

# REACH and its effects on Maltese Industry – Experiences of a local Company, ICP Ltd.

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Malta

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# Who are we

- **The Institute of Cellular Pharmacology is a Limited Liability Company**
- **We are a small SME**
- **We employ 13 people directly from various backgrounds.**
- **We deal indirectly with hundreds of people involved in agriculture and marine activities such as farmers and divers in Malta.**

# We are based at Mosta Technopark



# Principle activities at ICP

- **Production of extracts from biological sources (marine and terrestrial plants and alga).**
- **Research to determine the nature of active molecules.**
- **Production of Liposomes**
- **Tabulating and packaging.**

# **Principle Market segments :**

**Extracts for the production of active cosmetics**

➤ **Human Nutraceuticals**

➤ **Supplements for animal nutrition  
(aquaculture and poultry)**

# Principle Research Activity



*From the Plant to the Molecule*

From *Padina pavonica* to  
Maltanediol



# The process of producing Extract of *Padina pavonica* (EPP) :

- Cultivation
- Collection
- Drying
- Extraction
- Concentration
- Fractionation
- Registration

# The process of producing Extract of *Padina pavonica* (EPP) :

## ➤ Cultivation

The Algae is cultivated on specially designed farms built on the sea bed in order to maximise the yield.



# The process of producing Extract of *Padina pavonica* (EPP) :

The Algae is hand picked by divers from the farms as well as the wild.



# The process of producing Extract of *Padina pavonica* (EPP) :

## ➤ Drying

The Algae is then placed on racks and allowed to air dry without the use of heat.



# The process of producing Extract of *Padina pavonica* (EPP) :

## ➤ Extraction

The dry powdered algae is then placed in vessels where the active principles are extracted from the algae using a system of percolation.



# The process of producing Extract of *Padina pavonica* (EPP) :

## ➤ Concentration

The liquid extract is then concentrated using low pressure distillation.



Rotary  
Evaporator –  
for the  
concentration  
of the extract



Distillation  
Unit – for  
solvent  
recycling

# The process of producing Extract of *Padina pavonica* (EPP) :

## ➤ Fractionation

The liquid extract is then separated into different fractions containing different active molecules using Medium Pressure Liquid Chromatography.



# The process of identifying the active molecule of *Padina pavonica* (EPP) :

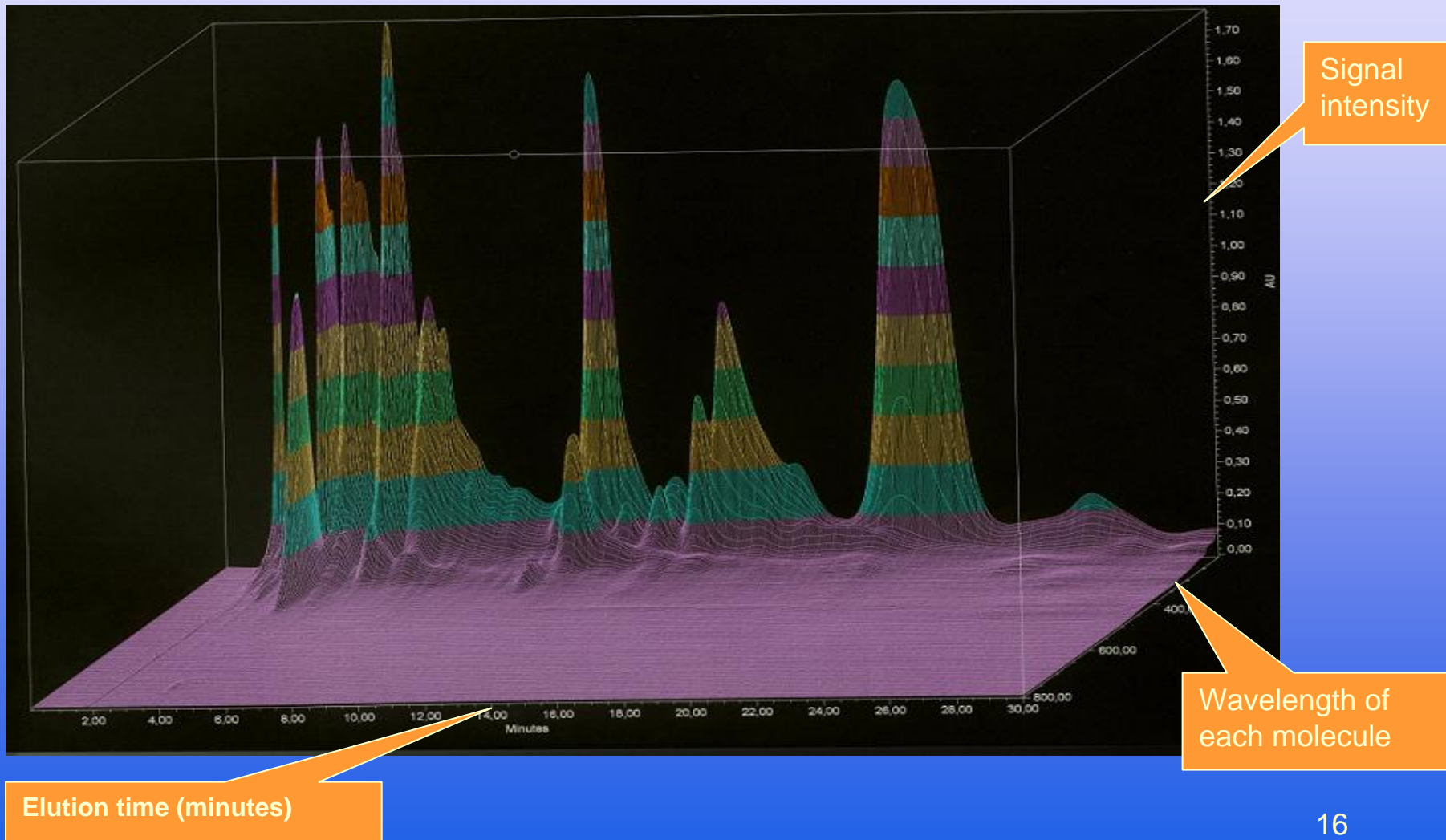
- Fractionation of crude extract using Medium Pressure Liquid Chromatography (MPLC).
- Pigments are removed using MPLC
- Each fraction is tested for activity using biological control (measurement of calcium fixation by osteoblast in culture).

