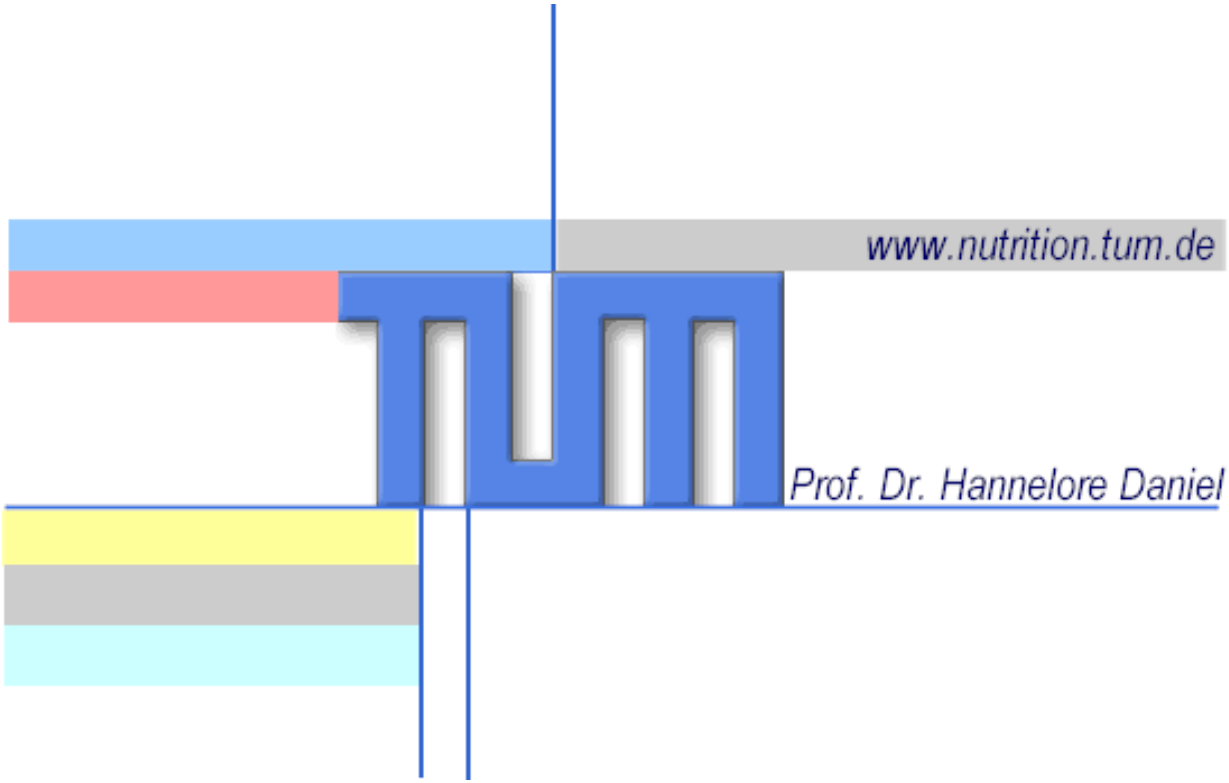

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FUNCTIONAL FOOD

Fashion or real progress in human nutrition ?

A critical science based review.

Although no legal definition of functional food is available yet within the EU, the products may be considered as foods that besides their general nutritional value affect specifically certain body functions that may be important in view of disease prevention or even as an adjuvant in therapy.

They are food by all means and should be distinguished from supplements or even dietetic foods.

The current state: between fraught, serious concepts and toxicological concerns

“erotic” bread

green tea extract enriched bread

low salt bread

iron fortified bread

where does functionality start and where does it end ?

functional foods

by use of conventional and/or classical biotechnological approaches

as functional food ingredients

- **soluble fibers (inulin, FOS, GOS, resistant starches)**
- **fatty acids, CLA, phospholipids**
- **special bacterial strains**
- **vitamins**
- **antioxidants (vitamins & others)**
- **flavonoids**
- **any other compounds**

→ **for use as additives and enrichment, as supplements**

functional foods

as transgenic products (plants) 2./3. generation GMO´s (Novel Foods)

Transgenic products for normal consumption, i.e.

- **with altered nutrient content/profile**
  - **Tomato with increased lycopen content**
  - **Rice with increased ß-carotene content**
- **with increased content of dietary fiber**
  - **Wheat with increased Inulin content**
- **with altered amino acid composition**
  - **increased in S-containing amino acids**
- **with altered fatty acid composition (PUFA-content)**

Dietary products for special needs, i.e.

