SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

Complexities in Evaluating Human Clinical and Observational Data for Ingredient Safety Assessment: Partially Hydrogenated Oils As a Case Study

November 7, 2014

Dose-Response Assessment Approaches to the Analysis of Noncancer Health Effects: *Current Practices, Advice from the National Academies, and 2014 WHO/IPCS Guidance*

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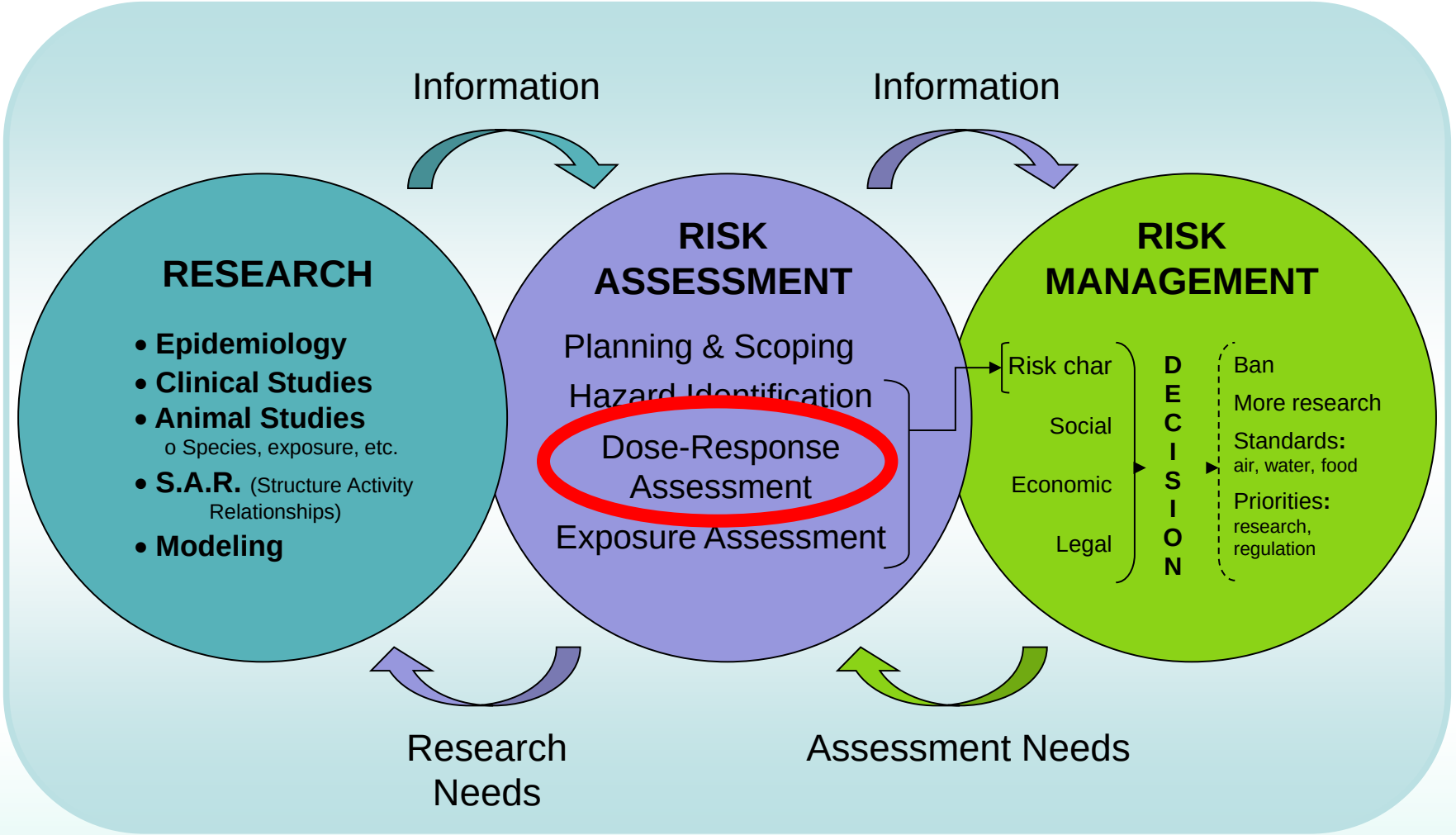
Outline

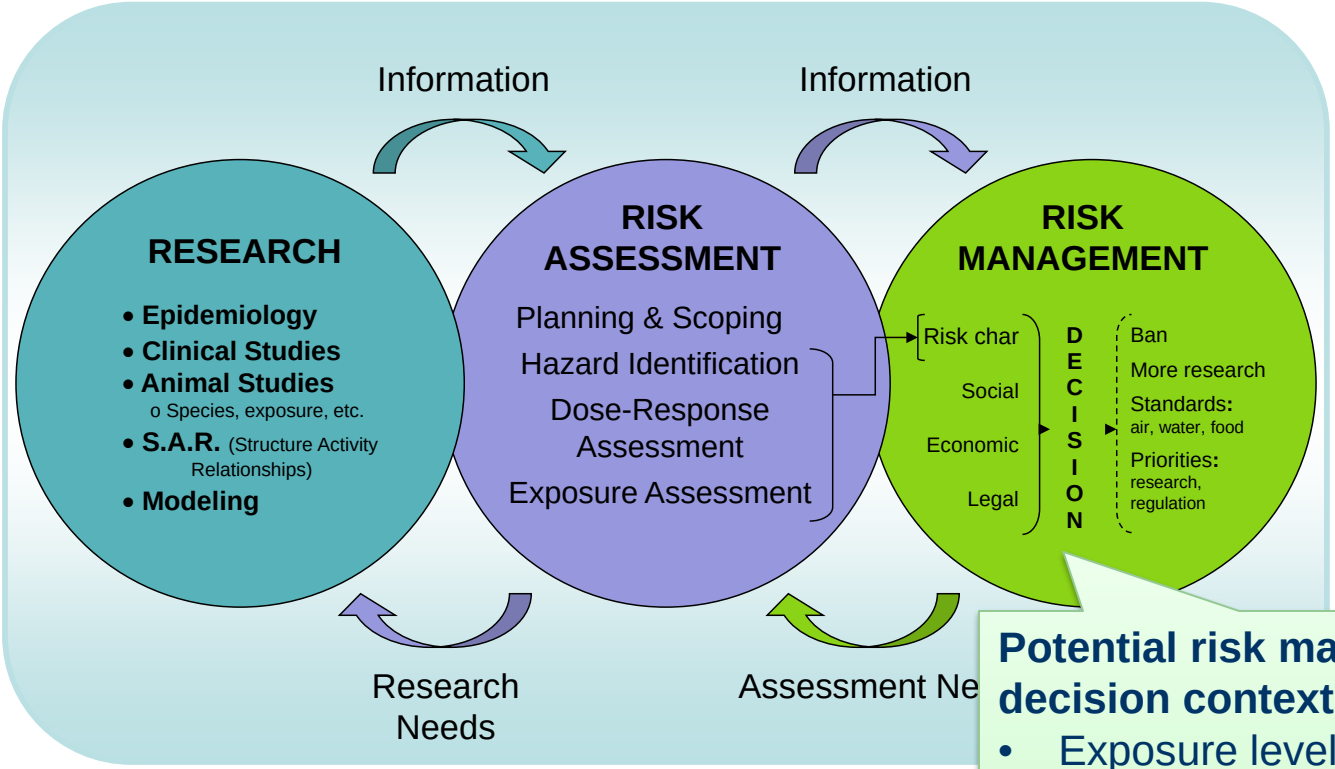
- Examples of current approaches for noncancer:
  - Reference Values
  - Residual Risk/Economic Benefits Analysis
- Recent (and not so recent) advice from the National Academies on dose-response assessment.
- Unified probabilistic framework for dose-response assessment from 2014 WHO/IPCS guidance.

- For each approach – issues in applying to PHOs.

Dose-Response Assessment in Context



What is the risk management decision context?



