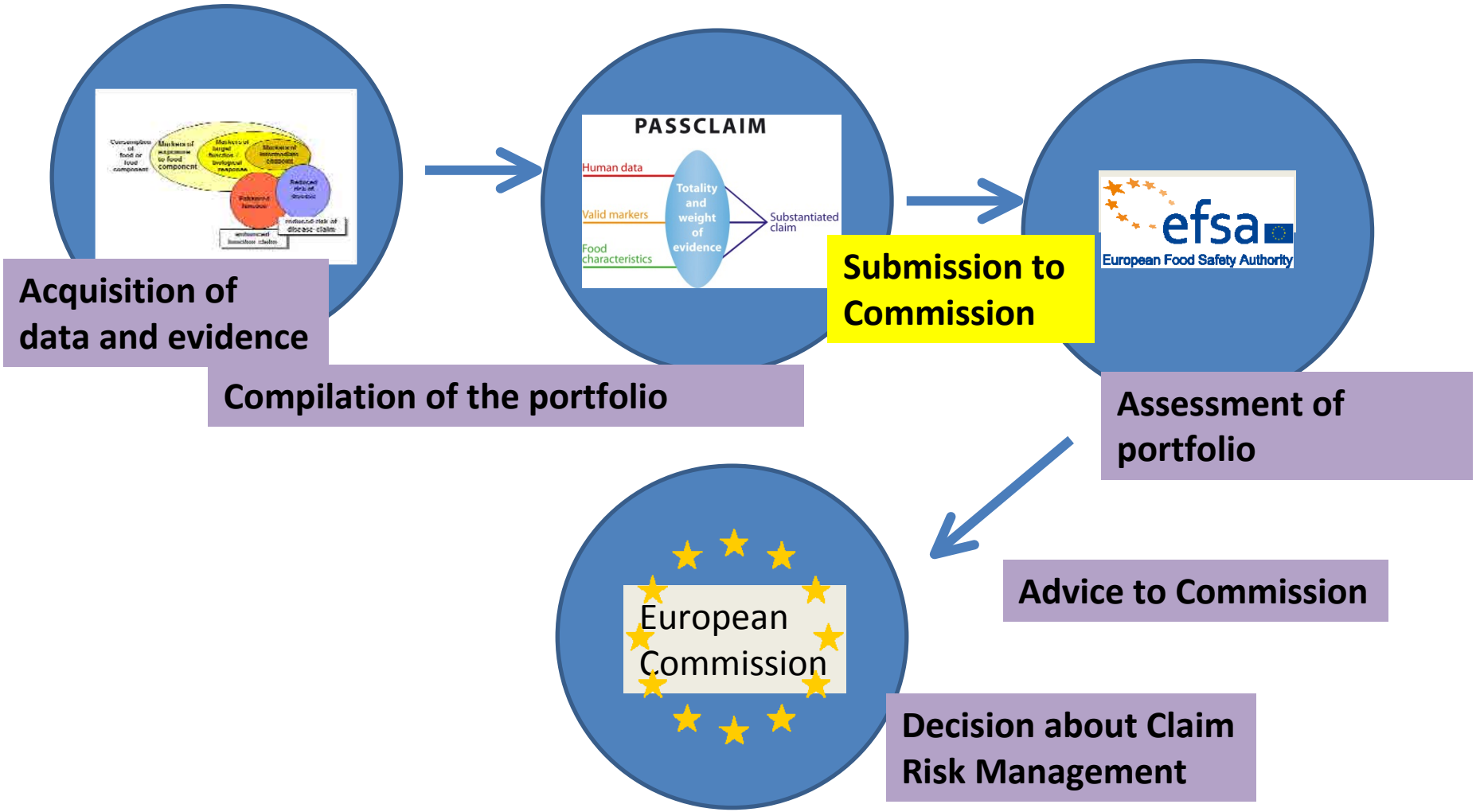
From PASSCLAIM to Health Claims

Professor Peter J Aggett
School of Medicine and Health
Lancaster University
profpjaggett@aol.com

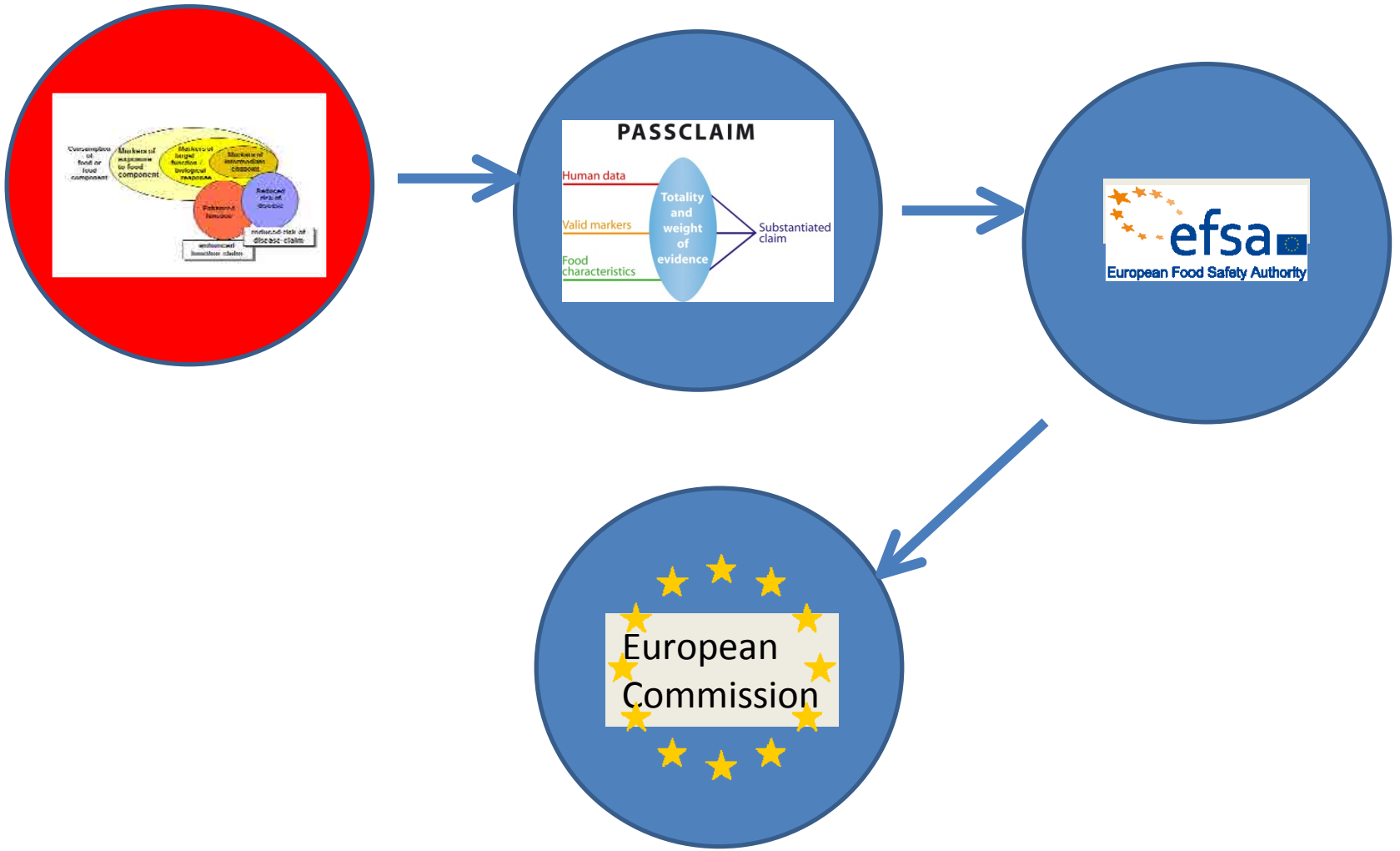
In the beginning there was FUFOSE

- Functional Food Science in Europe
- "Functional Food" was a convenient borrowing in Europe, by an ILSI Concerted Action, to boost governmental and industrial interest and investment in basic nutritional science as a basis for policy, practice, health promotion and improvement, and product development.
- In anticipation of legislation on Health Claims

