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

Brussels, 15 May 2014

COST 027/14

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action CM1402: From molecules to crystals - how do organic molecules form crystals? (Crystallize)

Delegations will find attached the Memorandum of Understanding for COST Action CM1402 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 CM1402
FROM MOLECULES TO CRYSTALS - HOW DO ORGANIC MOLECULES FORM CRYSTALS? (CRYSTALLIZE)

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 develop a fundamental understanding of the molecular mechanisms involved in the nucleation and crystal growth processes from the molecular scale to the macroscopic scale, leading to materials with targeted functions and properties.

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 72 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

Typically during chemical manufacturing, crystallization is employed as a purification step or to isolate the final product. Crystallization determines the quality of the product obtained but understanding the molecular mechanisms which occur during crystallization remains a scientific challenge, particularly for organic compounds.

Developments in advanced analytical techniques, molecular recognition probes and computational methodologies are beginning to provide insight into how molecules interact in solution, aggregate and, ultimately, form crystals. Together with studies in different phases, in confined systems, on surfaces and with impurities, this will improve our understanding of crystallization processes.

Europe plays host to recognised global leaders in different aspects of crystallization which, if brought together, will be in a unique position to drive the molecular understanding of the crystallization process.

Crystal Engineering has advanced so that there is understanding of the supramolecular interactions in molecular solids. The next step is to fully understand structure/function relationships in order to custom design new materials for specific applications. European researchers need to embrace this new paradigm in materials design, combine it with the developing insights into the crystallization processes, and exploit both of these to control crystallization processes with increased product yield and purity, and also reduced environmental impact and cost.

Keywords: Crystal nucleation and growth of molecular solids, crystal engineering, solvation structure and molecular probes, molecular dynamics and crystal structure prediction, organic molecules and biomolecules.

B. BACKGROUND

B.1 General background

Crystallisation from the solution phase is the last and, arguably, the most important step in many manufacturing processes, producing crystalline particulate products of high quality and purity with well-defined physicochemical properties. Problems persist in industry with variable control of these properties, which adds significant cost. One well-known case led to a loss of more than $250 M in sales alone.

2014, just designated the International Year of Crystallography by UNESCO, builds upon over two hundred years of scientific endeavour and over one hundred years of the use of X-ray

crystallography as the gold standard method of structure elucidation. However, even today there is little fundamental understanding of what happens in solution as molecules interact to form entities, nucleates, that eventually become crystals. The effect of impurities in the solution as nucleation and crystal growth occur is also poorly understood, as is the influence of surfaces and utilising surfaces to control crystal form. The latter is increasingly of importance as continuous manufacturing technologies are applied to the pharmaceutical industry. The last decade has seen significant interest in multi-component compositions for tuning the physical properties of materials, particularly Active Pharmaceutical Ingredients (APIs, also known as drug substances). However, these bring additional levels of complexity when considering their behaviour in solution and during crystallization processes. These are just some of the challenges facing the Crystal Growth Community.

Crystal engineering, the design and application of functional solids, has rapidly emerged as a scientific discipline over the past two decades. The challenges faced by the Crystal Engineering Community lie with how to control form and function for specific applications.

Both communities have developed effectively independent of each other, although some questions should be common, for example why are some molecules hard to crystallise, prone to polymorphism or prone to solvate formation? Computational methods have also advanced so that they can support the experimental scientists.

This COST Action will examine these challenges by bringing together both communities, along with theoretical and computational researchers with insight into the structure and supramolecular features of organic molecules and biomolecules.

Why COST? While Europe has a strong past in Crystallization research, it is fair to say that as the situation presently stands, this research effort is quite disperse and most actions are limited to a national level. Europe is in danger of losing the expertise as a world-leader in this area due to increasing competition from the US and certain Asian countries. There is little cooperation between the national networks and many countries only have groups in specific areas, for lack of an Action to allow the necessary networking between disciplines.

Furthermore many research teams interested in crystallization phenomena are restricted because the fundamental science requires significant resources. It is only through a pan-European collaboration that these resources can be brought to bear on this important scientific question and, importantly, ensure that Europe remains at the forefront of crystallization research.

This COST Action will facilitate development of a co-ordinated focus on the science and technology of crystallization by creating synergy between the leading European groups in crystal growth science and crystal engineering. Such an initiative will also provide networking opportunities for early career researchers across Europe, which will empower them in their future

careers. It will foster collaborations and allow European networks to be developed to access Horizon 2020 funding opportunities.