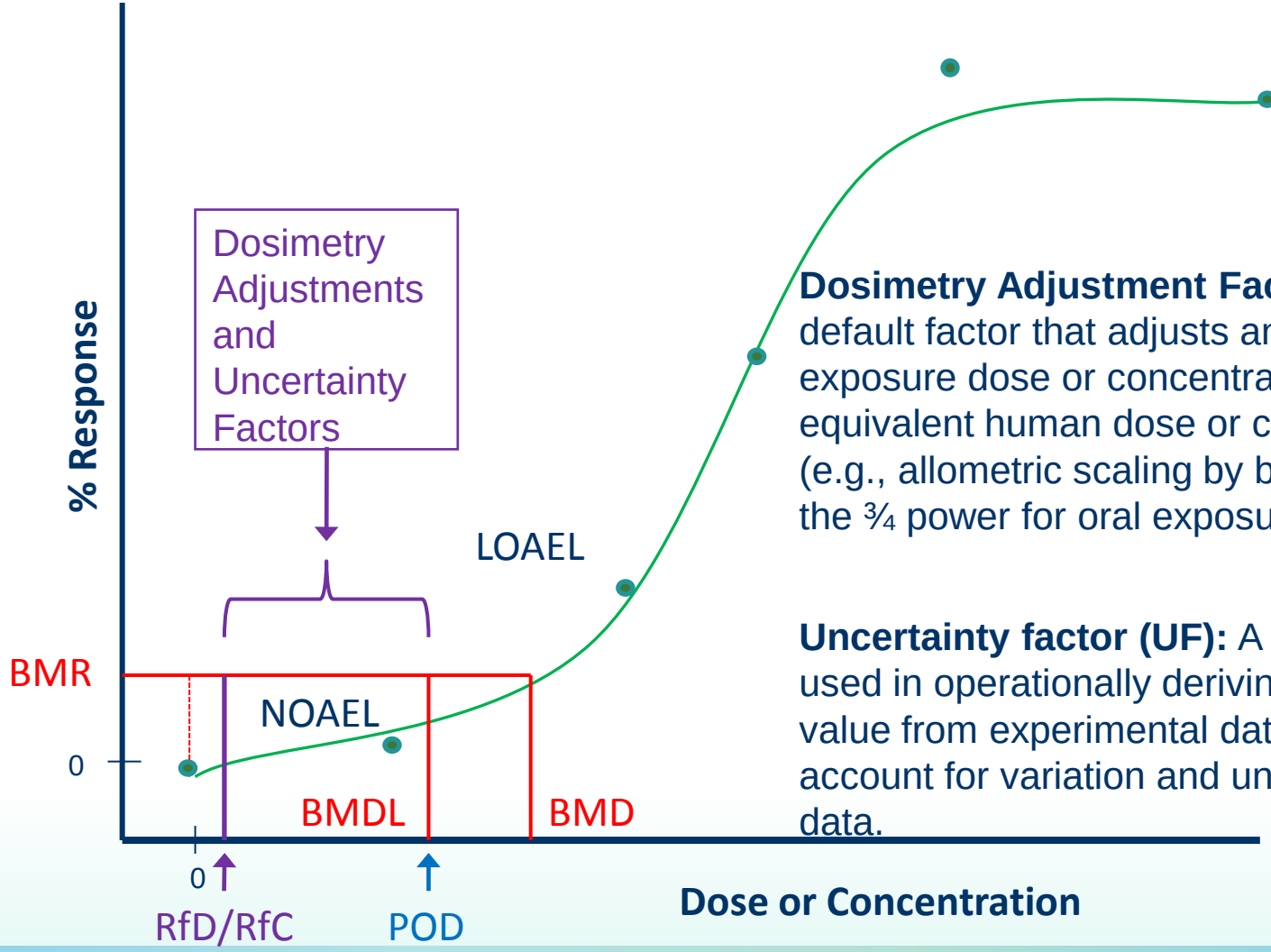
Potential risk management decision contexts:

- Exposure level "likely to be without appreciable risk?"
- Residual risk at current exposure levels?
- Economic benefit-cost of different exposure levels?

Current Practices for Noncancer Dose-Response Assessment in EPA's IRIS Program

- **Hazard Identification** identifies endpoints and effects where there is credible evidence of human health hazard.
- **Dose-Response Assessment** derives toxicity values for the human health hazards identified:
  - Select studies/endpoints suitable for dose-response analysis (including consideration of mode of action),
  - Derive point of departure (POD),
  - Apply dosimetry adjustments and uncertainty factors to derive RfD and/or RfC.
- **Methodology focuses on deriving a deriving an exposure "likely to be without appreciable risk" at the individual level.**

Points of Departure, Dosimetry Adjustments and Uncertainty Factors



Dosimetry Adjustment Factor (DAF): A default factor that adjusts an animal exposure dose or concentration to an equivalent human dose or concentration (e.g., allometric scaling by body weight to the ¾ power for oral exposures).

Uncertainty factor (UF): A default factor used in operationally deriving a reference value from experimental data intended to account for variation and uncertainty in the data.

Reference Dose or Concentration

- $POD_{HED\ or\ HEC}$ =
  (LOAEL or NOAEL or BMDL or BMCL) × DAF
- Uncertainty factors (some of which are =1)
  - UF_H = Human variability
  - UF_A = Animal-to-human extrapolation
  - UF_S = Subchronic-to-chronic extrapolation
  - UF_L = LOAEL-to-NOAEL extrapolation
  - UF_D = Database deficiencies
  - UF = "Composite" or "Total" uncertainty
    ($UF_H \times UF_A \times UF_S \times UF_L \times UF_D$)
- RfD or RfC =
  $POD_{HED\ or\ HEC} \div UF$

Can replace with chemical-specific, data-derived factors (CSAFs or DDEFs)

Reflect limitations in the available dataset (replace with "better" study)

Key issues for deriving an RfD for PHOs

PHOs in food → TFA ingestion → ↑ VLDL, ↑ LDL, ↓ HDL → Risk of myocardial infarction

TFA ingestion → Other mechanisms/ biomarkers (known and unknown) → Risk of myocardial infarction

What endpoint is the "key event" for conducting dose-response assessment (necessary precursor, explaining all subsequent toxicity)? LDL? HDL? Ratio? Earlier precursor?

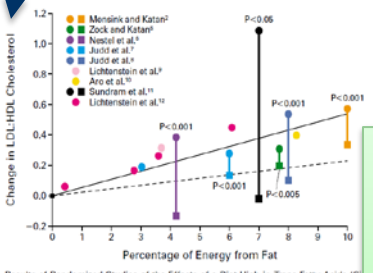
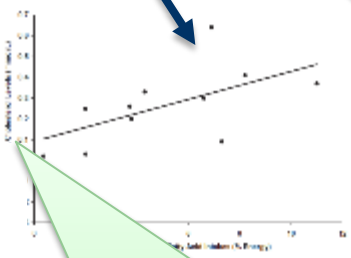


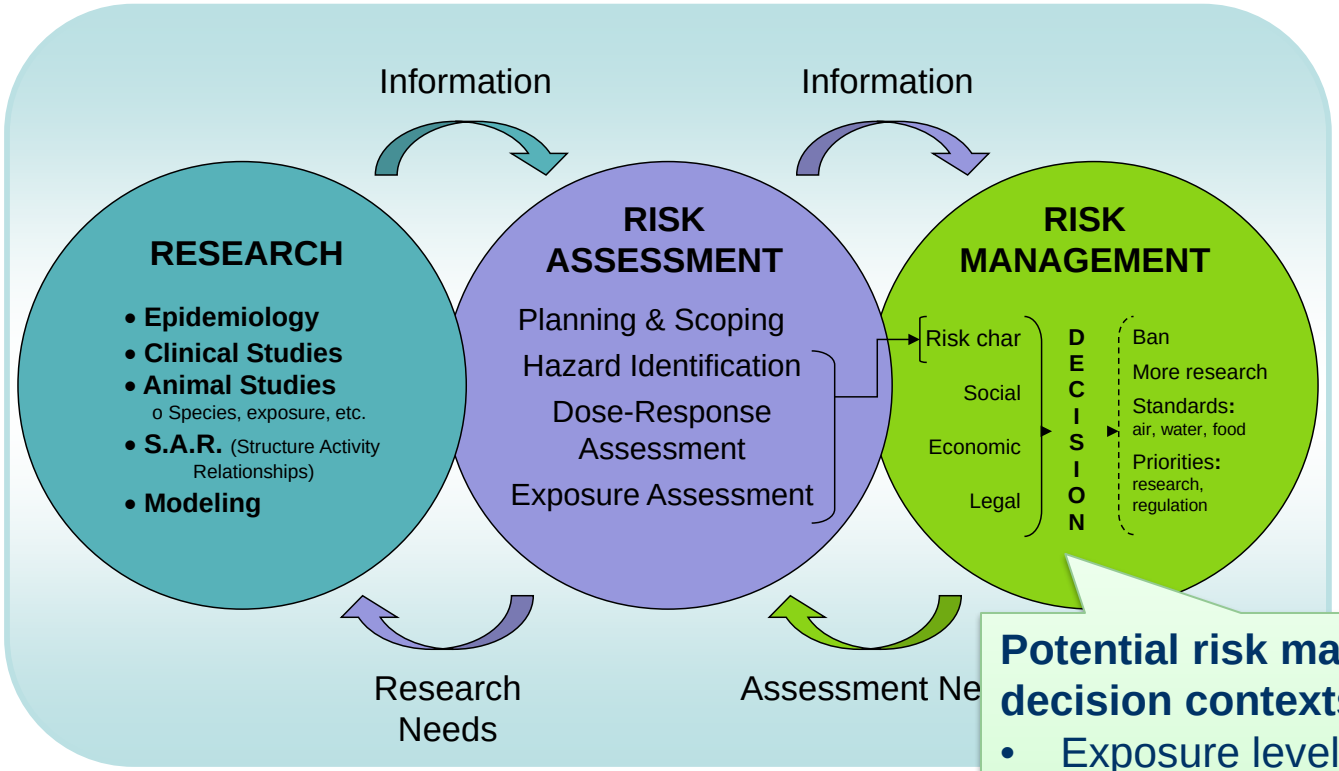
Figure 1. Results of Randomized Studies of the Effects of a Diet High in Trans Fatty Acids (C... Saturated Fatty Acids (Squares) on the Ratio of LDL Cholesterol to HDL Cholesterol.
A diet with isocaloric amounts of cis fatty acids was used as the comparison group. The soli... dicates the best-fit regression for trans fatty acids. The dashed line indicates the best-fit regre... saturated fatty acids.