- **with altered phenylalanine content for PKU**
- **with reduced gliadin content for celiac disease**
- **with eliminated epitopes for patients with allergies**

functional foods: by use of new ingredients

Food	Substance	Possible function or effect
		For the immune system
Milk	Casein peptide	Macrophage activation
Wheat	Lipopolysaccharide	Immunostimulation
Lobster	Chitin	Immunostimulation
Licorice	Glycyrrhetinic acid	Immunosupression
		For the endocrine system
Red pepper	Capsaicin	Antiobesic effect
Soybean	Trypsin inhibitor	Cholecystokinin secretion
		For the nerve system
Milk	Casein peptide	Opioid function
Milk	Casein peptide	Opioid antagonism
Wheat	Gluten peptide	Opioid function
		For the circulatory system
Milk	Casein peptide	Hypotensive effect
Corn	Zein peptide	Hypotensive effect
Soybean	Glycinin peptide	Hypotensive effect
Fish	Myofibril peptide	Hypotensive effect
Soybean	Glycinin	Lowering cholesterol
Lobster	Chitosan	Lowering cholesterol
Oilseeds	γ-Linoleic acid	Lowering cholesterol
Mushroom	Farnesylorcinols	Lowering cholesterol
Fish	Eicosapentanoic acid	Regulating coagulation
		For the digestive system
Milk	Casein phosphopeptide	Accelerated Ca intake
Serum albumin	Albutensin A	Peristaltic effect
Food proteins	Oligopeptide mixtures	Efficient amino acid intake
Wheat	High-glutamine peptide	Intestine activation
Many foods	Oligosaccharides	Microflora modulation
		For the cellular system
Milk	Lactoferrin	Antibacterial effect
Milk	Ganglioside	Antibacteriotoxic effect
Egg	Chicken cystatin	Antiviral effect
Rice	Oryzacystatin	Antiviral effect
Rice	γ-Oryzanol	Antioxidative effect
Sesame	Sesaminol	Antioxidative effect
Ginger	Gingerol	Antioxidative effect
Buckwheat	Lutin	Antioxidative effect
Carrot	Carotenoids	Antioxidative effect
Soybean	Saponins	Antioxidative effect

taken from: S. Arai, Studies on functional foods in japan, state of the art. Biosci. Biotechn. Biochem. 60(1), 9-15, 1996

Position of the American Dietetic Association: functional foods

It is the position of The American Dietetic Association that functional foods, including whole foods and fortified, enriched, or enhanced foods, have a potentially beneficial effect on health when consumed as part of a varied diet on a regular basis, at effective levels. The association supports research to further define the health benefits and risks of individual functional foods and their physiologically active components. However, each functional food should be evaluated on the basis of scientific evidence to ensure appropriate integration into a varied diet.

J Am Diet Assoc 1999 Oct;99(10):1278-85

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The basis of scientific evidence

What can be considered as "scientifically proven" as a basis for the development of functional foods ?

- increased intake of dietary fiber for reduction of colon cancer risk ?
- increased intake of folic acid for reduction of neural tube defects and prevention of homocystinuria ?
- increased intake of antioxidants for prevention of cardiovascular disease ?
- decreased intake of salt for prevention of hypertension ?

Increased intake of dietary fiber for reduction of colon cancer risk

Randomized, controlled trials have now shown us that the use of some of the diets and nutritional supplements thought to lower the risk of colorectal cancer has no short-term benefits with respect to preventing adenomas. There may be many reasons to eat a diet that is low in fat and high in fiber, fruits, and vegetables or to supplement the diet with a food high in cereal fiber, but preventing colorectal adenomas, at least for the first three to four years, is not one of them. With regard to questions about diet and colorectal cancer, though, definitive answers still seem to be beyond the reach of both observational epidemiologic studies and randomized, controlled trials.

Tim Byers, M.D., M.P.H.
The New England Journal of Medicine, April 20, 2000, Vol. 342, No. 16

Increased intake of folic acid for reduction of neural tube defects and prevention of homocystinuria

..... because no clear impact of folic acid supplementation and fortification on the prevalence of neural tube defects has as yet been documented; and furthermore a pause seems to have been reached in such studies.

Kalter H
Folic acid and human malformations: a summary and evaluation.
Reprod Toxicol 2000 Sep-Oct;14(5):463-76

Thus, only placebo-controlled intervention studies with tHcy-lowering B vitamins and clinical endpoints can provide additional valid arguments for the debate over whether tHcy is a causal CVD risk factor.

Ueland PM, Refsum H, Beresford SA, Vollset SE.
The controversy over homocysteine and cardiovascular risk.
Am J Clin Nutr. 2000 Aug;72(2):324-32.

Increased intake of antioxidants for prevention of cardiovascular disease

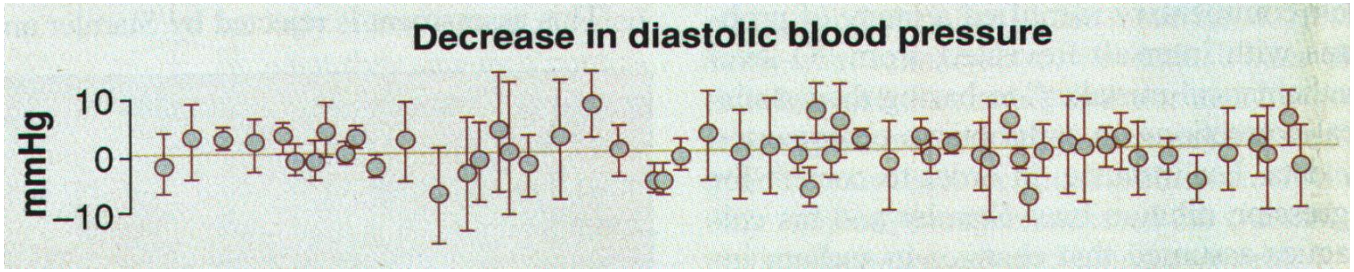
Observational and epidemiologic data, as well as randomized trials failed to provide clear cut indications, because of mixed results on the protective role of antioxidants against cardiovascular diseases.
In spite of the lack of a general consensus, recent data reinforce the concept that a regular intake of antioxidants present in food limits the progression of atherosclerosis. When it will be possible to monitor the efficacy of any antioxidant therapy with validated markers of oxidation, the potential influence of vitamins and antioxidants on coronary artery disease may eventually be resolved.