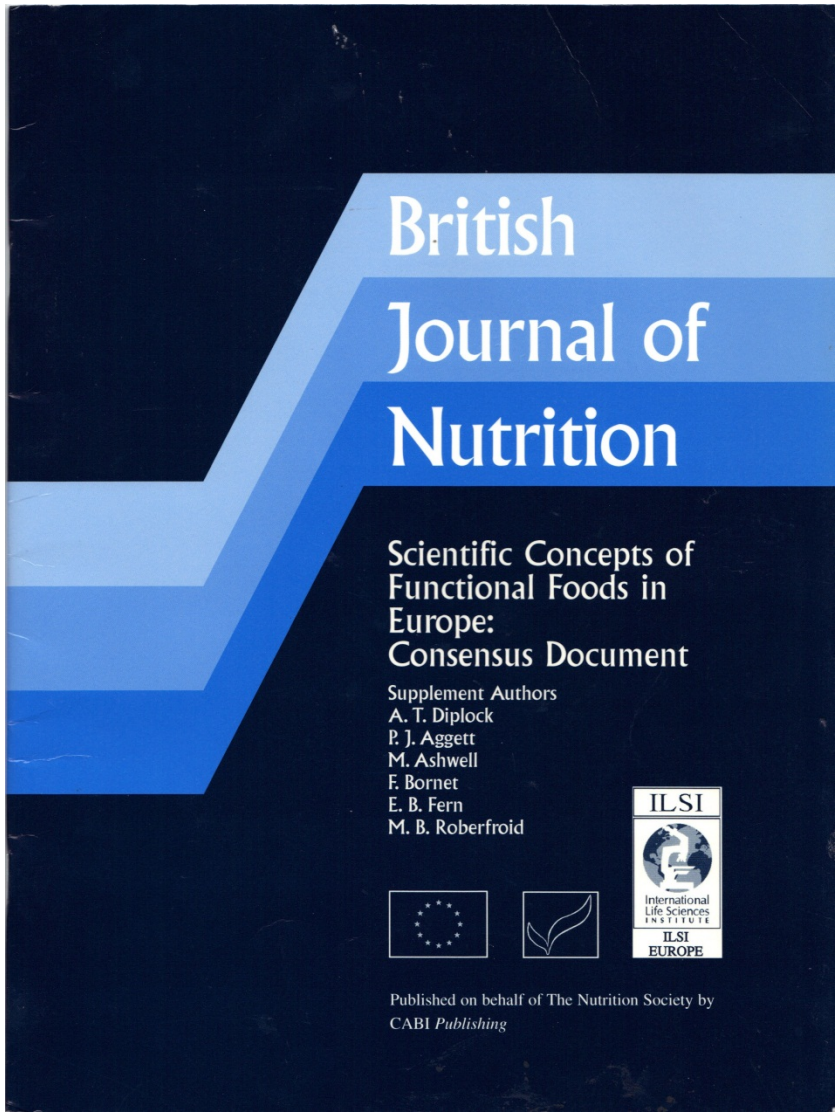
PASSCLAIM to Health Claims



PASSCLAIM to Health Claims



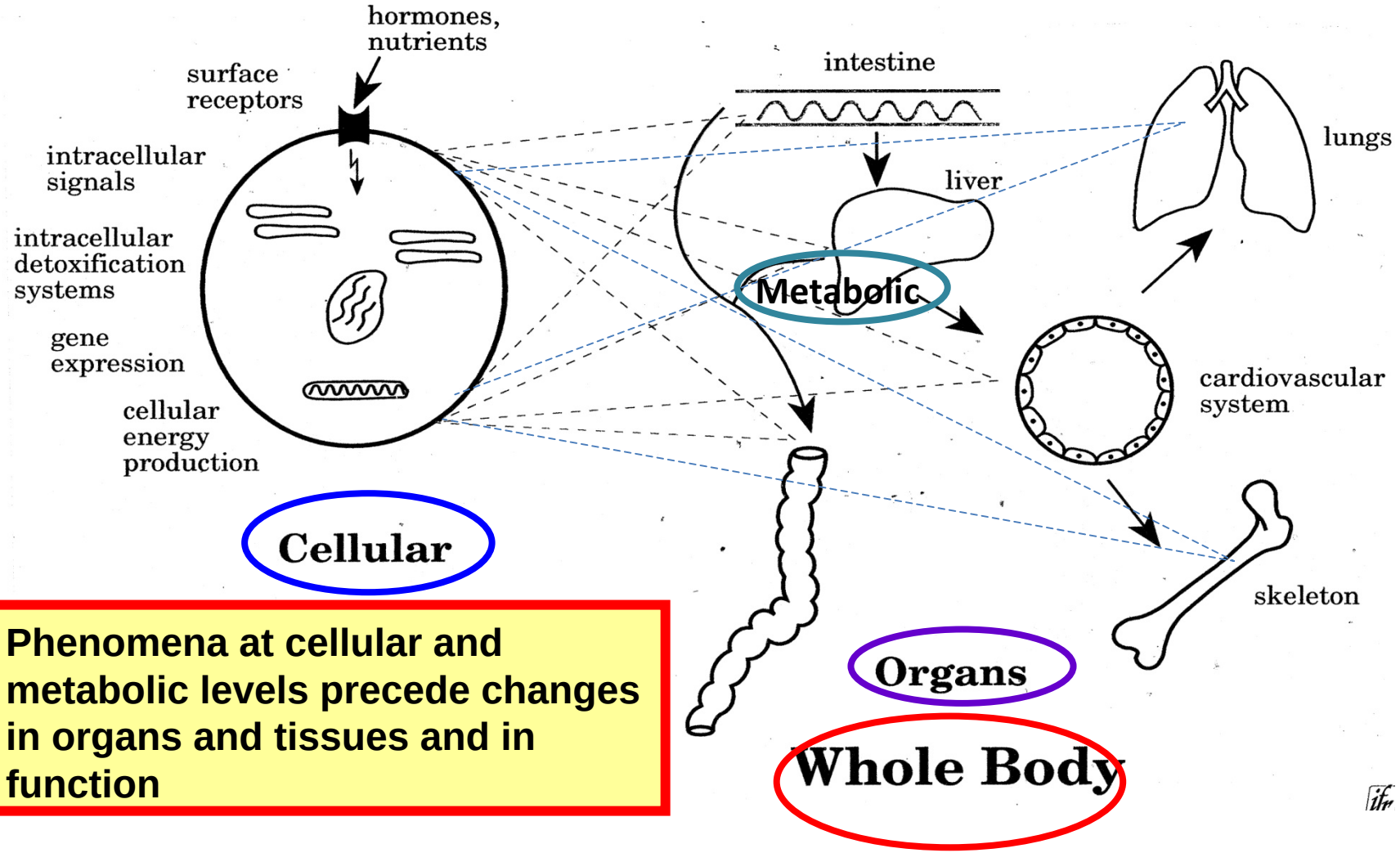
Good Quality Evidence: Science Based



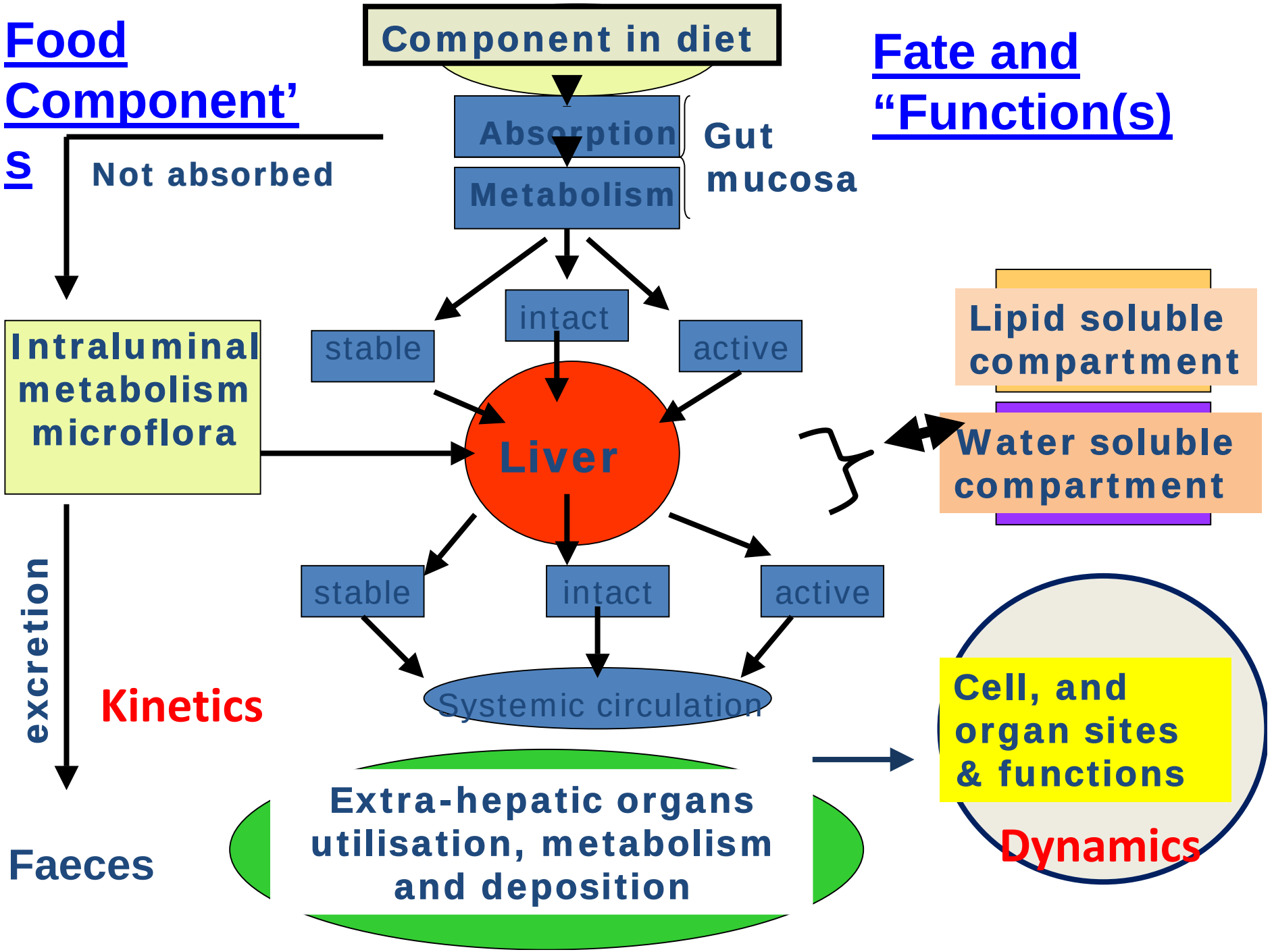
Functional Food Science in Europe 1994- 1998 (FUFOSE)
(Diplock et al BJN 1999)

- EU Concerted Action co-ordinated by the International Life Science Institute Europe
- "Evidence Based Nutrition"
- Explored existing science from a functional rather than a product perspective
- Hypothesis led science innovation and justification
- Assessed the science base required to provide evidence that specific nutrients positively affect functions
- Quality Assurance and Validation of Markers and Surrogates

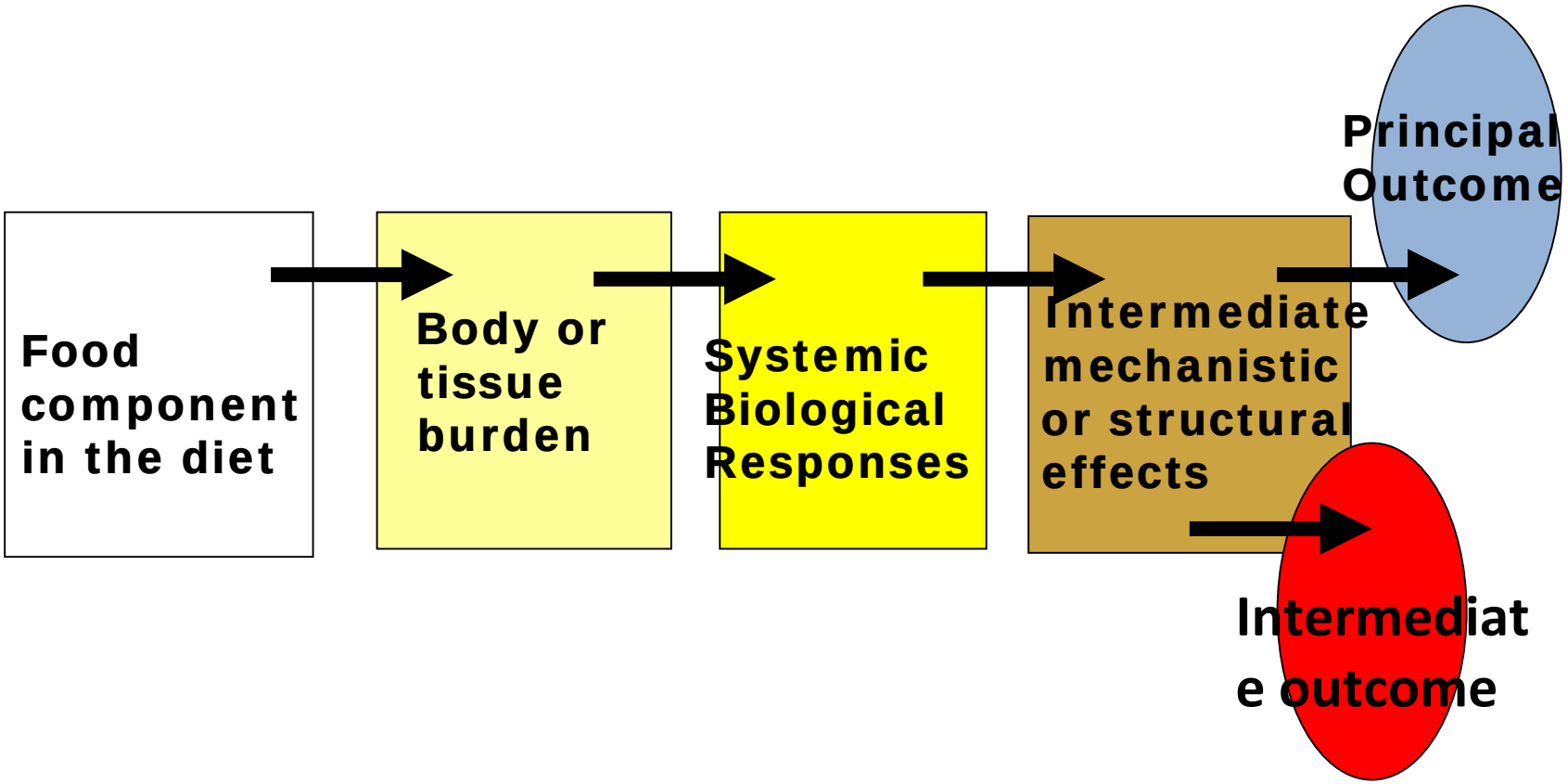
Metabolic and Functional Spectrum: Root Cause; Critical Control Points; and their Markers



