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

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Disclaimer: The views expressed in this presentation are those of the author, and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.
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.
- For each approach – issues in applying to PHOs.
Dose-Response Assessment in Context

Information

RESEARCH
- Epidemiology
- Clinical Studies
- Animal Studies
  - Species, exposure, etc.
- S.A.R. (Structure Activity Relationships)
- Modeling

RISK ASSESSMENT
- Planning & Scoping
- Hazard Identification
- Dose-Response Assessment
- Exposure Assessment

Assessment Needs

RISK MANAGEMENT
- Risk characterization
- Social
- Economic
- Legal
- Decision
  - Ban
  - More research
  - Standards: air, water, food
  - Priorities: research, regulation

Research Needs

SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety
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 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 $\frac{3}{4}$ 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**<sub>HED or HEC</sub> = (LOAEL or NOAEL or BMDL or BMCL) × DAF

- **Uncertainty factors (some of which are =1)**
  - UF<sub>H</sub> = Human variability
  - UF<sub>A</sub> = Animal-to-human extrapolation
  - UF<sub>S</sub> = Subchronic-to-chronic extrapolation
  - UF<sub>L</sub> = LOAEL-to-NOAEL extrapolation
  - UF<sub>D</sub> = Database deficiencies
  - UF = “Composite” or “Total” uncertainty
    \[(UF_H \times UF_A \times UF_S \times UF_L \times UF_D)\]

- **RfD or RfC** = 
  \[\frac{POD_{HED or HEC}}{UF}\]

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

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

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?

Risk of myocardial infarction

Other mechanisms/biomarkers (known and unknown)

↑ VLDL
↑ LDL
↓ HDL

PHOs in food → TFA ingestion → ↑ VLDL, ↑ LDL, ↓ HDL

PHOs in food ingest TFA, resulting in ↑ VLDL, ↑ LDL, ↓ HDL, leading to risk of myocardial infarction.
Different dose-response methodology needed for other contexts

- Epidemiology
- Clinical Studies
- Animal Studies
  - Species, exposure, etc.
- S.A.R. (Structure Activity Relationships)
- Modeling

Information

- Hazard Identification
- Dose-Response Assessment
- Exposure Assessment

Information

Research Needs

Assessment Needs

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) and the concentration-response relationship. Current exposures and 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.
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
Approach has been used in many analyses of policy options

Meta-analysis of clinical trials
Quantitative effects on cardiovascular risk factors and coronary heart disease risk of replacing partially hydrogenated vegetable oils with other fats and oils
D Mozaffarian¹,² and R Clarke³

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
Potential cardiovascular mortality reductions with stricter food policies in the United Kingdom of Great Britain and Northern Ireland.
O Flaherty M¹, 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

PHOs in food → TFA ingestion

- What policy options (including “no action”) are under consideration, and how will they affect TFA ingestion?
- Are the resulting exposures within the range of observation of the data?
  - Do effects on serum lipids explain all the cardiovascular toxicity of TFAs?

↑ VLDL  
↑ LDL  
↓ HDL

Other mechanisms/biomarkers (known and unknown)

Risk of myocardial infarction

- Are there other health effects that should be included?
## Comparison

<table>
<thead>
<tr>
<th>RfD/RfC approach</th>
<th>“Residual risk”/economic benefits approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Purpose is to estimate an exposure at which <strong>effects would likely not occur</strong>.</td>
<td>• Purpose is to estimate <strong>change in effects with change in exposure</strong>.</td>
</tr>
<tr>
<td>• Usually based on animal toxicology.</td>
<td>• Usually based on human data.</td>
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<tr>
<td>- Uncertainty factors used to extrapolate across and within species.</td>
<td>- In the relevant species</td>
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<tr>
<td>- Effects at different exposure levels are not estimated.</td>
<td>- If in the relevant exposure range, no need for low-dose extrapolation.</td>
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<td></td>
<td>- Provides estimates of effects at different exposure levels.</td>
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</table>
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?)