# The process of identifying the active molecule of *Padina pavonica* (EPP) :

The active fraction where we detect biological activity responsible for calcium fixation is purified using High Performance Liquid Chromatography (HPLC) coupled with three dimensional detector.



# The process of identifying the active molecule of *Padina pavonica* (EPP) :

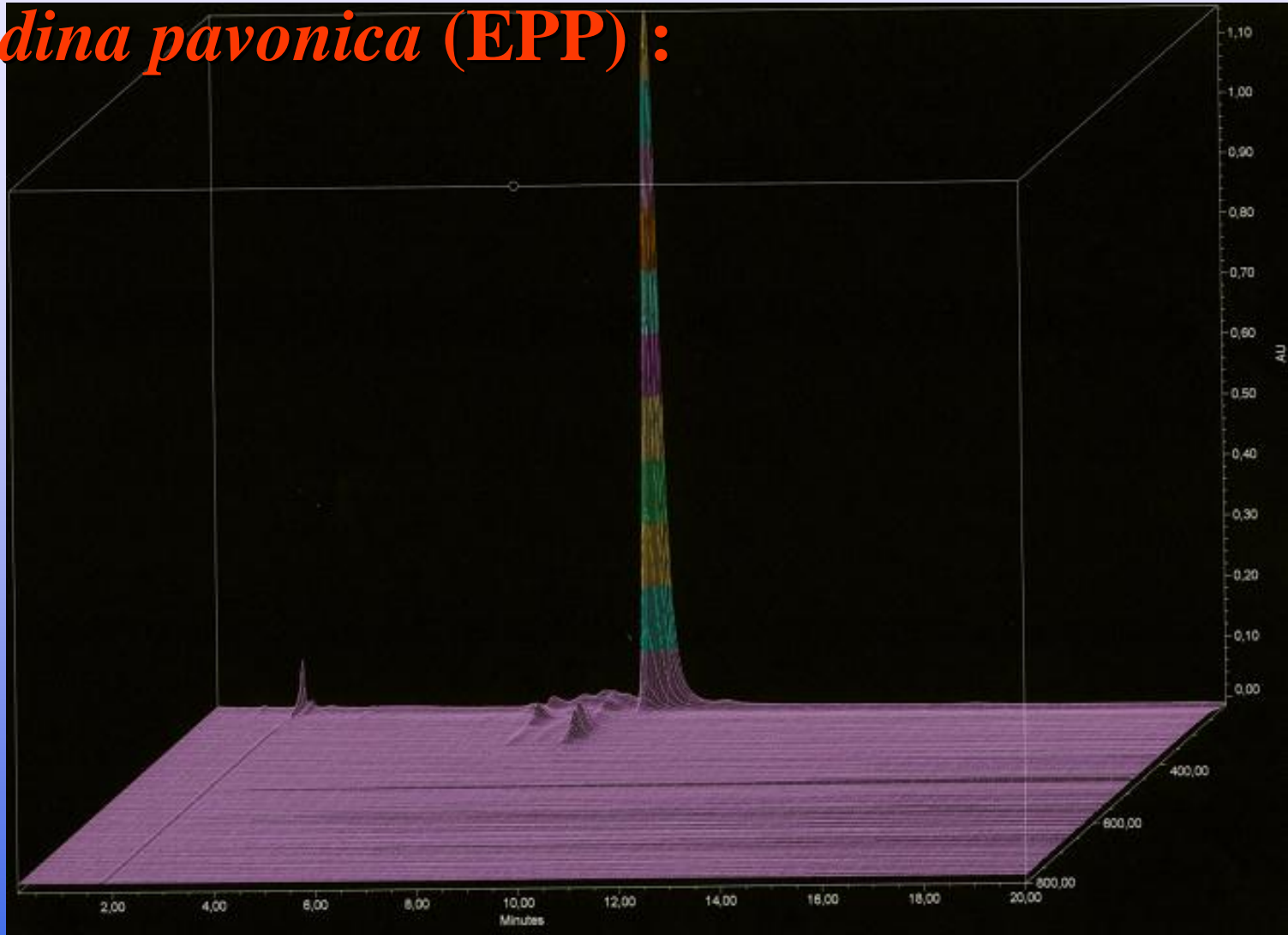


Signal intensity

Wavelength of each molecule

Elution time (minutes)