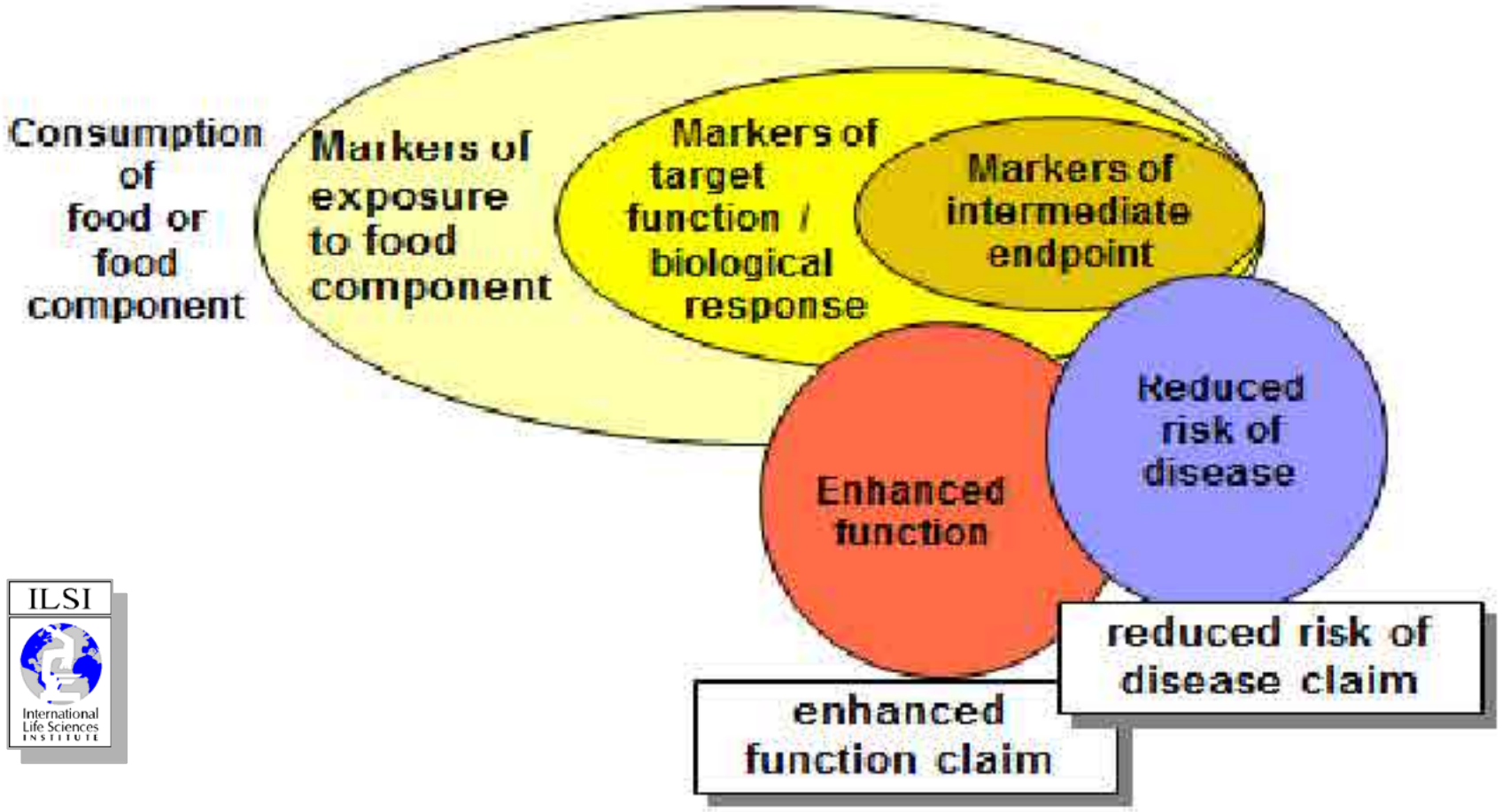
Phenomena at cellular and metabolic levels precede changes in organs and tissues and in function


Food Component's
Component in diet
Absorption
Metabolism
Gut mucosa
Not absorbed
Fate and "Function(s)
Intraluminal metabolism microflora
stable
intact
active
Liver
Lipid soluble compartment
Water soluble compartment
stable
intact
active
Systemic circulation
excretion
Kinetics
Cell, and organ sites & functions
Dynamics
Extra-hepatic organs utilisation, metabolism and deposition
Faeces

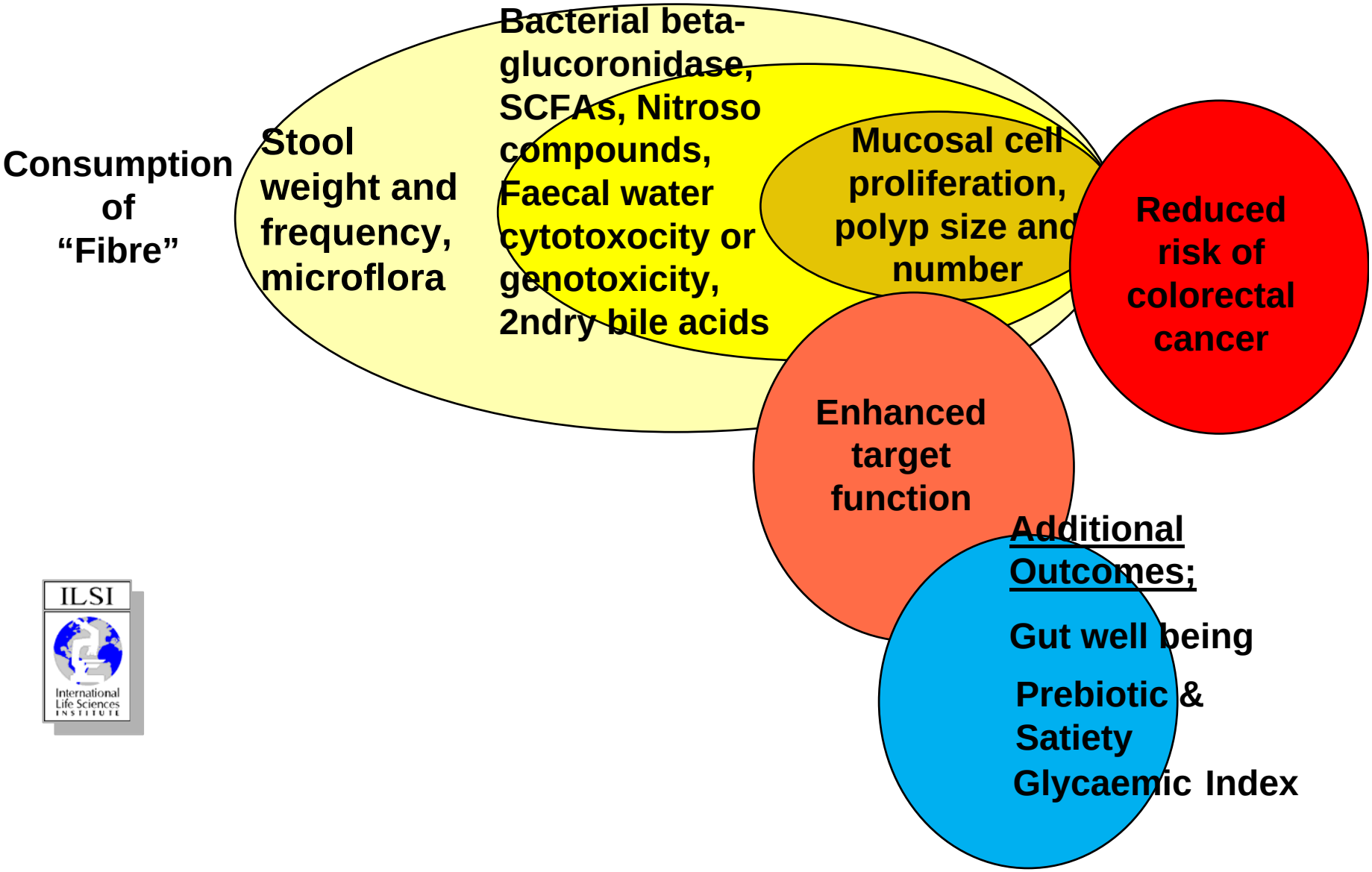
The FUFOSE Chain of Markers: Consumption to a single Outcome.



Functional Food Science in Europe: FUFOSE summary figure.



A scenario for markers and claims for for colorectal cancer (and other outcomes)



ILSI
International Life Sciences INSTITUTE

The FUFOSE mechanistic schema

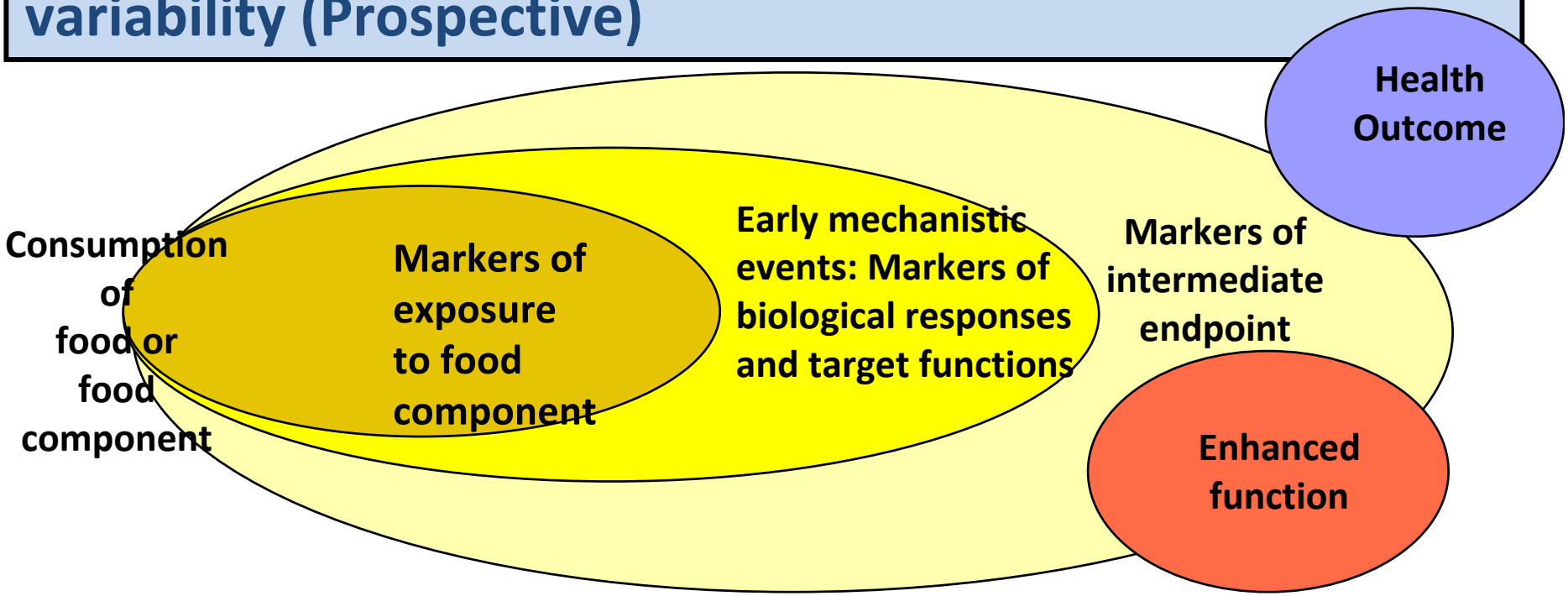
- A sequence of functionally related events
- Reflected in FUFOSE's differentiation of markers into factors and indicators
- Describes or Explains the cause, effect and dose response and intends to makes scientific sense
- Platform for assessing efficacy and safety; and for development

- “There is nothing more deceptive than an obvious fact”

- Sherlock Holmes

Sir Arthur Conan Doyle.

