National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

RBA methods

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The starting point

- A (food & nutrition) Policy Question

- convert to intake/exposure scenarios

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

Basic concepts

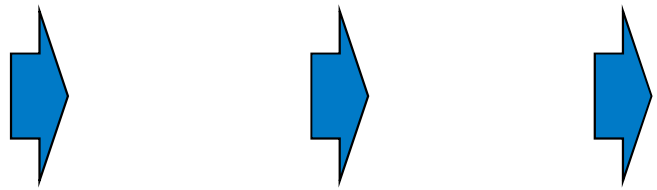
- reference exposure to assess against some alternative
- common health metric to compare different health effects
- tiered approach

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)



Basic method

substances or food of concern

adverse health effects
beneficial health effects

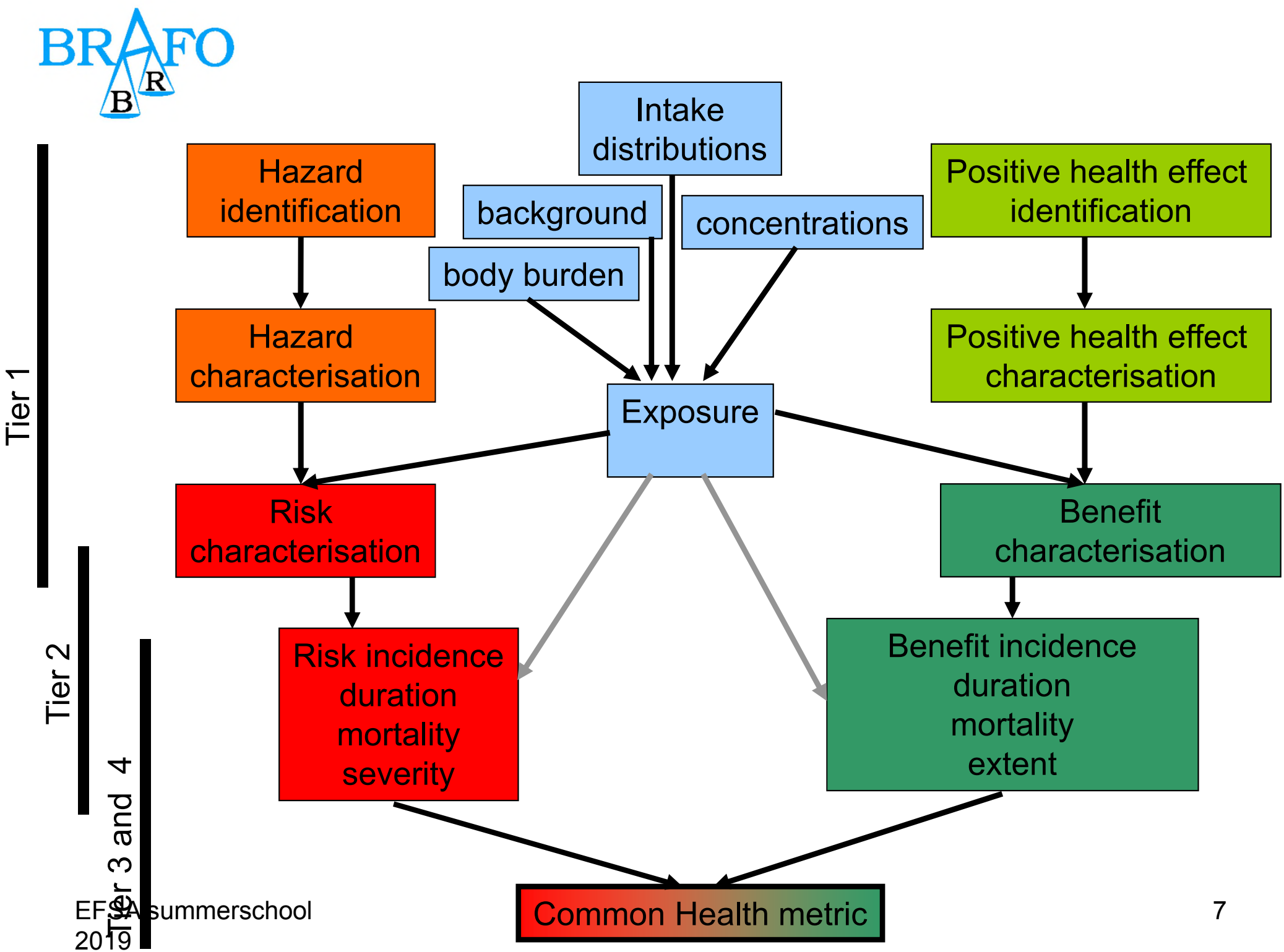
dose-response

intake reference vs.
alternative

extra and prevented cases
of different diseases and death

integrated
health metric

prefered scenario


Intake distributions
Hazard identification
background
concentrations
Positive health effect identification
body burden
Hazard characterisation
Positive health effect characterisation
Exposure
Risk characterisation
Benefit characterisation
Risk incidence duration mortality severity
Benefit incidence duration mortality extent
Common Health metric
Tier 1
Tier 2
Tier 3 and 4

Pre-assessment and problem formulation → **Reference scenario**
Alternative scenario

Tier 1
Characterisation & screening

- no benefit → **Stop: advise reference**
- no risk → **Stop: advise alternative**
- both risks and benefits ↓

Tier 2
Qualitative evaluation

- risks clearly dominates benefits → **Stop: advise reference**
- benefits clearly dominates risks → **Stop: advise alternative**
- no clear dominance ↓