B.2 Current state of knowledge

There have been a number of recent experimental and computational advances which have *started* to illuminate the understanding of the structure of solutions, aggregation, nucleation and crystallization processes. Due to space restrictions, only a few of these are discussed below. In a recent review it was indicated that the field of crystal nucleation is on the brink of major breakthroughs with the advent of sophisticated spectroscopic techniques and probability theory to gain insight into nucleation processes [*Angew. Chem. Int. Ed.* 2013, *52*, 1]. The authors are the pioneers in this area and the work needs wider coverage for immediate impact.
Another review shows that computationally efficient approaches have been developed in molecular dynamics to tackle the time- and length scale issues involved with nucleation and crystallization process [*Angew. Chem., Int. Ed.* 2011, 50, 1996]. However, to date these have not covered multiple time- and length scales at a time. Crystal structure prediction (CSP) has been used for single component systems and multi-component systems with fixed and limited range of stoichiometries, [*Chem. Soc. Rev*. 2014, DOI:10.1039/c3cs60279f.] Modelling of supersaturation depletion during nucleation with nanoscale models has been achieved [*CrystEngComm* 2013, 15, 2269].
Molecular recognition probes have been used to investigate solute-solute, solute-solvent and solvent-solvent interactions [*Nature Chem*. 2013, 5, 1006; *Chem. Soc. Rev*. 2012, 41, 3485]. It was shown the spatial and temporal control of nucleation in solution [*Phys. Rev. Lett*. 2011, 107, 025504] and microemulsions have been used to provide nanoscale crystals with thermodynamic control [*Cryst. Growth Des*. 2011, 11, 363]. Nanoscale patterned surfaces and self-assembled monoloayers have been used to investigate polymorphism control and chiral resolution [*J. Am. Chem. Soc*., 2009, 131, 18212; *CrystEngComm* 2011, 13, 24].
Crystal engineering is a mature field based on knowledge of molecular interactions in crystals, see the recent virtual issue [*Cryst. Growth Des*. 2013, vi6, 9,]. It is possible to design and control crystal form for a function as demonstrated for carbon capture [*Nature* 2013, 495, 80-84]. It has been shown that molecularly imprinted polymers and nanoporous materials can facilitate protein crystallization [*Proc. Natl. Acad. Sci*. 2011, 108, 11081; *J. Mater. Chem.* 2012, 22, 21928], and a review on protein crystal nucleation has been written [*Progr. Cryst. Grow. Charact. Mater*. 2013, 59, 133]. The recent advances in diffraction techniques are significant for future techniques for accessing information about the nanoscale [Spence *et al*., *IUCr*, 2014, 1, 19; *Curr. Opin. Struct.*

Bio, 2011, 21, 509].

The innovation that this Action will include the development of analytical methods to provide highly accurate molecular level information on the phases involved in crystallisation processes and allow validation of the methodology against existing higher level knowledge, the development of new nucleation theories combined with computational methods to probe the crystallization process from the molecular scale to the macroscale. It will introduce a new paradigm in crystal engineering based on knowledge of molecular interactions in solution, as well as using design to generate materials with desired functions. The interplay between the crystal growth of small organic molecules and protein crystallization will drive both fields forward.

B.3 Reasons for the Action

From an industrial perspective, there is an increased awareness of the need to understand the crystallization process. Presently Chemical Engineers in the pharmaceutical and chemical industries handle the transformation from the solution to the solid state in an empirical fashion which is not based on rigorous thermodynamic or kinetic principles. This approach is limited as molecular detail is omitted. A full understanding from a molecular scale perspective is required in order to gain a full picture of the time scales, length scales and the detail of the phase change from solution to crystal, which can only be achieved by bringing together a trans-European network of high-quality scientific researchers. This will facilitate a better understanding of the crystallization process, which will enable Europe to become the world leader in applying crystal nucleation science and technology to design crystallization processes that provide tailored products in terms of phase, morphology and size distribution; eliminating unfavourable manufacturing steps such as milling and granulation in pharmaceutical and fine chemical manufacturing.

B.4 Complementarity with other research programmes

This COST Action is complementary with the COST Action CM1005 “Supramolecular Chemistry in Water” in that both have a component (WG1) examining solution structure at high concentrations during the crystallization of organic molecules. However, the emphasis and application as well as much of the research in this Action is different to the COST Action CM1005.