Strategic use of the evidence base and markers to explore causality: Modifiers of effect uncertainty and variability (Prospective)



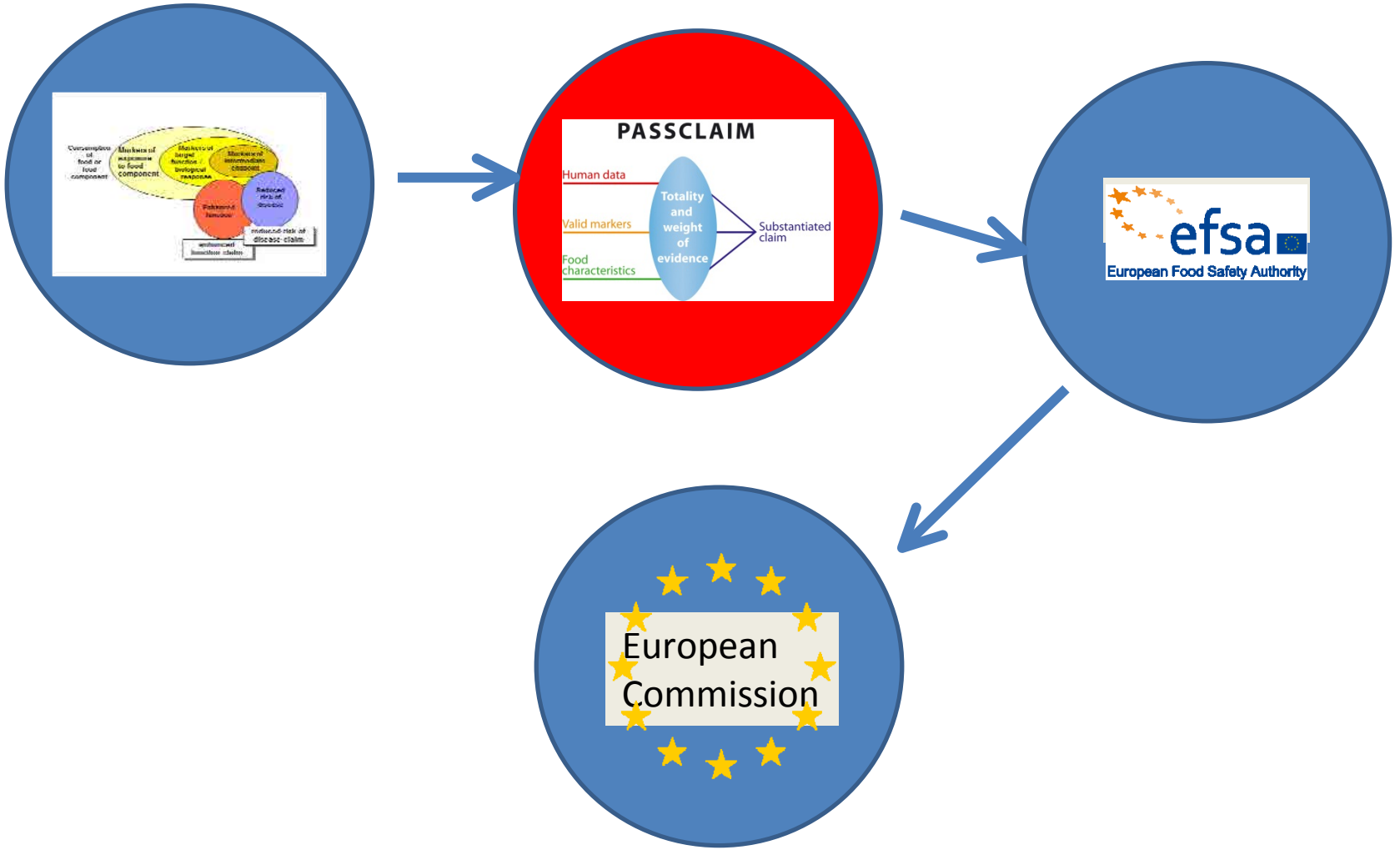
Markers of uncertainty, variability, susceptibility, confounders and for intervention and "targeting"

e.g. Age, maturation, growth, other dietary components, digestion and absorption, interaction with other nutrients, organ and tissue compartments' size and turnover, organ function, "functional and temporal proximity", polymorphisms, epigenome, reproduction and lactation, lifestyle, time.

Evidence Based Nutrition: Chain of Causality and Use of Markers

Better characterised populations
Early metabolic and functional responses to dietary interventions
Enhanced epidemiological studies
Nutrient - gene/receptor interactions
Markers of:
- susceptibility
- exposure
- body burden
- principal outcomes and intermediate effect (known predictive value)
- Desired outcomes and surrogate outcomes

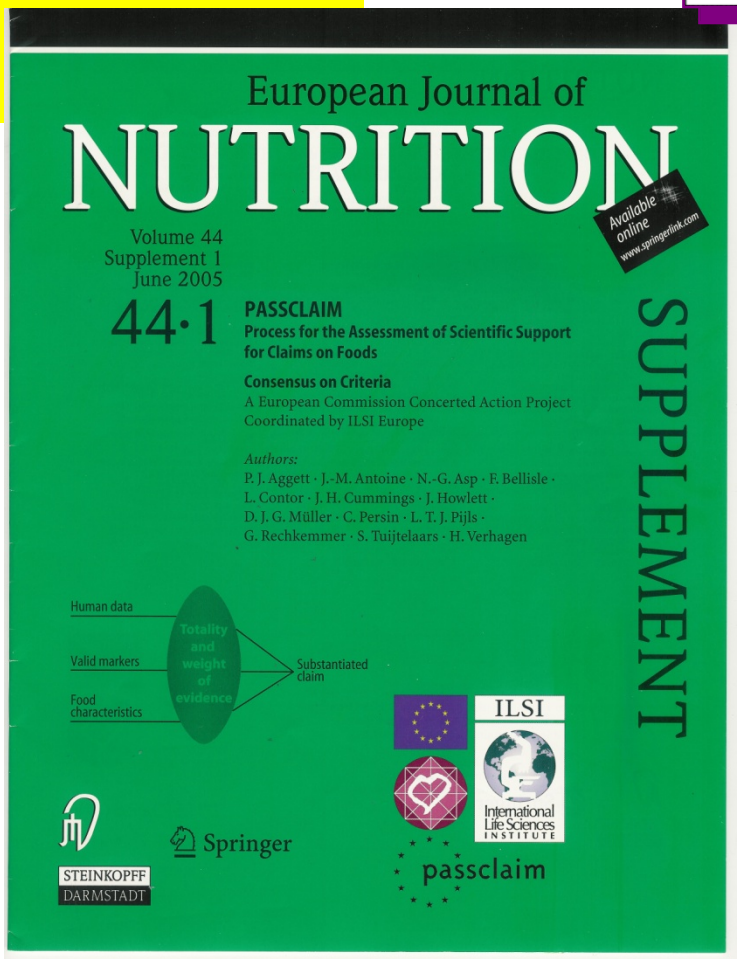
PASSCLAIM to Health Claims



The Process for the Assessment of Scientific Support for Claims on Food (PASSCLAIM) .

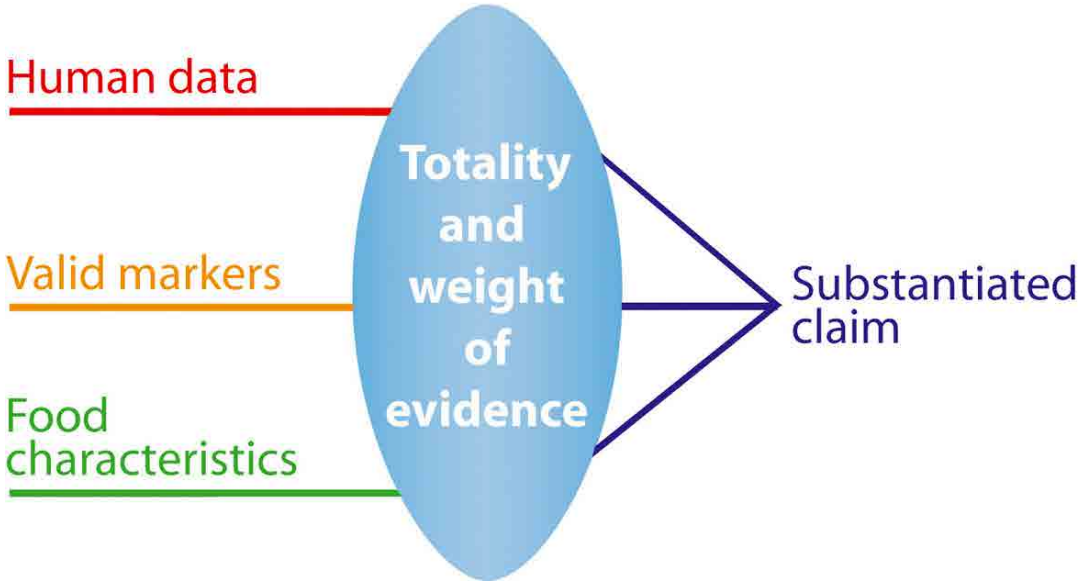
Aggett et al EJN 2005;Suppl 1; pp30

- Substantiating Health Claims
- Establishing Benefits
- Objective good quality data
- Application of validated markers



passclaim

PASSCLAIM



Underpinned by PASSCLAIM criteria for adequacy of the portfolio

passclaim

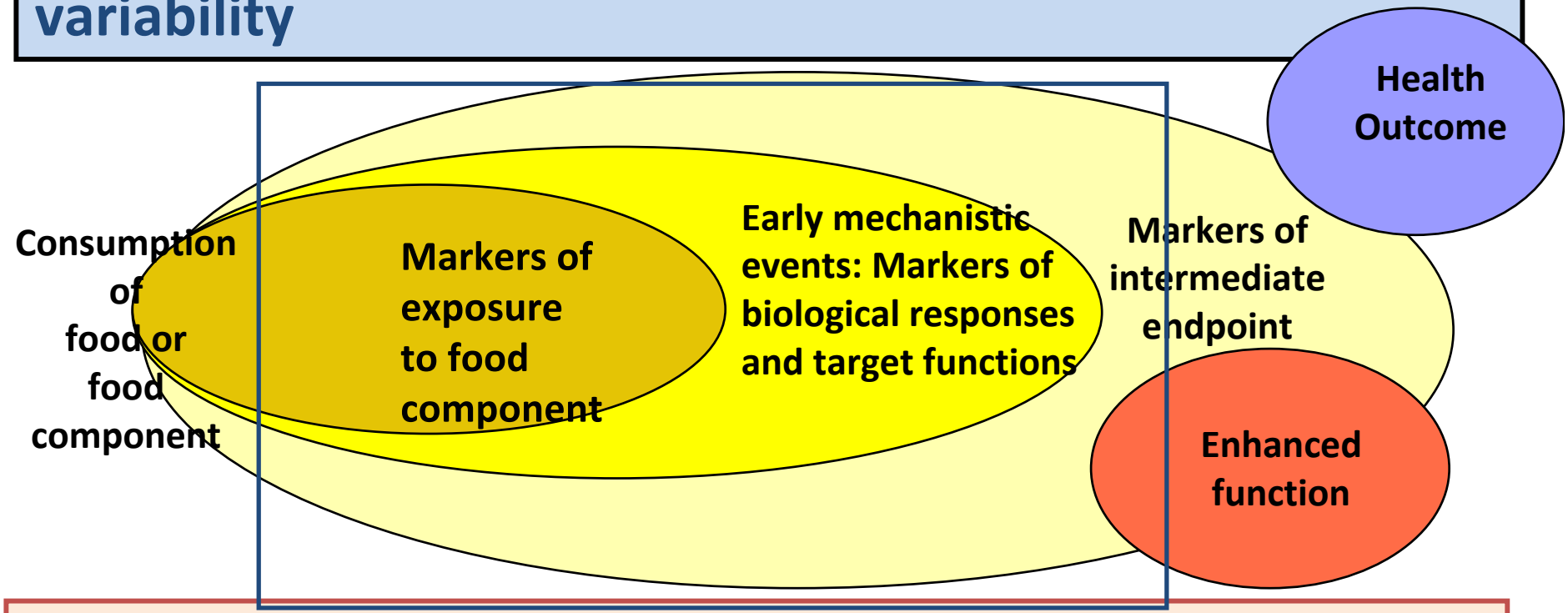
Hill Principles addressing Causation or Association?