What level of effect is "likely to be without appreciable risk?" 10%? 5%? 1%? 0.1%?

Do effects on serum lipids explain all the cardiovascular toxicity of TFAs?

Different dose-response methodology needed for other contexts



Potential risk management decision contexts:

- Exposure level "likely to be without appreciable risk?"
- Residual risk at current exposure levels?
- Economic benefit-cost of different exposure levels?

Current Practices for Noncancer Dose-Response Assessment of Air Pollution

- **Hazard Identification** results in a determination of endpoints/effects causally associated with air pollutant exposure.
- **Dose-Response and Economic Benefits Assessments**
  - Identifies studies suitable for modeling concentration-response relationships
  - Derives health-impact function (change in incidence of effects as a function of change in air quality)
  - For endpoints that can be assigned economic monetary value, estimates monetized economic benefits of change in incidence.
- **Focused on comparison among options of impact of exposure at the population level.**

Epidemiologic studies inform the magnitude of risk in the population

Changes in air pollution exposure (over space or time)

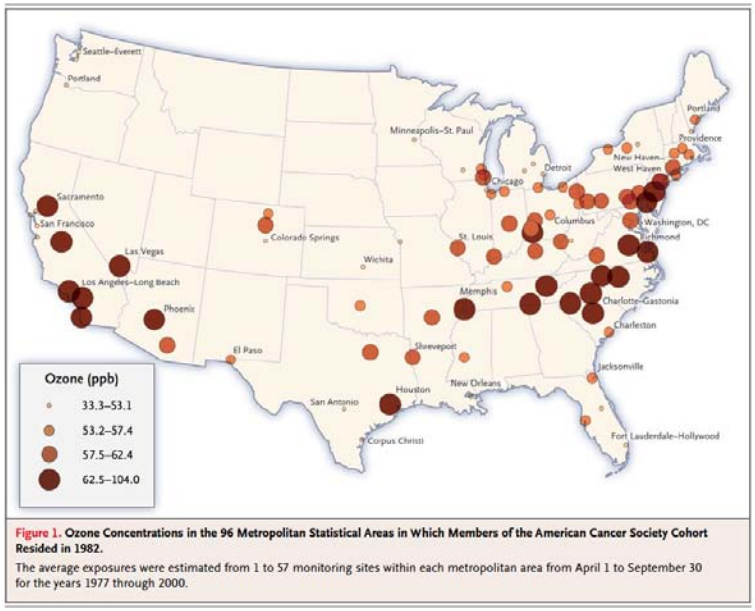
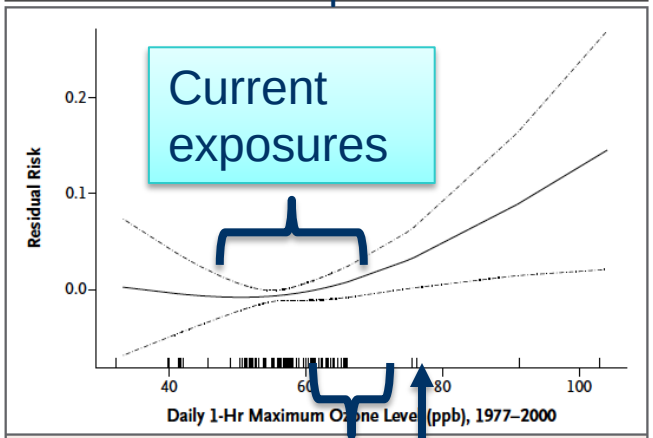


Figure 1. Ozone Concentrations in the 96 Metropolitan Statistical Areas in Which Members of the American Cancer Society Cohort Resided in 1982.

The average exposures were estimated from 1 to 57 monitoring sites within each metropolitan area from April 1 to September 30 for the years 1977 through 2000.

Concentration-response relationship



Current exposures

Figure 2. Exposure–Response Curve for the Relation between Exposure to Ozone and the Risk of Death from Respiratory Causes.

The curve is based on a natural spline with 2 df estimated from the residual relative risk of death within a metropolitan statistical area (MSA) according to a random-effects survival model. The dashed lines indicate the 95% confidence interval of fit, and the hash marks indicate the ozone levels of each of the 96 MSAs.

Current ozone standard

Revised standards being considered

Data can be “interpolated” to estimate the health impact (and economic benefits) of options for revising standard.

Adapted from slide by Neal Fan

Similarities with the case of PHOs

Within the range of observation, data could be "interpolated" to estimate the health effects (and economic benefits) of different exposure levels (including current exposures).

How would various risk management intervention options change exposure?

Current U.S. exposures

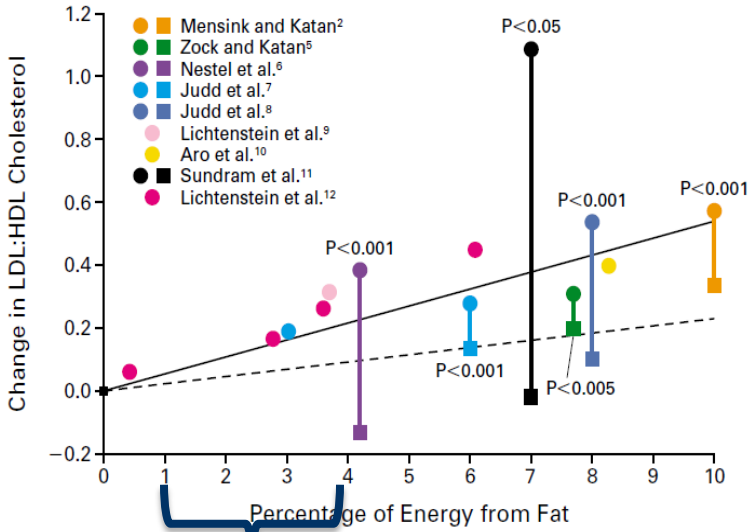


Figure 1. Results of Randomized Studies of the Effects of a Diet High in Trans Fatty Acids (Circles) or Saturated Fatty Acids (Squares) on the Ratio of LDL Cholesterol to HDL Cholesterol.

A [illegible] fatty acids was used as the comparison group. The solid line in- [illegible] s fatty acids. The dashed line indicates the best-fit regression for

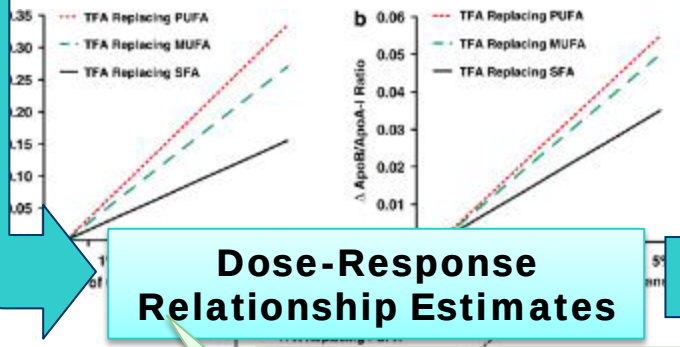
Approach has been used in many analyses of policy options

Meta-analysis of clinical trials

European Journal of Clinical Nutrition (2009) **63,** S22–S33; doi:10.1038/sj.ejcn.1602976

Quantitative effects on cardiovascular risk factors and coronary heart disease risk of replacing partially hydrogenated vegetable oils with other fats and oils

D Mozaffarian[1,2] and R Clarke[3]



Dose-Response Relationship Estimates

No need for low-dose extrapolation if we are in the range of the observed data ("interpolating," not extrapolating).

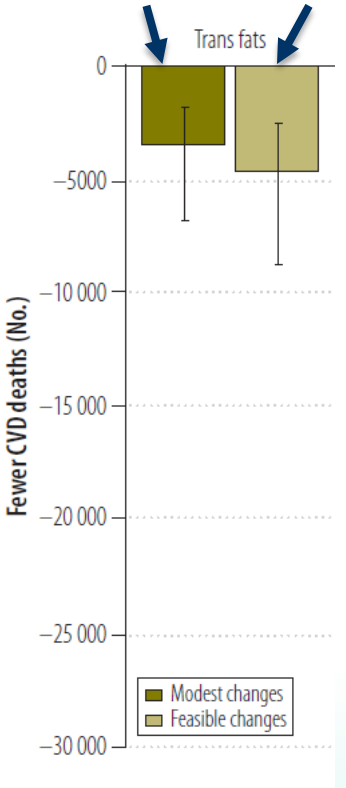
Model to Estimate of Impact of Policy Interventions

Bull World Health Organ. 2012 Jul 1;90(7):522-31. doi: 10.2471/BLT.11.092643. Epub 2012 Apr 12.