Tier 3
Deterministic computation of common health metric

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

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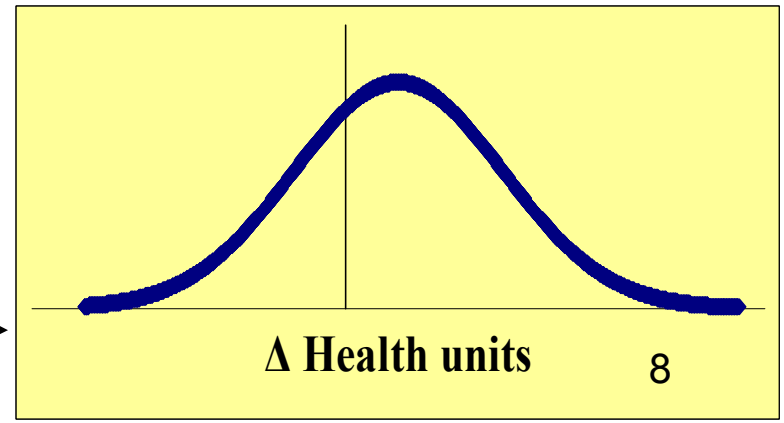
Tier 4
Probabilistic computation

- relatively small uncertainties → **Net benefit < 0 advise reference**
  Net benefit > 0 advise alternative
- large uncertainties →

BRAFO



Problem formulation

Pre-assessment and 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

Reference scenario
Alternative scenario

Question

Pre-assessment and problem formulation

- 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

Reference scenario
Alternative scenario

Pre-assessment and problem formulation

Scenario

- Reference scenario
  - Current
  - Business-as-usual
  - Hypothetical no-exposure
- Alternative scenario
  - Potential policy
  - Best-case, worst-case

- evaluate potential policies
- develop potential policies

Reference scenario
Alternative scenario

Scenario

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

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

Reference scenario
Alternative scenario

Tier 1
Identification and screening

Identification of risks and benefits

- Strength of the evidence (Human epi data)
  - e.g. WHO, WCRF criteria (convincing, probable)
  - Possible but high impact (uncertain)
- TDI/ADI thresholds (Animal experiments)
- Traditional and state-of-the-art risk assessment
  - most sensitive effect,
  - …
  - most severe effect

- Exclude from further assessment if you are confident
  - it is not relevant,
  - or will not occur

Stop
Perform either
Risk or
Benefit assessment

Tier 1
Identification and screening

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

Tier 2
Qualitative evaluation

- 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*

Tier 2
Qualitative evaluation

Compare

- Describe risks and benefits
  - In all four dimensions

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

Case studies

- Many stops in tier 1 & 2
- Not always a need for a common health metric
  - Plant sterols
  - Sweeteners

- Some case do need common health metric
  - Folic acid
  - Fish

Net health computation

- DALY/QALY computation

Tier 3
Deterministic computation of common health metric

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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