Applied to both single studies or portfolios of evidence.

- Strength of Association (probability)
- Consistency
- Specificity
- Temporality
- Dose/exposure-response relationship
- Plausibility
- Coherence
- Supportive data from other sources (Experimental evidence)
- Analogy

» (A. Bradford-Hill: Proc RSM1966)

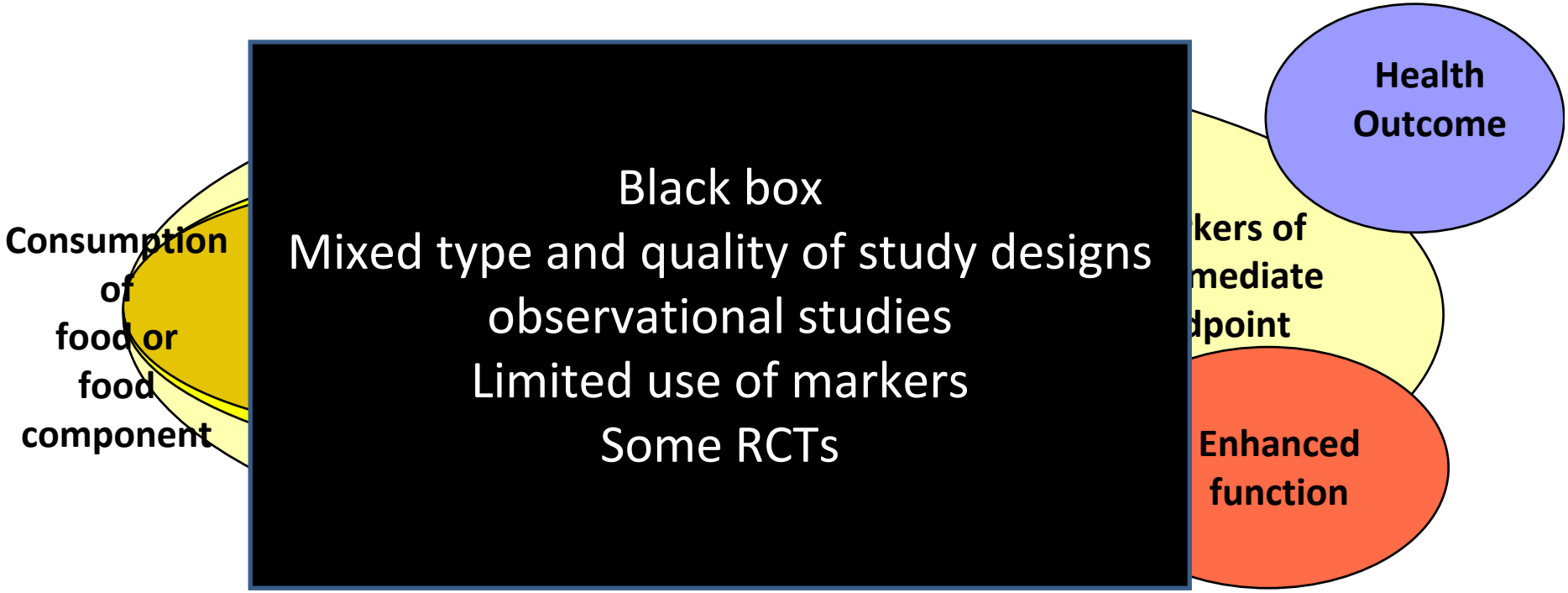
Strategic use of the evidence base and markers to explore causality: Modifiers of effect uncertainty and variability



Markers of uncertainty, variability, susceptibility, confounders and for intervention and "targeting"

e.g. Age, maturation, growth, other dietary components, digestion and absorption, interaction with other nutrients, organ and tissue compartments' size and turnover, organ function, "functional and temporal proximity", polymorphisms, epigenome, reproduction and lactation, lifestyle, time.

Strategic use of the evidence base and markers to explore causality: Modifiers of effect.



Markers of uncertainty, variability, susceptibility, confounders and for intervention and "targeting"

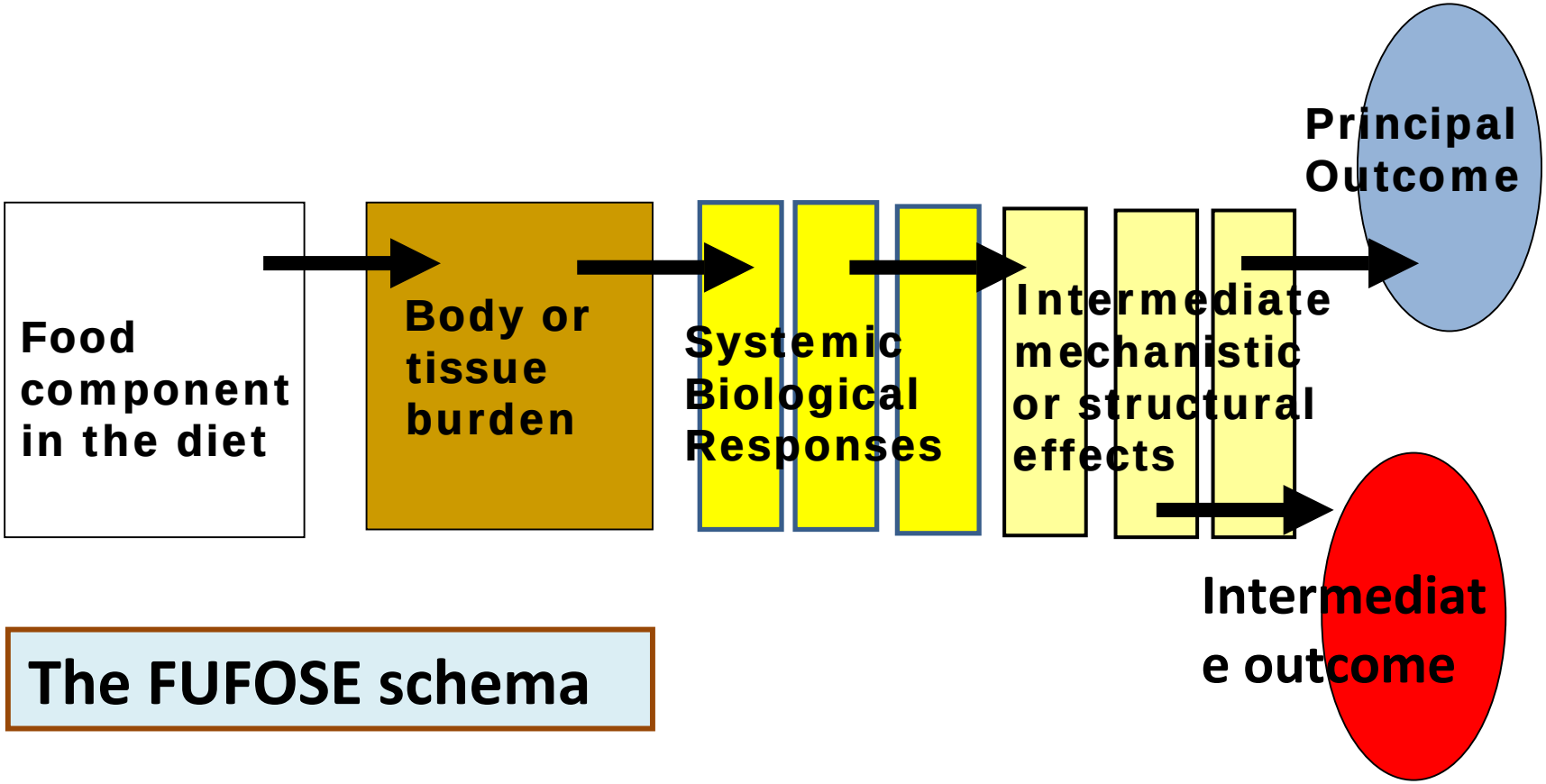
e.g. Age, maturation, growth, other dietary components, digestion and absorption, interaction with other nutrients, organ and tissue compartments' size and turnover, organ function, "functional and temporal proximity", polymorphisms, epigenome, reproduction and lactation, lifestyle, time.

Use of all Available Data

- Limited use of all data on causal or mechanistic chain; although there may be limited data
- Which data to use?
- What does it do and how does it do it?
- More than one component might influence the outcome of interest
- Any component might have multifunctional effects
- Mechanistic commonalities and synergies (root causes)

The FUFOSE Chain of Markers: Consumption to Outcomes.

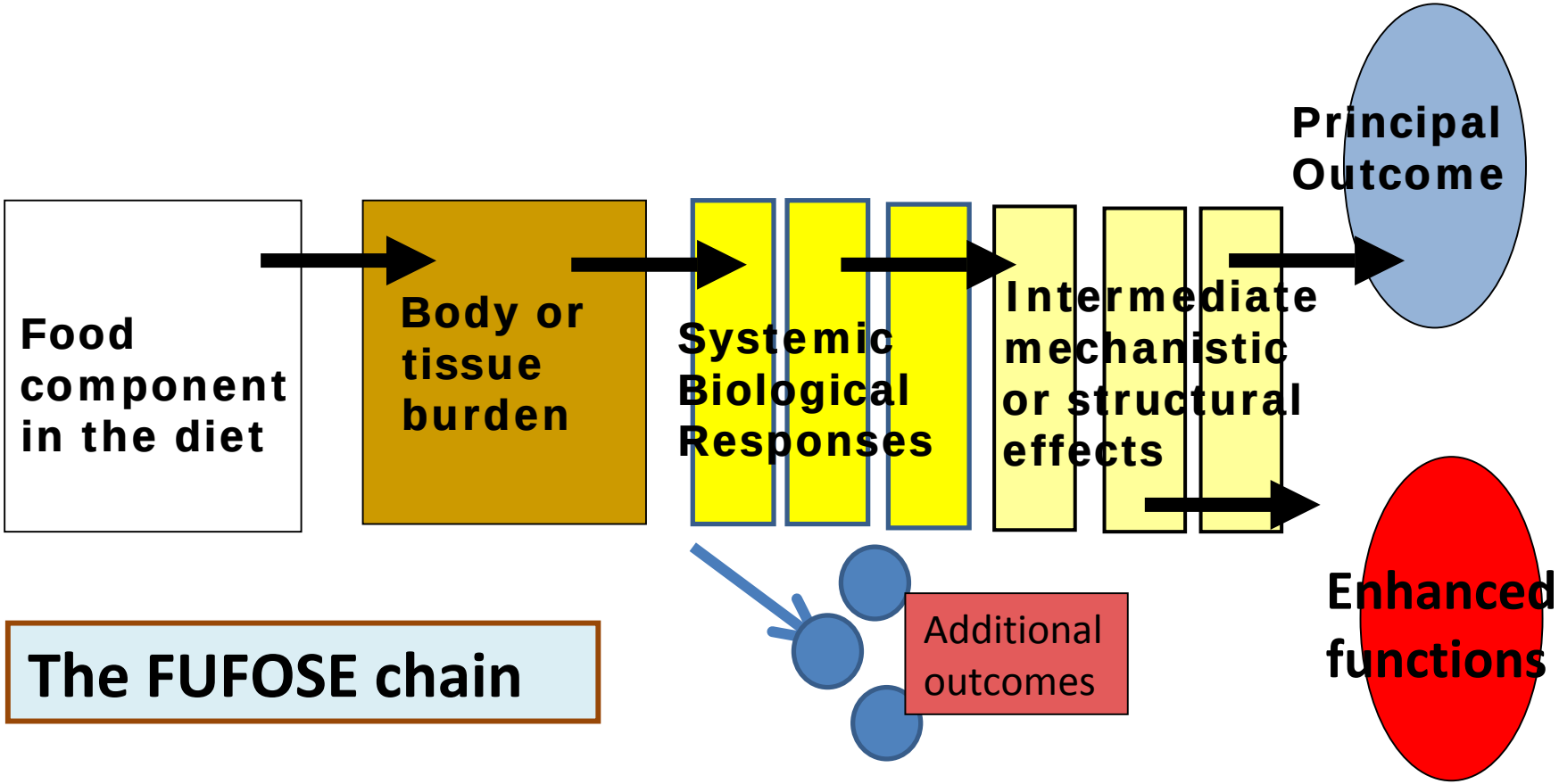
Principle of a causative chain in pathway



The FUFOSE schema

The Chain of Markers: Consumption to Outcomes.