C. OBJECTIVES AND BENEFITS

C.1 Aim

The main objective of the Action is to unite researchers from different disciplines to develop a fundamental understanding of the molecular mechanisms involved in the nucleation and crystal growth process across the length scales from the molecular scale to the macroscopic scale, leading to the formation of materials with targeted functions and properties.

C.2 Objectives

The structure of solutions and crystallization processes such as molecular self-assembly and nucleation are complex phenomena which are currently studied by many diverse scientific approaches. The COST Action will demonstrate the contribution of each approach so that a full molecular level understanding of these processes will emerge. The Action will pursue the following goals:

- Obtain insight into the molecular self-association processes found in solution in the crystallization of organic molecules (10 model compounds will be studied).
- Obtain an understanding of the spatial arrangements of the building units within clusters during crystallization from solution (10 model compounds will be studied).
- Optimize simulation protocols to determine solution structure, clustering of molecules and nucleus structure (10 model compounds will be studied).
- Develop methods for controlling cluster formation and polymorph outcomes (2 methods will be developed).
- Develop increased understanding of the role of surfaces, additives and impurities in nucleation (10 model compounds will be studied).
- Develop and validate simulation protocols for heterogeneous nucleation (10 model compounds will be studied).
- Improve our understanding and control of nucleation in multi-component systems which form multi-component materials such as co-crystals and organic salts (10 model compounds will be studied).
- Obtain insight into the influence of high pressure, external fields, and other energy sources upon nucleation (10 model compounds will be studied).
- Develop our ability to predict and control nanoparticle formation (10 model compounds will be studied).

- Develop increased understanding of the role of surfaces (including chiral surfaces), additives and impurities in crystal growth, with particular reference to continuous crystallization (10 model compounds will be studied).
- Examine new methods for process development (2 methods).
- Build on the fundamental knowledge outlined above by applying it in practical applications (6 applications).

In addition to these scientific objectives, the Action will enhance the profile of the researchers within the scientific community, the industrial community and at a policy level.
There will be five co-authored cross-discipline publications per year, in addition to an improved training environment for Early Stage Researchers. In the final year of the Action there will be workshops for industry, reports for policy makers, and published proceedings from a conference on nucleation. There will also be joint funding applications.

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

Training: Interdisciplinary training across the Action will provide Early Stage Researchers with a holistic approach to nucleation, crystallization and crystal engineering, giving them specialist training, broad awareness of the area and a full grounded toolset for the employment market.
Research: Enhanced research output will result from the Action as it will bring together researchers from experimental and theoretical backgrounds, as well as increased awareness of, and access to, the capabilities available at large scale facilities. There will be increased collaboration between researchers which will contribute to increased knowledge in the “Advanced Manufacturing and Processing” technology area as set out in Horizon 2020. This COST Action will achieve this through a variety of activities including workshops, conferences, Short-Term Scientific Missions, and Training Schools.

C.4 Potential impact of the Action

The Action will have a *profound impact* by: (i) opening new interdisciplinary collaboration opportunities, (ii) joining the knowledge and skills of research groups from different branches of chemical and physical sciences, (iii) creating a fertile framework to successfully address current challenging problems in crystallization science and (iv) taking advantage of state-of-the-art methods for nucleation and crystal growth developed in Europe. The Action will foster synergies not possible at national levels, particularly in the development of new methodologies for the monitoring

of solution properties, the detection of nucleation and increased access to large-scale facilities. In addition the integration of the Crystal Growth and Crystal Engineering Communities will make a substantial contribution to overcome the fragmentation of groups working on the fundamentals of crystallization processes and crystal engineering that currently exists.

The Action will make Europe highly attractive to the best young researchers in crystallization, which is currently under-represented in European research teaching programmes despite the existence for over a decade of dedicated journals and the recent introduction of an undergraduate textbook on crystal engineering. The COST Action members will find exciting career prospects in the steadily growing pharmaceutical sector, which is looking for new researchers with appropriate skills in crystallization, providing competitive advantage to European pharmaceutical and chemical industries.

The research activities have a strong initial focus on pharmaceuticals and the potential to create new opportunities in other materials systems where particle size/form control is critical, including energetics, dyes/pigments and agrochemicals, quantum dots, displays, electronics, sensors, solar cells and inks, for example. This will help attract and retain business Research and Development (R&D) investment in Europe.