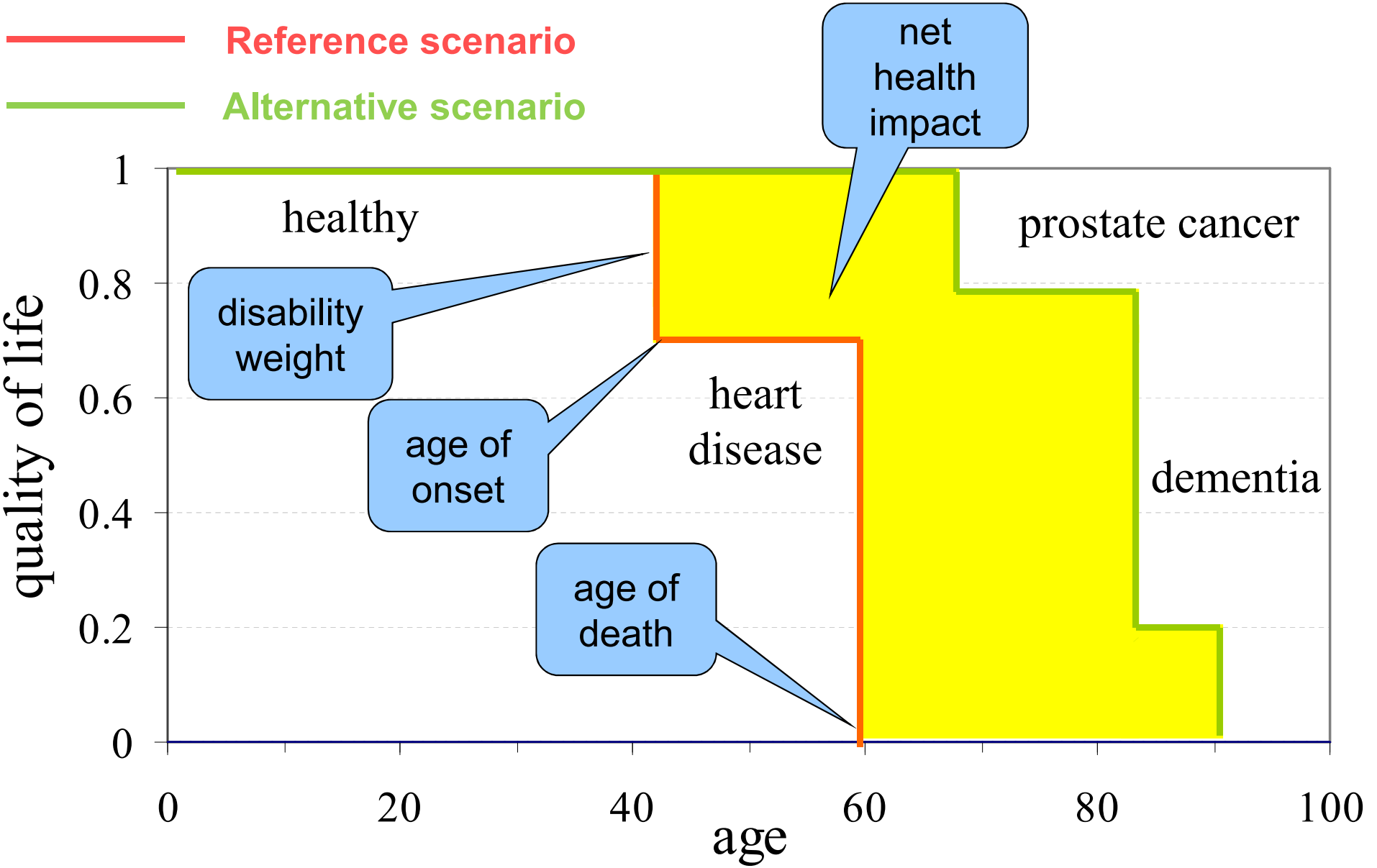
Integrated health metrics

Tier 3
Deterministic computation of common health metric

- DALY/QALY
- Combines mortality and morbidity
  - unit is time (years / healthy life years)
- Valuation of life with disease

- DALY = w YLD + YLL
  - YLH: Years Lived Healthy
  - w: disability weight
  - YLD: Years Lived with the Disease
  - YLL: Years of Live Lost through the disease

- DALY weights: WHO, IHME, global burden of disease studies


Reference scenario
Alternative scenario
net health impact
healthy
prostate cancer
disability weight
heart disease
age of onset
dementia
age of death
quality of life
1
0.8
0.6
0.4
0.2
0
0
20
40
60
80
100
age

How

- Combine
  - Exposure, intake distributions
  - **Dose-response functions**
    - › epi meta analysis
    - › convert animal experiments
  - Disease characteristics

- Resulting in
  - Incidence and mortality
  - DALY calculations

- Use e.g. QALIBRA: www.qalibra.eu

Tier 3
Deterministic computation of common health metric

---

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

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Tier 4
Probabilistic computation

Data needed

- Population info (age, sex, etc.)
- Intakes (reference & alternative)*
- Dose-response functions*
- Recovery probabilities*
- Mortality probabilities*
- Disease weights*
- Disease durations*
- Life expectancies

Tier 3
Deterministic computation of common health metric

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worst/bad case analysis
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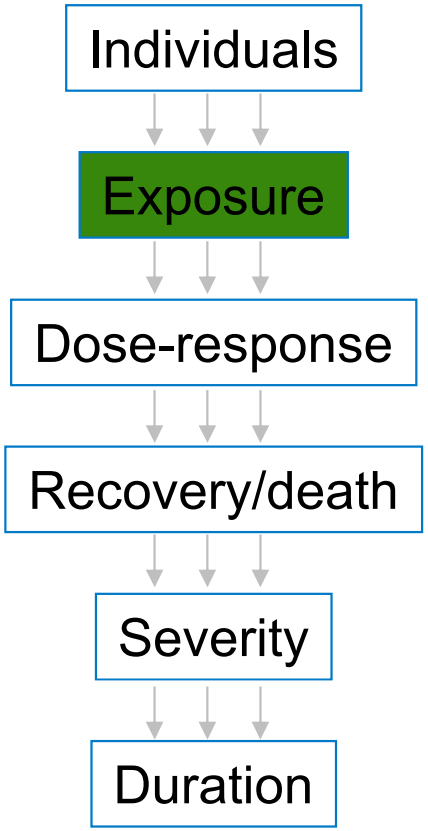
Tier 4
Probabilistic computation

* Needed for each health effect considered

Input data: exposure



- **Intake of chemical or food item** associated with a health effect
  - for Reference & Alternative scenarios
- **a single value**
  - (e.g. typical or worst case)
- **or a distribution**
  - for different subpopulations
- **usual intake, background exposure**
- **Can use output from existing dietary models (e.g. MCRA)**

exposure example: Salt

- Data
  - FFQ, Salt content per product, all scenarios
- Models
  - MCRA, spade
  - Salt intake distribution, depending on **age** and **sex**

