Overview on Current State of the Science on Dietary Exposure Assessment

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Carolyn Scrafford, PhD (cscrafford@exponent.com)

Nga Tran, DrPH (ntran@exponent.com)

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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

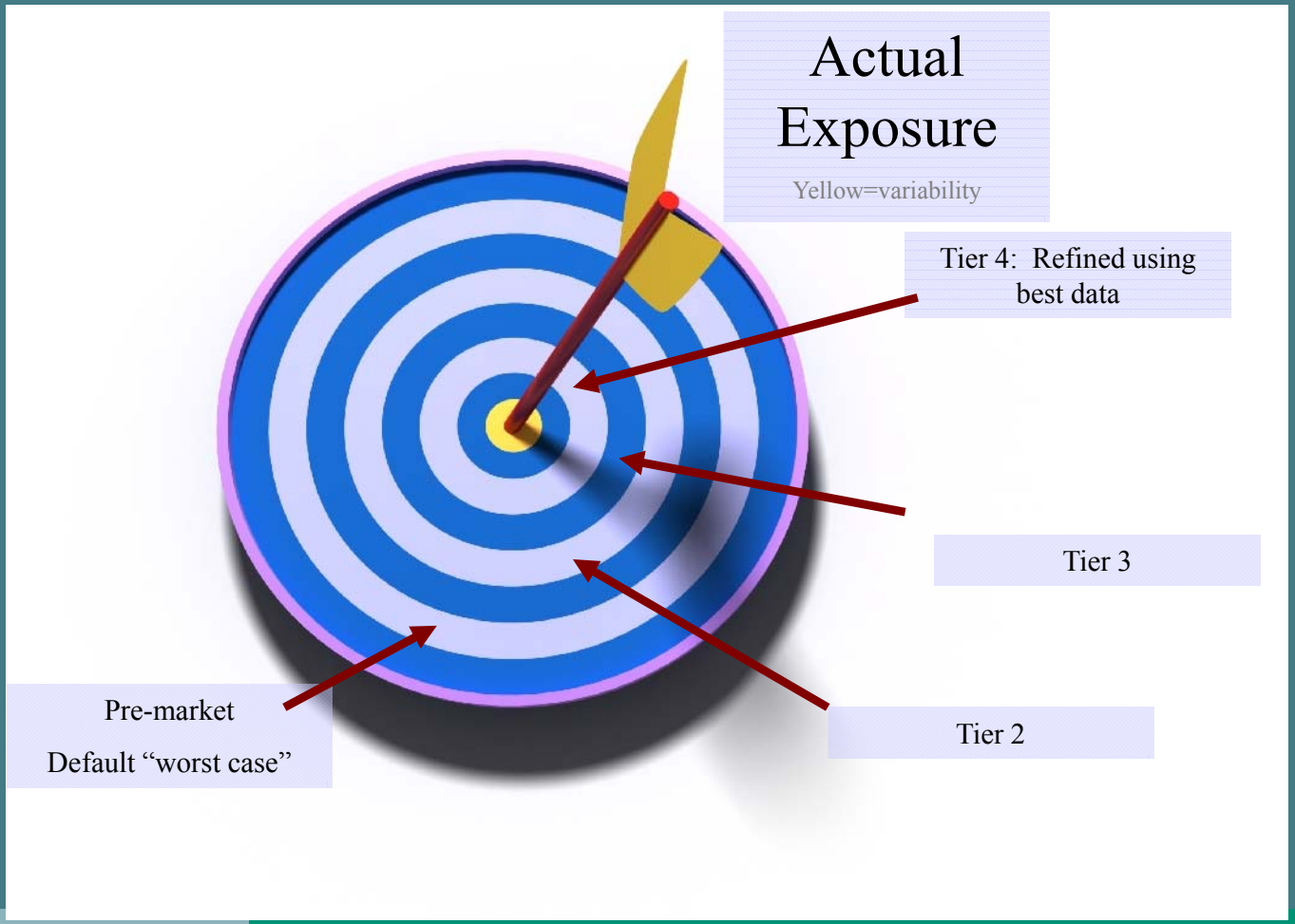
Dietary Exposure Equation:

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

⇒ Intake (mg/kg bw/day)

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

Tiered Approach to Estimating Exposure



Approaches To Quantify Dietary Exposure

	Direct	Indirect
Definition	Direct, real time measurements of contaminant, food additive, or nutrient in the food as consumed	Link measured (or estimated) concentrations in foods with information on human consumption patterns
Example	Duplicate diets	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
Strengths	Can be best indication of actual exposures in sampled population	Easiest, can be done quickly, cheapest, screening assessment
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

- CSFII 1994-96, 1998
- 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

	Pre-market approval	Nutrient assessment	Post-market issues
Example Scenarios	Intentionally added: Food additive, color additive, GRAS substance	Adequacy or quality of diet compared to DRIs	Contaminants: Proposition 65 labelling, recall management
Objective	Safety assurance: conservative intakes, high-end consumers	Understand true population exposure	Safety assurance: Current/realistic intakes, typical or high-end consumers
Approach	Conservative: Short term consumption (e.g., 2-day averages), maximum use rates, focus on high-end consumers (i.e., 90th percentile)	Realistic: Usual intake modelled from 2 days of 24 hour recalls, focus on mean levels	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

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: ∑ [concentration of constituent in food] x [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

Cumulative EDI, US population, NHANES 2003-2006

			EDI (mg of X/kg bw/day)			
			Per Capita		*Per User*	
	Food types	% Users	Mean	90th	Mean	90th
Proposed New Uses	**Bars**	8%	0.19	0	2.35	4.74
	Fruit flavored drinks	5%	0.11	0	2.14	4.35
	Flavored water energy sport drinks	5%	0.07	0	1.39	2.89
Background Sources	**Blueberries**	18%	0.07	0.09	0.40	0.87
	Grapes	16%	0.11	0.12	0.69	1.80
Cumulative	***SUM @ individual level***	***39%***	***0.54***	***1.76***	***1.41***	***3.44***

