Overview on Current State of the Science on Dietary Exposure Assessment

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Outline

- Background on dietary exposure assessment
  - Indirect vs direct methods of assessment

- Current approach:
  - Pre-market safety assessments
  - Nutrient assessment
  - Post-market Proposition 65 assessments

- Limitations

- Conclusion
BACKGROUND
Dietary Exposure Equation:

\[
\text{Food Ingredient/Contaminant Level (mg/kg food)} \times \frac{\text{Consumption (kg food/person/day)}}{\text{bodyweight (kg)}}
\]

\[
\text{Intake (mg/kg bw/day)}
\]

Compare intake to safe exposure level or relevant toxicological dose (e.g. ADI)
Tiered Approach to Estimating Exposure

Actual Exposure
Yellow=variability

Tier 4: Refined using best data
Tier 3
Tier 2
Pre-market
Default “worst case”
## Approaches To Quantify Dietary Exposure

<table>
<thead>
<tr>
<th></th>
<th><strong>Direct</strong></th>
<th><strong>Indirect</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Direct, real time measurements of contaminant, food additive, or nutrient in the food as consumed</td>
<td>Link measured (or estimated) concentrations in foods with information on human consumption patterns</td>
</tr>
<tr>
<td><strong>Example</strong></td>
<td>Duplicate diets</td>
<td>Two-compartment model for exposure scenarios that combine human consumption data (e.g., FFQ or dietary recalls) with proposed, measured, or estimated concentrations in food</td>
</tr>
<tr>
<td><strong>Strengths</strong></td>
<td>Can be best indication of actual exposures in sampled population</td>
<td>Easiest, can be done quickly, cheapest, screening assessment</td>
</tr>
</tbody>
</table>
| **Weaknesses**       | Exposure sources not always clear, methods not always available, burdensome, chemical specific, only applicable to sampled population for time period sampled | Limited accuracy  
Difficult to validate  
**Steady state assumption** |
Modeling an Exposure Assessment (FIT FOR PURPOSE)

- Simple model but implementation can be complex
- Does it ask the right questions
  - What will the assessment be used for?
    - Premarket approval
    - Post market issues
    - Labeling
    - Research
    - Priority setting
  - What is the toxicological concern?
  - Do we want to be conservative or precise?
  - What data do we have?
Data Sources

Dietary Consumption Surveys
- NHANES 1999-2012
- WHO Cluster diets
- Private surveys
- Custom surveys

Nutrient/Food Ingredient/Contaminant Data
- USDA
- Manufacturer
- Literature
- FDA TDS
Consumption Data

NHANES has 3 major components

– 2-day/24-hour Recall Survey
  • “How much?”
– Food Frequency Survey (FFQ)
  • “How often?”
– Dietary Supplement Use Survey
Data Analysis: Issues to Consider

• Derive estimates for:
  – *Per capita vs. per user* (consumers only)
  – Subpopulations with different diets
  – Typical consumer (average, median) or high consumer (upper 90th percentile), etc.

• Short term v long term intake:
  – Per eating occasion, 24-hr daily intake, N-day average intake, Modeled usual long term intake?

• On a g/day or g/kg bw/day basis

• Precision of the estimate
CURRENT APPROACH
### Considerations before choosing approach

<table>
<thead>
<tr>
<th>Example Scenarios</th>
<th>Pre-market approval</th>
<th>Nutrient assessment</th>
<th>Post-market issues</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intentionally added: Food additive, color additive, GRAS substance</td>
<td>Adequacy or quality of diet compared to DRIs</td>
<td>Contaminants: Proposition 65 labelling, recall management</td>
</tr>
<tr>
<td>Objective</td>
<td>Safety assurance: conservative intakes, high-end consumers</td>
<td>Understand true population exposure</td>
<td>Safety assurance: Current/realistic intakes, typical or high-end consumers</td>
</tr>
<tr>
<td>Approach</td>
<td>Conservative: Short term consumption (e.g., 2-day averages), maximum use rates, focus on high-end consumers (i.e., 90th percentile)</td>
<td>Realistic: Usual intake modelled from 2 days of 24 hour recalls, focus on mean levels</td>
<td>Realistic: Usual, long-term intake can be estimated by amount consumed with frequency of consumption, focus on mean levels, “Average rate of intake or exposure for average users” Shorter-term, high end exposure for recall management</td>
</tr>
</tbody>
</table>
PRE-MARKET APPROVAL EXAMPLE
Pre-market Approval/Safety Assurance Example

Ingredient X is proposed to be added to several foods, including:

- Energy and Nutrition Bars: 150 – 200 mg/serving
- Flavored water, Energy, and Sport Drinks: 25-50 mg/serving
- Fruit-Flavored Drinks: 80 – 100 mg/serving

X is also naturally occurring in blueberries and grape. Based on the published literature, the average level is 2,000 ppm in blueberries and 1,000 ppm in grapes.