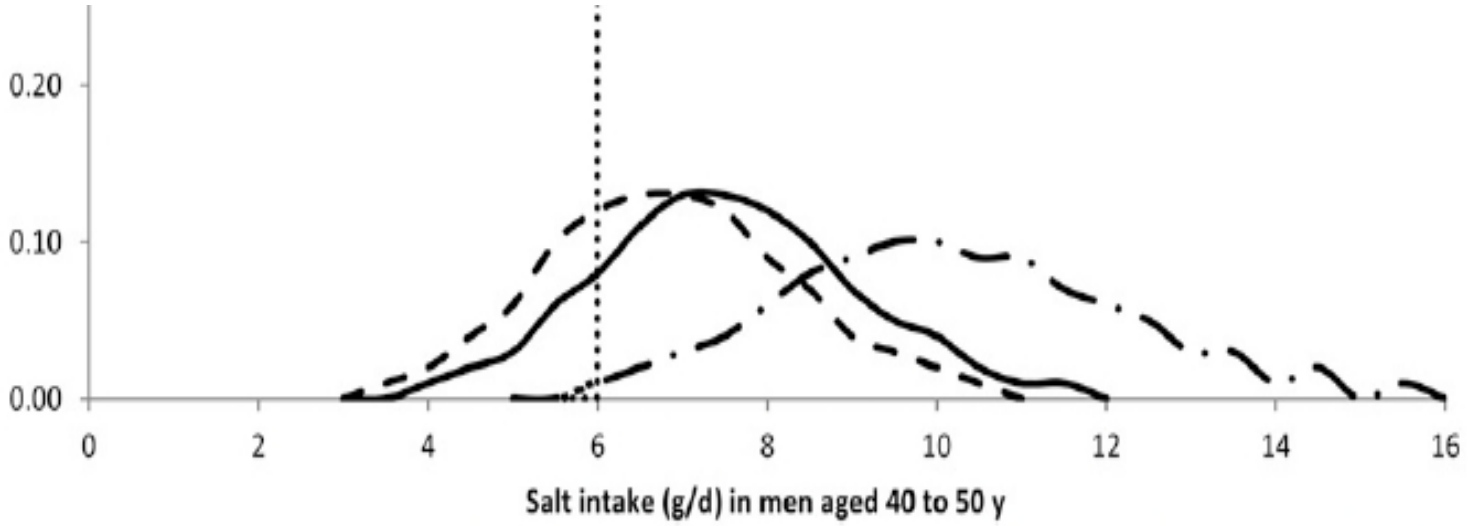


FIGURE 1. Distributions of salt intake in the current salt intake and the 3 salt-reduction scenarios in men aged 40–50 y.