C.5 Target groups/end users

The research knowledge and expertise generated in this Action will be relevant to wide variety of end-users in academia as well as the pharmaceutical and agrochemical sectors, both small and large-scale companies, including chemical synthesis, analytical and process monitoring. Both healthcare biotech and pharmaceuticals invest heavily in research (15-25% of revenues) creating high value jobs in Europe. Indeed, publicly-quoted biotechnology companies in Europe have a market cap of over €50 billion and employ over 87,000 people. This COST Action will also facilitate transfer of knowledge and innovation from the science base to industry in line with the 'EC Bio4EU Action Plan', and will capitalise on breakthroughs in science and technological development. The Action will deliver the ability to design organic products with better physical properties and more efficient crystallization processes, guaranteeing that only the desired crystal phase will be produced. This will lead to better and cheaper manufacturing due to a reduction in batch failure and, ultimately, cheaper product costs, especially for medicines. It will help European chemical and pharmaceutical companies to remain competitive in the increasingly intense global competition and will reduce the cost of medicines for patients and healthcare systems.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

This COST Action aims at a fundamental understanding of the molecular mechanisms of crystallization processes for organic molecules by uniting researchers interested in crystal engineering, crystal growth and protein crystallization. This will include crystallization from the solution phase, in the solid, liquid and gas phases and from complex phases such as microemulsions. Therefore four complementary Working Groups (WGs) have been defined as outlined below.

WG1: Solution Structure
Investigation into molecular self-association in solutions of different concentrations, and melts using in-situ techniques for probing solution structure and the supersaturated state, in synergy with multi-scale modelling.

WG2: Nucleation
This Working Group will examine the formation of the nucleus, its structure, and its influence on the resultant crystalline phase and methods to control nucleation. The influence of impurities in determining nucleation outcomes will be examined.

WG3: Crystal Growth
This Working Group will investigate methods for controlling crystal growth. It will examine the kinetics of crystallization as well as how impurities and surfaces affect crystal growth in terms of crystal size, shape and distribution.

WG4: Integrating Crystal Engineering and Crystal Growth Philosophies for Applications
This Working Group will explore how the different methodologies and philosophies used in the crystal engineering and crystal growth communities can be combined. The focus will be on incorporating knowledge of the solution structure and the nucleus into the crystal engineering paradigm, which is presently driven by crystallographic and synthetic philosophies, as well as understanding how structure impacts on function. Allied to this, it will build on the fundamental knowledge obtained in the other WGs by applying it in practical applications.

Within the WGs scientists from diverse experimental and molecular simulation research fields in

biology, chemical engineering, chemistry, pharmacy and physics will be brought together to create multi-disciplinary teams of scientists targeting crystallization processes from both a fundamental viewpoint and exploitation into practical applications.
The resources already available for the tasks outlined in these Working Groups will include (i) PhD students (ii) PDRAs (post-doctoral research associates) (iii) technical support and (iv) Principal Investigators (PIs). The latter include experienced PIs and those at the beginning of their careers. In addition, the infrastructure available includes (i) high quality laboratories, (ii) specialist equipment for analysis and characterisation, (iii) large scale facilities and (iv) software for the computational aspects.

D.2 Scientific work plan methods and means

The scientific methodologies that will be utilised in the Working Groups are outlined below.
1. The use of spectroscopic and diffraction techniques in both the laboratory and in large scale facilities to access information about intermolecular interactions (WG1 and WG2).
There are a wide range of different analytical techniques that are in theory available for the in-situ analysis of concentrated solutions and pre-critical nuclei. Often one of the major requirements in this work is the detailed analysis of the data obtained. The Action will have access to Infrared and Raman Spectroscopy, Dynamic Light Scattering, Nuclear Magnetic Resonance, X-ray Photoelectron Spectroscopy, Near Edge X-ray Absorption Fine Structure Spectroscopy, Small and wide-angle X-ray Scattering and Neutron Diffraction. Acoustic levitation allows droplets of material to be suspended and analysed while the solvent evaporates, allowing for structural changes due to concentration effects to be monitored in real time. High pressure and hydrostatic pressure techniques allows access to new crystal phases. This provides insight into the molecular building blocks which influence nucleation processes and allows manipulation of the crystallization outcomes.
2. The use of designed chemical probes for accessing information about molecular assembly, solvation shells and pre-critical clusters (WG1 and WG2).
Potential approaches for examining the transition between the liquid and solid states is to use folding molecules or intramolecular balances and supramolecular complexes for studying the behaviour of partially pre-organised states that mimic the early stages of crystallization. Such approaches provide a quantitative means of studying structural aspects such as pre-organisation, rigidity, and effective molarity on the aggregation of organic solutes. Furthermore, these systems facilitate systematic investigation of solvent effects, and their interplay with the electrostatic and

dispersion interactions that drive self-association. Impurity probes will be designed and synthesised so as to selectively disrupt specific supramolecular motifs, such as amide dimers and hydrophobic interactions. The studies will probe the connection between solution state interactions and the formation of pre-critical clusters containing crystallographic motifs.

