

**ADVISORY COMMITTEE ON ANIMAL FEEDINGSTUFFS**

**41<sup>st</sup> Meeting of ACAF on 5 March 2008**

**Information Paper**

**LIPGENE PROJECT – THE PRODUCTION OF LONG CHAIN  
POLYUNSATURATED FATTY ACIDS IN TRANSGENIC  
PLANTS**

**PRESENTATION BY PROFESSOR JONATHAN NAPIER –  
ROTHAMSTED RESEARCH, HARPENDEN**

**February 2008**

# The production of long chain polyunsaturated fatty acids in transgenic plants:

## Towards a sustainable source of LC-PUFAs

*Prof. Johnathan A. Napier*

Rothamsted Research, Harpenden, UK



E-mail: [johnathan.napier@bbsrc.ac.uk](mailto:johnathan.napier@bbsrc.ac.uk)



## Why are fish oils important in human diet?

- Specific fatty acids found in fish oils are prevalent in specialised organs (such as the brain, eyes). These are the n-3/omega-3 long chain polyunsaturates
- Mammals have a very limited ability to synthesise these fatty acids, so we need to obtain them from our diet
- Some human genetic disorders are directly linked to an inability to make these fatty acids. There is also some evidence of a reduced capacity to synthesise them in old age and/or diseased states.
- The fatty acids found in fish oils are NOT the same as those in vegetable oils
- Omega-3 fatty acids play a role in anti-inflammatory responses

## Fish Oils play important roles in the prevention of human diseases

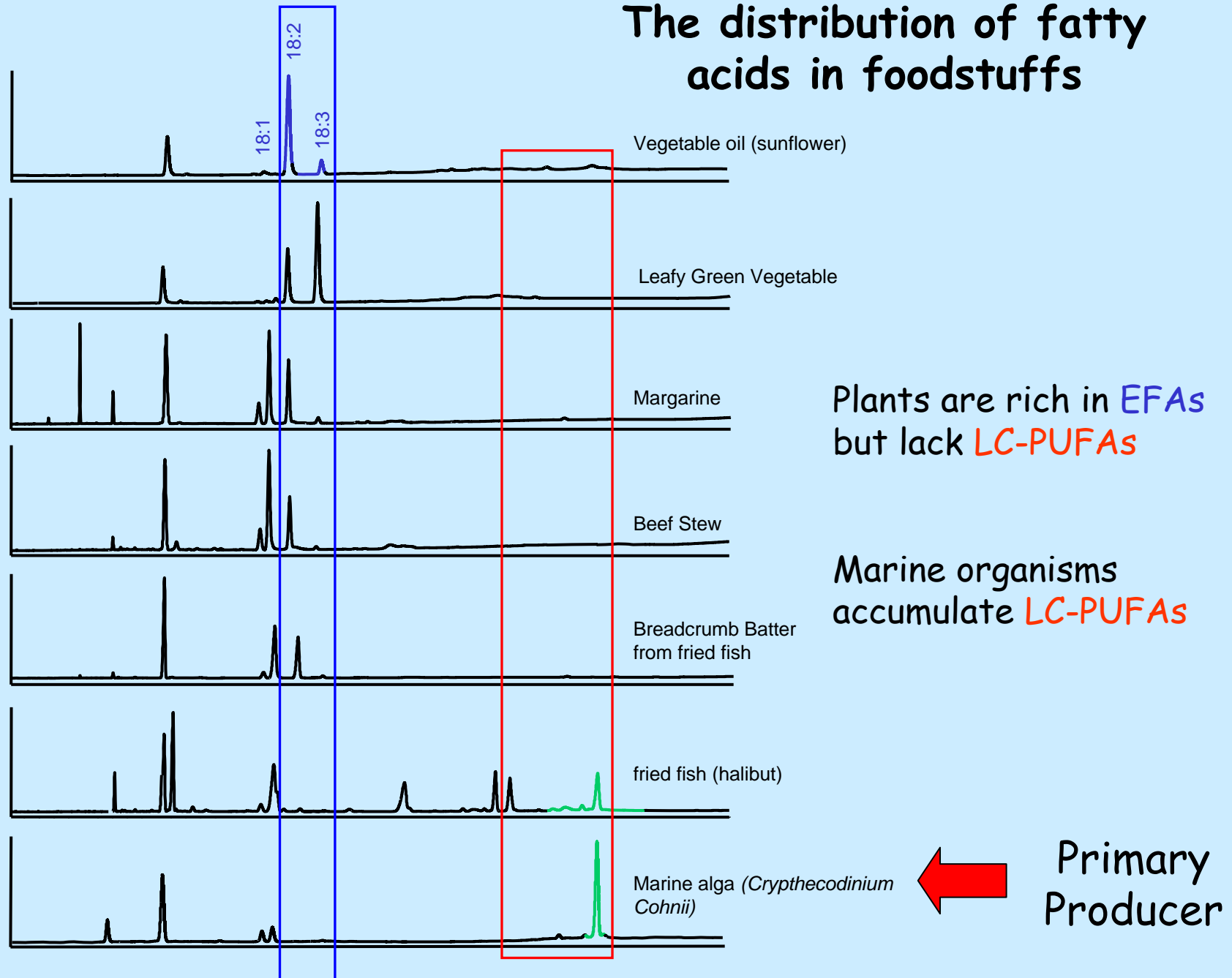
- Moderate daily intake of fish oils can avert progression towards type 2 diabetes and CVD
- Fish oils can help prevent the re-occurrence of cardiac infarction
- A diet rich in fish oils may slow the progression of metabolic syndrome
- Fish oil fatty acids may play roles in moderating arthritic conditions
- Improves the balance of omega-3/omega-6 fatty acids
- May possibly play roles in cognition and mood