# The process of identifying the active molecule of *Padina pavonica* (EPP) :



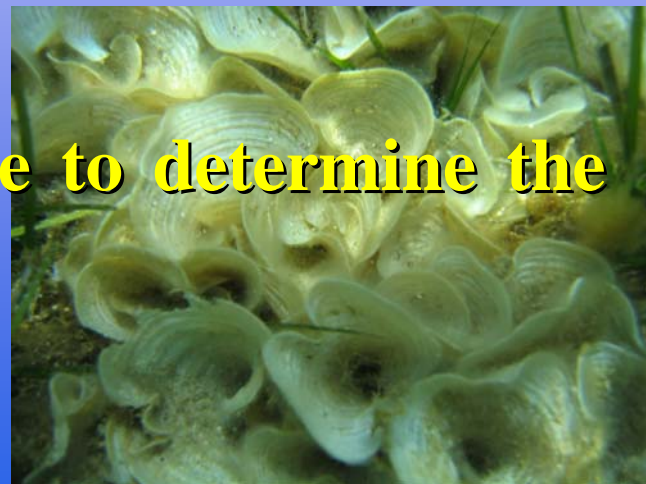
We remove all the other molecules from the semi purified fraction. We purify this fraction further using HPLC.

# The process of identifying the active molecule of *Padina pavonica* (EPP) :

We determine the mass of the pure molecule using Mass Spectrophotometer coupled with Gas Chromatography.

We determine the weight of the molecule up to the fifth decimals.

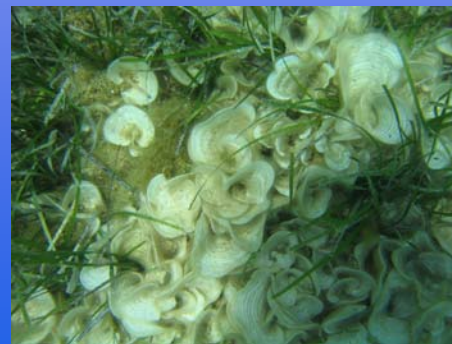
With such precision it is possible to determine the exact formula of the molecule.



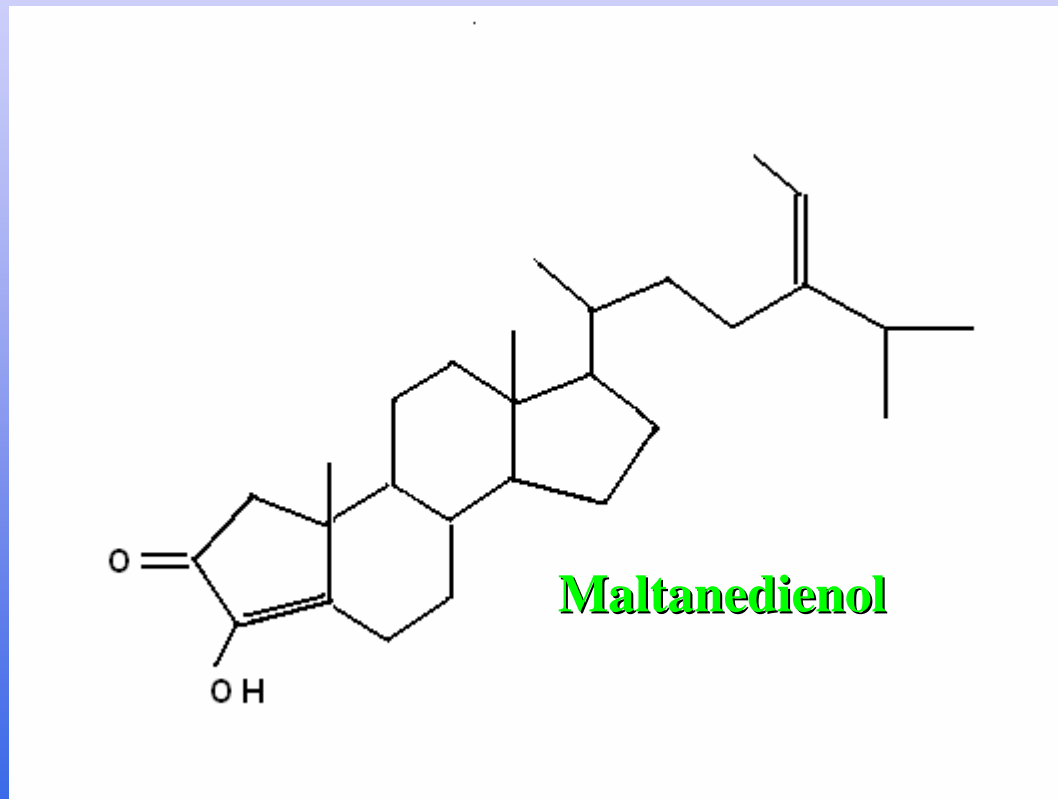
# The process of identifying the active molecule of *Padina pavonica* (EPP) :

The molecule is dissolved in an inert Nuclear Magnetic Resonance (NMR) solvent and we determine the resonance of the protons and  $^{13}\text{C}$ .

By coupling the two spectrums using computer imagery, we determine the spatial structure of the molecule.