<table>
<thead>
<tr>
<th>Ranking from different types of prioritization:</th>
<th>Lower bound</th>
<th>Central Estimate</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
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Dose at which I% experiences effect size M
NAS/NRC recommendations for advancing dose-response

- *Science and Decisions* report (NRC, 2009) recommended incorporating
  - Mode of action, vulnerable populations, background exposures, and
- *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

1. Selecting conceptual model based on MOA, background exposure and disease processes, and vulnerable populations.

2. Incorporating probabilistic methods, redefining “Uncertainty Factors” and the RfD and RfC probabilistically.

3. Resulting dose- or concentration-response function could support multiple decision contexts.

Available Health Effects Data

Endpoint Assessment

Mode of Action Assessment

Vulnerable Populations Assessment

Background Exposure Assessment

Conceptual Model Selection

Dose Response Method Selection

Dose-Response Modeling and Results Reporting
Application of MOA, vulnerable populations, and background assessment to PHOs

Available Health Effects Data

Endpoint Assessment

Mode of Action Assessment → Vulnerable Populations Assessment → Background Exposure Assessment

PHOs in food → TFA ingestion

Unmodifiable factors: Heredity, sex, age, etc.

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

↑ VLDL

↑ LDL

↓ HDL

Risk of myocardial infarction

Other mechanisms/biomarkers (known and unknown)
Issues in application 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)

• 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.

<table>
<thead>
<tr>
<th>Conceptual Models for Low-Dose-Response</th>
<th>Individual Dose-Response</th>
<th>Population Dose-Response</th>
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</thead>
<tbody>
<tr>
<td>1. An individual’s: Non-linear</td>
<td>Probability of Effect</td>
<td>Fraction of Population Affected</td>
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<td>The population: Linear</td>
<td>Background dose Dose</td>
<td>Dose</td>
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- 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).
  - 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” $\text{HD}_M^I$, and its uncertainty:

  $$\text{HD}_M^I = \text{the human dose at which a fraction (or incidence) } I \text{ of the population shows an effect of magnitude (or severity) } M \text{ or greater (for the critical effect considered).}$$

- 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).

Calculating an RfD versus calculating an $H_{D M}^I$

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

- Interspecies Factor*
- Intraspecies Factor

- No Observed Adverse Effect Level
- Magnitude of effect not specified
- Fraction of the population protected not specified

$$H_{D M}^I = \frac{BMD_M}{AF_{\text{Inter BS}} \times AF_{\text{Inter TKTD}} \times AF_{\text{Intra I}}}$$

- Interspecies Factor for Body Size differences*
- Interspecies Factor for remaining TK and TD differences*
- Intraspecies Factor for Incidence I

*Omitted if based on human data

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\%)

uncertainty

95% coverage

$\text{HD}_M^I$ 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
- Unmodifiable factors: Heredity, sex, age, etc.
- Modifiable factors: Other diet, physical activity, BMI, etc.
- Risk of myocardial infarction

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

Unmodifiable factors:
- Heredity, sex, age, etc.

Other mechanisms/biomarkers (known and unknown)

Individual dose-response

Human variability and susceptibility

- Probabilistic RfD
- “Residual risk” or economic benefits assessment

\[ \text{HD}^I_M = \frac{\text{BMD}_M}{\text{AF}_{\text{Intra-I}}} \]
Issues in application of probabilistic dose-response to PHOs

- PHOs in food → TFA ingestion
  - Unmodifiable factors: Heredity, sex, age, etc.
  - Modifiable factors: Other diet, physical activity, BMI, etc.

- Risk of myocardial infarction
  - VLDL↑, LDL↑, HDL↓
  - Other mechanisms/biomarkers (known and unknown)

- If deriving a probabilistic RfD, what levels of $M$ and $I$ are appropriate?
- What is the uncertainty in the individual dose-response?

How can human variability in dose-response (and its uncertainty) be quantified?
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.

  - 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.

  - 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?

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RISK MANAGEMENT
Decision
• Ban
• More research
• Standards: air, water, food
• Priorities: research, regulation

Research Needs
Assessment Needs

Information
Information
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?
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