## Some Fact about Fatty Acids

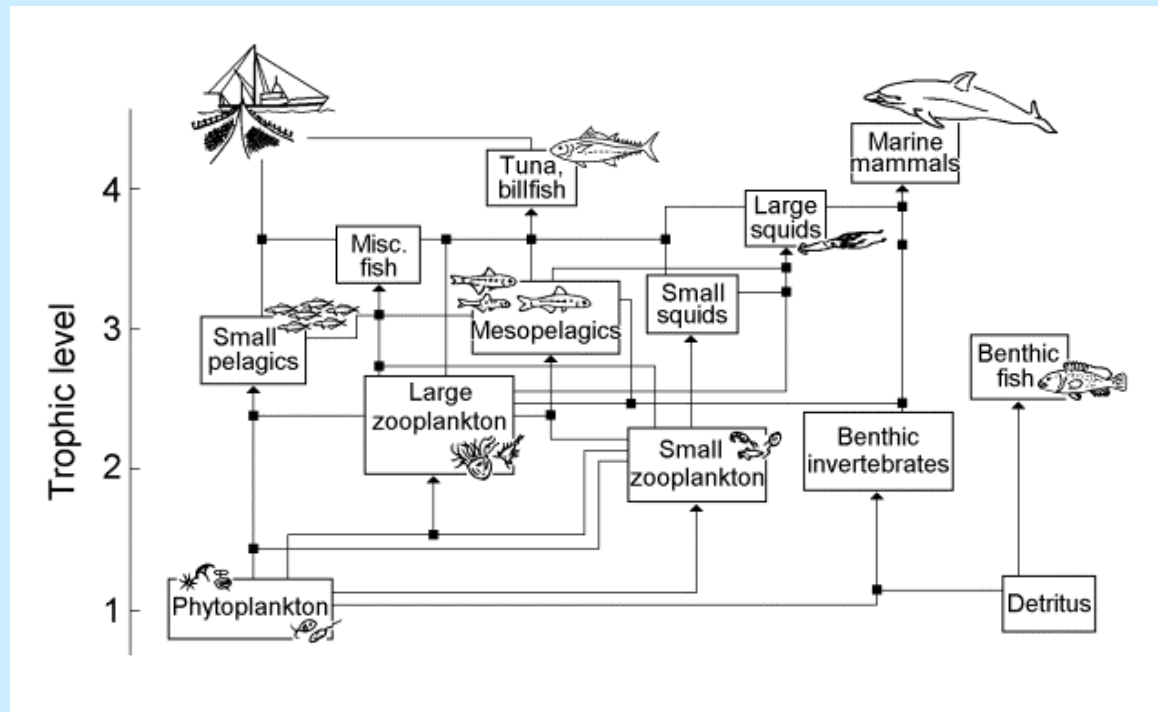
- Mammals have two Essential Fatty Acids, which they must obtain from their diet: linoleic acid (LA) and  $\alpha$ -linolenic acid (ALA)
- Fish oils are rich in omega-3 Long Chain polyunsaturated fatty acids (LC-PUFAs)
- Although the EFAs are precursors for LC-PUFAs, animals can only convert them at a low rate (1%)
- Plant oils do NOT contain LC-PUFAs
- Fish do NOT actually synthesise LC-PUFAs; they obtain them from their diet (microalgae at the bottom of the food web)