# The process of identifying the active molecule of *Padina pavonica* (EPP) :



# Determining Biological activity of the Extract of *Padina pavonica* (EPP) :

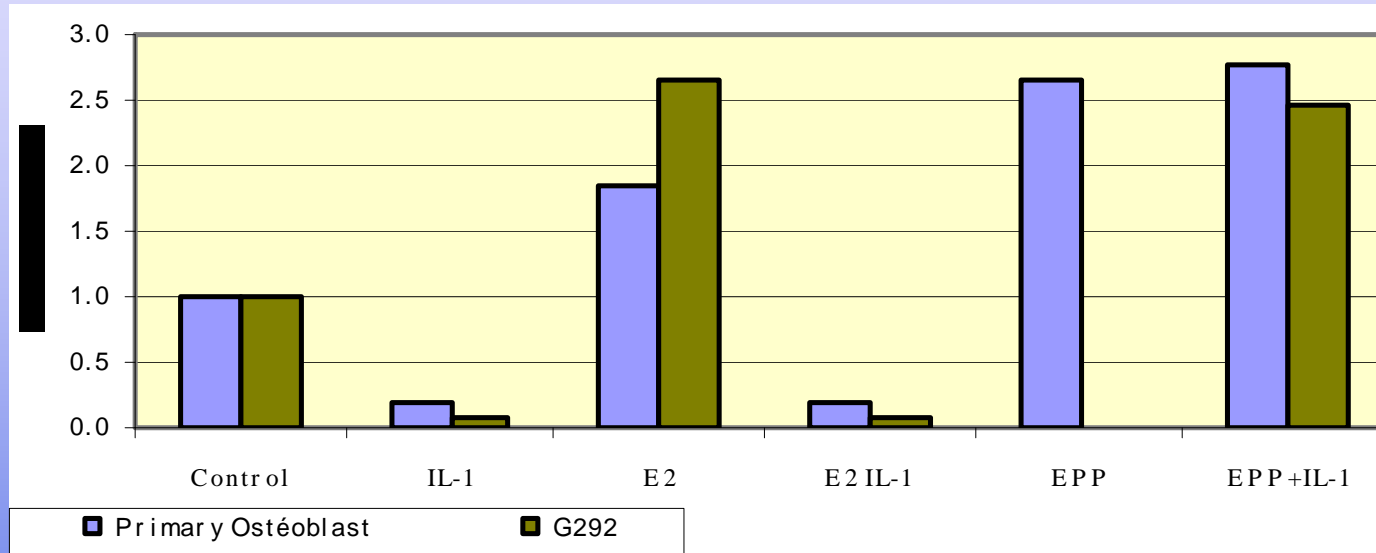


In vitro laboratory for  
tissue culture studies

Atomic absorption unit  
for measurement of  
calcium fixation by cells.