Principle of a causative chain or pathway

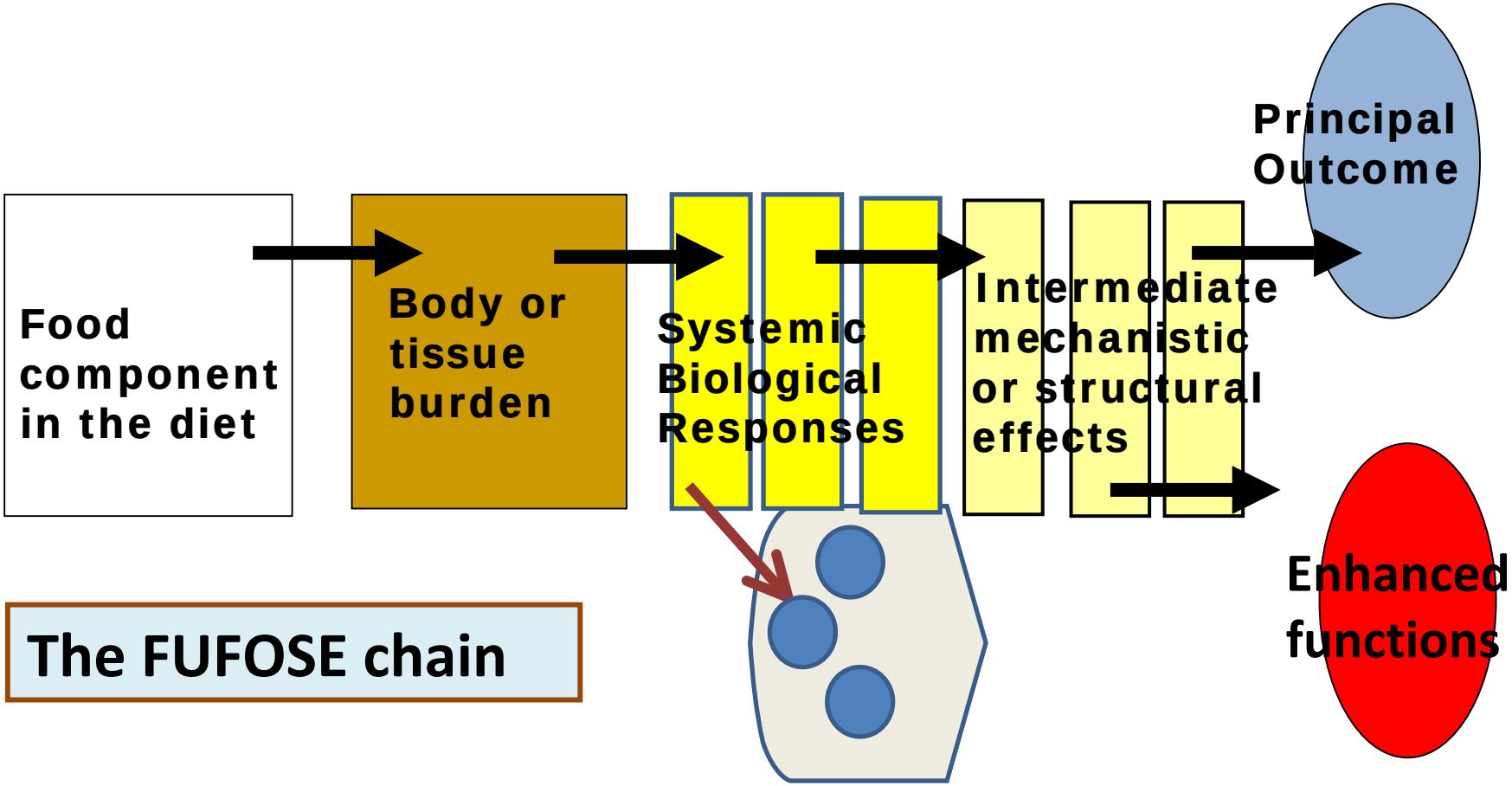


One Change: Knock on and Multiple Effects

- Dietary Component: Polyunsaturated Fatty Acids
- Altered cell membrane fluidity
  - Altered signal transduction
    - Enhanced Neuronal function,
    - retinal function (preterm neonates)
    - Increased insulin sensitivity (adiposity, glucose tolerance, reduced glycosylation of proteins, reduced atherosclerosis)

The Chain of Markers: Consumption to Outcomes.

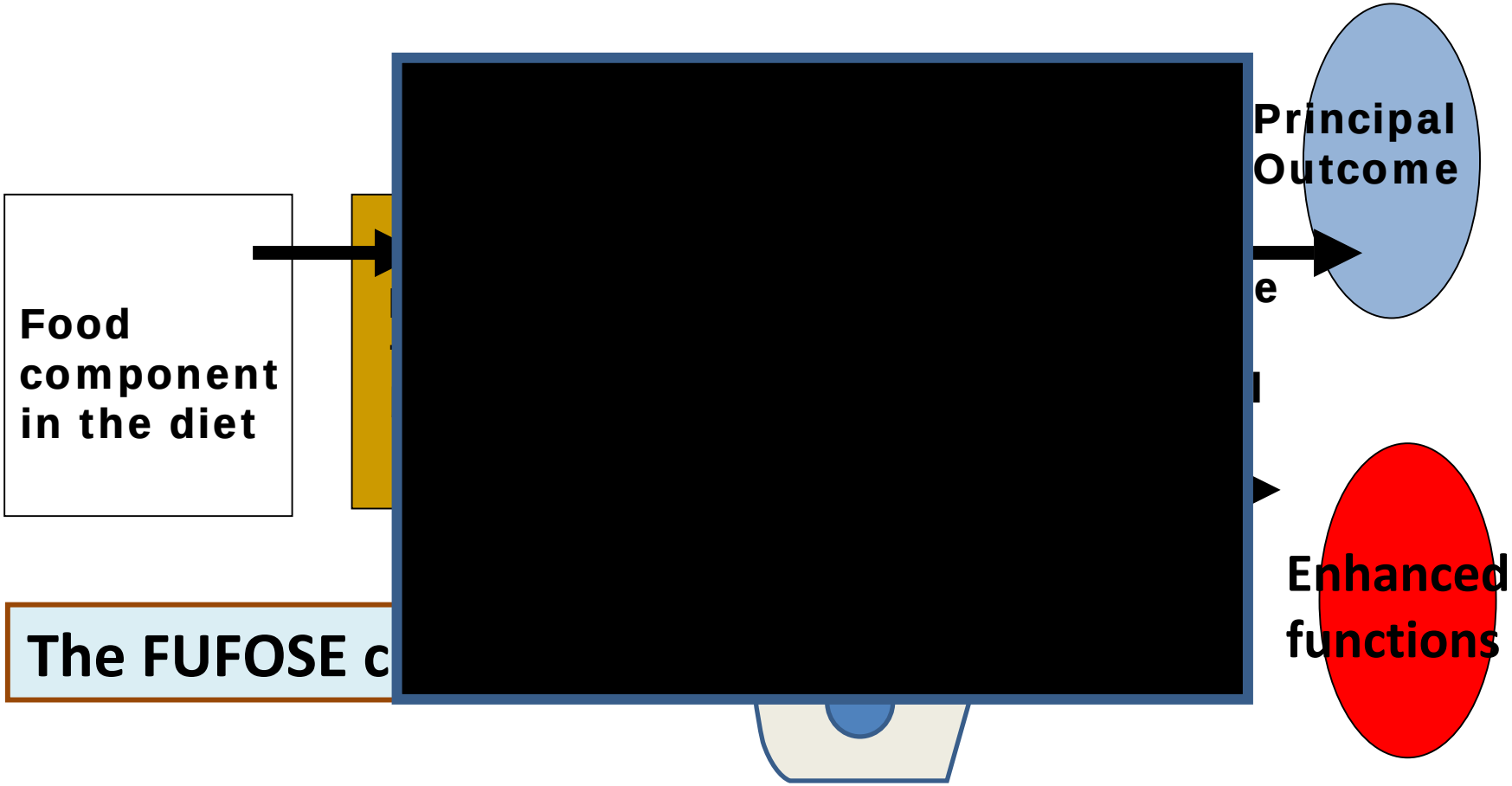
Principle of a causative chain in pathway



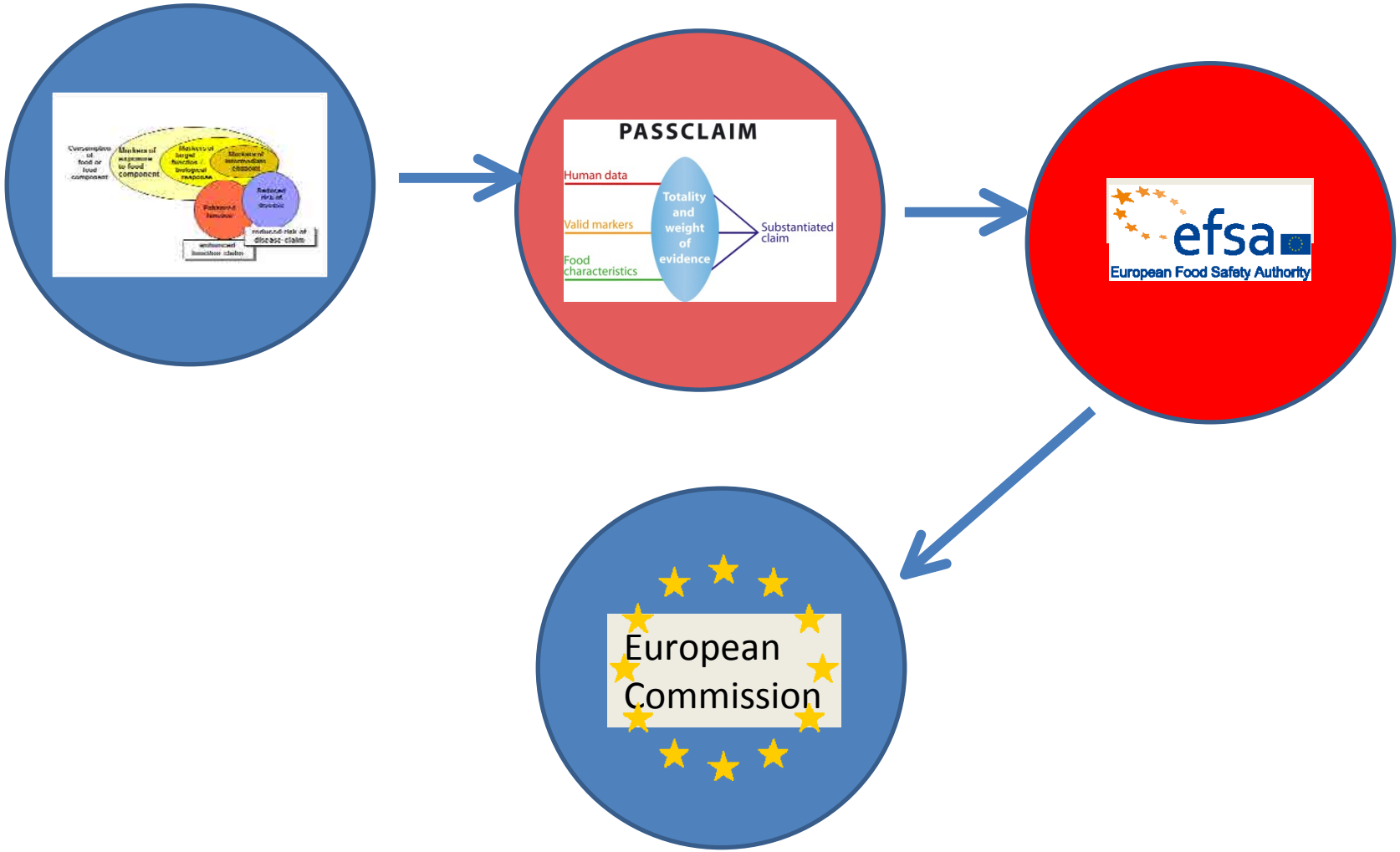
The FUFOSE chain

The Chain of Markers: Consumption to Outcomes.