# The distribution of fatty acids in foodstuffs



Fish oils can be “passaged” through animal feeds, yielding an animal-derived foodstuff enriched in omega-3 LC-PUFAs.



This is analogous to what occurs in the marine foodweb, with the progression of omega-3 LC-PUFAs to the top of the food chain

# Fish Oil is currently an unsustainable resource

## Considerations:

Fish oils have a vital role to play in human health & nutrition

Fish oils are known to protect against heart disease & Metabolic Syndrome

Vegetable oils CANNOT provide the same level of protection or health benefits

## Additionally...

Natural fish stocks are in major decline & suffer from pollution

Aquaculture of marine fish requires fish oils (i.e. non-sustainable)

Aquaculture of marine fish CANNOT use vegetable oils as a 100% substitute

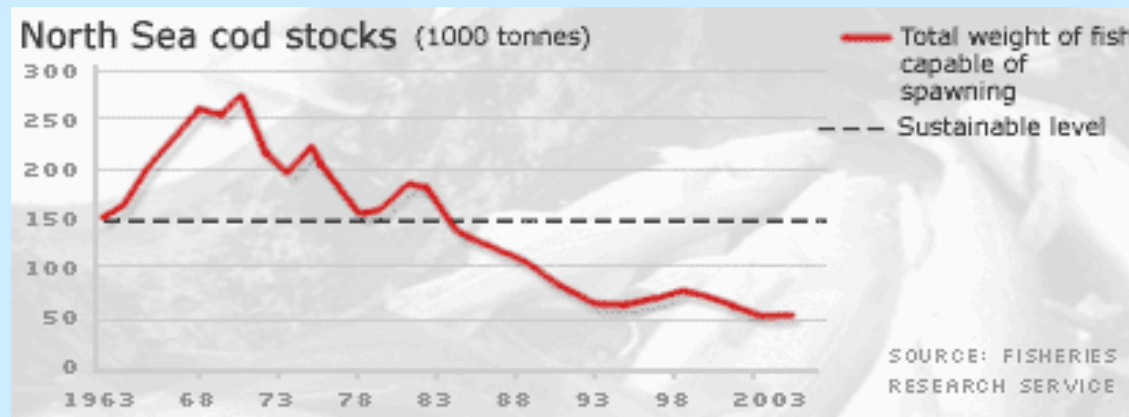
Aquaculture is projected to consume 97% of the current production of fish oil

We therefore need an alternative, sustainable source of fish oils for both human nutrition and aquaculture.





**There is an urgent need for a sustainable source of fish oils -current marine stocks are in perilous decline**



**Transgenic plants engineered to produce fish oils can provide a safe & sustainable source of these important compounds for human health and nutrition**