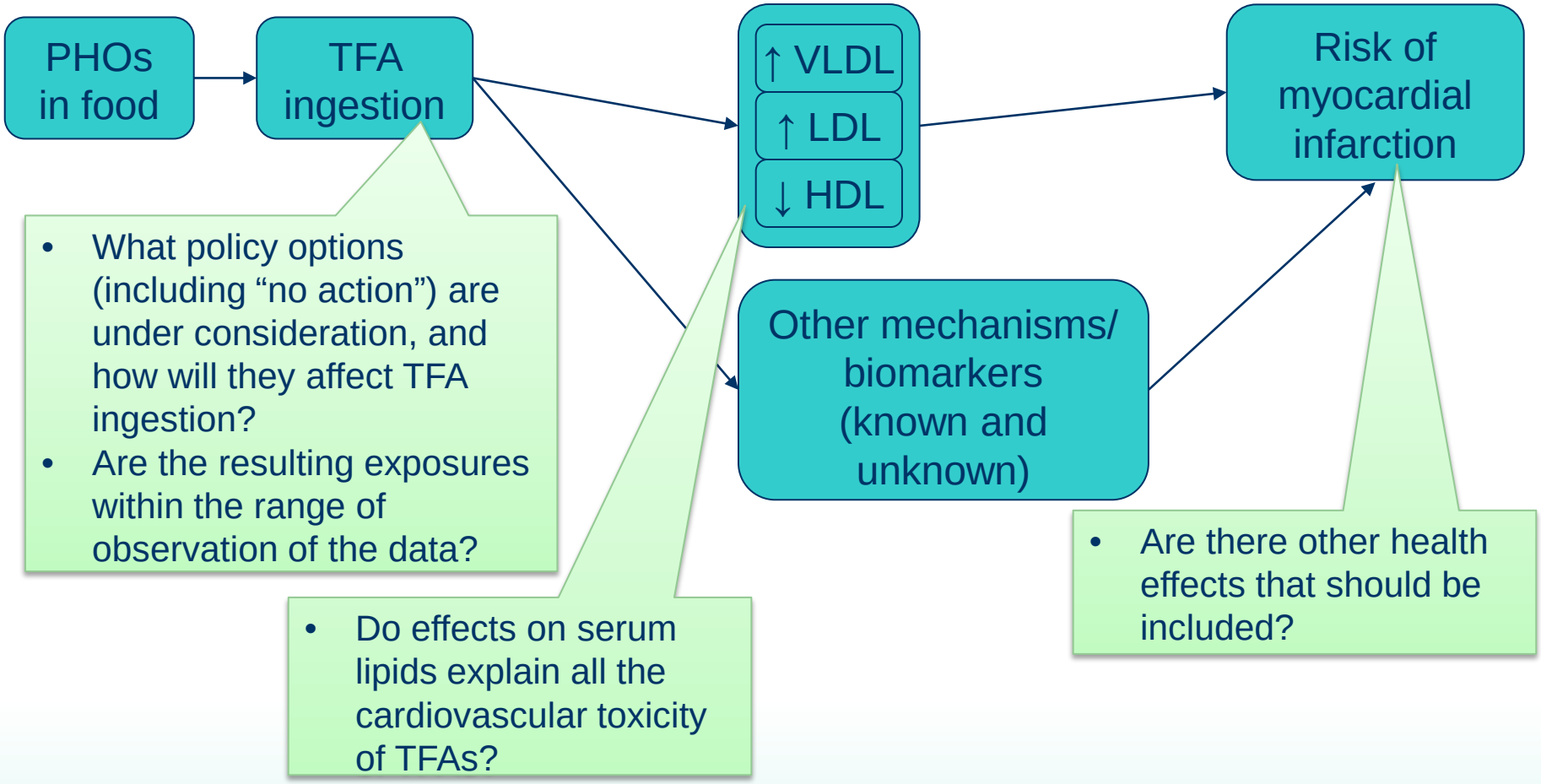
Potential cardiovascular mortality r eductions with stricter food policies in the United Kingdom of Great Britain and Northern Ireland.

O Flaherty M[1], Flores-Mateo G, Nnoaham K, Lloyd-Williams F, Capewell S.

Reduce by 0.5% or 1%



Key issues for supporting “residual risk” and economic benefits for PHOs



Comparison

RfD/RfC approach

- Purpose is to estimate an exposure at which effects would likely not occur.
- Usually based on animal toxicology.
  - Uncertainty factors used to extrapolate across and within species.
  - Effects at different exposure levels are not estimated.

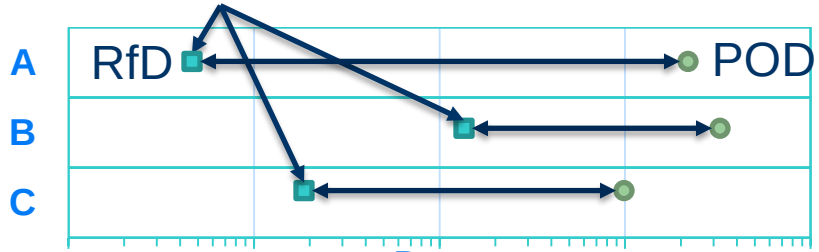
"Residual risk"/economic benefits approach

- Purpose is to estimate change in effects with change in exposure.
- Usually based on human data.
  - In the relevant species
  - If in the relevant exposure range, no need for low-dose extrapolation.
  - Provides estimates of effects at different exposure levels.

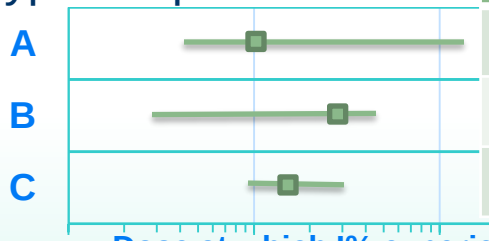
Reference values provide a limited characterization of uncertainty

- Uncertainty factors are not just "uncertainty"
  - Mixture of adjustment, uncertainty, and variability
  - Presumed to be "conservative"
- "Compounding conservatism" could arise from multiplying factors
- Some decision contexts benefit from more than just the "conservative" bound
  - Choosing among alternatives
  - Allocating resources
  - Economic benefits analyses
  - Residual risk / "risk above RfD"

"No appreciable risk"
(same % confidence?)



Ranking from different types of prioritization:

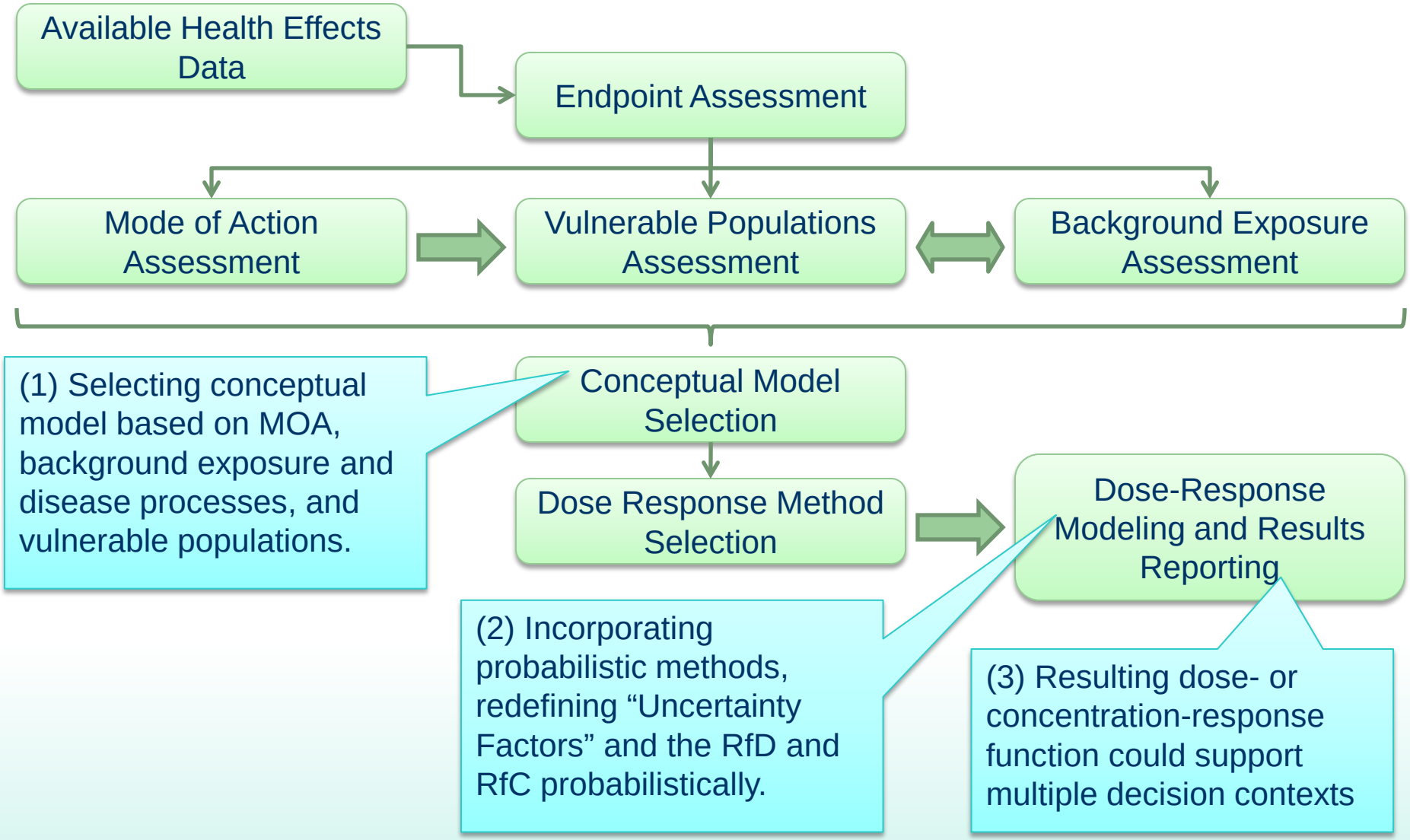


Lower bound	Central Estimate	Range
2	1	3
1	3	2
3	2	1

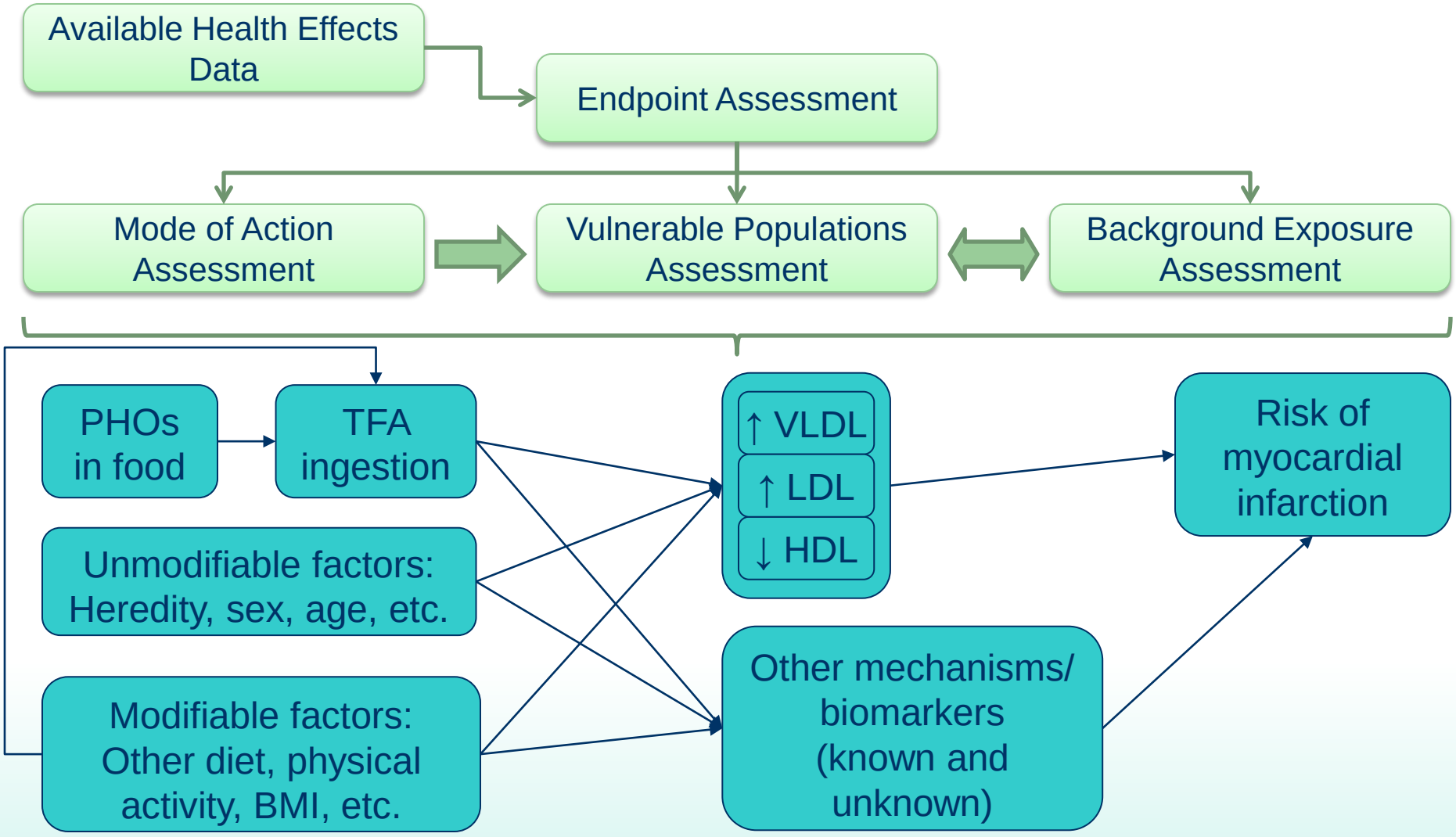
NAS/NRC recommendations for advancing dose-response

- *Science and Judgment* report (NRC, 1994) recommended presenting quantitative representation of uncertainty.
- *Science and Decisions* report (NRC, 2009) recommended incorporating
  - Mode of action, vulnerable populations, background exposures, and
  - Probabilistic methods for assessing uncertainty.
- *Review of the IRIS Program* report (NRC, 2014) recommended systematic use of uncertainty analysis and expanded use of Bayesian methods.
- All recommendations caveated with considerations as to "feasibility" and "fit-for-purpose."

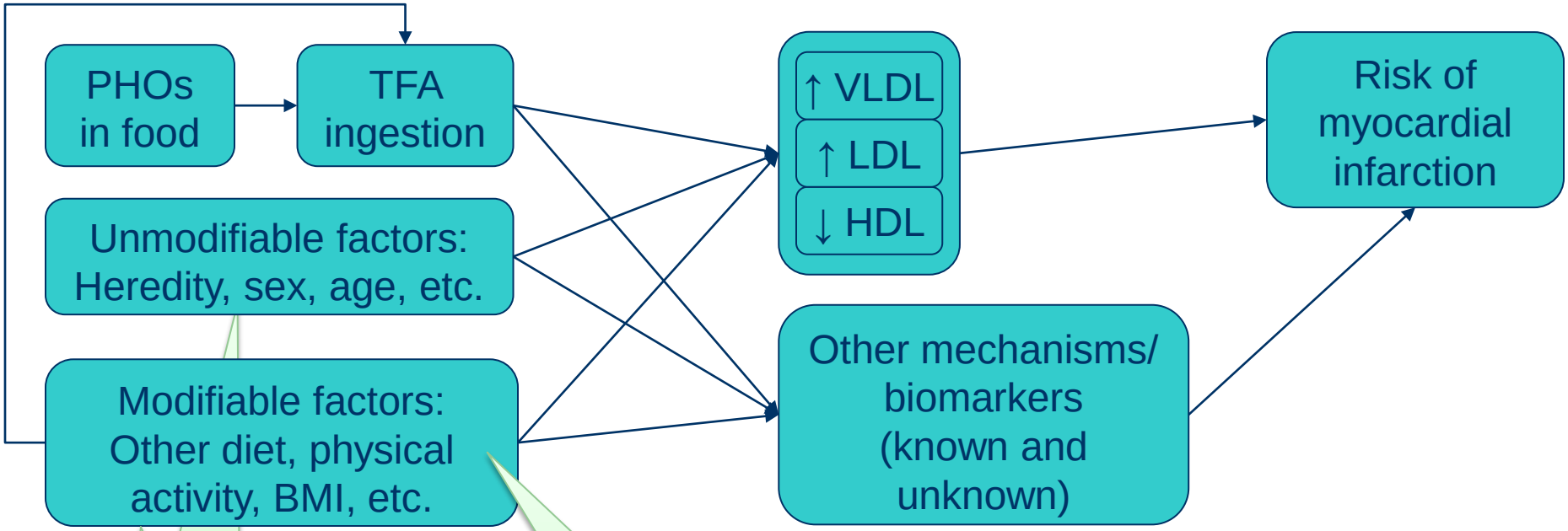
Science and Decision's "Unified Approach" to Dose-Response Assessment



Application of MOA, vulnerable populations, and background assessment to PHOs



Issues in application to PHOs

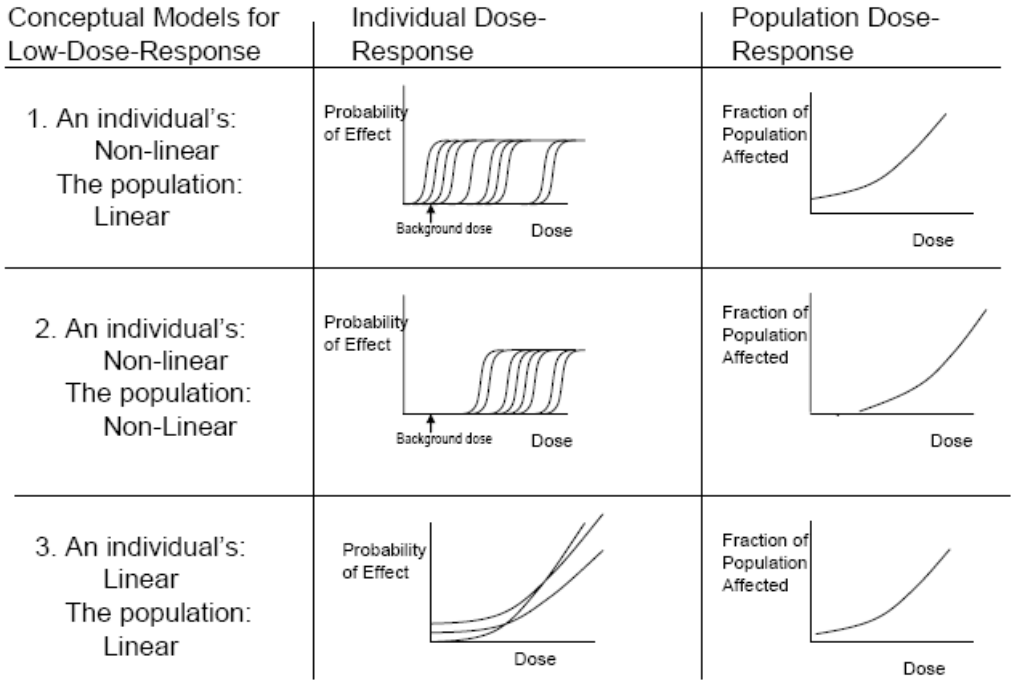


- What factors modulate an individual's dose-response relationship for TFAs?

