

6	<b>Trifolio-M GmbH</b> (FRG)	Dr. H. Kleeberg	Extraction, Formulation
7	<b>Free University of Brussels</b> , (B)	Prof N. Koedam & Prof Jaziri	Natural Resource Management and Ecology, Plant Biotechnology
8	<b>OEL</b> (D) Institute of Organic Farming	dr. Gerold Rahmann	Certification Quality Systems, Environmental impact, Energy and water savings, Socio-Economic aspects, Trading
9	<b>University of Leiden</b> , (NL)	Prof. R. Verpoorte	Molecular biology, Biochemistry and Plant Biotechnology
10	<b>Essence Srl</b> (IT)	Avv. Oliva	Extraction and formulation
11	<b>Hopital Salpetrière</b> (F)	Dr. O. Chosidov	Dermatology
12	<b>Medical Entomology Centre Ltd</b> , (UK)	Dr. I. Burgess	Epidiomology, Vector control, Economical analysis
13	<b>University of Pisa</b> (IT)	Dr. L. Pistelli	Extraction, isolation and structural elucidation of secondary metabolites from plants
14	<b>De Montfort University</b> (UK) School of Pharmacy	Dr. Jack Woolley	Mode of action.
15	<b>Cambridge University</b> , Department of Chemistry, (UK)	Prof. S. Ley	Purification, Isolation and Synthesis
16	<b>European Tropical Forest Research Network (ETFRN)</b> (NL)	Dr. W. Brinkman ETFRN Coordinator	Dissemination of results, particularly regarding the aspects related to tree breeding and cultivation Virtual meeting point, discussion forum and on-line library
17	<b>Bioparco</b> (IT)	Dr. K. Friedrichs	Management of Zoological gardens
18	<b>Napels University</b> (IT)	Dr. A. Ritieni	Food science.
19	<b>Danish International Development Assistance</b> (DANIDA). (DK)	Dr. L. Graudal	International co-operation in forestry

### **Integration and Structuring Effect:**

Many of the partners mentioned above have a long standing tradition in Neem research and have always been at the cutting edge of this field. Other partners are present in their respective fields as recognised centres of excellence and their contribution is necessary to find and implement economically viable applications which are wholly, or in part, based on Neem derived products. Within this partnership all necessary competences are represented in order to address both fundamental research aspects as well as more applicative aspects. The socio-economic impact these innovative solutions might have will also be considered.

The role of the ENN will be to offer a platform where all the different disciplines and competences involved in very diverse aspects of Neem and its applications can find a point of exchange which in a second moment can lead to synergisms and close co-operation on specific projects. The ENN will also have an important role to play in interfacing with both international (FAO, WHO, UNEP, World Bank) and national (from governments to local administrations, professional and consumer associations) organisations. Another important aspect is that the Neem tree does not grow in any Member State of the EU (and never will) so that it will be important to create close links with as many countries as possible where it grows but where it remains an untapped resource.

This way it will be possible on the one hand to further awareness (already pretty well developed in some DCs) and economic growth in those countries around the Neem added value chain and on the other hand favour an increased use of Neem based products, which come from a renewable resource, that can underpin a more sustainable form of development in many different sectors of the EU economy and enhance consumer protection.

# Alternative Biocides

## Need and Relevance

By 2006 a EU directive (98/8/CE) has indicated the phasing out of a certain number of unsound biocides. (Methyl Bromide, rodenticides and others) because of their environmental impact and/or health hazard. Neem is known for its antimicrobial effects and has shown promise against some major plant pathogens e.g. powdery mildews The ENN would study in which cases Neem derived products could be a useful alternative either as a biocide or as an alternative mean of controlling harmful organisms. This might particularly be true for the control of sinanthropic organisms (mice, rats and pigeons). Indeed the reversible anti-fertility effect of Neem oil has been studied in mice, rats, primates and chickens and the results confirm the effectiveness on fertility without compromising the health of the animals nor their sexual behaviour or their libido. As in urban areas the control of both rats and pigeons populations represent a large expense for the local communities alternative control measures to the rodenticides and the physical suppression of pigeons would be preferable. The same approach (i.e. reversible fertility control) can be adopted for all those animals in natural parks or zoos which exceed the carrying capacity of either the protected area or the zoo structure, thus intervening by milder means.

Also for the control of ecto-parasites (both animal as human) Neem based formulations could assure effective control without exposing the either the treated subjects or the operator to negative side effects.

Adopting Neem derived products could also offer an opportunity for controlling both insects and micro-organisms at the same time since it appears that although the limonoids control insects other neem compounds, but not the major limonoids, are likely to be the active agents against microbes.

## Excellence:

Neem research within different EU countries has a long standing historic tradition of excellence. Combining different research groups of excellence (their resources or capacity for finding them) from Neem research with specific competences in plant biotechnology, biochemistry, organic chemistry and areas more geared towards the applications (Malaria, Veterinary, Vector control etc....) would greatly facilitate the development of effective novel means for addressing the different applications envisioned above.

