BRAFO methodology and application to the case studies

27 November 2012

6th Asian Congress on Food and Nutrition Safety

Dr Alessandro Chiodini
FUFOSE 1995-1999
Benefit assessment

Passclaim 2001-2005
Benefit assessment

FOSIE 2000 – 2004
Risk assessment
Benefit-risk problems

- Policy consideration
- Allow a food on the market
- Make a recommendation
- Fortify a food
- Change a production process
- Start an intervention
- Investigate if you can improve health
- …
Benefit-risk problems
Tiered approach

• Stop when you can answer the question

• Don’t answer the question too accurately

• Full quantitative risk-benefit assessment is very data demanding

• Involves large effort (time and money)
Pre-assessment and problem formulation

Tier 1
Characterisation & screening

both risks and benefits

Tier 2
Qualitative evaluation

no clear dominance

Tier 3
Deterministic computation of common health metric

worst/bad case analysis
Sensitivity analysis
Increasingly assessing more and more parameters probabilistically

Tier 4
Probabilistic computation

Net benefit < 0 advise reference
Net benefit > 0 advise alternative

Reference scenario
Alternative scenario

Stop: advise reference
Stop: advise alternative

no benefit
no risk

risks clearly dominates benefits
benefits clearly dominates risks

relatively small uncertainties

large uncertainties

Δ Health units

BRAF0
Problem formulation

• Set the scope and limitations of the assessment

• Describe reference and alternative scenario

• Iterative process

• Interaction with policymaker, risk assessor, maybe other stakeholders
Question

• Does scenario A, or B, C… result in net health gains or losses compared with the reference scenario?

• Is one alternative better than another, considering health only?

• Scenarios can be refined or updated as more information becomes available from tiers 1 and 2.
Scenario

• Reference scenario
  - Current
  - Business-as-usual
  - Hypothetical no-exposure

• Alternative scenario
  - Potential policy
  - Best-case, worst-case
Scenario

- The risk factor(s) under consideration
- The (sub) population
- The exposure

- Intake distributions
  - Habitual intake
  - Depending on age, sex, …
  - including background exposure
  - body burden, accumulation
  - potential substitutions

Pre-assessment and problem formulation

Reference scenario
Alternative scenario
Screening

• Genuine risk-benefit question?
• Can it be answered already?*
  • Worst/best case assumptions

• The alternative scenario introduces changes in both risks and benefits
  • More risk, more benefit
  • Less risk, less benefit
  • Less risk, more benefit *
  • More risk, less benefit *

Stop
Perform either
Risk or
Benefit assessment
Dimensions

- Number of people involved (incidence)
- Severity of the health effects (disability weight)
- Duration (years lived with the disease) and induced extra mortality (years of life lost)

Assessed qualitatively or quantitatively, according to what is feasible & useful to reach a decision
Compare

• Describe risks and benefits
  • In all dimensions

• If either risks or benefits clearly dominates
  • In all dimensions
  • In those dimensions qualitatively judged to be the most important

• Stop

Tier 2 Qualitative evaluation
Net health computation

• DALY/QALY computation

Tier 3
Deterministic computation of common health metric

- worst/bad case analysis
- Sensitivity analysis
- Increasingly assessing more and more parameters probabilistically

Tier 4
Probabilistic computation

Net benefit < 0 advise reference
Net benefit > 0 advise alternative
**DALY**

*Disability Adjusted Life Years* is a measure of overall disease burden, expressed as the cumulative number of years lost due to ill-health, disability or early death.

\[
\text{DALY} = \text{YLD} + \text{YLL}
\]

- **YLD**: Years Lived with Disability
- **YLL**: Years of Life Lost

---

**Tier 3**

Deterministic computation of common health metric

- worst/bad case analysis
- Sensitivity analysis
- Increasingly assessing more and more parameters probabilistically

---

**Tier 4**

Probabilistic computation
How

• Combine
  • Exposure, intake distributions
  • Dose-response functions
  • Disease characteristics

• Resulting in
  • Incidence and mortality
  • DALY calculations

• Use e.g. QALIBRA: www.qalibra.eu
# Case studies

<table>
<thead>
<tr>
<th>Natural Foods</th>
<th>Dietary Intervention</th>
<th>Heat Processing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy</td>
<td>Folic acid</td>
<td>Acrylamide</td>
</tr>
<tr>
<td>Fish</td>
<td>Macronutrient</td>
<td>Benzo(a)pyrene</td>
</tr>
<tr>
<td></td>
<td>replacements</td>
<td>Heat Treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>of milk</td>
</tr>
<tr>
<td>Natural Foods</td>
<td>BENEFITS</td>
<td>RISKS</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
</tbody>
</table>
| **Farmed salmon** (ω-3 PUFA) | - lower risk of coronary heart disease  
- healthy development of foetuses and infants | **Farmed salmon** (dioxin/PCB, methyl-Hg)  
- cancer development  
- developmental changes in the foetus |
| **Soy protein** (isoflavones) | - reduced risk of prostate cancer  
- reduced risk of osteoporosis  
- reduced risk for CVD | **Soy protein** (isoflavones)  
- increased risk of breast cancer  
- effect on thyroid gland  
- sperm quality |
Natural Foods – Soy and Salmon

Problem formulation
What are the health effects if people consume more farmed salmon/soy protein instead of their current consumption?