3. Modelling of molecules, molecular clusters and solvated species using both crystal structure prediction methods, molecular dynamics and, where appropriate, Monte Carlo simulations (All WGs). Molecular dynamics and, where appropriate, Monte Carlo simulations on a specific confined environment system will be used to investigate different solution concentrations, and configurations for clusters of varying sizes to gain insight into the nucleation process and the transition point between cluster and crystal. Analysis will be performed on the most stable cluster structure to determine the size of the cluster when it has similar stability to the bulk crystal. Crystal structure prediction methods will be used to generate models for investigating alternative nuclei structures and the effects of solvent and size on stability. A reliable quantum chemical method will be developed to generate force-field parameters for packing and to explore reactive steps such as proton transfer during solute aggregation. Modelling involving impurities and surfaces will allow their influence on the solution structure, nucleus structure and crystallization outcomes to be examined. Aligned to this is the need to develop tools to facilitate exchange of structural and simulations datasets involving a variety of different programs.

4. Direct experimental methods for investigating and controlling nucleation and crystallization conditions (WG2 and WG4).

A direct approach to explore the critical nucleus will be the use of confinement synthetic strategies, or the use of external fields, which in some cases can also allow control of the spatial and temporal distribution of the particles. It would be know where and when a definite number of nucleation events would occur. One promising area for the study of the nucleation process is the control of the properties of the generated particles, for instance generation of nano-sized particles with controlled size.

Microemulsions will be used for the synthesis of confined nanoparticles since they can exert thermodynamic control (rather than kinetic control) over the crystallization process, thereby generating stable polymorphs directly. This is in contrast to Ostwald’s empirical rule of stages, whereby the stable polymorph is often obtained after a series of metastable phases have been formed.

5. Indirect methods for investigating nucleation, and modelling nucleation and crystallization kinetics (WG2). The kinetic and thermodynamic factors underlying nucleation will be examined by using induction time and metastable zone width experiments to probe nucleation processes. This

indirect approach requires performing a large number of experiments because of the stochastic nature of nucleation: it is not know where and when an indefinite number of nucleation events will occur. The influence of impurities on both the thermodynamics and kinetics of nucleation will also be examined. The influence of cluster size on nucleation kinetics and how it changes dynamically during crystallization as the supersaturation decreases will be modelled.

6. Methods to investigate crystal growth and control polymorphism (WG3 and WG4).

Other crystallization technologies, such as crystallization of organic molecules in gel media with organic solvents, interfacial crystallization between two liquid phases and counter-diffusion methods (which will also allow time-resolved measurement of concentration gradients and pre-critical size distribution) will be used to investigate crystallization processes and outcomes. The influence on crystal growth will be examined by (i) the addition of impurities to the crystallising solution, and (ii) the use of specifically functionalised surfaces. Atomic force microscopy and scanning tunnelling microscopy will allow characterisation of different surfaces and the early assemblies of molecules as a function of external conditions. The increasing demand for enantiopure organic molecules means that chiral recognition needs to be investigated, using chiral impurities and chiral surfaces. Calculations of lattice matching will inform the choice of molecules for surface functionalization, along with application of the Bond Selection Mechanism (BSM) theory. This will include crystallization from the vapour phase and the use of seeding and hetero-seeding.

The anticipated milestones are:

- Experimental and theoretical analysis of the relationship between nucleation behaviour and crystallization conditions.
- Experimental and theoretical analysis of the relationship between nucleation behaviour and molecular properties.
- Experimental and theoretical analysis of the influence of surfaces and impurities on crystal growth.
- Experimental and theoretical analysis of relationships between racemic and homochiral crystals.
- Experimental and theoretical analysis of model compounds from the molecular scale to the macroscopic scale.