The competences involved will be organic chemists (extraction, purification, identification of Neem SMs) parasitologists (in vitro testing on parasite), entomologists (testing on vector, crop pests and biocides), plant physiologists and microbiologists, medical disciplines (epidemiology, immunology etc....) and formulators (SMEs).

**Partners: (those listed can form a core group, it is open to more interested partners and stakeholders)**

N°	Organisation	Name	Competences
1	ENEA (IT)	S. A. van der Esch	Plant Biotechnology, Veterinary, Microbiology, Entomology, Immunology, DSP
2	University of Aberdeen, (UK),	Dr.. J. Mordue & Dr. E. Allan	Entomology, Plant Biotechnology, Mode of action, Microbiology
3	Keele University, (UK),	Prof G. Jones Prof. E.D. Morgan	Development of analytical method, stability of products, and enhancement of activity through chemical modification.
4	University of Camerino(IT)	Prof. F. Esposito & Dr. A. Hableutzel	Parasitology (Malaria), Entomology, Veterinary
5	Max Planck Institute Chemical Ecology, (FRG),	Dr. B. Schneider	Biochemistry, Purification, Identification

(Sustainable development, global change and ecosystems). This R&D cross cuts the different thematic areas in accordance to the end products or applications envisioned. All the same a lot of the multidisciplinary and integrated research necessary to obtain an end-product or application in one of the thematic areas mentioned is actually in common. This is one of the fundamental reasons to present a Network of Excellence which is explicitly centred on the Neem tree and its products.

The Network will then function as a common think tank and co-ordination point for the definition and preparation either of EU Integrated Projects or other projects supported by local or national and international R&D programmes.

Below different examples will be illustrated of how the ENN can intervene on the three different thematic areas mentioned beforehand. All these activities will have in common those competences and research groups which already have a position of excellence concerning activities of the Neem added value chain (Plant biotechnology, extraction, purification and identification of complex organic compounds, formulation). For each different example mentioned more specific competences and capabilities will be necessary and thus involved on more specific themes such as “Malaria”, “Safer and environmentally friendly production methods and healthier foodstuffs”. For each activity a short illustration of **Need and Relevance** will be made, while the **Excellence and Integration and Structuring effect** will be valid for all of them.

## **Malaria (thematic area 1.1 subtheme 1.1.2.3)**

### **Need and Relevance:**

The **need** for novel approaches for the control of malaria are self evident as both the vector and the parasite are becoming resistant to commonly used biocides and pharmaceuticals and the prevalence is increasing. Within the thematic area 1.1 the sub-thematic area 1.1.2.3 (confronting the major communicable diseases linked to poverty) is appropriate as Neem derived secondary metabolites have shown to be active against *Plasmodium falciparum* (malaria parasite) and towards Anopheles (vector for malaria parasites). These preliminary results are very interesting but before effective Neem based products can be developed both for vector and parasite control a multidisciplinary approach must be adopted. In most countries where malaria is a serious problem Neem trees grow and often aren't exploited for these specific properties. Thus the **relevance** of the R&D to be carried out by the network is to verify if Neem based products can effectively combat malaria through the use of unexploited resources present in the countries where it is a huge medical and socio-economic problem.

## **Safer and environmentally friendly production methods and healthier foodstuffs. (thematic area 1.5)**

### **Need and Relevance**

The use of Neem derived products in pest control in crop cultures is already a reality albeit not largely used. The environmental benign character of these preparations and low toxicity towards both the operator exposed and the end-user (consumer) are good arguments in favour of using Neem derived products. All the same as the effects on the pests isn't of a “knock-down” nature better information on the modes of action and application are necessary if a wider use is to be stimulated. Another important sector where Neem derived products are showing promising results is in the field of improvement of animal husbandry and animal welfare. Although evidence is still sporadic these products could be very useful for the control of ecto-parasites especially in the fibre added value chain and for the control of disease bearing vectors like *Culicoides* (Blue tongue). The ENN will focus on the question if Neem derived products can become a valid alternative to be used as veterinary drugs thus improving animal welfare from housing to slaughter.

properties and promise, some impediments have yet to be overcome and many uncertainties clarified before neem's potential can be fully realised.

Although research on many different aspects of the Neem tree are underway –in many different countries (India, USA, Canada, Germany, United Kingdom, Italy, Australia)- they generally are individual initiatives lacking adequate financial support and lack co-ordination between groups.

Neem SMs have been disclosed by participating scientist and therefore cannot be patented, an important consideration, so that it is difficult to obtain, as a producer, a secure position with patent protection. This discourages investments by big chemical and pharmaceutical companies. Indeed the neem production world is one dominated by SMEs and cottage industries.