Salt example: MCRA exposure, RBA input

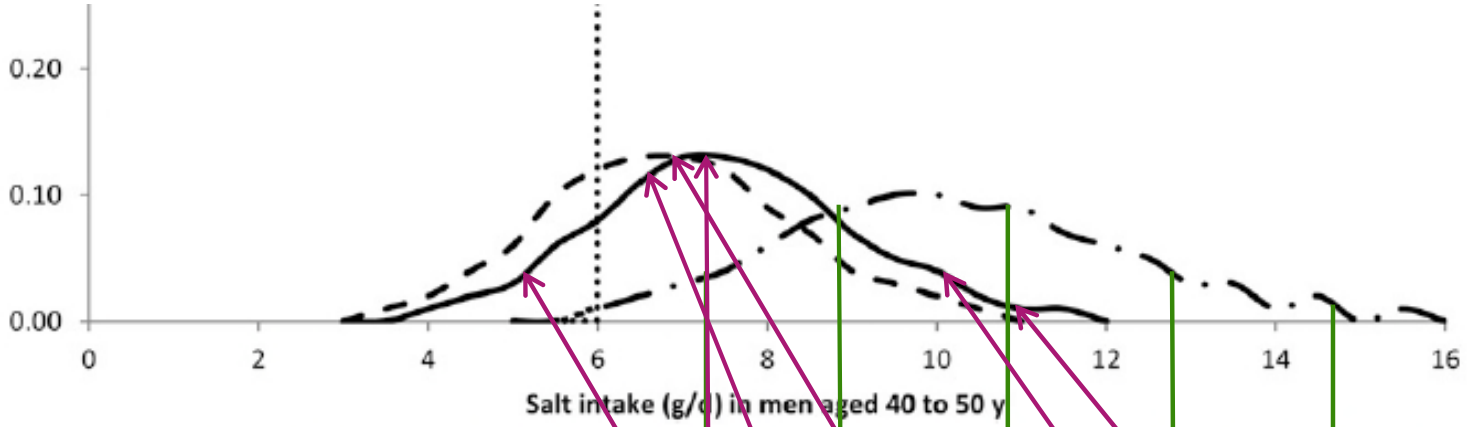
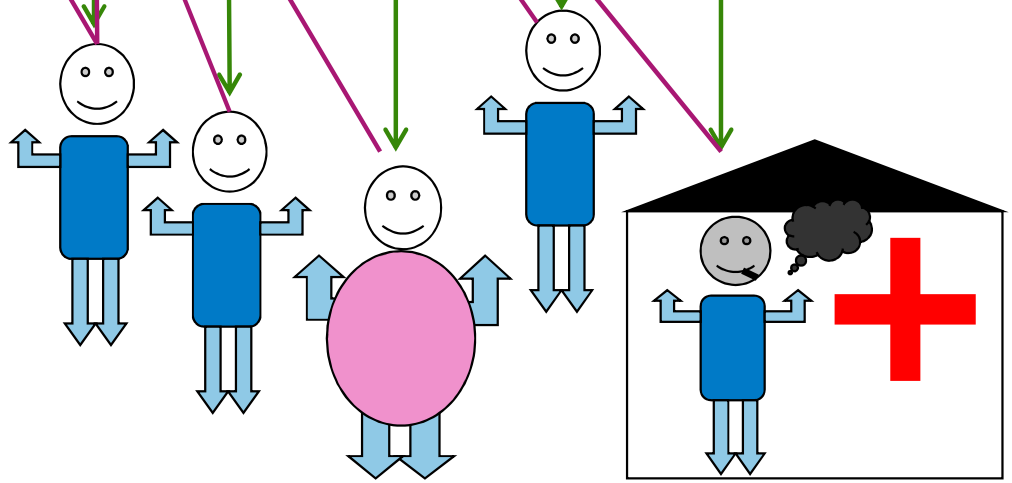
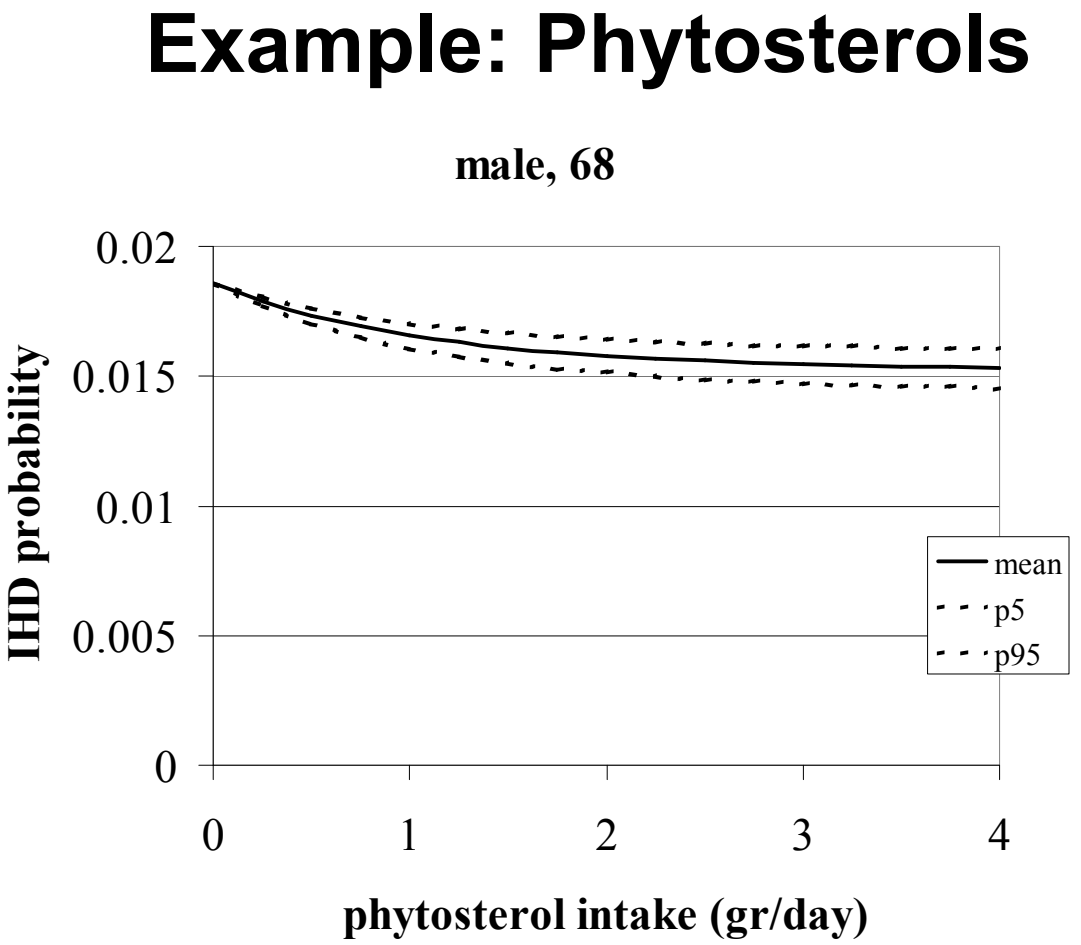