Principle of a causative chain in pathway



PASSCLAIM to Health Claims



Scientific substantiation of health claims:

- The EFSA NDA advises the European Commission on the extent to which:
- The claimed effect of the food is beneficial for human health
- A cause and effect relationship has been established between consumption of food and outcome detected in humans and whether the magnitude of the effect is related to the quantity consumed (e.g. strength, consistency, specificity, dose-response and biological plausibility of the relationship).
- (DPRichardson)

The European commission must seek EFSA's advice on the extent to which:

- The quantity of the food and pattern of consumption required to obtain the claimed effect could reasonably be consumed as part of a balanced diet.
- The specific study group (s)in which the evidence was obtained is representative of the target population for which the claim is intended.
- (DPRichardson)

Using the Evidence to Best Effect?

- Producing an RCT?
  - Does not necessarily help with mechanisms
  - Neither explanatory nor pragmatic RCTs are always feasible or ethical for nutrition science
  - Does not use all the available data
  - Time scale
  - May not give a clear outcome from a dose range representative of intended use because of temporal and mechanistic remoteness.
- Root cause or critical metabolic point might be useful as a component factor (marker) or surrogate outcome

Using the Evidence to Best Effect?

- FUFOSE schema for acquiring and using data mechanistically appealing
- Its would enable logical use of much data
- Complement other information and enable its analysis in toto against Hill Principles

An Alternative “Hierarchy” of Evidence

(i) Experiments which probably can give the strongest idea of mechanisms with an immediacy between exposure and outcome

(ii) Randomised Controlled Trials (RCTs); explanatory, pragamatic purposes

(iii) Regression continuity designs

(iv) Natural experiments (these are random non-manipulative biomedical occurences in populations which can be quantitatively and systematically analysed) e.g. Inborn Errors of Metabolism

Types of Evidence: An alternative Hierarchy?

(v) non-experimental studies including cohort studies, case-control studies, and ecological designs

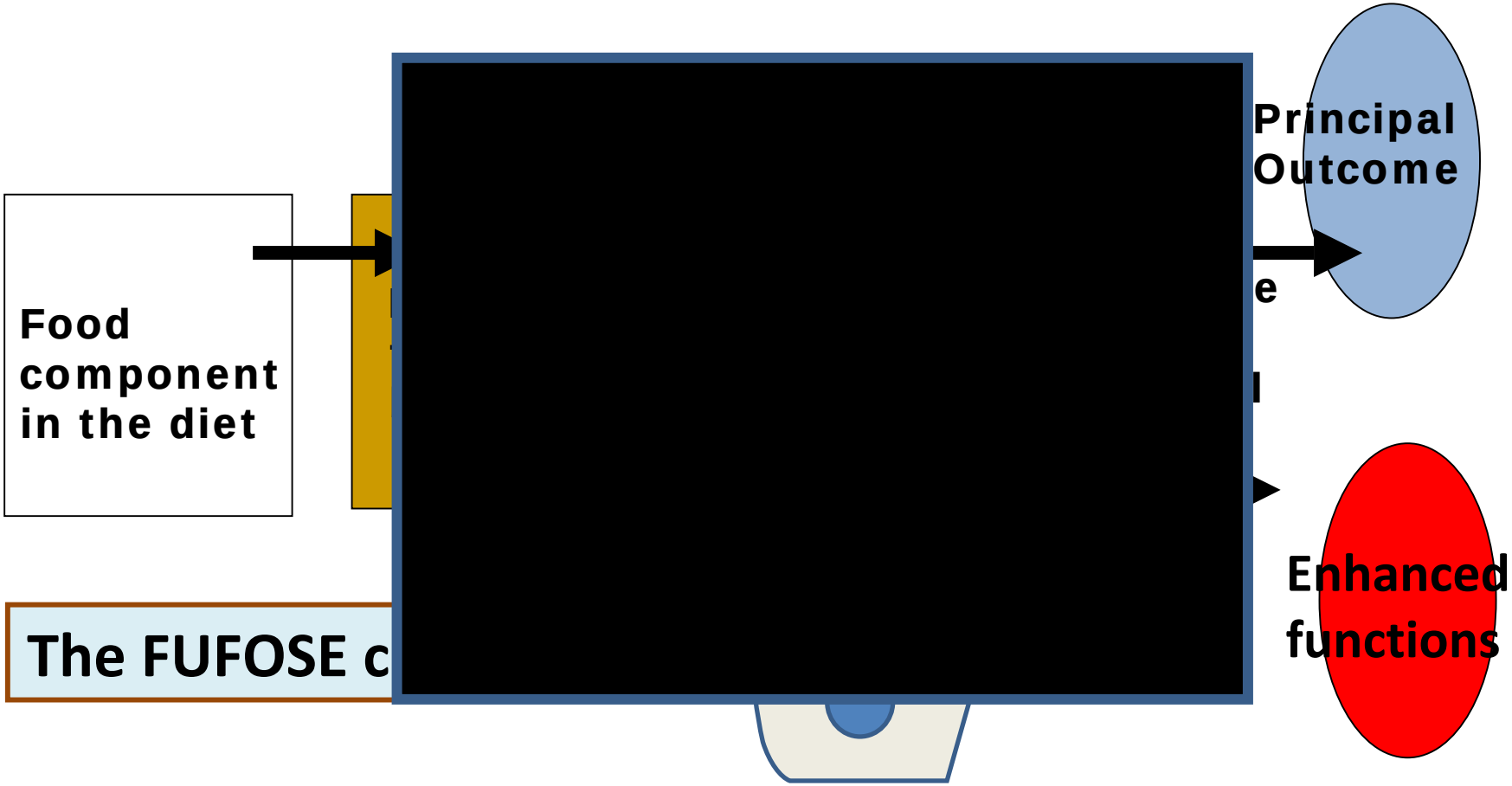
- All of these, with or without corroborative information from animal studies can be used to substantiate the extent to which causality can be demonstrated

(The Academy of Medical Sciences 2007).

- All markers need to be quality assured and validated.

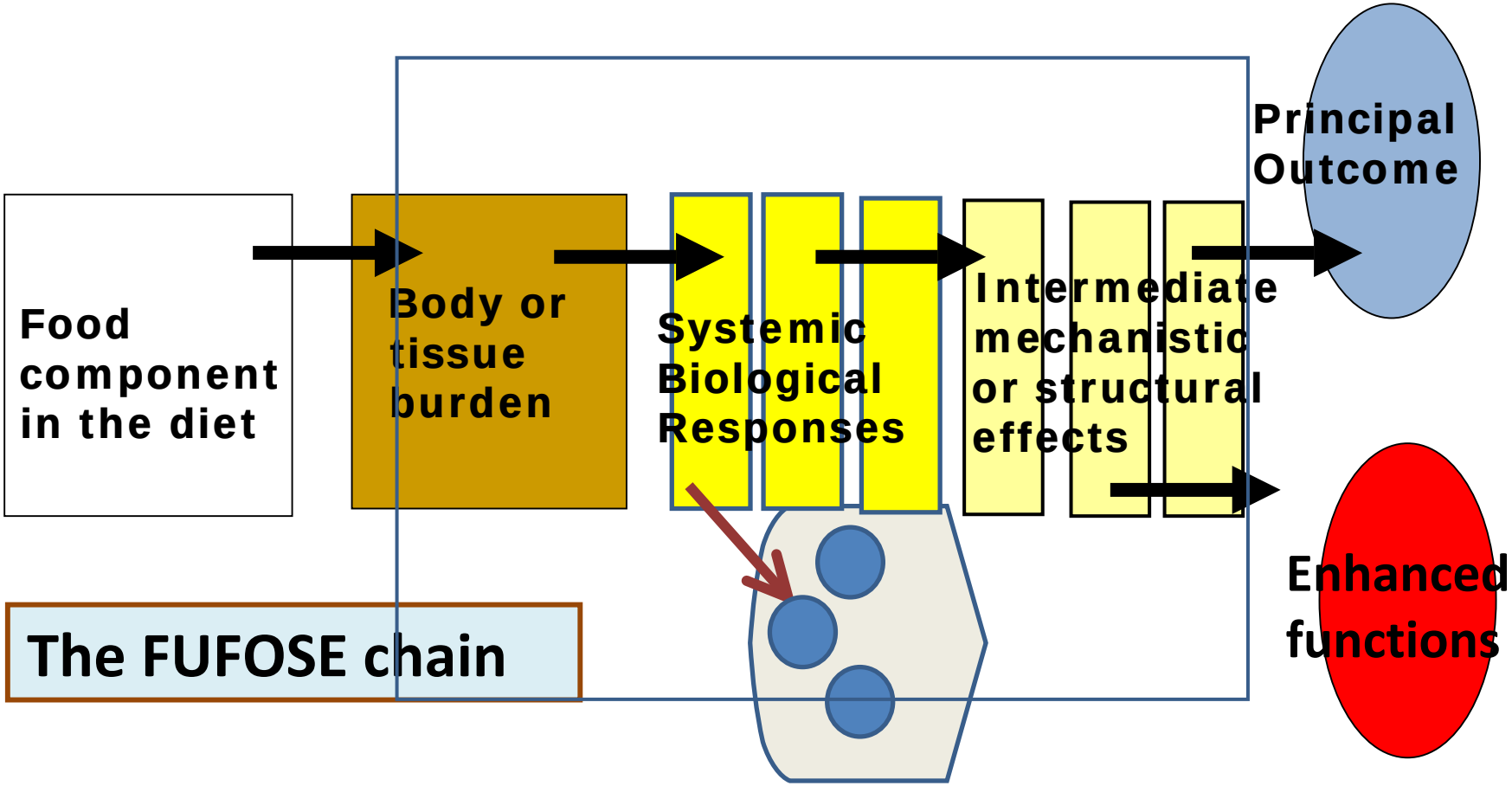
The Chain of Markers: Consumption to Outcomes.

Principle of a causative chain or pathway



The Chain of Markers: Consumption to Outcomes.