- How can background exposures (to TFAs and/or other risk factors) be addressed quantitatively?

Issues in implementing subsequent steps from *Science and Decisions*

- NRC (2009) conceptual models focused on quantal endpoints, but many noncancer effects (e.g., serum lipids) are continuous endpoints.



- Prominent recommendation of linear extrapolation as a "default" for noncancer has lead to substantial controversy and has overshadowed the other recommendations, and the whole approach in general.

New WHO/IPCS Guidance on Characterizing Uncertainty

- Previous guidance published on probabilistic exposure assessment (IPCS, 2008).
- New guidance (IPCS, 2014) focuses on “hazard characterization” (WHO nomenclature for dose-response assessment).
  - Focused on quantitative approaches to evaluating and expressing uncertainty in dose-response.
  - Re-examines the fundamental principles behind dose-response assessment, resulting in a unified approach across all types of endpoints (continuous, quantal, cancer, noncancer).
  - Also addresses uncertainties that are not easily quantified.
- Provides tools and data (distributions) to implement a probabilistic approach to dose-response assessment.

WHO/IPCS approach to implementing a probabilistic framework for toxicity values

- Replaces concept of "safe" dose with a "target human dose" HD_M^I, and its uncertainty:

> **HD_M^I** = the **human dose** at which a **fraction (or incidence) I of the population** shows an effect of **magnitude (or severity) M or greater** (for the critical effect considered).

- Calculated similar to a RfD:
  - Can use fixed factors (non-probabilistic), like an RfD.
  - Can also use probability distributions instead of fixed factors.
  - In either case, magnitude of the effect **M** and the incidence **I** in the population made explicit and transparent.
- Can be used to derive a "probabilistic RfD."
- Can provide dose-response function (e.g., to support "residual risk" or economic benefits analysis).

Source: WHO/IPCS Guidance Document *Evaluating and Expressing Uncertainty in Hazard Characterization* (2014)

Calculating an RfD versus calculating an HD_M^I

$$RfD = \frac{NOAEL}{AF_{Inter} \times AF_{Intra}}$$

- NOAEL: No Observed Adverse Effect Level
  - Magnitude of effect not specified
- AF_{Inter}: Interspecies Factor*
- AF_{Intra}: Intraspecies Factor
  - Fraction of the population protected not specified

$$HD_M^I = \frac{BMD_M}{AF_{Inter-BS} \times AF_{Inter-TKTD} \times AF_{Intra-I}}$$

- BMD_M: Benchmark Dose for Magnitude of effect M
- $AF_{Inter-BS}$: Interspecies Factor for Body Size differences*
- $AF_{Inter-TKTD}$: Interspecies Factor for remaining TK and TD differences*
- $AF_{Intra-I}$: Intraspecies Factor for Incidence I

*Omitted if based on human data

Source: WHO/IPCS Guidance Document *Evaluating and Expressing Uncertainty in Hazard Characterization* (2014)

Moving from "RfD" to "HD_M^I" provides quantitative definition of "safe" through a "probabilistic RfD"

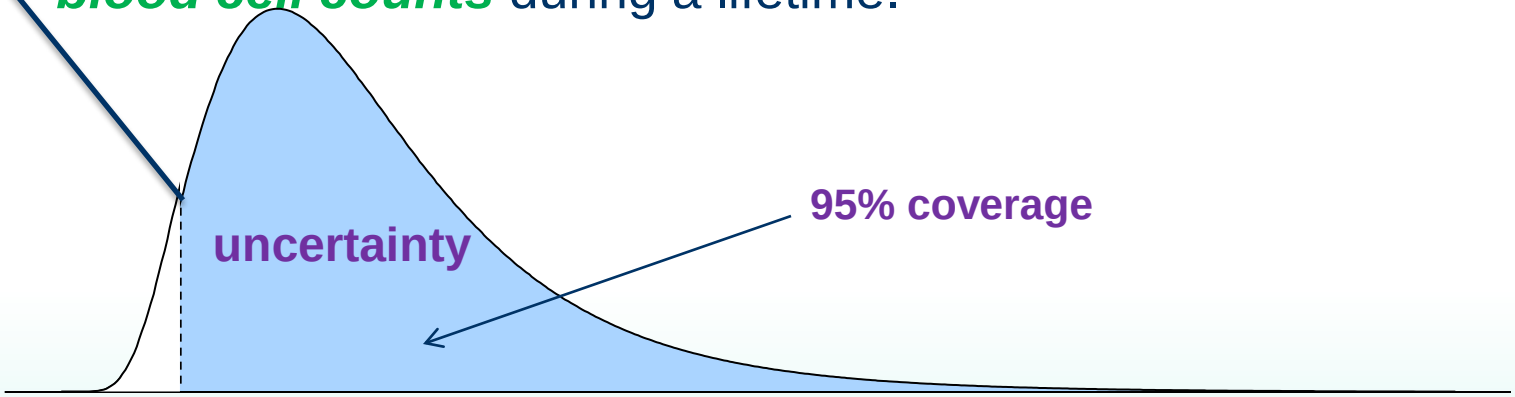
Deterministic RfD

… a daily oral exposure to the ***human population (including sensitive subgroups)*** that is ***likely*** to be ***without an appreciable risk*** of ***deleterious effects*** during a lifetime.

Probabilistic RfD (with 95% coverage)

… a daily oral exposure where, with ***95% coverage (confidence)***, ***less than fraction 1% of the human population*** shows ***more than 5% decrease in red blood cell counts*** during a lifetime.

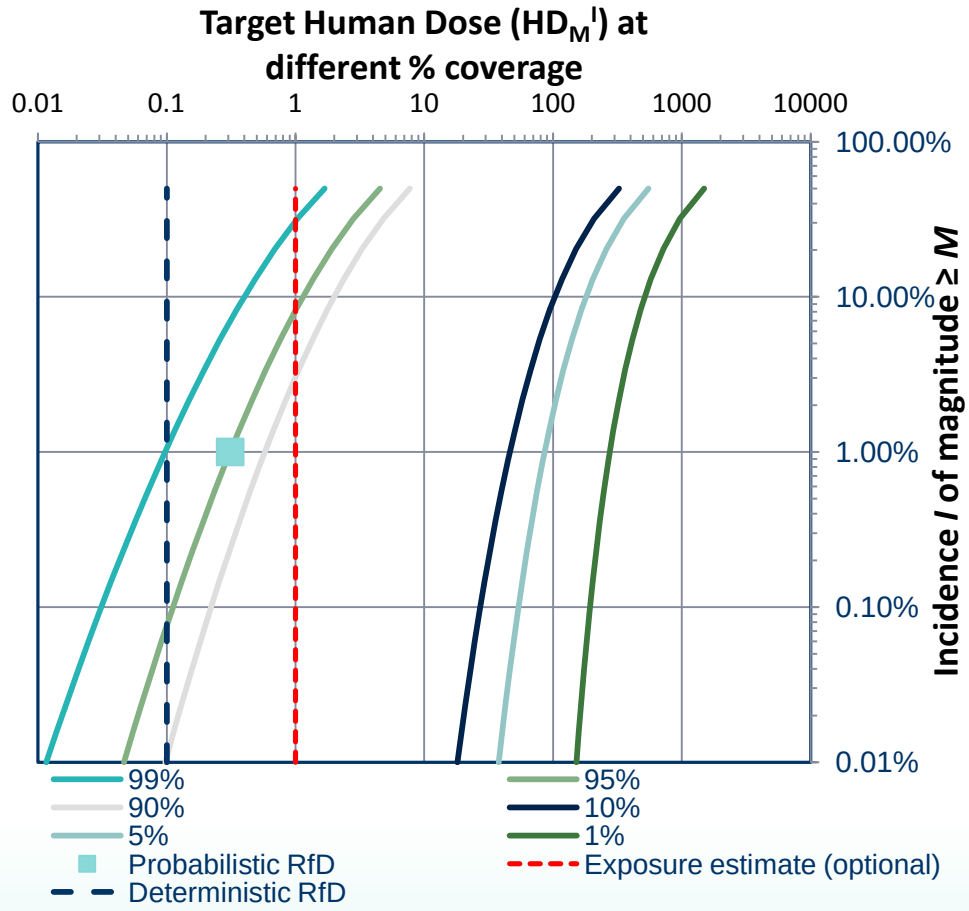
Target human dose HD_M^I (e.g., $HD_{M=5\%}^{I=1\%}$)



Adapted from WHO/IPCS Guidance Document *Evaluating and Expressing Uncertainty in Hazard Characterization* (2014)

HD_M^I can be estimated at multiple levels of magnitude and incidence of effect

- A single "unified" methodology for both
  - RfD/RfC derivation (being explicit about levels of M and I).
  - "Residual risk" or economic benefits assessment (population risk as a function of exposure)
- Probabilistic approach provides quantitative estimates of uncertainty.