FIGURE 1. Distributions of salt intake in the current salt intake and the 3 salt-reduction scenarios in men aged 40–50 y.

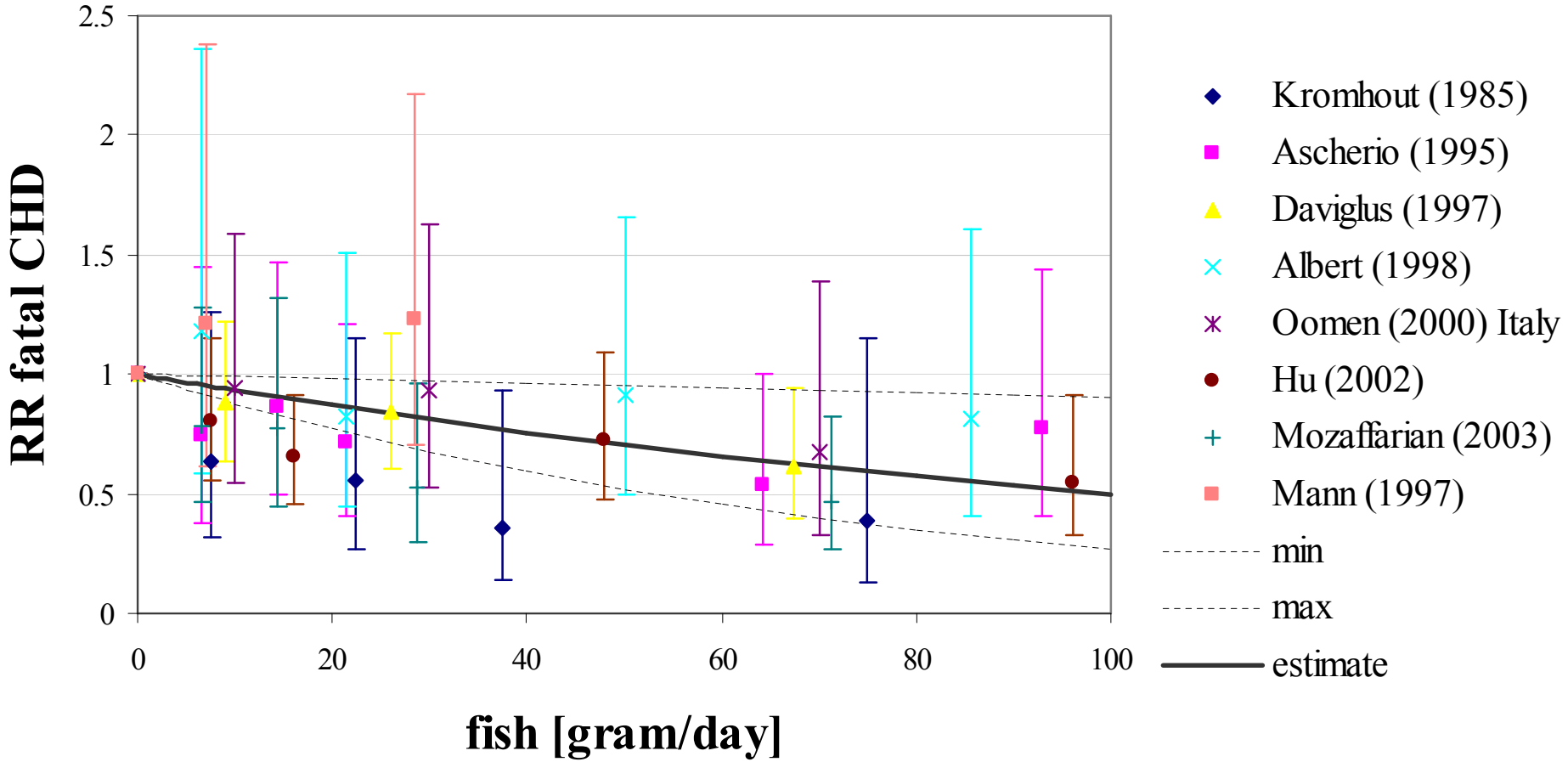


example: dose-response

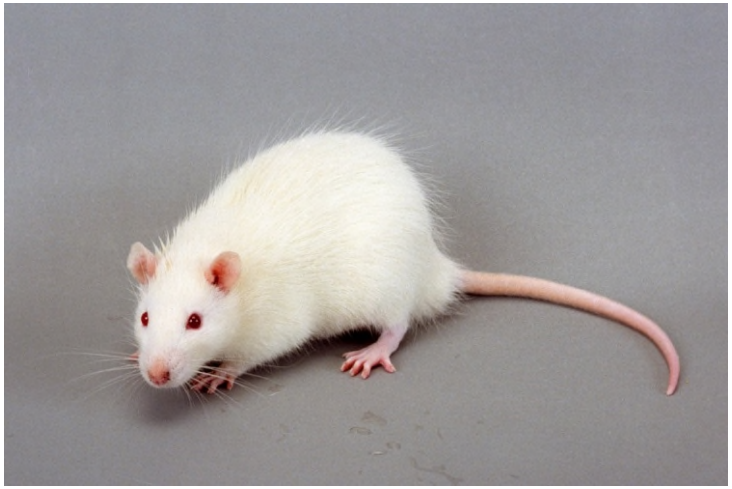
- Combine studies and data
  - Sterol intake → %LDL cholesterol reduction
  - Baseline LDL cholesterol level
  - Absolute LDL cholesterol reduction → reduction in IHD incidence
  - Baseline IHD incidence