Catapano AL, Tragni E
Antioxidants and coronary artery disease.
Curr Atheroscler Rep 1999 Nov;1(3):221-9

Decreased intake of salt for prevention of hypertension

Three decades of controversy over the putative benefits of salt reduction show how the demands of good science clash with the pressures of public health policy

The (political) Science of Salt



Adding up the evidence: In a meta-analysis of 56 clinical trials done since 1980 in people with normal blood pressure, extreme salt reduction offered little benefit.

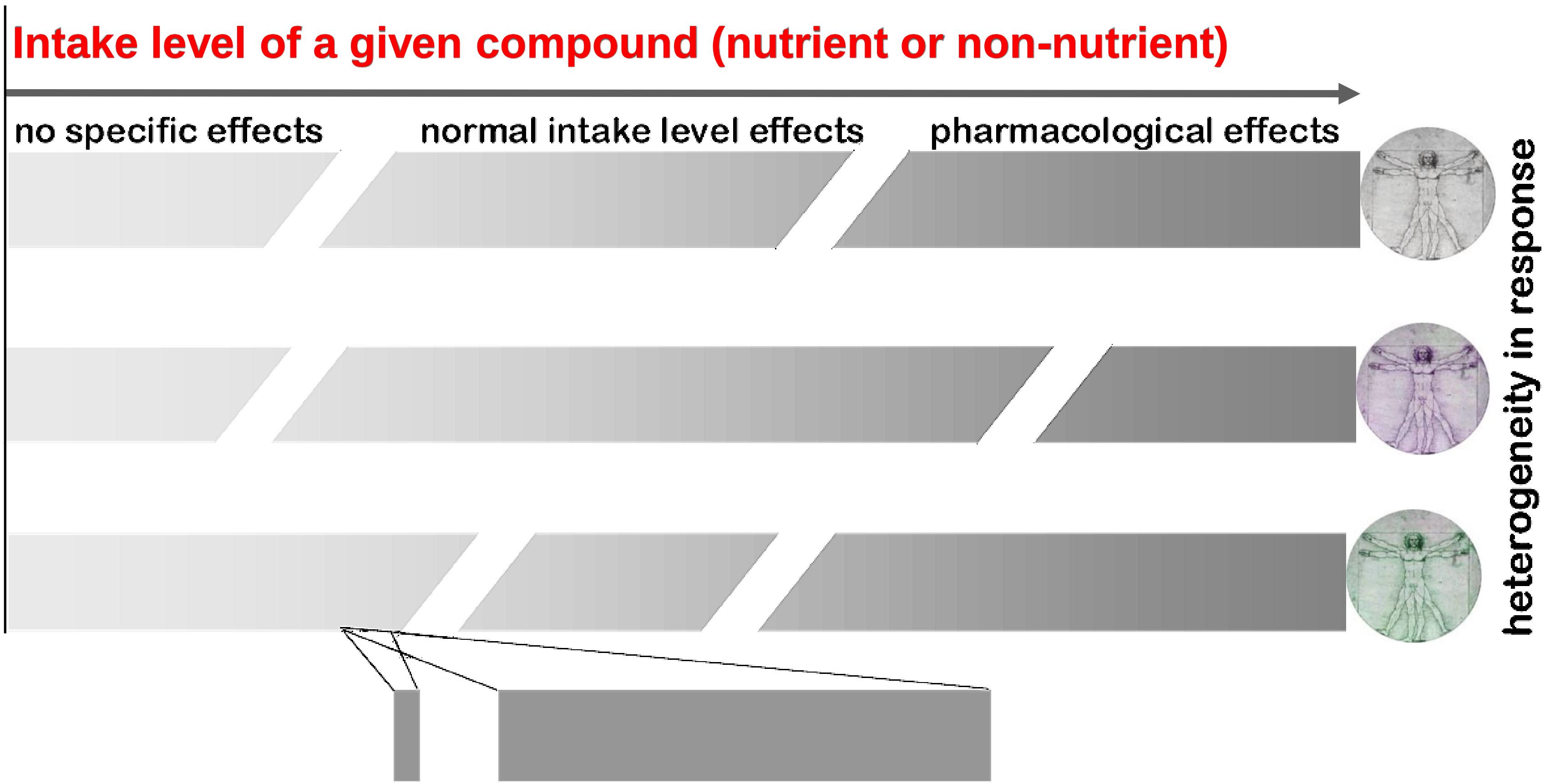
Science, 14.8.1998, 898-907

Conclusion:

There is already (in most cases) a conflict in the definition of a particular food functionality as far as scientific prove and scientific consensus is concerned.