Reference scenario
No intake of farmed salmon/soy protein

Alternative Scenario
200 g/week farmed salmon
25 g/d soy protein
Figure 1. Flow chart of the BRAFO tiered approach

Pre-assessment and problem formulation ➔ Reference scenario
                                         Alternative scenario

Tier 1
Identification and screening

Genuine RB question
yes ➔ no
risks clearly dominates benefits
benefits clearly dominates risks

Tier 2
Qualitative evaluation

no clear dominance ➔ Stop; advise reference
Stop: advise alternative

Net benefit < 0 advise reference
Net benefit > 0 advise alternative

Tier 3
Deterministic computation of common health metric

worst/bad case analysis
Sensitivity analysis
Increasingly assessing
more and more parameters
probabilistically

Tier 4
Probabilistic computation

large uncertainties

ΔQALY
Farmed salmon

Reference/policy scenario
Current intake of farmed salmon vs. increased intake of farmed salmon

Benefit-risk factor(s) under consideration
Natural food containing beneficial/adverse constituents

The population
Dutch general population

Exposure
Background exposure to beneficial/adverse constituents including n-3 LCPUFA, Hg, and PCB
Yes, benefits and risks are involved in comparing the scenarios of low/high intakes of farmed salmon.

**Benefits:**
CHD, cognitive functions

**Risks:**
Cancer, impaired infant development

**History of use:** Available for farmed salmon

**Epidemiological/clinical data:** Available for oily fish
Qualitatively weigh benefits against risks:

Requirements:
- Exposure of general population/subgroups (known for fish).
- Dose-response function for benefit/risk (CHD/cancer), but multiple benefits/risks to consider
- Assess magnitude of health effect (severity of disease)
- Assess number of individuals affected
- Estimate effects of variable contaminant concentrations

>>> With multiple benefits/risks no clear outcome from qualitative evaluation!
**Exposure estimation:** Worst case/best case possible for farmed salmon

**Health effects:** Incidence of CHD and cancer possible, infant development

**Dose-response-relationship:**
- Response must relate to a clinical endpoint which can be expressed in DALYs
- Possible for farmed salmon (CHD) but various benefit factors are effective.
- Variables to calculate DALYs (disease weight, time of onset, time of death) not available for the risk factors. Degree of uncertainties?

**Computation of health effects:**
- DALYs calculation with the QALIBRA tool
Outcomes at tier 3:
The alternative scenario (based on the benefit for CHD) results in a decreased number of DALYs.
Soy protein

Reference/policy scenario
Current soy protein intake vs. increased soy protein intake

Benefit-risk factor(s) under consideration
Natural food containing beneficial/adverse constituents

The population
Dutch general population

Exposure
Background exposure to beneficial/adverse constituents of isoflavones
Yes, benefits and risks are involved in comparing the scenarios of low/high intakes of soy protein.

**Benefits:**
CHD, osteoporosis, cancer,

**Risks:**
Cancer, cognitive functions, sperm quality

**History of use:**
Available for soy (soy protein)

**Epidemiological/clinical data:** Available for soy (soy protein)
Qualitatively weigh risks against benefits:

Requirements:
Exposure of general population/subgroups known.
Dose-response function for benefit/risk (CVD/cancer)
Assess magnitude of health effect
Estimate effects of isoflavones?

Benefit of increased soy protein intake outways risk!

Stop at level tier 2, advise alternative scenario
Conclusion for the case studies

• The application of the BRAFO methodology for the BRA of:
  - farmed salmon reported a reduction of DALYs for the alternative scenario (tier 3 level)
  - soy protein reported that the benefit of the alternative scenario significantly outweighs the risk (tier level 2)

• The BRAFO tiered approach methodology is suitable for the qualitative BRA of natural foods

• The quantitative BRA of the BRAFO methodology requires support from QALIBRA

• The quantitative BRA presents the overall outcome in one common scale (DALYs)

• BRA requires statistical data (incidence, etc.) from the population for which the BRA has to be done (mostly not available)
What do you need?

• A well formulated problem
• Expertise
  • Toxicology
  • Nutrition
  • Modelling
• Data
  • Exposure distributions, concentrations
  • Dose-response
  • Disease characteristics, incidences, weights, mortality
• Common Sense/brain
  • Follow the guidance document but think, use proxy data, short-cuts etc.
Overall Conclusions

• Problem formulation is essential

• Tiers are useful

• Data is often a problem
  • Dose-response in higher tiers
  • Converting animal experiments to human disease characteristics
  • Confounding in cohort studies, intakes poorly measured
Thank you

www.ilsi.eu