## Defining the targets for nutritional enhancement

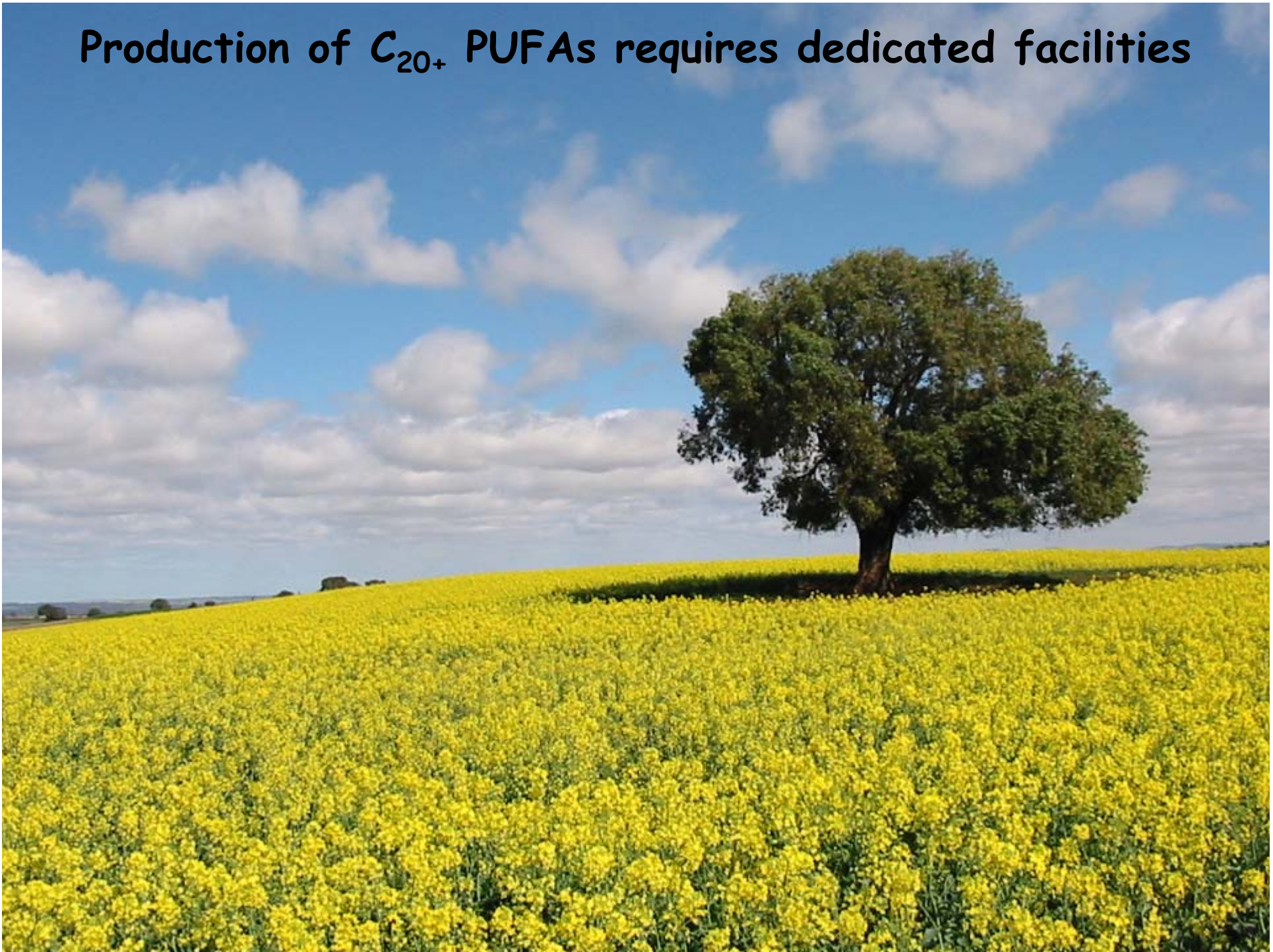
### Current best natural sources of LC-PUFAs

SDA (18:4, n-3)	<i>Echium spp.</i>	~10%
<i>ARA (20:4, n-6)</i>	<i>Mortierella alpina</i>	~25%
EPA (20:5, n-3)	<i>Phaeodactylum tricornutum</i>	~35%
DHA (22:6, n-3)	<i>Cryptothecodinium cohnii</i>	~45%
EPA & DHA (n-3)	<i>Isochrysis galabana</i>	15%, 8%
(% of total fatty acids)		

