a coordinated international perspective.

The **Management Committee** (MC), led by the Chair and Vice-Chair, will manage the Action according to the COST rules. The MC will be responsible for the overall strategy of the Action and for the coordination of the international network and platform activities.

The **Steering Committee** (SC) is scheduled to meet twice a year. The SC meetings will be coordinated with those of the MC and WG meetings. It is envisaged that the SC will include WG co-chairs, Grant Holder, a Dissemination Manager, an Equal Opportunities Manager (including ESRs), Training Officer, as well as a STSM Officer. Under the instruction of the MC the SC will review the work programme of the WGs.

WG meetings will be coordinated by a Chair and Co-Chair who will be responsible for the organisation of the transdisciplinary WG meetings. WG meetings are scheduled annually for the duration of the Action. Communication between the WGs and the SC will be electronic and supported by video conferencing if required. The WGs will together coordinate the Action's workshops and conferences.

Workshops are one of the key COST tools for this Action, bringing together scientists working in very different fields. It is envisaged that the scope of the workshops will become more transdisciplinary and exploratory as the Action progresses. Short-Term Scientific Missions (STSMs) and the mobility of ESRs will also be important, as they will facilitate knowledge exchange and transdisciplinary research. The MC will appoint a **STSM Coordinator** to coordinate these activities.

Training Schools will allow for best-practice, knowledge transfer, avoid repetition and accelerate

uptake of the approach. The MC will appoint a *Training School Coordinator* to coordinate these activities. The Action will coordinate the production of both scientific and popular scientific information for dissemination through both conventional and social media. A task to be performed by the MC appointed *Dissemination Manager*. All of the Action's activities will be reviewed by a Equal Opportunities Manager, who will also secure the positive involvement of ESRs in the Action.

E.2 Working Groups

Three WGs will facilitate the effective realization of the Action. WG1 will address the rapid analytical and technological advancements being made in the field; WG2 will look at the innovative application of the technology for community health assessment, while WG3 will take these innovative data to the next level through their integration with existing epidemiology and social sciences. An ESR and a mentor will lead each WG, with each WG made up of team of experts with relevant competences. The transdisciplinary nature of the Action will mean that certain individuals will be members of multiple WGs. Each WG will meet a minimum of once a year in addition to workshops, training schools and conferences. The draft output of any WG will be circulated to the other two WGs prior to publication for comment and discussion to ensure that the transdisciplinary nature of the Action is maintained.

E.3 Liaison and interaction with other research programmes

The Action will closely liaise and interact with FP7 ITN SEWPROF and other international projects. Those researching into this field both in the EU and internationally (e.g. in the USA or Australia) will be invited to the Action's meetings and to contribute to the agenda for future development in the field. The Action will also draw from other indirectly related projects by inviting representatives to the meetings. Due to the interdisciplinary and cross-sectorial nature of the Action, active collaborations in closely aligned research areas will be sought throughout the duration of the Action. The Action will allow for an exchange of ideas between those involved in SEWPROF and other related projects funded at national level in different countries.

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

This Action will respect appropriate gender balance in all its activities and the Management Committee (MC) will place this as a standard item on all its MC agendas. The Action is committed

to the considerable involvement of early-stage researchers. This item will also be placed as a standard item on all MC agendas. A MC member will be appointed as an equal opportunities champion to ensure that all of the Action’s activities are proactive towards gender balance and the positive role of ESRs. Actions will be taken to achieve a gender balance through promoting the participation in the MC and the WGs. At every management meeting a gender distribution plot showing the balance between male/female and ESR taking part in the activities of the Action will be presented. In organizing workshop and conferences, gender balance will be taken into account when selecting (keynote) speakers, as this Action is an excellent means to reach out to both female and male participants. ESRs will be encouraged to actively take part in the conferences and training schools by organizing and setting up the program, taking a leading role in dissemination, with particular focus on social media. ESRs will also be encouraged to take part in Short Term Scientific Missions (STSM). To ensure the largest impact on both male and female participants, a balance in gender amongst the participants will be sought.

F. TIMETABLE

The four year Action will be initiated with a First Management Committee Meeting during the first quarter of year 1 and followed by a coordination and dissemination meeting which will be held in the first quarter of each year. The Action’s website and web-based discussion platform will be established and maintained by the Grant Holder with meetings organised bi-annually. Working Group meetings will be organised in a way to allow information from each to feed into the other two WGs and allow cross-WG activities. The existing Europe-wide testing platform will be coordinated to run bi-annually with workshops occurring in between for planning and results evaluation. The hugely successful Testing the Waters Conference will be hosted by the Action in years 2 and 4 to facilitate further dissemination, global interaction and publication of the conference special issue.