The only initiative to address in a more coordinated way research and development of Neem has been taken by the FAO (Food and Agricultural Organisation). Indeed the FAO has furthered the creation of an International Neem Network (INN) which essentially concentrates on the forestry aspects of the neem tree in those countries where it grows. Although this is important for studying the biodiversity and optimising growth conditions the INN does not address a whole range of important aspects linked to Neem added value. These range from harvesting through extraction and purification, to formulation of products followed by specific application protocols and finding new and wider applications. It is exactly these latter activities which can have the greatest impact as an economical resource for those countries where it is widely present but unexploited (Africa) or scarcely exploited (South America). Only in India is there a mature industry and, for the moment, the major provider of all the neem products which have commercial applications (cosmetics, natural pesticides, medical applications).

Greater input of resources into Neem products and research in the EU would help the developing nations with new industry and at home lead to a better environment and safer pesticides and other products.

## **The European Neem Network:**

To achieve these aims, we propose to form a European Neem Network (ENN) (Network of Excellence) which comprises all European stakeholders (scientists, producers, formulators, end-users and consumers) which should address the following issues:

### **A) Specifically geared towards the European Research Area (ERA)**

- Identification of impediments and uncertainties that hinder more widespread use of Neem products in the EU (regulatory, safety, awareness etc.)
- Standardisation of analytical protocols for neem substances
- Standardisation of application protocols
- Identification of novel and innovative applications
- Fundamental research both for understanding the biosynthetic pathways underlying the synthesis of the biologically active compounds as the mode of action of those compounds.
- Fundamental research for studying in depth the biodegradation products of the active compounds and their fate both in the environment as in the human body.

### **B) Promoting co-operation between European Research Area (ERA) and Developing Countries (DCs)**

- Capacity building in those countries where Neem is abundant but not exploited (mainly Africa)
- Flanking FAO, UNEP, World Bank, WHO with scientific and technological advice for furthering Neem exploitation

The thematic areas where Neem research (integrated with other research areas) could be important are 1.1 (Genomics and biotechnology for health), 1.5 (Food Quality and Safety) and 1.6

# Expression of Interest

## EUROPEAN NEEM NETWORK (ENN)

The intense and widespread use of synthetic pesticides (SP) and biocides (SB) during the past half century for the control of household, agricultural and forest pests, as well as human and animal disease vectors has caused concerns regarding the toxicity and environmental impact of these agents. Some inherent features and use patterns of the conventional SPs and SBs that lead to these concerns are (i) toxicity to mammals -including livestock, fish, birds, and beneficial organisms; (ii) adverse effects on the environment, causing contamination of soil, water and air; (iii) resurgence of pest populations because of the emergence and widespread occurrence of physiological resistance to conventional SPs; (iv) the high costs of the development of new synthetic pesticides, which put the new agents out of reach of pest control programmes in the developing World and (v) not meeting the modern aim of Integrated Pest Management programmes.

Pesticides and biocides are necessary for the control of organisms that are harmful to crops (SPs) and human or animal health and for the control of organisms that cause damage to natural or manufactured products (SBs). The negative health and environmental impact of synthetic products compels us to find valid alternatives which have much less harmful effects. Therefore a search for new, environmentally safe, target-specific SPs and SBs is being conducted all over the world. The most prominent phytochemical pesticides studied in recent years are those based on neem (*Azadirachta indica* (A. Juss)) derived Secondary Metabolites (SM).

For 2000 years the Neem tree has been prized in India, because of its numerous useful properties, traditionally used in agriculture and health care (Ayurvedic medicine). The tree, of the mahogany family has been carried across the world and is now established throughout the drier tropics. Among the many SMs found in the tree -- of which not all properties have been fully studied -- the triterpenoid compounds known as limonoids are presently the most interesting because of their biological activities. Neem derived SMs are capable of producing multiple effects on pests such as antifeedancy, disruption of growth, fecundity suppression, sterilisation and oviposition repellency, and changes in biological fitness. Some or all of these effects have been observed on more than 400 different pest insects. These compounds are at the same time highly biodegradable and only slightly toxic to beneficials while their toxicity towards humans, and mammals in general, has been declared to be of category IV (EPA and EU norms) which is non-toxic. Another important component of the Neem seeds is the oil it contains. Recent studies have put into evidence the reversible anti-fertility effect of this oil in mice, primates and fowl (no anti-fertility effect on mammals is present when one uses the polar limonoids from the neem seeds).

Not only is the Neem tree of major interest as a source of phytochemicals for more environmentally sound SPs and SBs, it can also play a role as an instrument in the arena of global climatic changes. It is listed, among other trees, as an excellent carbon dioxide sink. It is fast-growing, and because of its ability to resist high temperatures and drought, and grow in degraded, eroded and acid soils it can be used to try and halt the desertification process (windbreaks, leaf-litter and fuelwood to poor populations where fuel is becoming a scarce resource), and to restore fertility to exhausted soils.

Taken together, these properties place the neem tree in central importance among tropical plants (excluding food plants) as a natural resource, which could advance sustainable development and foster economic development in those areas of the world most requiring it. The phytochemical products can provide environmentally sound pesticides for the developed world, bringing income to the tropical regions, and promoting safety and quality of food and quality of life in general.

Four decades of research on Neem products have revealed promising results in many disciplines and attracted the interest of scientists both in the developing and developed world. Despite all its