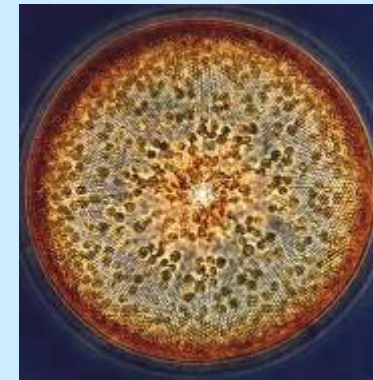
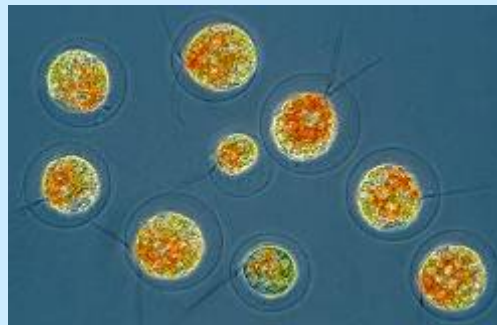
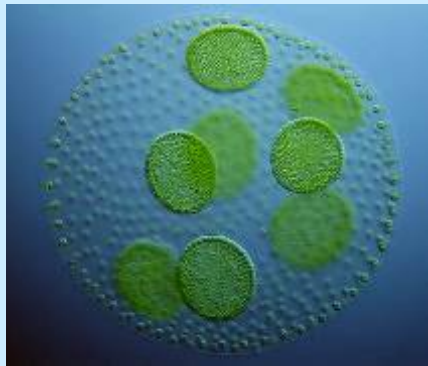
However, not all these sources are easy to cultivate. Some processes are expensive and difficult to optimise or maintain



Production of  $C_{20+}$  PUFAs requires dedicated facilities

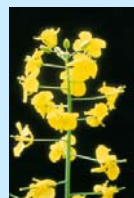


# The "Designer" Oilseed Concept



The obvious sources of genes for LC-PUFA biosynthesis are marine algae

Identify gene(s) for trait of interest (e.g. synthesis of LC-PUFAs) and transfer into new host



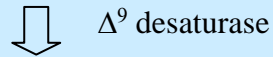
Regenerate transgenic plants with novel fatty acid traits.