NUTRIENT ASSESSMENTS

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

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

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

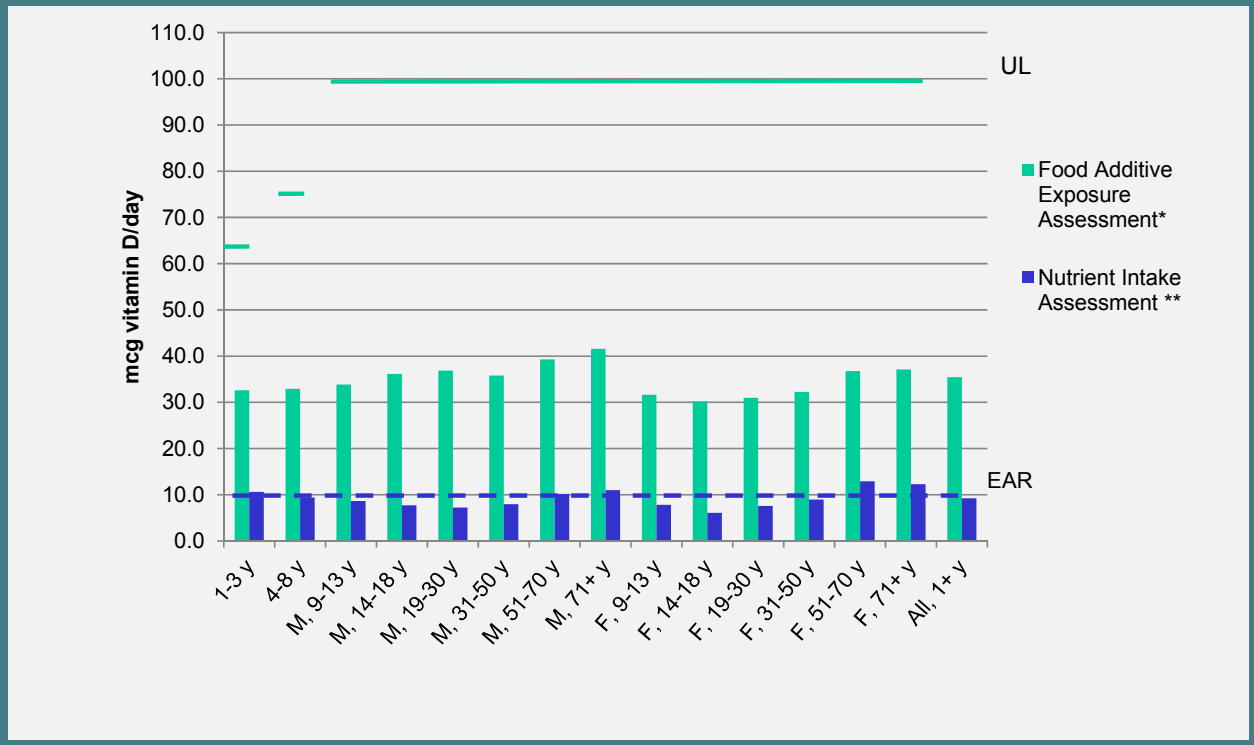
Nutrient Intake

- 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

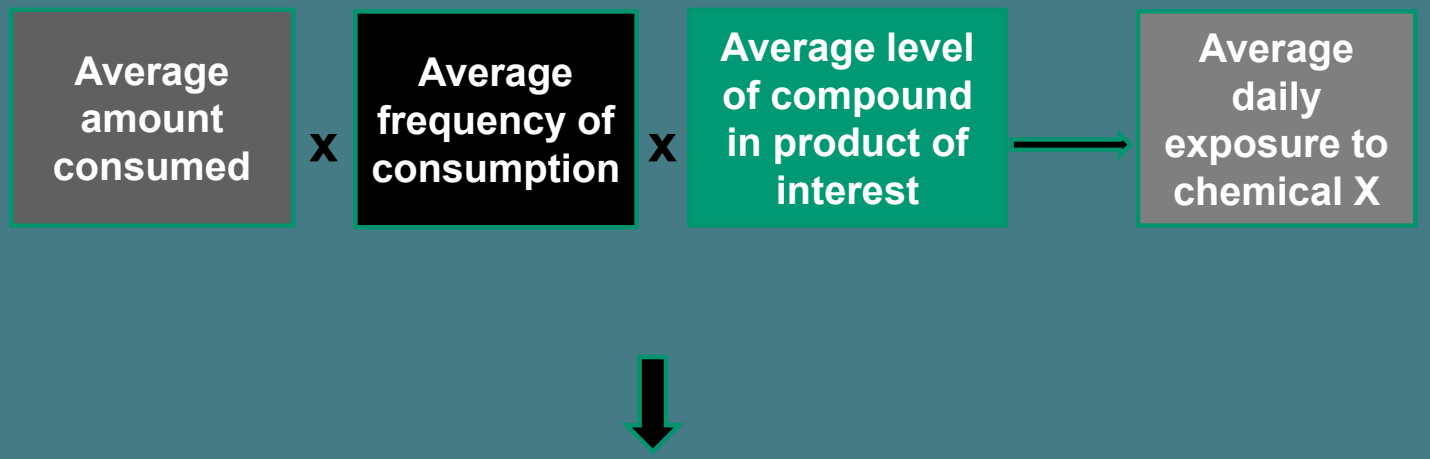
Key Considerations (from the Exposure Assessor Viewpoint) under Proposition 65

- 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:



- 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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