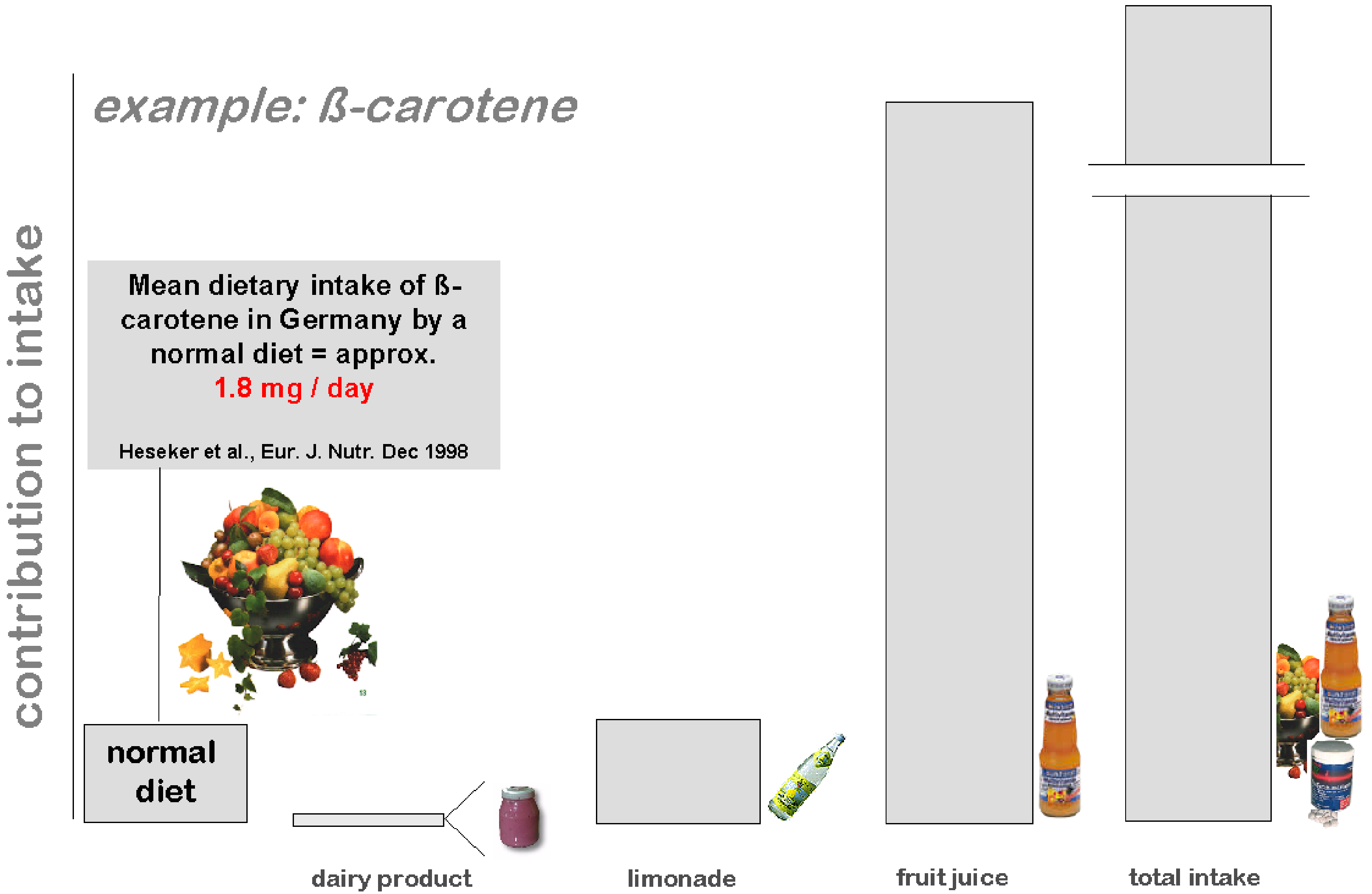
The **effective level** of a functional food or ingredient

where does functionality start and where does it end ?



how much does a certain food ingredient contribute to total intake and which role does the genetic heterogeneity play in the response?

where does functionality start and where does it end ?



where does functionality start and where does it end ?

Although ß-carotene has been studied extensively…
intervention studies show that ß-carotene supplementation may be fatal !