What is the cumulative estimated daily intake (EDI) of X?

- Cumulative EDI = Proposed + Background
  
  - Proposed: \( \sum \) \([\text{concentration of constituent in food}] \times \text{[amount of food]}\)
  
  - Background: Add intake from current uses, naturally occurring sources in the diet and dietary supplements (where applicable)
Estimating Daily Intake (EDI) From Proposed Uses: Indirect Model Approach

- Tier I assessment
  - Maximum proposed use level
  - Consumption typically based on 2 days of 24-hour dietary recalls from NHANES
  - Assign proposed use levels to representative NHANES food codes
<table>
<thead>
<tr>
<th>Food types</th>
<th>% Users</th>
<th>Per Capita</th>
<th>90th</th>
<th>Per User</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bars</td>
<td>8%</td>
<td>0.19</td>
<td>0</td>
<td>2.35</td>
</tr>
<tr>
<td>Fruit flavored drinks</td>
<td>5%</td>
<td>0.11</td>
<td>0</td>
<td>2.14</td>
</tr>
<tr>
<td>Flavored water energy sport drinks</td>
<td>5%</td>
<td>0.07</td>
<td>0</td>
<td>1.39</td>
</tr>
<tr>
<td>Blueberries</td>
<td>18%</td>
<td>0.07</td>
<td>0.09</td>
<td>0.40</td>
</tr>
<tr>
<td>Grapes</td>
<td>16%</td>
<td>0.11</td>
<td>0.12</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Cumulative SUM @ individual level</strong></td>
<td><strong>39%</strong></td>
<td><strong>0.54</strong></td>
<td><strong>1.76</strong></td>
<td><strong>1.41</strong></td>
</tr>
</tbody>
</table>

**Cumulative EDI, US population, NHANES 2003-2006**
Nutrient Assessments

• Estimate distributions of *usual* nutrient intakes by general population and various age/gender groups

• Use data from 2 days of dietary recall in NHANES combined with USDA nutrient data to approximate long-term intakes
  – Iowa State University Method (C-Side)
  – NCI Method (publicly available code)

• Representative of the typical food supply at the time of the survey
Nutrient assessment example – Vitamin D

• Nutrient of public health concern
  • A large proportion of the U.S. population consumes suboptimal levels of vitamin D

• Risks with excessive intake
  • Need to ensure intakes are within safe level

• Vitamin D is a naturally occurring nutrient in a limited number of foods (fatty fish, egg yolk, meat), and as identified in 21 CFR, it is permitted as an additive in select foods with limits on the concentration.
## Overview of Vitamin D in the Food Supply

<table>
<thead>
<tr>
<th>Category of Food</th>
<th>Maximum Level (21 CFR)</th>
<th>Actual Level (USDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soy-based food products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soy-based beverages</td>
<td>All products, 50 IU/100 g</td>
<td>Some, 50 IU/100 g</td>
</tr>
<tr>
<td>Soy-based beverages</td>
<td>All products, 89 IU/100 g</td>
<td>Some, 89 IU/100 g</td>
</tr>
<tr>
<td>Soy-based butter substitute spreads</td>
<td>All products, 330 IU/100 g</td>
<td>Some, 330 IU/100 g</td>
</tr>
<tr>
<td>Soy-based cheese substitute</td>
<td>All products, 270 IU/100 g</td>
<td>Some, 270 IU/100 g</td>
</tr>
<tr>
<td>Calcium-fortified fruit juice and drinks</td>
<td>All products, 100 IU per 240 mL</td>
<td>Most, 100 IU per 240 mL</td>
</tr>
<tr>
<td>Soy protein based meal replacement bevs</td>
<td>All products, 140 IU per 240 mL</td>
<td>Most, ≤140 IU per 240 mL</td>
</tr>
<tr>
<td>Meal replacement or other type bars</td>
<td>All products, 250 IU/100 g</td>
<td>Some, ≤250 IU/100 g</td>
</tr>
<tr>
<td>Cheese and cheese products</td>
<td>All products, 81 IU/30 g</td>
<td>Some, ≤81 IU/30 g</td>
</tr>
<tr>
<td>Breakfast cereals</td>
<td>All products, 350 IU/100 g</td>
<td>Some, typically &lt;175 IU/100 g</td>
</tr>
<tr>
<td>Grain products and pasta</td>
<td>All products, 90 IU/100 g</td>
<td>Limited, ≤90 IU/100 g</td>
</tr>
<tr>
<td>Milk</td>
<td>All products, 42 IU/100 g</td>
<td>Nearly all, 42 IU/100 g</td>
</tr>
<tr>
<td>Milk products</td>
<td>All products, 89 IU/100 g</td>
<td>Some, ≤89 IU/100 g</td>
</tr>
<tr>
<td>Infant formula</td>
<td>All products, 100 IU per 100 kcal</td>
<td>All products, typically ~60 IU per 100 kcal</td>
</tr>
</tbody>
</table>
**Nutrition**