dose-response example: fish vs. fatal CHD



example dose-response:
Dioxines, Spermcel production in offspring

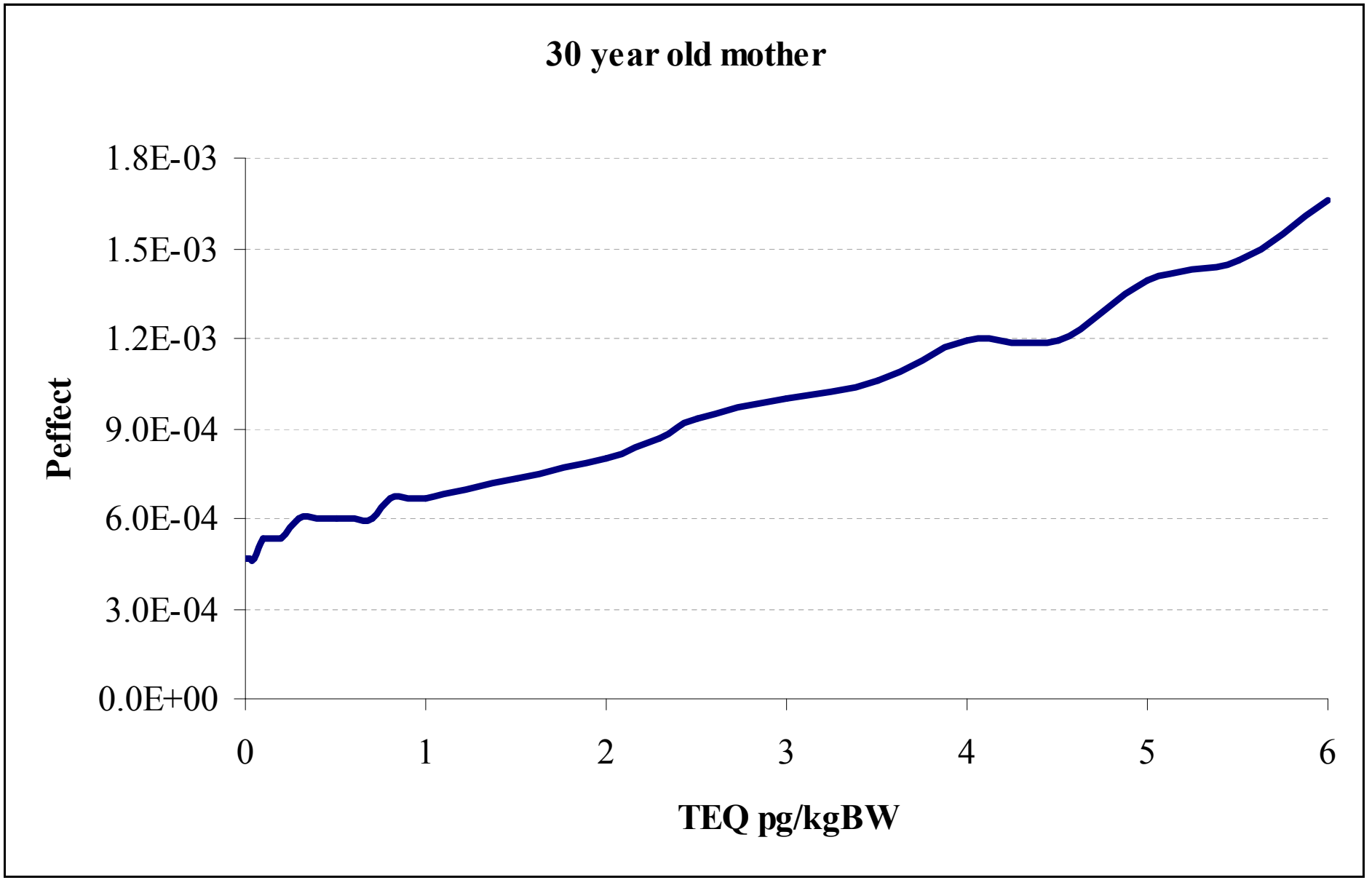


- Animal experiment

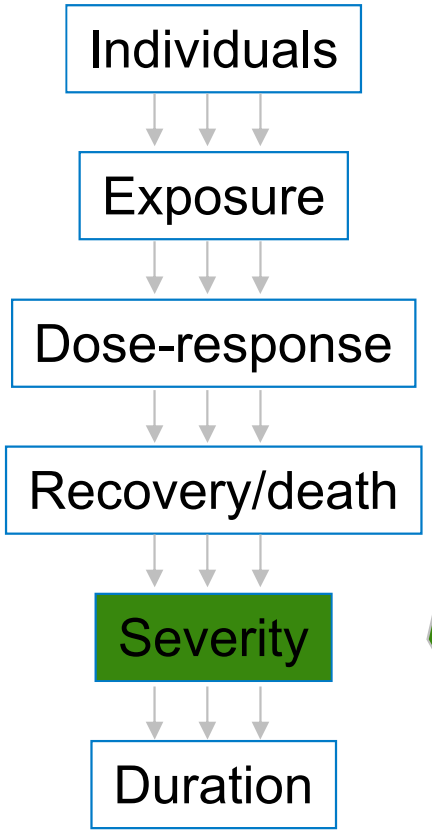
- Effect in sons of exposed mothers
- 15% reduction = infertile

- cumulative exposure

- Probability of having a child (depends on age)
- Probability it is a son 51%, CBS

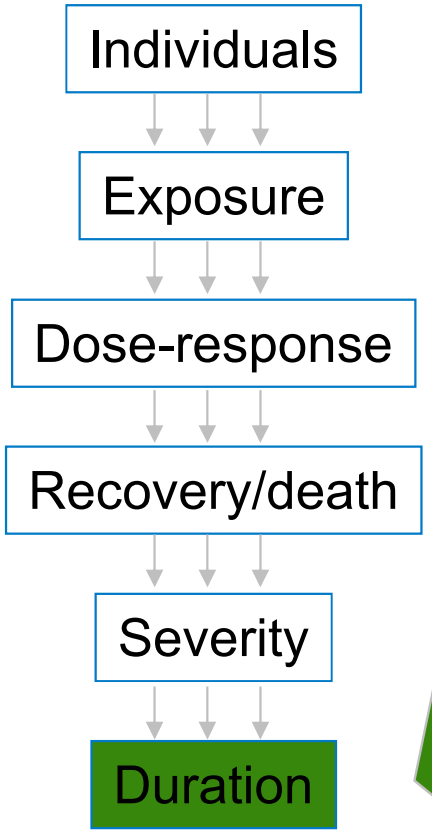

30 year old mother
1.8E-03
1.5E-03
1.2E-03
9.0E-04
6.0E-04
3.0E-04
0.0E+00
Peffect
0
1
2
3
4
5
6
TEQ pg/kgBW

health effects: severity



- **DALY or QALY weights** available from published sources (e.g. WHO)
- **Usually a single number**, but:
  - may differ for those who recover or die
  - may depend on age, sex, etc.
  - may depend on intake
  - may be a function of a continuous effect (e.g. IQ)
- **Complications:**
  - national differences
  - disease with >1 stage or level of severity
  - uncertain for animal endpoints

Health effects: duration



- **Duration of health effect**
  - e.g. from national statistics
- **Often a single number**, but:
  - may differ for those who recover/die
  - may depend on age, sex, etc.
  - may depend on intake
- **Complications:**
  - may depend on cause
  - uncertain for animal endpoints

What do you need?