## Conventional PUFA Biosynthetic Pathway

### Animals

18:0 stearic acid

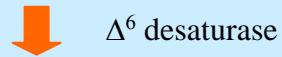


18:1 oleic acid

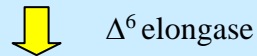


*n-6*

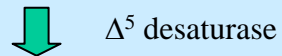
18:2 linoleic acid



18:3  $\gamma$ -linolenic acid

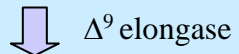


20:3 di-homo  $\gamma$ -linolenic acid

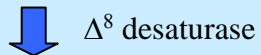


20:4 arachidonic acid

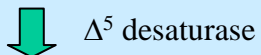
18:2 linoleic acid



20:2 eicosadienoic acid



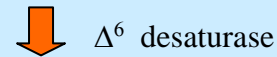
20:3 di-homo  $\gamma$ -linolenic acid



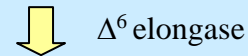
20:4 arachidonic acid

*n-3*

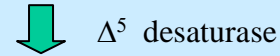
18:3  $\alpha$ -linolenic acid



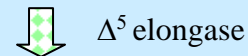
18:4 octadecatetraenoic acid



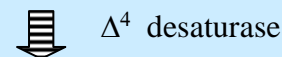
20:4 eicosatetraenoic acid



20:5 eicosapentaenoic acid



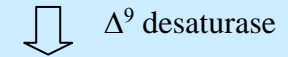
22:5 docosapentaenoic acid



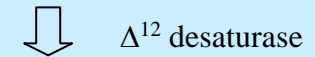
22:6 docosahexaenoic acid

### Plants

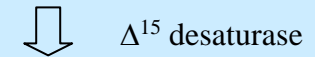
18:0 stearic acid



18:1 oleic acid



18:2 linoleic acid

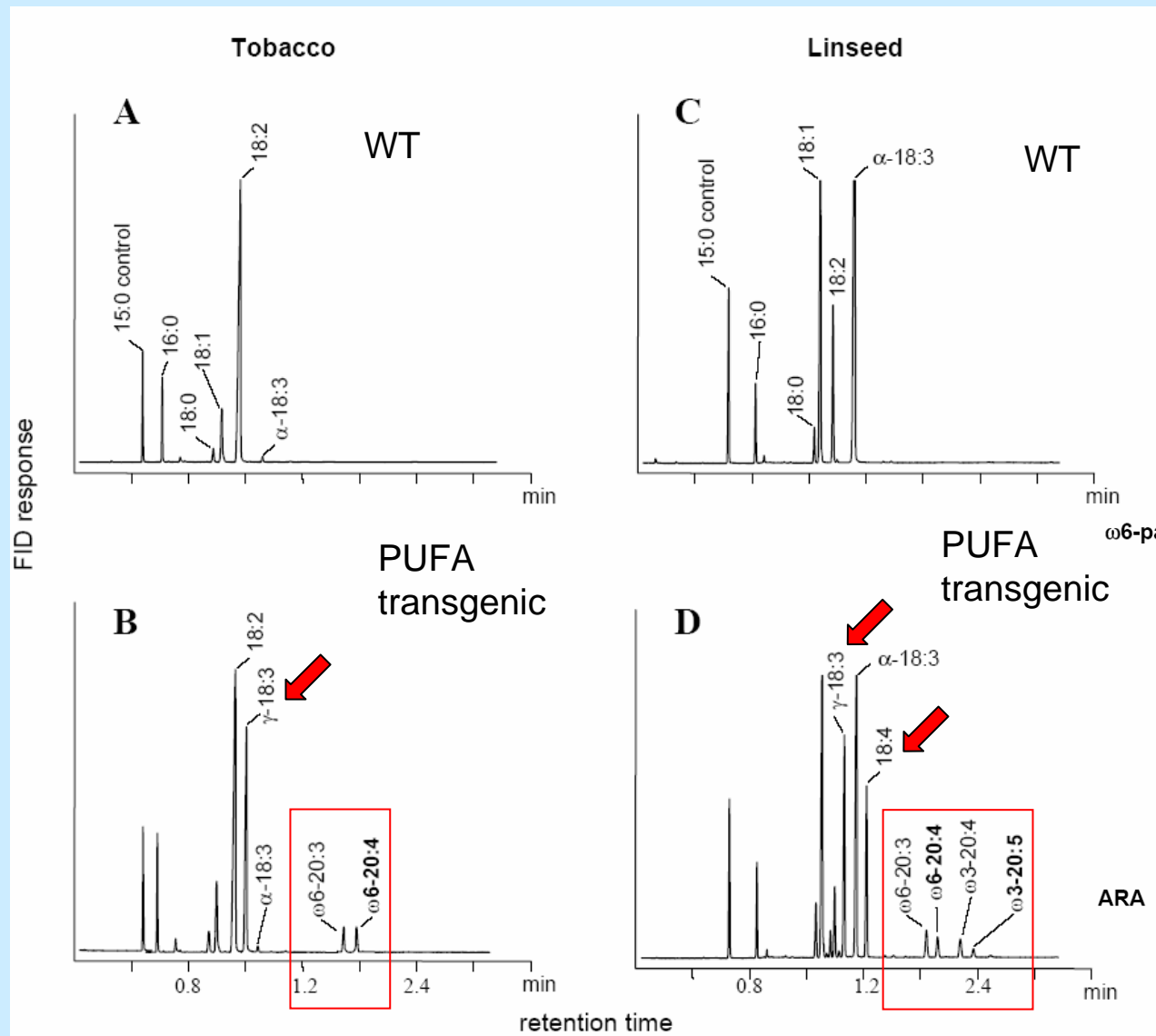


18:3  $\alpha$ -linolenic acid

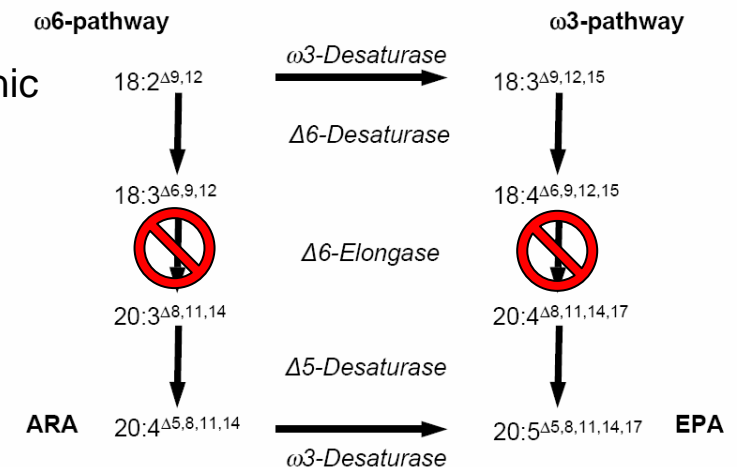
### Algae

Many heterologous enzymes are required to engineer LC-PUFA synthesis into transgenic plants

# Expression of LC-PUFA biosynthetic genes in transgenic plants



High levels of C<sub>18</sub> products, low levels of C<sub>20</sub>. Blocked after first ( $\Delta$ 6)-desaturation (i.e. elongation is rate-limiting)



## Expression of LC-PUFA biosynthetic genes in transgenic soybean and *Brassica juncea*



**10-15% EPA  
in seed oils**



Soy and Brassica may contain endogenous activities that can overcome the substrate dichotomy problem

*-endogenous acyltransferases with a broader substrate specificity than those found in linseed?*

**The shuffling of fatty acids between the PC and acyl-CoA pools during the biosynthesis of LC-PUFAs may be more efficient than in linseed:**

**This could be due either positive or negative factors modulating acyl-exchange**

## Delivery of transgene-derived LC-PUFAs into the human food chain.

1. Direct ingestion
2. Indirect via enrichment of animal feeds (terrestrial)
3. Indirect via enrichment of animal feeds (marine)

Work within the EU FP6 LIPGENE has focussed on (2) - Work of Prof Ian Givens, University of Reading BUT only as a proof-of-concept using non-GM oils.