**Adequacy of Vitamin D Intake**

- What are current dietary sources of vitamin D?
- What are intakes of vitamin D from these sources?
- How do intakes compare to EARs?
  - Prevalence of nutrient inadequacy
  - EAR cut-point method: % < EAR

**Safety**

**Potential Risks of Vitamin D Intake**

- What are all potential maximum sources of vitamin D?
- What are potential intakes of vitamin D from these sources?
- How do intakes compare to ULs?
Estimating Intakes of Vitamin D

**Nutrient Intake**
- Naturally occurring
- Fortification reflective of current practices
- Dietary supplements (as reported)
- Estimate distributions of usual nutrient intakes by general population and various age/gender groups
  - Approximate long-term intakes from 2-days dietary recall

**Safety Assessment**
- Naturally occurring
- Fortification reflective of maximum allowable levels in all permitted use categories, and maximum proposed new use(s)
- Dietary supplements (can conservatively assume all individuals use a supplement)
- 90th per user daily intake based on an average of 2-days dietary recall.
Vitamin D Nutrient Intake vs. Safety Assessment, NHANES 2003-8

* 90th percentile of maximum potential exposure: naturally occurring vitamin D, maximum level of all potential food additive uses, and conservative assumption of dietary supplement use by all individuals (10 mcg/d for ages 1-50 y, 15 mcg/d for ages 51+ y)

** Mean intake of current exposure: naturally occurring vitamin D, current food additive uses, and use of dietary supplements by respondents
DIETARY EXPOSURE ASSESSMENTS FOR PROPOSITION 65
Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65)

- Passed by voter initiative in 1986
- 800+ listed chemicals as carcinogens/reproductive toxicants
- A knowing and intentional exposure to a listed chemical requires a warning unless:
  - Exposures do not exceed thresholds
- Applies to businesses in the chain of distribution with 10 or more employees
- Statute and regulations provide guidance as to data and methods to be used for assuring compliance
- Includes exposure assessment as a key component
Key Considerations (from the Exposure Assessor Viewpoint) under Proposition 65

- Assessment should be for the average (typical) consumer of that food
  - Average is not further defined
  - Consumer is not further defined
  - Realistic, long-term usual exposure
  - Contaminant levels based on analytical measurements of finished product

- Not brand specific but can be for the appropriate category
Estimating Rate of Exposure

- Differs from pre-market safety assessments in accounting for **frequency** of consumption

- **How much AND how often?**
  - How much – grams per EO
    - NHANES 24-hour dietary recall
  - How often – EO per day
    - NHANES FFQ 2003-2006
    - The NPD Group, Inc. (formerly National Purchase Diary) National Eating Trends (NET) survey
      - Includes 14-day diaries that provide “how often”
      - Allows for more specific food categories compared to NHANES FFQ
      - Total U.S. population (including infants)
      - Can be used in combination with the NHANES dietary recall data
Dietary Exposure Calculation:

- Average amount consumed
- Average frequency of consumption
- Average level of compound in product of interest
- Average daily exposure to chemical X

• Compare to relevant Prop 65 safety thresholds of “safe harbor levels” (i.e., NSRL/MADL)

NSRL = No Significant Risk Level (carcinogens)
MADL = Maximum Allowable Dose Level (reproductive toxicants)
LIMITATIONS
Dietary Exposure Indirect Model Limitations

• “Simple” equation, but:
  – A given person does not eat the same foods at every meal/day, or the same amount of food at every meal/day
  – Different people have different dietary patterns: different foods/different frequency of consumption/varying amounts
  – Contaminant/nutrient levels in/on food are variable
  – Contaminant/additive/nutrient may be present in multiple foods

• “Snap shot” level data to predict long-term exposure
Conclusions

- Inherent limitations in the underlying data and the indirect approach to dietary exposure assessment

- The current model is based on the best publically available data and from a safety prospective, allows for conservative estimates related to negligible risk of adverse outcomes in the U.S. population.

- Thoughtful consideration of the correct approach and use of available data to match the objective of the assessment will yield intakes that are useful and directly applicable for risk management decisions to ultimately protect the public’s health.
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