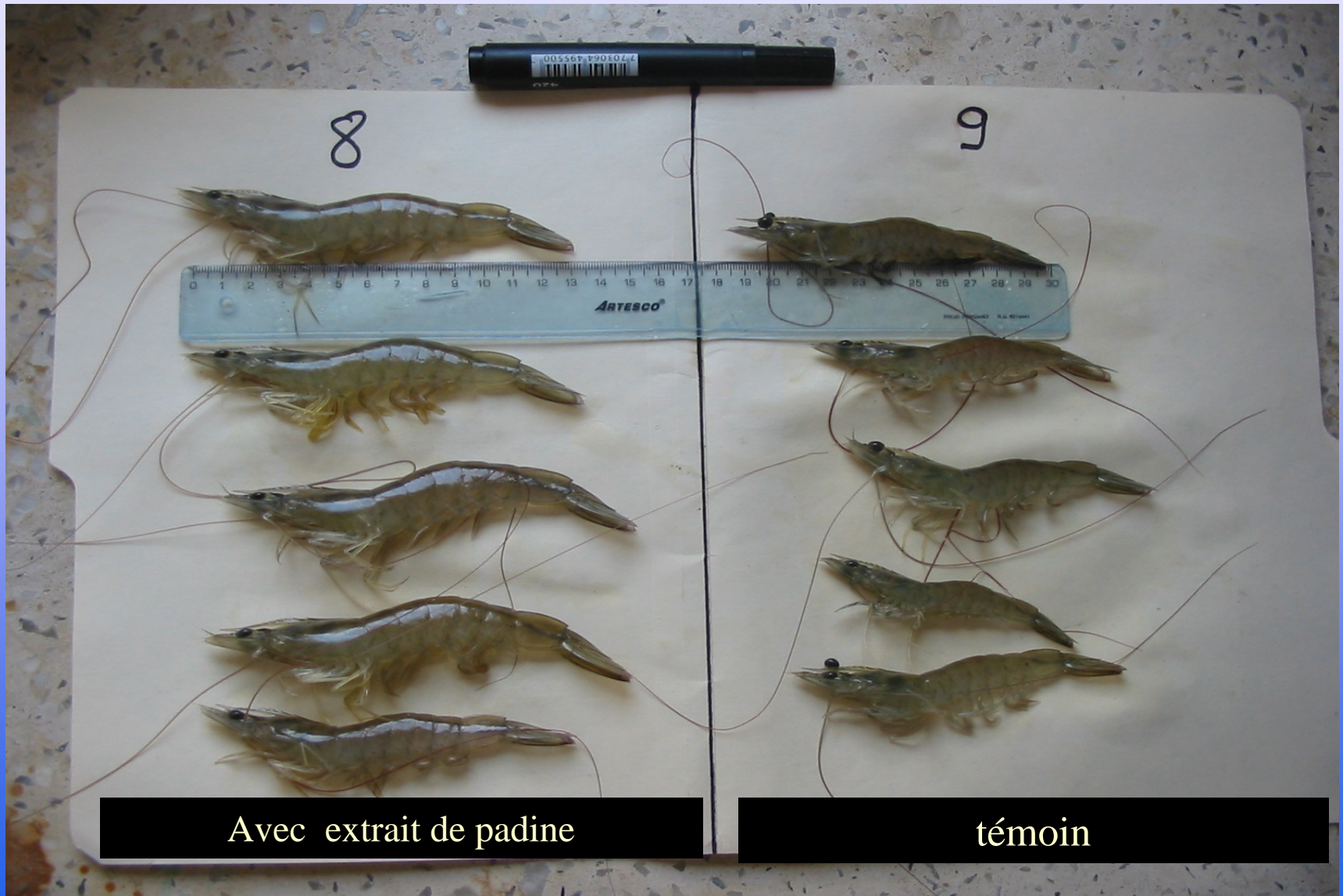


# Determining Biological activity of the Extract of *Padina pavonica* (EPP) :



**EPP induces Calcium fixation in osteoblasts in the presence of Interleukin 1. This is not the case with Oestradiol**

# The use of the Extract of *Padina pavonica* (EPP) :



# The use of the Extract of *Padina pavonica* (EPP) :

The results show that it is possible to increase the growth rate of shrimps and shorten the growth cycle through the incorporation of EPP in the diet.

# The use of the Extract of *Padina pavonica* (EPP) :

## ➤ Poultry Industry

EPP is being used in the poultry industry to:



- Increase egg shell thickness
- Increase bone density and strength
- Improve the rate of healing of skin lesions following bacterial and viral infections.
- Increase mineral transfer from the egg shell to the embryo

# **The use of the Extract of *Padina pavonica* (EPP) :**

## **➤ Human Nutraceuticals**

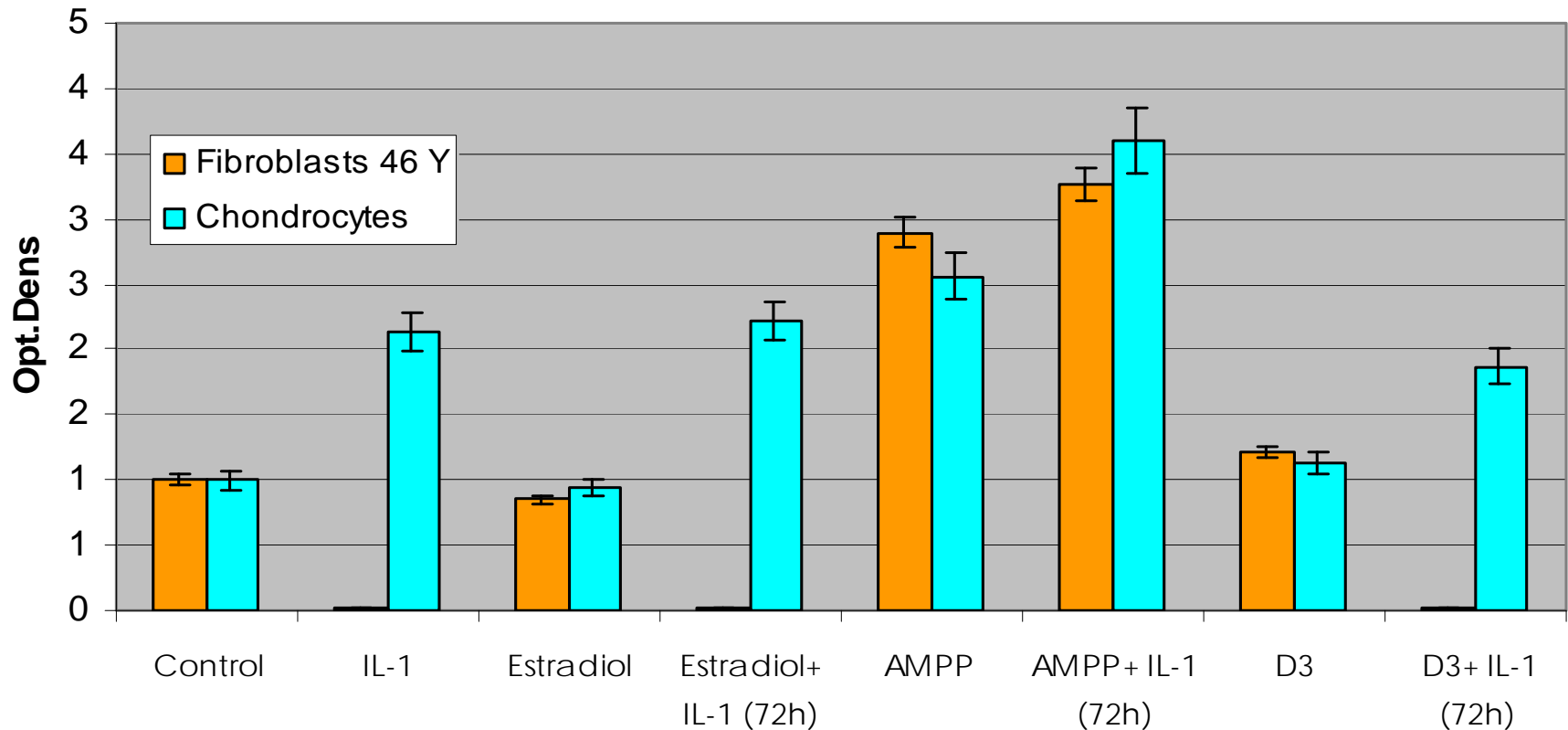
**EPP is being used as a Nutraceutical product to strengthen bone density by increasing glycosamino glycan synthesis and increasing calcium fixation.**