Work at Rothamsted (not part of LIPGENE) is currently focussed on (3) in conjunction with academic and industrial collaborators.



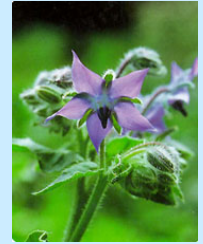
## Issues relating to the use of GM-derived plant oils enhanced with the presence of omega-3 LC-PUFAs.

If extracted oils are used it would be difficult to use DNA-based diagnostics to identify a product containing such GM material

If used to indirectly enhance a food product (via animal feeding) it would become even more difficult to use DNA techniques for identity-preservation.

Need new lipid-based analytical approaches to identify such material (but need also to distinguish between GM plant and algal diets)

## Summary



- The production of LC-PUFAs in transgenic plants is feasible and likely to be enhanced by further refinements.
- This should provide a safe, sustainable and environmentally-benign source of these important fatty acids for either human nutrition or as an animal feed. In particular the aquaculture industry is urgently seeking a cheap(er), cleaner source of fish oils
- Using transgenic plants to synthesis health-protective dietary components such as LC-PUFAs may help persuade the public of the benefits of GM technologies to deliver functional nutrition and reduced environmental impact (?).



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SIXTH FRAMEWORK PROGRAMME



## Lipgene

Welcome to the Lipgene project website

Lipgene is an EU Sixth Framework Integrated Programme being conducted by 25 research centres across Europe. Collectively, these 25 research partners are the 'Lipgene consortium'.

The full title of the project is "Diet, genomics and the metabolic syndrome: an integrated nutrition, agro-food, social and economic analysis". It will run from 2004 to 2009.

The primary focus of Lipgene is the interaction of nutrients and genotype in the metabolic syndrome. The metabolic syndrome is the term used to describe a clustering of several risk factors for cardiovascular disease, namely obesity, abnormal blood lipids (e.g. high blood cholesterol & raised triglyceride levels), insulin resistance and high blood pressure (hypertension).

The project (2004-2009) is being coordinated by Professor Mike Gibney and Professor Helen Roche of University College Dublin.

Contract number: FOOD-CT-2003-505944

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Diet, genomics and the metabolic syndrome: an integrated nutrition, agro-food, social and economic analysis. Funded by the EU.



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