- A well formulated problem
- Expertise
  - Toxicology, microbiology
  - Nutrition
  - Modelling
- Data
  - Exposure distributions, concentrations
  - Dose-response
  - Disease characteristics, incidences, weights, mortality
- Common Sense
  - Learn from examples, follow guidance documents, use proxy data, short-cuts etc.

What makes risk-benefit difficult?

! Interaction with problem owner

- A well formulated problem
- Expertise
  - Toxicology, microbiology
  - Nutrition
  - Modelling
- Data
  - Exposure distributions, concentrations
  - Dose-response
  - Disease characteristics, incidences, weights, mortality
- Common Sense
  - Learn from examples, follow guidance documents, use proxy data, short-cuts etc.

Learning by doing, work in teams

YES

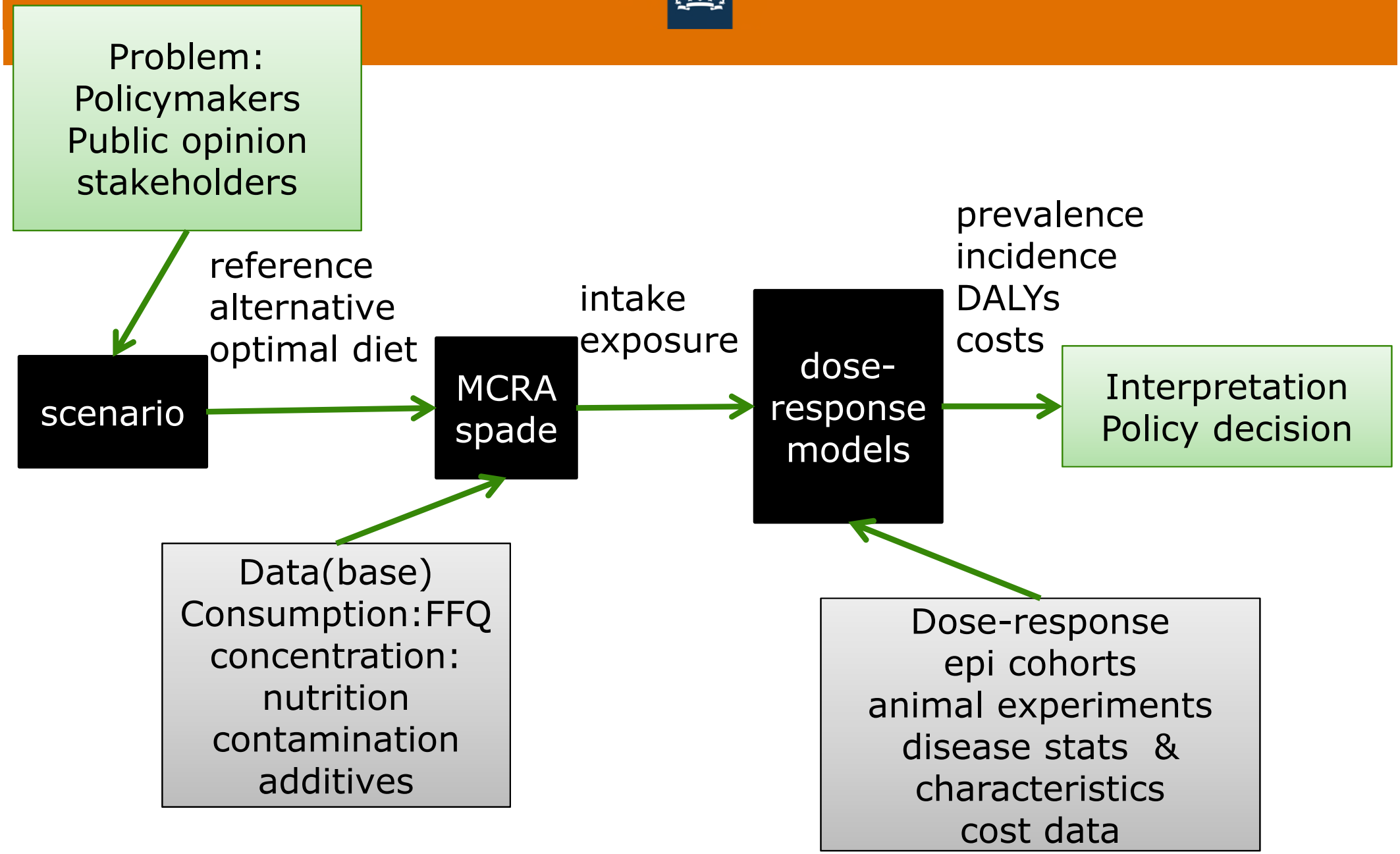
Partial solution to the data problem

Conclusions

- Tiers are useful
  - Many case studies stop before tier 3
  - But not all

- Problem formulation is essential

- Data is often a problem
  - Dose reponse in higher tiers
  - Converting animal experiments to human disease characteristics
  - Confounding in cohort studies, intakes poorly measured, not a controlled experimental setting


Problem:
Policymakers
Public opinion
stakeholders
reference
alternative
optimal diet
scenario
MCRA
spade
intake
exposure
dose-
response
models
prevalence
incidence
DALYs
costs
Interpretation
Policy decision
Data(base)
Consumption:FFQ
concentration:
nutrition
contamination
additives
Dose-response
epi cohorts
animal experiments
disease stats &
characteristics
cost data

Thank you