The α-Tocopherol, ß-Carotene Cancer Prevention Trial

National Cancer Institute and the National Public Health Institute of Finland

Sample size	29.133 male smokers in Finland (50-69 years of age)
Supplement	50mg Tocopherol, 20 mg ß-Carotene or both (Placebo controlled)
Time period	5-8 years
Result	18% more lung cancers, 8% increased mortality

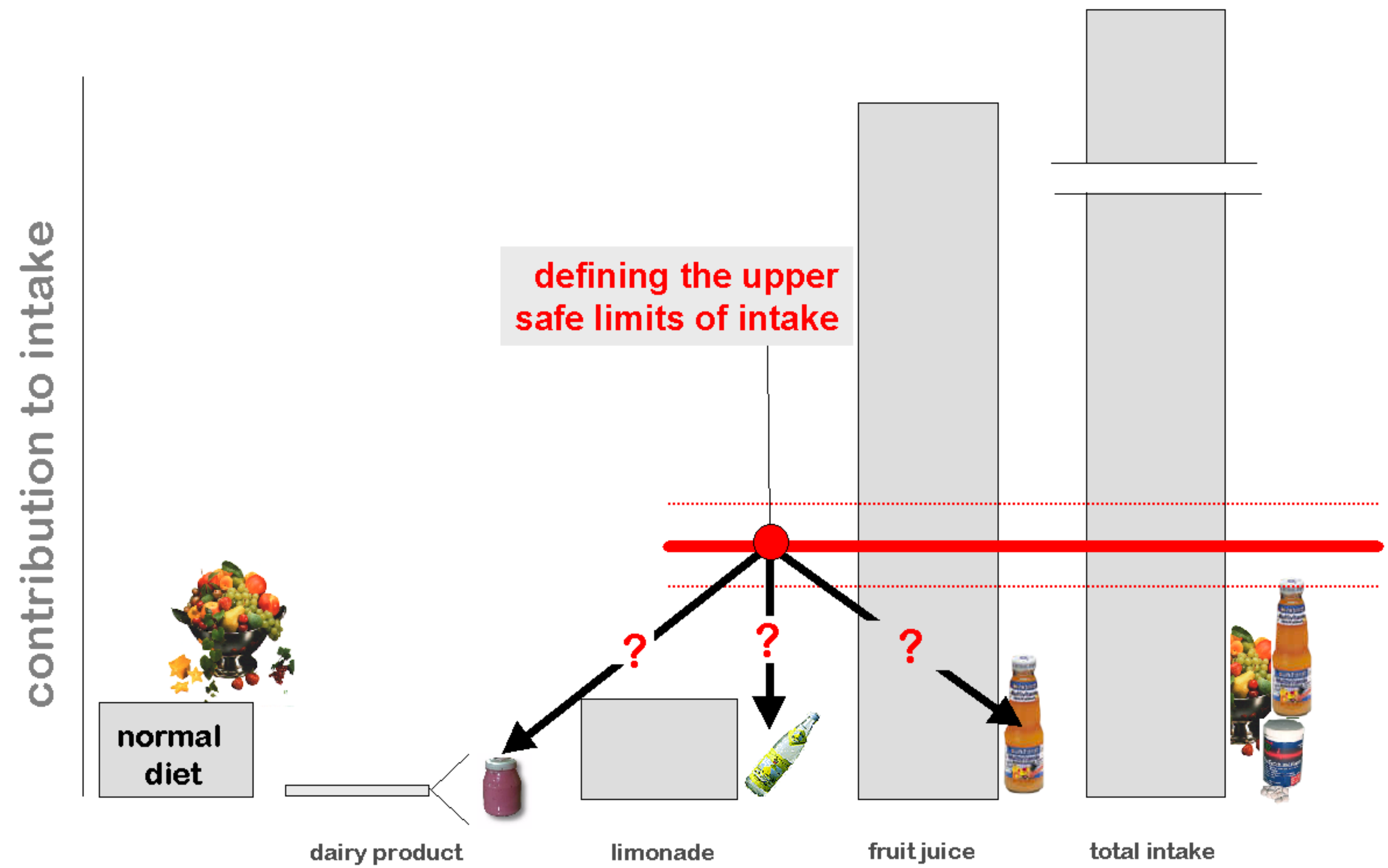
The ß-Carotene Cancer and Retinol Efficiency Trial (CARET)

National Cancer Institute (USA)

Sample size	18.314 participants (50-69 years), smokers & those that stopped smoking
Supplement:	Retinol und 30 mg ß-Carotene (Placebo controlled)
Time period	4 years
Result	46% more lung cancers in smokers, 17% increased mortality