E. ORGANISATION

E.1 Coordination and organisation

The management and organisation of this Action will conform to the "COST Action Management" (document COST 4114/13) and "Rules for Participation in and Implementation of COST Activities" (document COST 4112/13). The Action will run for 4 years and will be managed by a Management Committee (MC). The MC will be responsible for the overall management of the Action, including managing the budget, coordinating Action activities and reporting to the relevant COST Committees.

The Action Chair (AC), Vice-Chair (VC) and Working Group Leaders (WGLs) will be appointed at the 1st MC meeting. The MC will meet every 6 months to evaluate progress and plan future activities. The AC will be the official point of contact between the Action and the COST Office.

A Core Group will be set up consisting of:

- Action Chair (AC) and Vice-Chair (VC)
- The Working Group Leaders (WGLs)
- The Training Coordinator (TC)
- The Short-Term Scientific Mission (STSM) Coordinator
- The Website and Dissemination Manager

This Core Group (CG) will prepare MC meetings, agendas and minutes. The CG will also oversee the implementation of the Action, interaction with the Scientific Community, including recruitment of new research groups, as well as dissemination of results and activities to academia, industry and the wider community. There will be close liaison between all members of the CG.

To maximise participation of European scientists the Action will be widely publicised by advertising in relevant journals and webpages, at conferences, via mailing lists and social networking resources (*e.g.* LinkedIn, ResearchGate etc.).

The first task of the WGs will be to compile lists of the current research activities and expertise of their members to be distributed to all participants and placed on the Action website, enabling enhanced networking opportunities and cross-fertilisation of ideas. The list will be kept up-to-date to allow easy monitoring of the success of the Action.

The Website and Dissemination Manager will oversee the creation of the Action website and will be responsible for its upkeep. The website will include details of research capabilities, Action activities and events including STSMs, Workshops, Training Schools, research publications, presentations and reports. The website will have a restricted access section for Action members only where participants can discuss current projects, ideas for future projects and post results.

Milestones include (i) successful election of all members of the CG, (ii) assignment of participants to WGs, (iii) establishment of new research collaborations, (iv) publication of annual reports and (v) successful completion of Action activities [2 conferences, 2 Training Schools, 5+ STSMs per year].

E.2 Working Groups

The research of this COST Action will be organised in four Working Groups (details in Section D). Each WG will be led by a Working Group Leader (WCL) with a Vice-Leader. Wherever possible, one of these positions in each WG will be held by an ESR in order to promote leadership capability within the Action. The majority of Action members will be involved in more than one Working Group. This will help efficient communication between the different Working Groups and maximise the benefit from the Action.
Each WG Leader, together with the Vice-Leader, will be responsible for: (i) setting and monitoring WG milestones, (ii) co-ordinating the WG meetings, (iii) leading the scientific discussions, (iv) interacting with the STSM Coordinator for managing the STSMs within the WG, (v) participating in the Core Group, (vi) co-ordinating WG contributions to the website, (vii) interacting with the Website and Dissemination Manager, (ix) requesting and collecting Annual Reports from individual participants, (x) writing reports of the WG activities, (xi) liaising with the Training Coordinator. These are essential elements of the Action and will require care and commitment to ensure the success of the Action.
The progress of the different activities, especially the STSMs involving ESRs, will be recorded in the annual Monitoring Progress Report.

E.3 Liaison and interaction with other research programmes

This COST Action has complementarity with COST Action CM1005 “Supramolecular Chemistry in Water”, and certain joint activities involving, in particular their WG1 and WG3 of the above mentioned Action, could be envisaged, for example workshops and seminars. There will be close interaction between the members of the CG of this Action with the management and Core Group of COST Action CM1005. This will be extended to relevant new COST Actions that begin during the lifetime of this Action.

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

This COST Action will respect an appropriate gender balance in all its activities and the Management Committee will place this as a standard item on all its MC agendas. The Action will also be committed to considerably involve early-stage researchers. This item will also be placed as a standard item on all MC agendas.

An effort will be made to maintain a good gender balance in the elected members of the COST Action and maintain national diversity in all teams. ESRs will be encouraged to become actively involved in the Action including joining the running of the Training Schools and co-ordination of the WGs. Training within the Action will be focussed on the training needs and requirements of ESRs. When allocating STSMs, priority will be given to those projects involving ESRs.

To enhance capacity building the following mentoring activities will be enacted:

- Involvement of ESRs in all aspects of the management and implementation of the Action.
- Support for ESRs in developing new ideas and projects.
- Encourage ESRs to organise different activities within the Action and to get involved in STSMs.
- Action activities will encourage ESRs to network (both within the Action and beyond).
- ESRs will be encouraged to lead research reviews and engage with industry stakeholders.