**In medical estatic EPP is being used to promote collagen synthesis.**

# The use of the Extract of *Padina pavonica* (EPP):



Glycosamino glycanes synthesis



# The use of the Extract of *Padina pavonica* (EPP) :

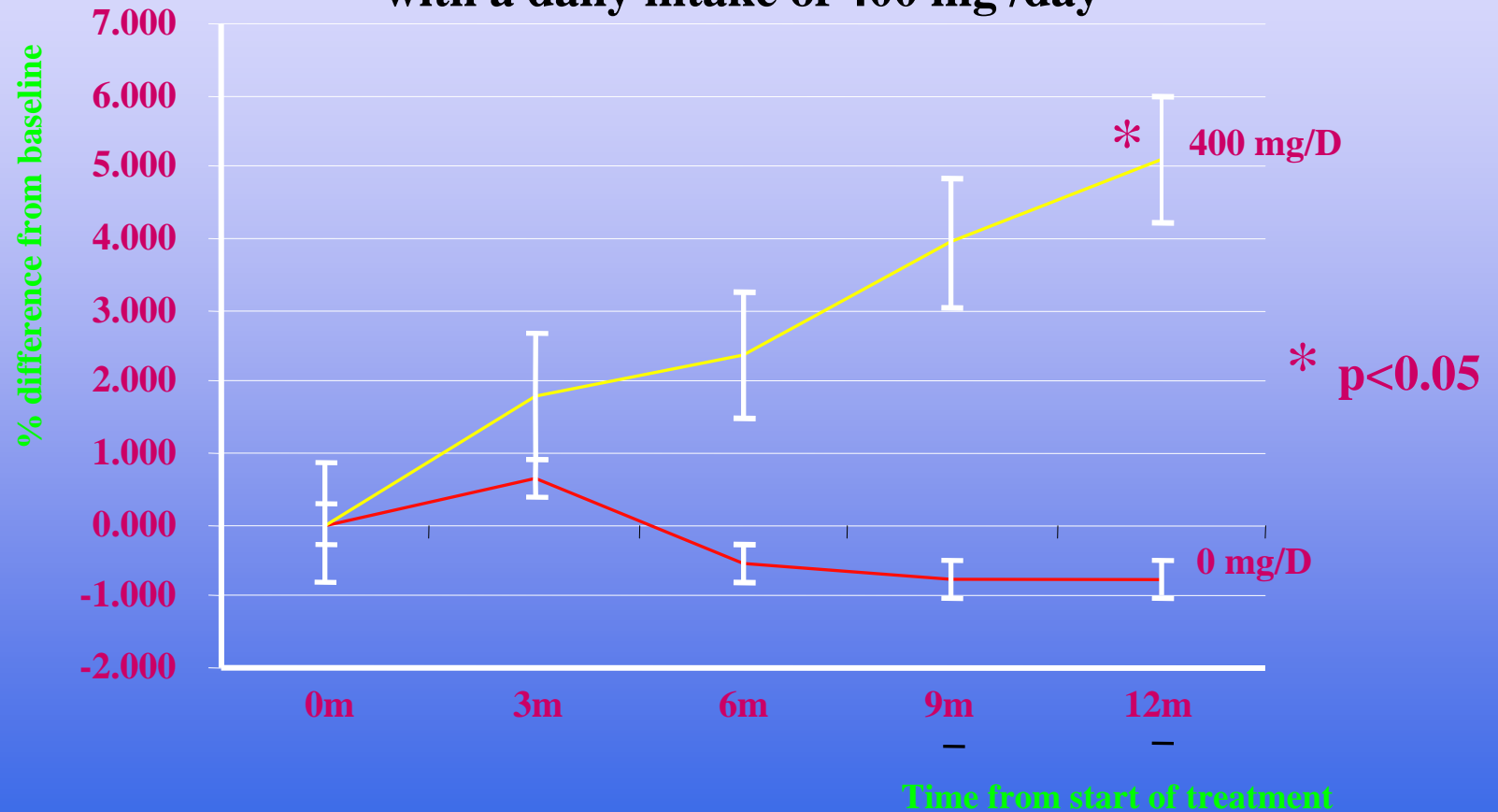
## ➤ Human Nutraceuticals

EPP is being used as a Nutraceutical product to increase **Bone Mass Density (BMD)**.

The results of a clinical study were published in **FIGO** showing that it is possible to increase **Bone Mass Density** in post menopausal woman.