Year	1				2				3				4			
Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
SCORE Kick-off	X															
Coordination &	X				X				X				X			

dissemination meeting																
Website setup and maintenance	X		X		X		X		X		X		X		X	
MC Meeting	X				X				X				X			
SC Meeting		X				X				X				X		
WG1 Meeting		X				X				X				X		
WG2 Meeting		X				X				X				X		
WG3 Meeting		X				X				X				X		
European testing platform		X		X		X		X		X		X		X		X
SCORE Workshop				X				X				X				
Testing the Waters Conference					X								X			

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: BE, CH, CY, CZ, DE, DK, EL, ES, FI, FR, HR, IT, NL, NO, PT, SK, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 68 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?

This Action aims to maintain and extend a pan-European inter- and transdisciplinary network to further develop a novel approach for assessing health related factors at the community level and to provide new insights into how sewage biomarker analysis can be improved and used to inform on different aspects of community health. This unique platform will involve early stage and experienced researchers from diverse scientific disciplines such as environmental engineering, chemistry, pharmacology, epidemiology, social- and forensic science, as well as decision makers, stakeholders and health workers.

The transdisciplinary character of the Action foresees several scientific benefits as described in Section C. With this excellent Action that combines innovative approaches with state-of-the-art techniques, a wide scientific and non-scientific audience will be reached for the dissemination of the results. Next to the scientific goals, special emphasis will be made on applied scientific issues and the social benefits. Communication of the experimental results to public authorities, national and local governments, and to the general public will play a key role. Therefore, the involvement of policy makers and end-users, such as the United Nations (WHO, UNODC), EU (ECDC, EMCDDA, EAHC), as well as to local stakeholders and health authorities is highly important. The integration of scientific and social spheres will also help to identify and address critical issues. Several end-users (researchers, decision makers) and stakeholders (focal points, water companies) are already participating in the network and form a strong basis for the Action. Others have been contacted and have expressed interest to follow the progress of the programme and will be involved to maximize benefits.

H.2 What?

The following dissemination methods will be used in order to communicate the research outcomes of the Action to each target audience:

Scientific audience

- Publications in peer-reviewed journals of the highest international standing
- Presentations at thematic workshops, seminars and international conferences.
- Training programmes (advanced courses and technical workshops).

- Monographs (e.g. best-practice of wastewater analysis for determining drug use, evaluating community health etc.)

Policy makers, stakeholders, health authorities

- Invitations to workshops and workgroup meetings.
- Reports ‘non-scientific’
- Dialogs

General public

- Popular media (internet, television, radio, newspapers)
- Public website
- Social network platforms (Facebook, Twitter)
- e-newsletter

H.3 How?

Outreach activities are considered to be of great importance to the Action for the wide and diverse dissemination of research outcomes. Communication will be appropriate for each kind of target audience.

The scientific audience will mainly be addressed via scientific publications in peer-reviewed journals of high ranked journals and thematic workshops, seminars and international conferences. Students and young scientists (ESRs) will be especially encouraged to present their results at scientific conferences.

The training programme will consist of courses and workshops, covering a specific area of expertise, and will focus on young scientists and new members of the Action. They will be organized concurrently and will be open to all practitioners and end-users. The Action will host technical and information workshops. These events will meet the double goal of: (i) presenting (scientific) results and (ii) training technical staff of public bodies, industries and other concerned stakeholders on the aspects covered by the Action.

Standardization of sewage analysis for determination of drug use and the participation of inter-laboratory comparison studies on a regular basis is essential for facilitating reliable and comparable results that can complement prevalence data from epidemiological studies and played a key role to the success of earlier comparative studies. A guideline of “best practice” for executing sewage studies will be made available and new participants will be invited to expand this activity and take part in training activities.

The Action will hold regular meetings, both at the Action and WG level. These meetings and the workshops together with reports will serve as a connector and open dialogs between the different disciplines i.e. scientists, policy makers and stakeholders. The constant exchange of information in a transdisciplinary network is essential for evaluation and updating the dissemination plan during the course of the Action.

A public website will play a prominent role in dissemination and outreach for the Action. It will give access to all the relevant documents generated (reports, guidelines, etc) and include a discussion forum where specific questions can be posted. The website and a web-based e-newsletter will keep the members of the network informed, but will also serve to disseminate the outcomes to the general public. Furthermore, considering the importance of social network and popular media, these platforms will also be used for the dissemination of the Action in order to reach the public in an understandable ‘non-scientific’ language.