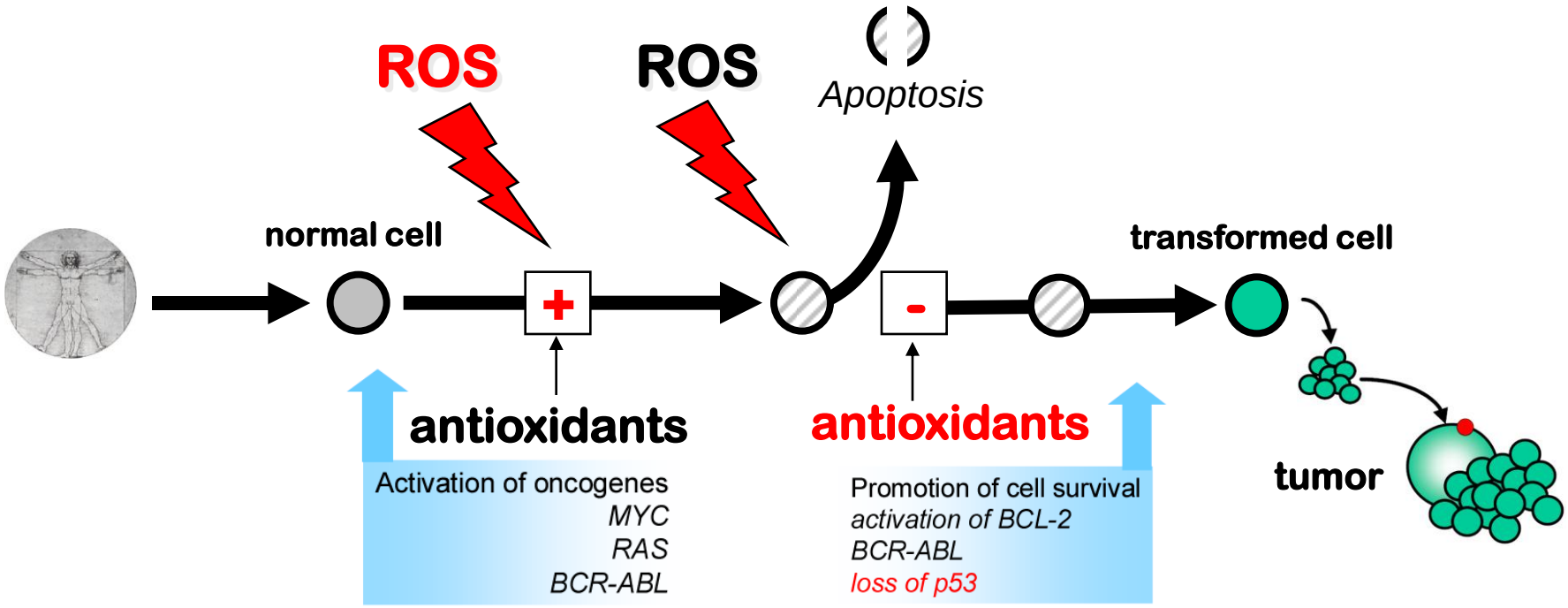
Sources: N. Engl. J. of Med. 331, 141-147, 1994
N. Engl. J. of Med. 331, 189-191, 1994
N. Engl. J. of Med. 334, 1189-1190, 1996
Am. J. Clin. Nutr. 62, 1517S-1520S, 1995