# *Bone Density Lumbar spine*

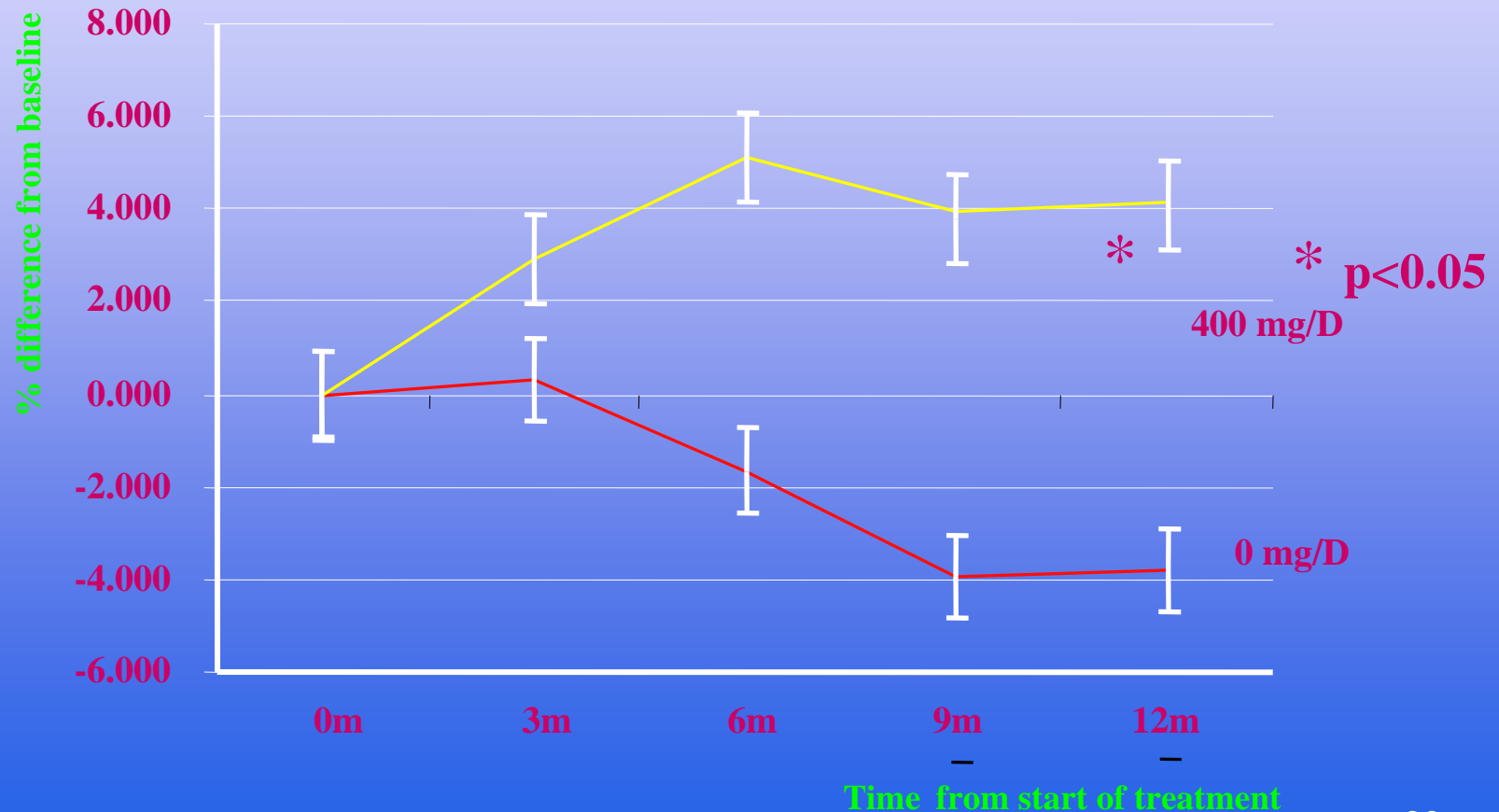
Graph showing % difference BMD over the treatment period in L2 - L4 with a daily intake of 400 mg /day



# *Bone Density*

# *Femur Neck*

Graph showing % difference BMD over the treatment period in Femur Neck with a daily intake of 400 mg /day



# **REACH**

**Regulation EC N°. 1907/2006 concerning the  
Registration, Evaluation, Authorization and  
Restriction of Chemicals or (REACH)**

**What has REACH meant for us**

**What did the process involve**

**What are the disadvantages of REACH**

**What are the advantages of REACH**

**Where do we go from here**

**REACH** *Regulation EC Nº. 1907/2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemical*

**What has REACH meant for us to date :-**

**For a large number of our products natural extracts and minerals, REACH did not have any significant affect for two reasons.**

**Volume Sold**

**Nature of Product**

# **REACH** *Regulation EC N°. 1907/2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemical*

## **What has REACH meant for us**

### **Volume Sold**

**According to the regulation, any substance as such or included in preparations, manufacture or imported in quantity equal or above 1 Tonne per year per manufacturer or importer will have to be registered.**

**Our extracts are highly concentrated and very active. A concentration factor of approximately one million is normally used for the production of most of our extracts. This means that we are producing Kilogram quantities of extract and not Tonne quantities of extract so we do not fall under this category.**

# **REACH** *Regulation EC N°. 1907/2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemical*

## **What has REACH meant for us**

### **Nature of Product**

**According to the regulation, appendix IV (list of substances) and V (point 7 :”minerals” and point 8: “substances which occur in nature”), minerals and plant extracts are not considered as “substances” according to REACH but as preparations constituted of a solvent and/or a carrier.**

**So in fact the extracts that we produce do not need to be registered but the carriers that we used were registered.**

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Registration, Evaluation, Authorization and Restriction of  
Chemical*

**What has REACH meant for us**

**So in fact we did not need to register these  
materials under REACH unless we chose to.**

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## **What has REACH meant for us**

**We also produce Liposome in quantities greater than one Tonne per annum and these materials needed to be registered under REACH. Initially we followed the guidelines requested by our customers in this field.**

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## **What did the process involve**

**Compilation of all the materials produced not derived from minerals or plant extracts and produced in quantities over 1Tonne.**

**Compilation of all the raw materials (every single ingredient) used to manufacture these materials.**

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## **What did the process involve**