Summary of WHO/IPCS approach to probabilistic uncertainty analysis

- Moving to the HD_M^I concept enables (but does not require) uncertainty to be characterized probabilistically.
  - Uncertainty factors replaced with probability distributions.
  - Factors combined probabilistically.
  - Outputs that are explicit as to the magnitude and incidence of effects
    - Can support broader array of decision contexts, including “residual risk” and economic benefit-cost analysis.
    - “Agnostic” as to linear/non-linear extrapolation, instead acknowledging that uncertainty increases
      - For estimating very small incidences (e.g., I<1%)
      - For estimating very small magnitudes of effect (e.g., M<1% change)
- WHO/IPCS focused on animal toxicology data, but the same principles apply when using human data.

Applying probabilistic dose-response approaches to PHOs

PHOs in food

TFA ingestion

↑ VLDL

↑ LDL

↓ HDL

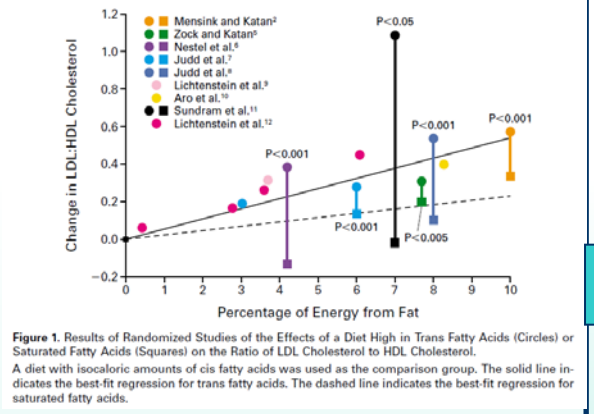
Risk of myocardial infarction

Unmodifiable factors: Heredity, sex, age, etc.

Modifiable factors: Other diet, physical activity, BMI, etc.

Other mechanisms/ biomarkers (known and unknown)

Individual dose-response



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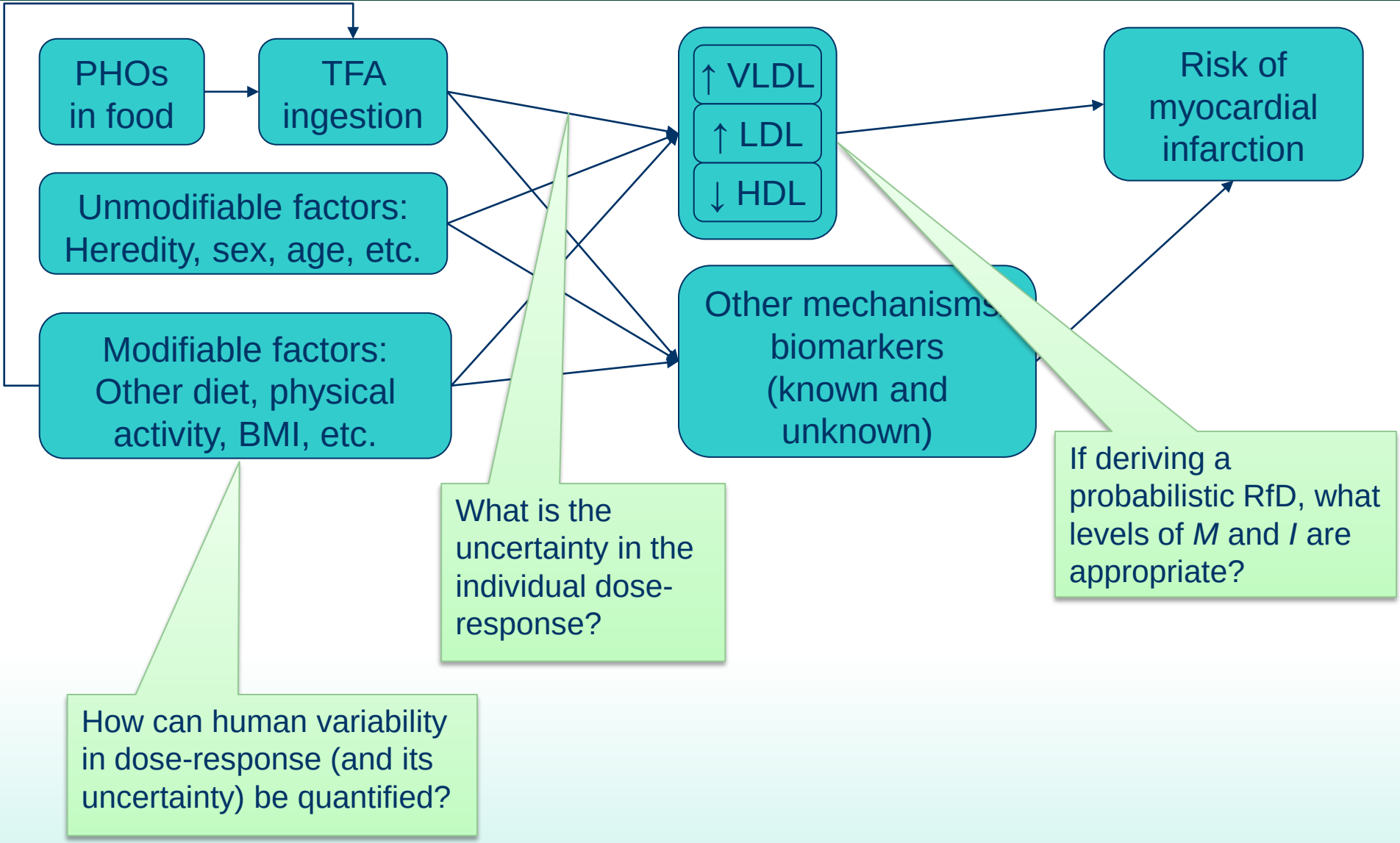
A diet with isocaloric amounts of cis fatty acids was used as the comparison group. The solid line indicates the best-fit regression for trans fatty acids. The dashed line indicates the best-fit regression for saturated fatty acids.

Human variability and susceptibility

$$HD_M^I = \frac{BMD_M}{AF_{Intra-I}}$$

- Probabilistic RfD
- "Residual risk" or economic benefits assessment

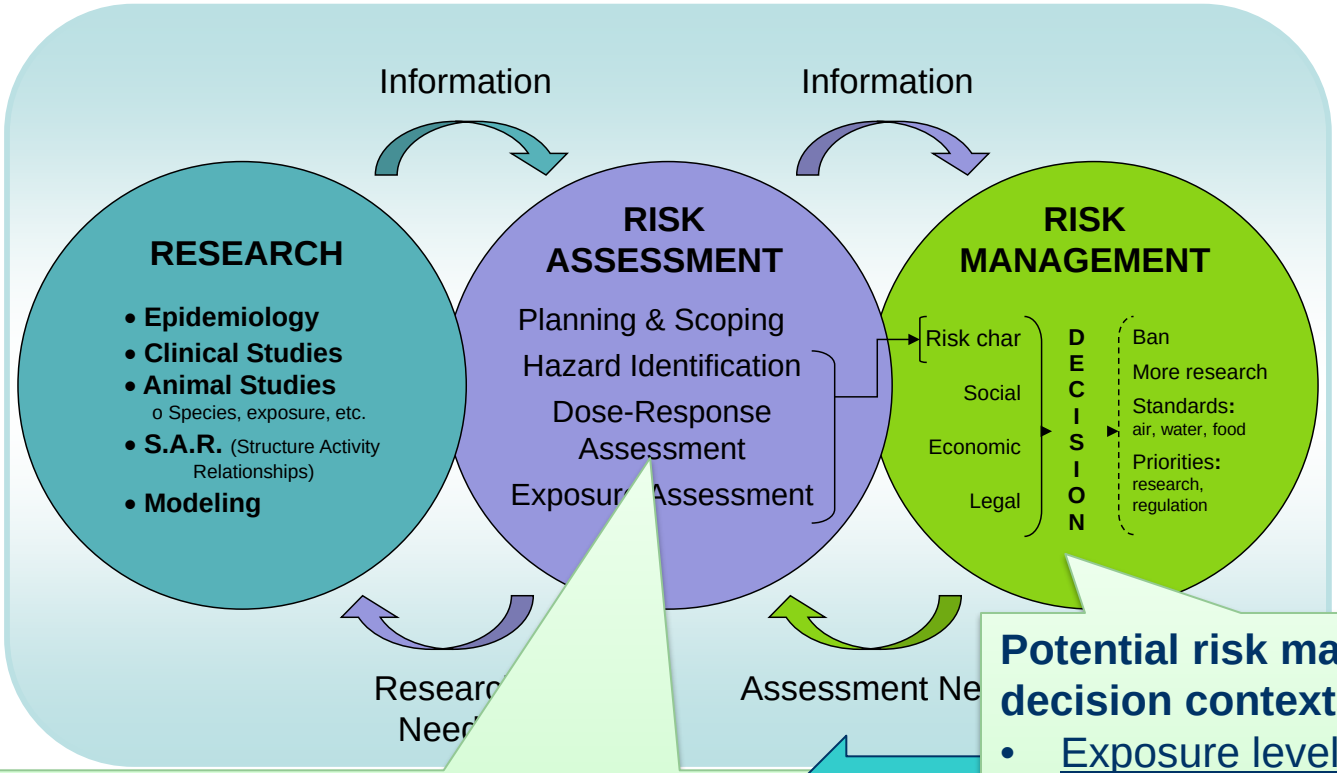
Issues in application of probabilistic dose-response to PHOs



Summary: Dose-response approaches for noncancer effects

- Examples of current practices for noncancer effects.
  - Reference values defining levels “likely to be without appreciable risk.”
  - Dose-response functions to support “residual risk” or economic benefit-cost analyses.
- National Academy recommendations (1994-2014).
  - Quantitatively characterize uncertainty and variability.
  - Incorporate mode of action, vulnerability, and background exposure.
  - “Unified” approach to dose-response assessment can more broadly support different decision contexts.
- WHO/IPCS guidance on uncertainty (2014).
  - Reflects additional progress on developing a probabilistic approach.
  - Based around estimating a “human target dose” HD_M^I for a specific magnitude of effect *M* and incidence in the population *I*.