New requirements: defining upper safe limits of intake



New requirements: identification of groups of higher risk

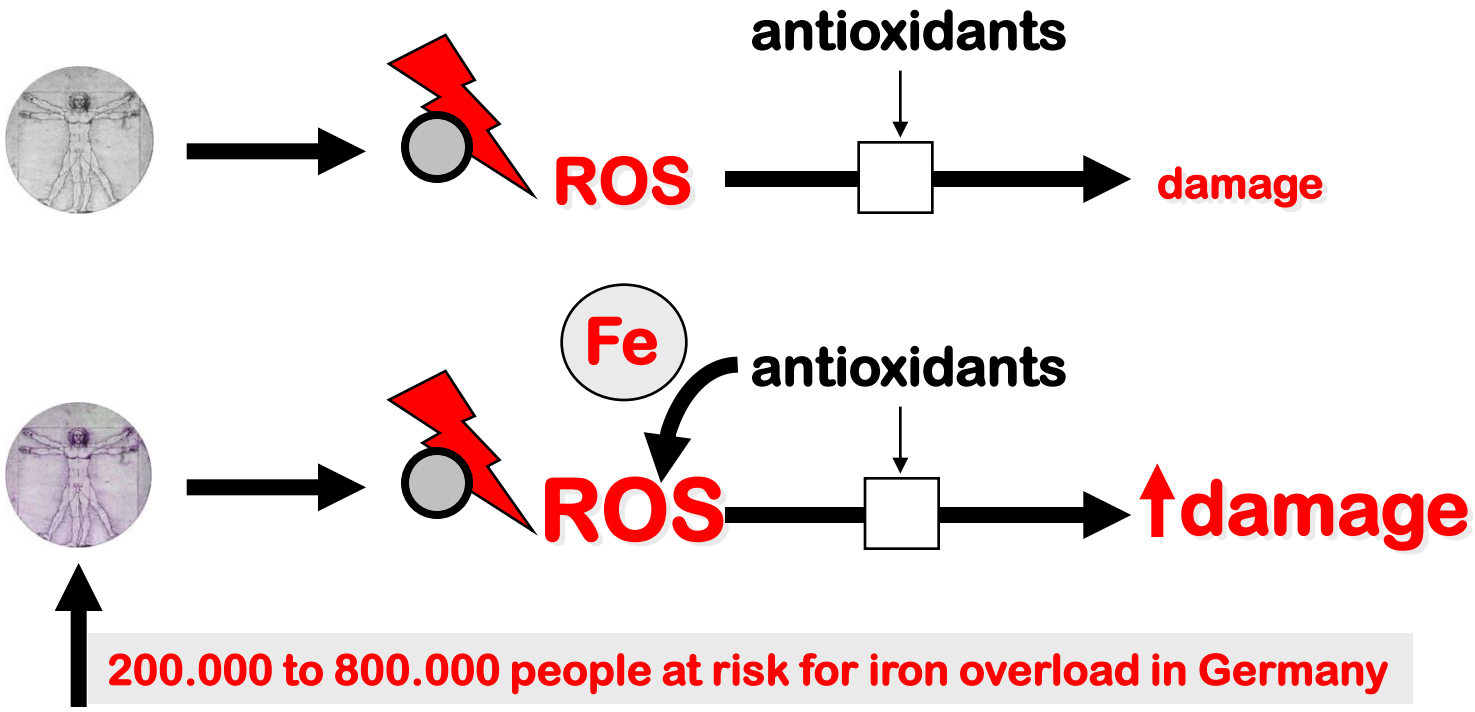
example: intake of antioxidants



→ the effect of a functional food ingredient depends on the physiological/pathophysiological state !

New requirements: identification of groups of higher risk

example: genetic heterogeneity



CONCLUSIONS: Iron deficiency was more common in women, and iron overload was more common in men. Among male employees, iron overload was almost as common as iron deficiency.

Niederau C, et al.
Screening for hemochromatosis and iron deficiency in employees and primary care patients in Western Germany. Ann Intern Med 1998 Mar 1;128(5):337-45

It can´t be accepted that every producer can add any ingredient to any food, regardless of how positive in might be in an individual case.

Prof. Bockisch, CEO UNION Deutsche Lebensmittelwerke GmbH/Unilever

But how to regulate ?

Unwanted effects of a functional food or particular ingredient are in most cases not immediate and causal and are therefore hard to detect.

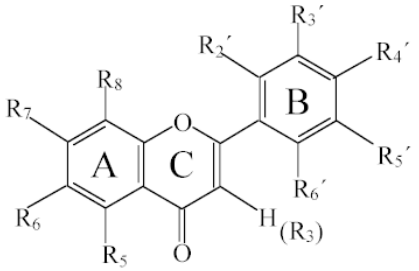
However, there are important and immediate effects too, if it comes to food-drug interaction!

…. an example

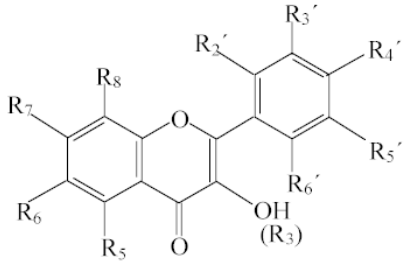
An example with emerging new “active” food ingredients

Proposed health promoting effects

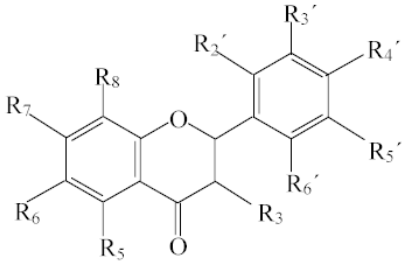
- as antioxidants
- as anticarcinogenic compounds
- as cardioprotective compounds



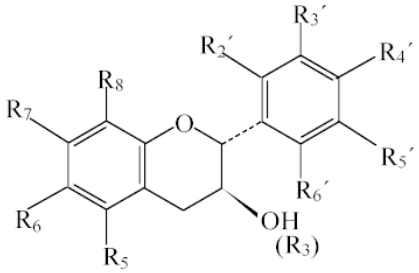
Flavones



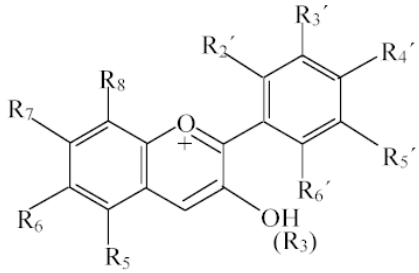
Flavonols



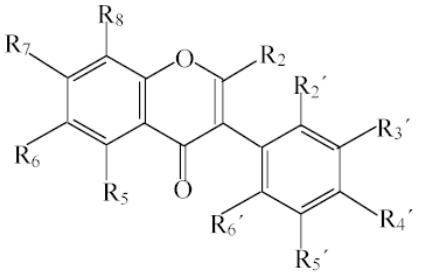
Flavanones



Catechines (Flavanols)