Principle of a causative chain in pathway



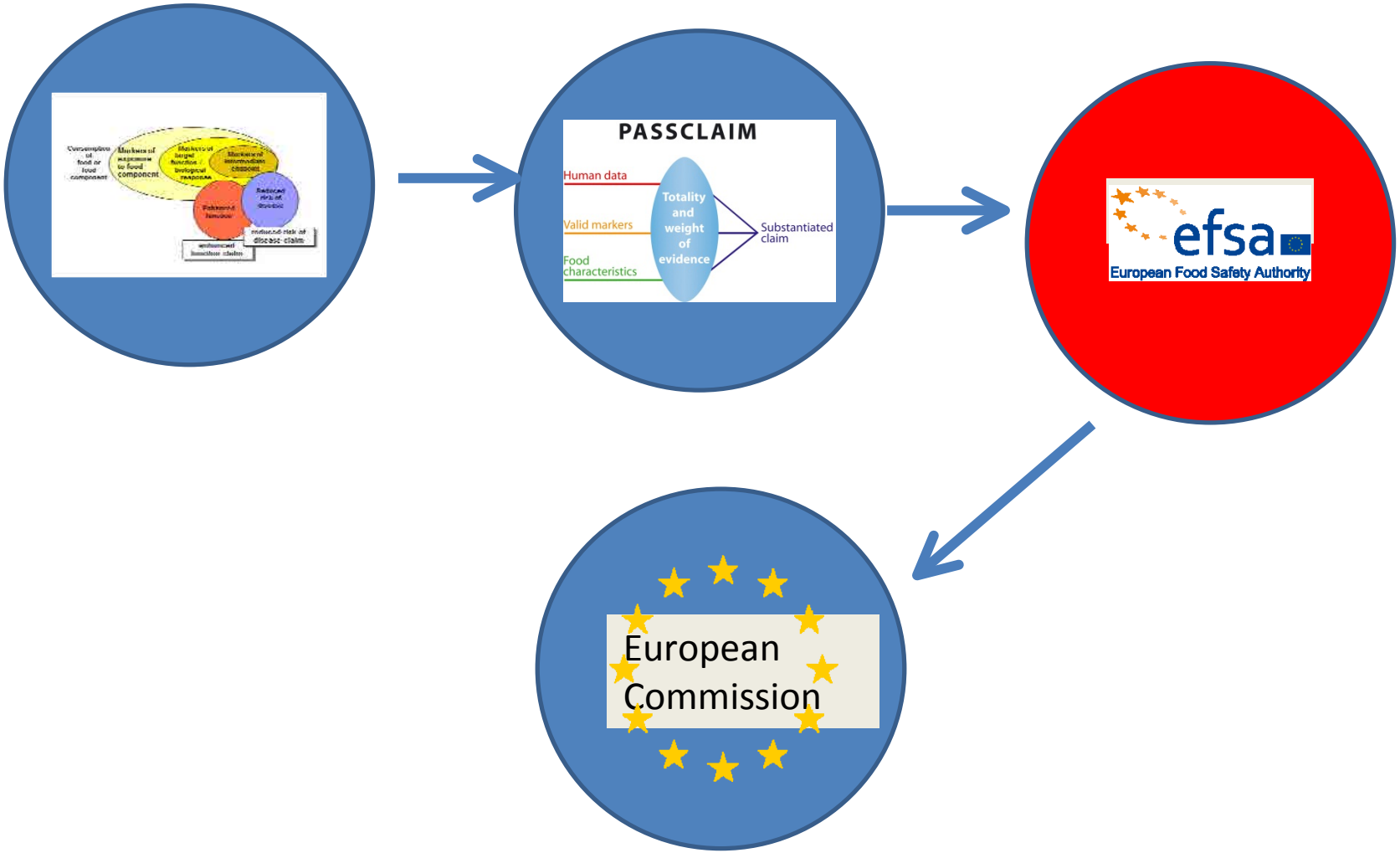
Evidence Based Mechanistic Reasoning

- Uses mechanisms to explore infer causal associations
- Testing associations
- An inferential chain resembling that applied by FUFOSE
- Still needs high quality markers and reasoning

    - (Howick et al, J R Soc Med 2010:433-441)

Is it time critically to reappraise the use of evidence in submitted portfolios and in the process of EFSA NDA evaluation and decision making?

PASSCLAIM to Health Claims

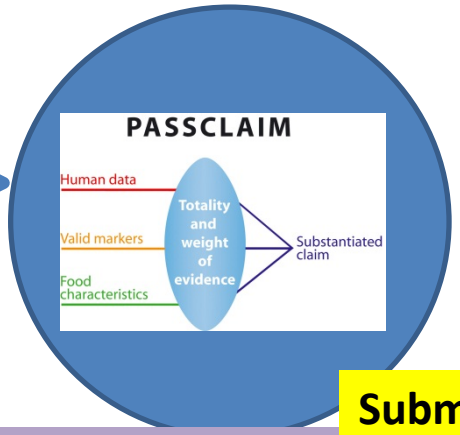


The Assessment

- EFSA NDA is following its principles. It is not condoning weak science
- Variable quality of portfolios submitted
- Guidance provided by EFSA, which derives from PASSCLAIM, is not followed
- “PASSCLAIM set to high a standard”
- Is the process as transparent as it could be, and is there effective feedback? Uncertainties and Variables
- EFSA is probably being blamed unfairly for a weakness in the system

PASSCLAIM to Health Claims

Acquisition of data and evidence



Compilation of the portfolio

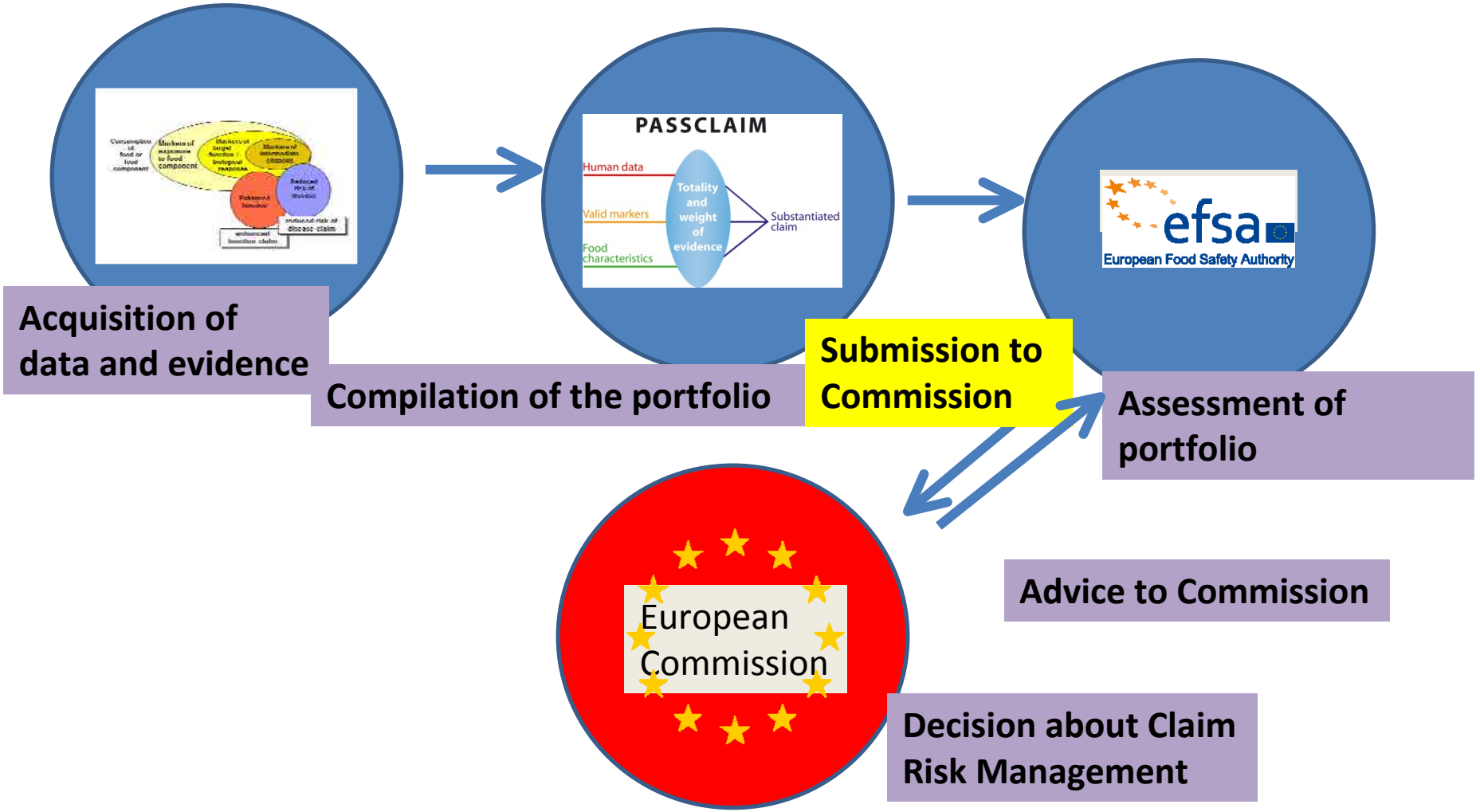
Submission to Commission

Assessment of portfolio

Advice to Commission

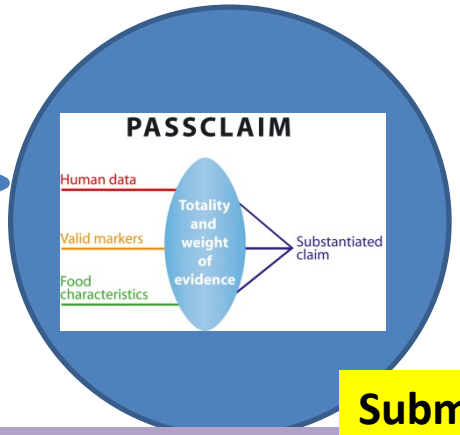
Decision about Claim Risk Management

PASSCLAIM to Health Claims



Causality and Claims are not the same

Acquisition of data and evidence



Compilation of the portfolio

Submission to Commission

Assessment of portfolio

Advice to Commission

Explicit uncertainties and variabilities

Engage other stakeholders
Consider classes of claims with distinct conditions

Decision about Claim Risk Management

Key Points

- Good Quality of Science
- Totality lies in using all the evidence to tell a sound story according to a logical schema (FUFOSE)
- Including key elements to justify causality and address the broader relevance; the complete story (PASSCLAIM)
- Self Assessment of evidence (FUFOSE and PASSCLAIM) alert to gaps
- More “open approach” to the evidence by all participants; (Evidence Based Mechanistic Reasoning not just RCTs)

Finally

- Causality and Claims are not the same
- There are Considerations of Public Health Protection and Improvement, as well as commercial issues;
- Views of Member States, Commission Directorates, and public interest groups may be at variance.

Bibliography

- Aggett PJ, Antoine JM, Asp NG, Bellisle F, Contor L, Cummings JH, Howlett J, Müller DJ, Persin C, Pijls LT, Rechkemmer G, Tuijtelaars S, Verhagen H. PASSCLAIM: consensus on criteria. Eur J Nutr. 2005;44 Suppl 1:i5-30.

- Blumberg J, Heaney RP, Huncharek M, Scholl T, Stampfer M, Vieth R, Weaver CM, Zeisel SH. Evidence-based criteria in the nutritional context. Nutr Rev. 2010; 68:478-84.

- Diplock AT, Aggett PJ, Ashwell M, Bornet F, Fern EB, Roberfroid MB. Scientific concepts of functional foods in Europe. Consensus document. Br J Nutr. 1999;81 Suppl 1:S1-27.

- Howick J, Glasziou P, Aronson JK. Evidence-based mechanistic reasoning. J R Soc Med. 2010;103:433-41.

- The Academy of Medical Sciences. Identifying the environmental causes of disease: how should we decide what to believe and when to take action? Report synopsis, London November 2007, pp. 144.