Key issues in application of RfD methodology to PHOs



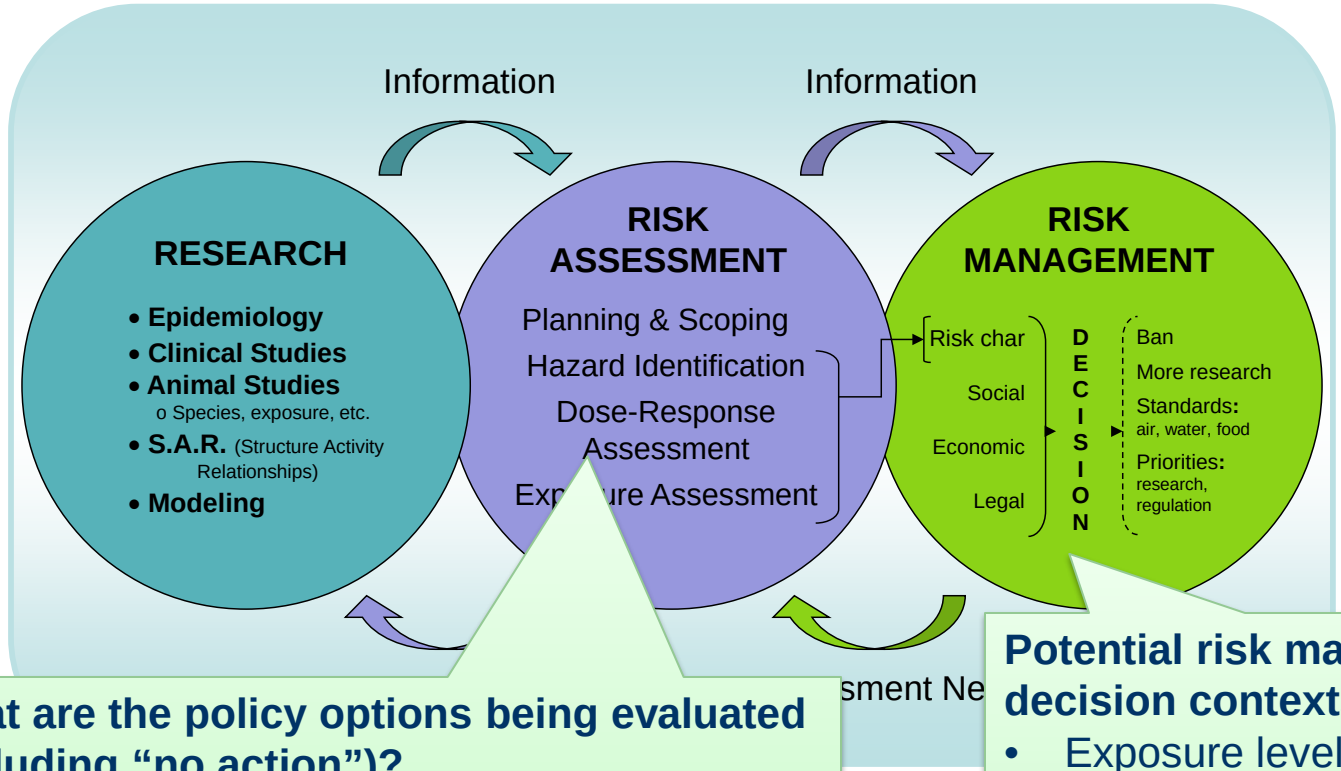
For deriving an RfD

- Identifying "key event" for conducting dose-response assessment.
- What level of effect is "likely to be without appreciable risk?"

Potential risk management decision contexts:

- Exposure level "likely to be without appreciable risk?"
- Residual risk at current exposure levels?
- Economic benefit-cost of different exposure levels?

Key issues for residual risk or economic benefits analysis for PHOs



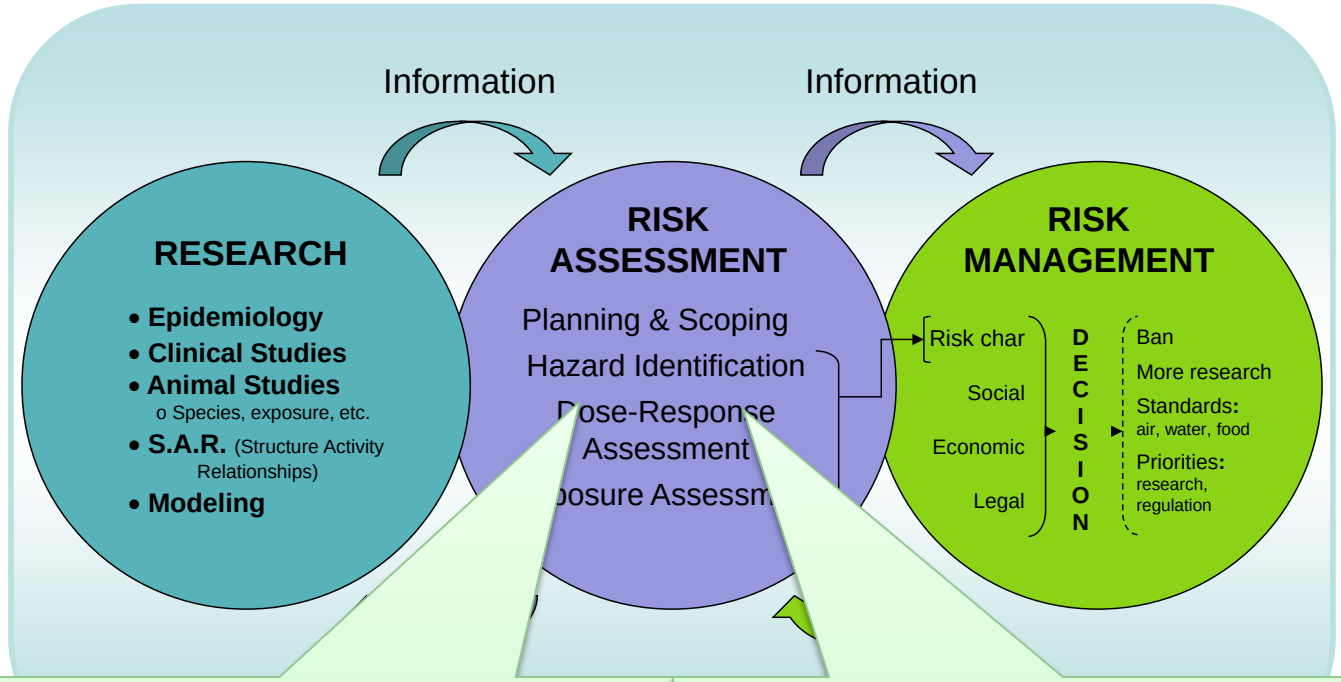
What are the policy options being evaluated (including "no action")?

- What is "residual risk" or "economic benefit" being compared against?
- Are the resulting exposures still within the range of observed data ("interpolation" versus "extrapolation")?

Potential risk management decision contexts:

- Exposure level "likely to be without appreciable risk?"
- Residual risk at current exposure levels?
- Economic benefit-cost of different exposure levels?

Key issues in incorporating new NRC and WHO/IPCS methods



Mode of action, vulnerability, and background exposures

- What factors modulate an individual's dose-response relationship for TFAs?
- How can background exposures (to TFAs and/or other dietary components) be addressed quantitatively?

Probabilistic dose-response

- What is the uncertainty in the individual dose-response?
- How can human variability in dose-response (and its uncertainty) be quantified?
- If deriving a probabilistic RfD, what levels of *M* and *I* are appropriate?

Acknowledgments

WHO/IPCS 2014 final drafting group

David Bussard, U.S. EPA
Wout Slob, RIVM
Theo Vermeire, RIVM
Matthias Herzler, BfR, Germany
Andy Hart, FERA, UK
Dale Hattis, Clark University
George Fotakis, ECHA rep.
Bernard Bottex, EFSA rep.
Carolyn Vickers, IPCS
Kathy Hughes, IPCS (on detail from Health Canada)

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