Anthocyanidines



Isoflavones

Flavonoids (coumarins) affect drug metabolism

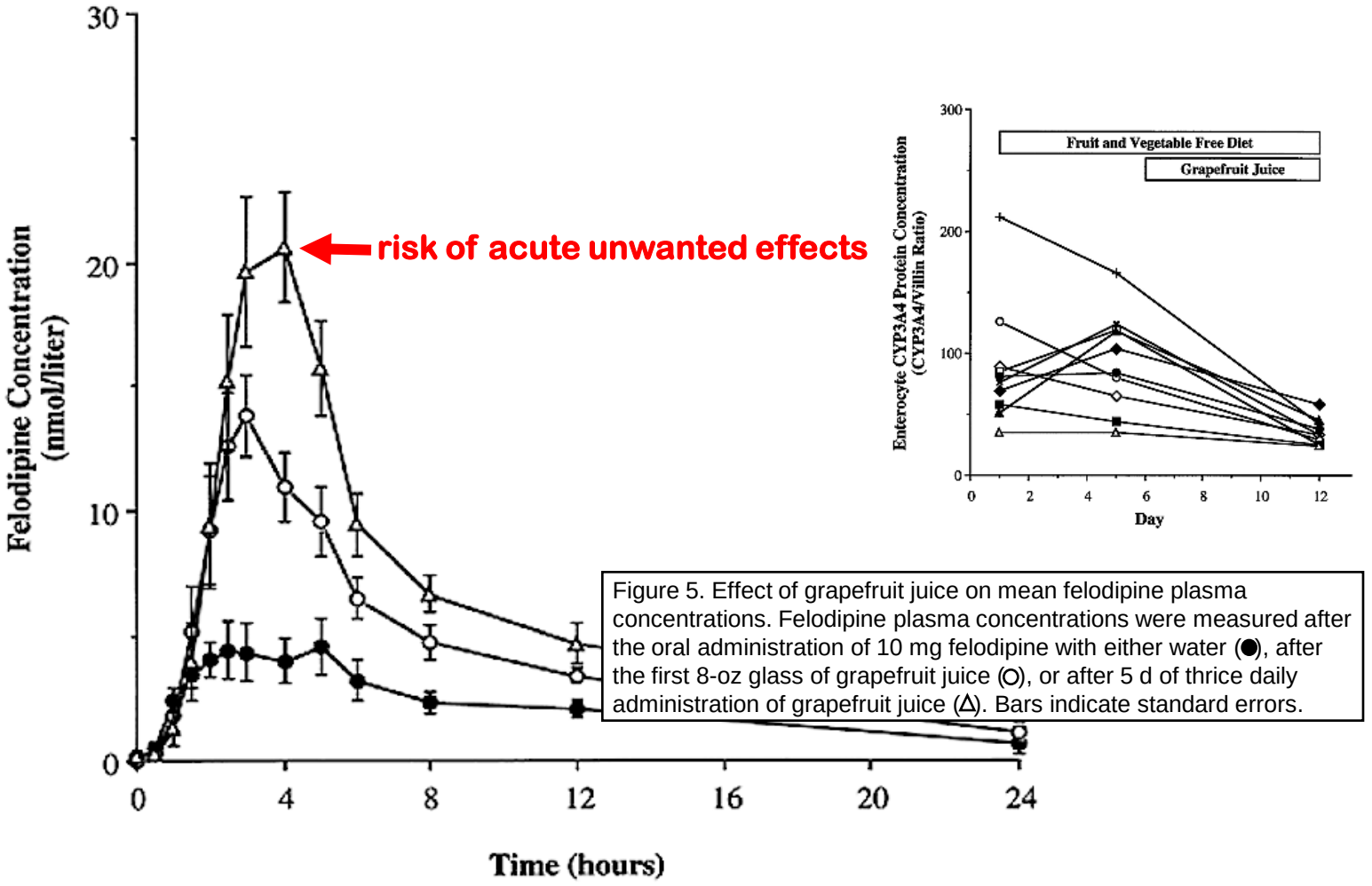


Figure 5. Effect of grapefruit juice on mean felodipine plasma concentrations. Felodipine plasma concentrations were measured after the oral administration of 10 mg felodipine with either water (●), after the first 8-oz glass of grapefruit juice (○), or after 5 d of thrice daily administration of grapefruit juice (△). Bars indicate standard errors.

Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. Lown KS, et al., J Clin Invest 1997 May 15;99(10):2545-53

Flavonoids (coumarins) affect drug metabolism

Severe interactions of grapefruit juice compounds with drug metabolism mainly by inhibition and down-regulation of intestinal CYP3A4

Experimentally shown for these drugs in studies with human volunteers just taking these test compounds

Dihydropyridines	**triazolam**	**increased risk for unwanted effects**
verapamil	**lovastatin**	
cisapride	**astemizol**	
amiodarone	**terfenadine**	
saquinavir	**cyclosporin**	
midazolam	**and others**	

Needs to be taken into account when assessing safety of new foods enriched with flavonoids or supplements !

Bailey DG, Malcolm J, Arnold O, Spence JD, Grapefruit juice-drug interactions. Br J Clin Pharmacol 1998 Aug;46(2):101-10

SUMMARY

Ingredients that target specific body functions need to be evaluated with respect to different consumer groups and their individual risks (genetic heterogeneity).

Although safety and functionality is assessed on product basis, the principle of action is in most cases taken to other products that consequently requires a new risk-benefit analysis (but there is no proper pathway of regulation).

New compounds/ingredients given in doses that can not be achieved with a normal diet need rigorous testing of safety and functionality.

However, this is all is not trivial !

The NEEDS

This all is likely to need new research strategies that take advantage of emerging information from genomics and proteomics to produce evidence of safety, efficacy and applicability. Ethical exploitation of the rapid growth in interest in 'functional foods' by the food industry will require a level of investment in biomedical research unusual in the past.

Mathers JC
Dietary strategies to reduce the burden of cancer and cardiovascular disease in the UK.
Br J Nutr 2000 Dec;84 Suppl 2:S211-6