**Compilation of all the procedures used in the manufacture of the materials in a step by step manner.**

**Classification of the materials into various categories:**

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## **What did the process involve**

**Classification of the materials into various categories:**

**Antioxidant**

**Stabilizer**

**Preservative**

**Solvent**

**Colorant**

**Bleaching agent**

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## **What did the process involve :**

**For each ingredient under each classification the following information was collated in tabular form :**

- **The name of the ingredient**
- **The INCI name of the ingredient**
- **The CAS number of the ingredient**
- **The quantity of the ingredient present in the final product**
- **The quantity if any of other materials added to this ingredient in the manufacturing process**
- **The nature and the level of any by-product present in this ingredient**
- **The nature and level of impurities (primarily heavy metals) present in this ingredient**
- **The presence and level of Glycol, Ether, and Phthalates**
- **The presence and level of the microbiological load**
- **If the ingredient was sterilised using irradiation**
- **Toxicity data**
- **Eco toxicity data**
- **If the ingredient has been tested using animals testing**
- **If the ingredient is classified under CMR (carcinogenic, mutagenic or to toxic for reproduction)**
- **The inventory status of the product using the EINECS number**
- **Details of the establishment and person responsible**

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## **What did the process involve :**

**For each ingredient the GMO status as well as the country of origin had to be identified including information regarding manufacturing process of the ingredient such as:**

- **The ingredient itself**
- **The raw materials used to manufacture the ingredient**
- **Any organism that may have been used to manufacture the ingredient**
- **Any processing aids such as enzymes that may have been used to manufacture the ingredient**

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## **What did the process involve :**

**For each ingredient the Allergen status as well as the possibility of the ingredient coming in contact with allergens had to be identified including :**

- **The ingredient itself**
- **The raw materials used to manufacture the ingredient**
- **The possibility of cross contamination of the ingredient with allergens**
- **The possibility of handling, cleaning or processing material containing allergens coming in contact with the ingredient.**

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## **What did the process involve :**

**As can be seen, this is quite a comprehensive list of information that needed to be gathered for every ingredient used in production of our finished products.**

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**What did the process involve :**

**Each liposome contains on average ten ingredients as raw materials.**

**So the multiplication factor on the amount of data that needed to be collated was daunting.**

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## **What did the process involve :**

**We made contact with all of our suppliers of raw materials and asked them to provide us with the information needed in order to allow us to compile our data for registration purposes.**

**Most of our suppliers were willing to help us in this process since they were also involved in the same process for their registration.**

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**What did the process involve :**

**When all the data was collected and the files compiled we forwarded these file to our customers for their registration.**

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## **What are the disadvantages of REACH**

- **The process of collating and processing all of the data is very time consuming.**
- **Not all of the suppliers were in position to provide us with the information requested.**
- **We needed to ensure where possible that we will use the same materials from the same suppliers for future production since any change in any of the raw materials will mean that we will need to adjust our documentation.**

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## **What are the disadvantages of REACH**

- **In some instances we had to change the supplier as the existing supplier could not give us the data that was required. This very often meant that we had to purchase the same raw material for a higher cost from a different supplier.**
- **We had to assign a person almost on a full time basis to process this documentation and keep up with the changes needed.**

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## **What are the disadvantages of REACH**

- **In summary we had to use more man power and increase the cost of raw materials in order to come in line with the REACH directive. This obviously has a direct affect on the bottom line.**

# **REACH** *Regulation EC Nº. 1907/2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemical*

## **What are the advantages of REACH**

- **We have a more controlled, standardised system for our production due to the control of suppliers of raw materials and the expectations of our customers.**
- **We have access to data about our production and processing collated in a standardised system that is identical to all our suppliers and customers.**

# **REACH** *Regulation EC N°. 1907/2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemical*

## **What are the advantages of REACH**

- **Before we had many similar systems but not exactly the same for the different suppliers and customers so we had to adopt many different systems for the different contacts.**
- **Now there is one single template that we have to use as opposed to many.**

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## **What are the advantages of REACH**

- **Since we are using this standardised system there is the need for less physical control such as audits by our customers than before since the audit is standardised paper audit common to all producers.**

# **REACH** *Regulation EC N°. 1907/2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemical*

## **What are the advantages of REACH**

- **In summary we now have one standardised system of recording data that is acceptable to both suppliers and customers.**
- **This has in fact streamlined the way in which we process data since we are now only dealing with one system.**

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## **Where do we go from here :**

- **Since we adopted the REACH system :-**
- **We diverted resources for the management of the system so now we have to maximise the benefits of the system.**
- **We have now adopted the REACH system for all of our products including the materials not covered by REACH.**
- **This will in fact save us time and money in the long term as our supplier and customer base increases. We will not need to discuss, adopt, audited or be audited for different systems for each supplier and customer to the same degree as before.**

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## **Where do we go from here :**

- **The process of pre-registration was very simple**
- **We registered the company with a registration body ECHA in order to get a registration number.**
- **Then we used the company registration number along with the EC number and CAS number (were it existed) to register each product.**
- **For naturally occurring substances one standard number was used.**
- **This process was carried out directly over the net.**
- **A pre-registration number was received for each submission made.**

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## **Where do we go from here :**

- **In Conclusion :-**
- **REACH has been a paper exercise.**
- **There was an initial cost both in terms of human as well as financial resources.**
- **When the system is adopted and put in place, it should save time and money through the use of a recognised standardised system acceptable by all producers in Europe.**



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