F. TIMETABLE

The timetable below is indicative of the activities to be implemented over the 4 years of the Action. The numbers of the STSMs and workshops will be determined by the MC. The timing of the Training Schools is dependent on the exact start date of the Action. As far as practical, MC and WG meetings will be held concurrently with Action events to reduce travel costs, maximise attendance and ensure more funding is available for the STSMs and training activities. CG and MC meetings will occur every six months. In addition, CG teleconferencing meetings will occur at three month intervals between MC meetings.

Activity	Year 1				Year 2				Year 3				Year 4			
	¼	½	¾	1	¼	½	¾	1	¼	½	¾	1	¼	½	¾	1
1st MC meeting	X															

Establish WGs	X															
MC meeting		X		X		X		X		X		X		X		X
Annual meeting		X				X				X				X		
WG meeting				X				X				X				
Workshops				X										X		
Training Schools								X							X	
STSMs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Final Conference																X

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: AT, BE, BG, CH, CZ, DE, EL, ES, FI, FR, HR, IE, IT, NL, PL, PT, SE, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 72 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?

The target audiences for the Action are:

1. The participants of the Action
2. The Scientific Community (the wider crystal growth / crystallization / crystal engineering community both within Europe and beyond, the more general scientific community including learned societies and students in Higher Education)
3. Policy makers (including national and European funding agencies, and regulatory bodies, e.g. European Medicines Agency)
4. Industry (including the pharmaceutical, agrochemical and fine chemical industries)
5. The general public (including schoolchildren and their teachers)

H.2 What?

The results and activities of the Action will be disseminated via a variety of methods suited to the target audience. The normal methods of scientific communication will be utilised, including publications, oral and poster presentations at conferences and seminars, websites and social networking sites. Action activities like conferences, STSMs, Training Schools and Workshops will promote dissemination of knowledge within the Action and beyond. Meeting reports and Annual reports will be available on the website. These will also be sent electronically to all interested parties and stakeholders. The final report on the Action will be made available in both electronic and printed formats and distributed to all stakeholders. All target audiences will have access to the website, which will contain:

• News and announcements to the members of the Action and to the general public,
• Current schedule of meetings and STSMs.
• A searchable description of the project, together with up-to-date results,
• A variety of web-based mailing lists (grouped by target audience) and an archived discussion forum.
• Databases of articles, data and other information compiled for knowledge transfer,
• The software developed in the Action for communication between the different software packages used in the research programs will be available for Action members.

The website will be available to users at two levels. The Activity reports, publications and news items will be accessible by all users. There will also be a secure member's only section of the website for uploading data, draft reports and unpublished material.

In addition, researchers will make short videos showing their research for a wider public audience. These will form a "Practical guide to…." series showcasing their research techniques, experiments or key findings. These will be available via the website and other social media websites (e.g. YouTube).

H.3 How?

The first target audience will be reached using the communication tools of the Action, including the website, e-mail distribution list and in internet discussion forum.

The second target will be reached by publications in leading scientific journals, preferably by joint publications, and including review articles, contributions at national and international conferences and workshops, and the yearly and annual reports.

The third target will be reached (where appropriate) by research proposals, e-mail distribution lists and social networking, and the yearly and annual reports.
The fourth target will be reached using the communication tools of the Action, including the website, e-mail distribution lists, in internet discussion forum, and the yearly and annual reports.
The fifth target will be addressed by public media. This will include articles written for a general audience and published in news media and other media platforms (for example general social networking sites such as Facebook), and publication of non-technical reports in non-specialised journals.
To help recognition of the research and activities of the Action, the following procedures will be put in place:

- Each Action participant should acknowledge COST if a peer-reviewed paper is published in the broad context of solution structure and nucleation of organic compounds as an outcome of collaborative work carried out within the Action.
- Each Action member will mention and briefly describe the Action if she/he gives a lecture or a talk anywhere outside the Action.
- The COST and Action’s logo will routinely appear on the acknowledgement slide of talks and on conference posters.
- Each Action member who is invited to contribute to a TV or radio interview, or to a general overview article in a journal addressing the general public, will announce that his or her work is involved with this COST Action on understanding the crystallization of organic compounds.
- The Action will proactively contact the press each time a breakthrough result has been freshly published in a high-level journal.