Regulatory Challenges and Hurdles for Bioactive Compounds

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Objectives

- Review key elements for GRAS
- Examine proposed criteria for DRI of bioactives
- Compare and Inspect criteria for several bioactives in red palm oil
- Encourage quality research → health claims

GRAS Key Elements

- Description of substance
  - Process
  - Finished product description
  - Quality control measures
  - Stability assessment
- Intended
  - Effects
  - Population
- History of use
- Intended use
  - EDI
  - ADI
- Safety
  - ADME
  - Animal studies
  - Clinical studies

Delaney Clause

- …"[n]o additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal.
- Applicable to food additives (FDCA, Section 409), animal drugs in meat and poultry (FDCA, Section 512), and color additives (FDCA, Section 721)
- Note:
  - All "commodities" or natural foods, such as apples, cabbages and carrots, contain carcinogens and mutagens; these are not subject to the Delaney Clause

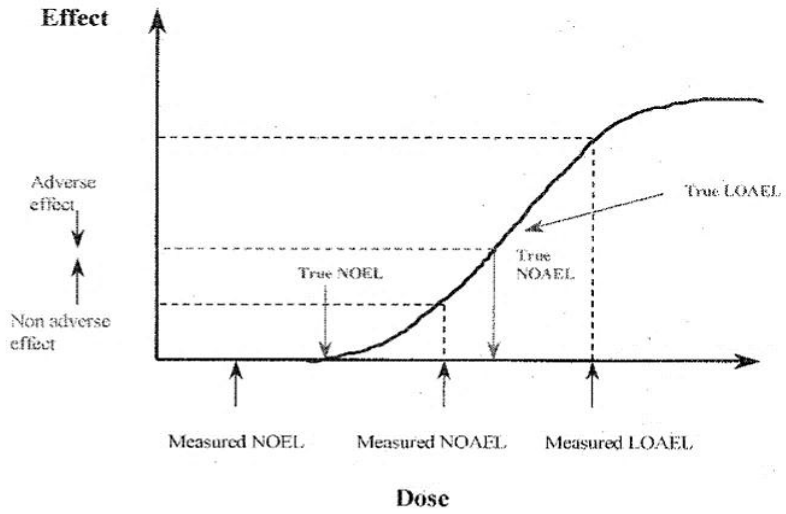
Bioactives: What are Tolerable Upper Limits?

- Currently, there are ULs for 24 of 37 vitamins and minerals
- Safety requires understanding of toxicology → ULs
- ULs are based on NOAEL or LOAEL plus applicable uncertainty factor
- Is this approach applicable to bioactives for which dietary withdrawal does not produce classic deficiency presentations?
- What is the minimum intake to maintain health?
- What biological endpoints should be acceptable for the DRI process?

Yates et al., Reg Toxicol Pharmacol 2017; doi: 10.1016/j.yrtph.2017.01.002

Bioactives: What are Tolerable Upper Limits?

- What's involved in risk assessment?
- Are current nutrient databases adequate to assess EDI for bioactives, such as flavonoids?
- Are there sufficient data to establish a risk/benefit curve?
- Key elements for consideration
  - Identification of critical effect
  - Determine point of departure from dose response curve
  - Application of appropriate uncertainty factor



Yates et al., Reg Toxicol Pharmacol 2017; doi: 10.1016/j.yrtph.2017.01.002
Lewis et al., Toxicol Pathol 2002; 30(1):66-74

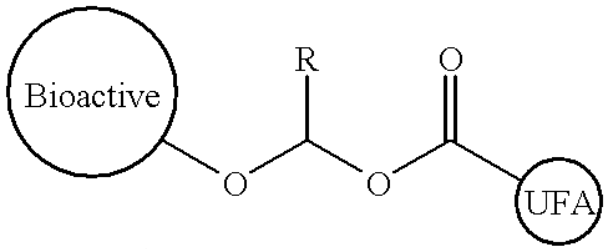
Bioactives: Lutein Case Study

- Traditionally, why RDAs?
  - To "prevent" nutrient deficiency
- Traditionally, why DRIs?
  - To reduce chronic disease endpoints
  - There are 42 DRI nutrients; many do not meet traditional criteria for essentiality (e.g., fiber, fluoride, choline)
  - Where does lutein fit? Are there sufficient data to establish DRI?
    - Data suggest lutein may reduce risk of AMD (age-related macular degeneration)
    - What should be the criteria for establishing a DRI?

Yates et al., Reg Toxicol Pharmacol 2017; doi: 10.1016/j.yrtph.2017.01.002

Bioactives: Criteria for DRI Consideration

- Definition of substance
- Establish and validate analytical method for substance in food
- Establish quantitative bioactive database
- Conduct and evaluate prospective cohort studies
- Conduct classic ADME studies



- Conduct and collect dose-response data
- Establish and evaluate EDI and ADI data
- Conduct systematic reviews
- Establish biological plausibility of efficacy
- Compile data for safety assessment and DRI establishment

Lupton et al., Eur J Nutr 2014; doi: 10.1007/s00394-014-0666-3

Natural Variation in Plant Composition

Plant Source Material

- **Species and Variety**
  - Any known adulterant or frequently substituted species?
- **Plant part**
  - Leaf, fruit, flowers, seed, stem, root, rhizome, total above grour
- **Agricultural conditions, including country of origin**
  - Growing conditions: stressed plants produce more defense molecules
  - Time of year to harvest: content of active(s), markers
  - Pesticide/herbicide/insecticide application: chemical contamination
  - Pollution: heavy metal content, etc.
  - Harvesting and handling practices: mycotoxin content, mold, microbes, moisture
- **Processing/Extraction Procedure**

Rosemary Spice

Booth et al., Food Chem Toxicol 2012; doi: 10.1016/j.fct.2012.03.075

Bioavailability

- Fed or fasted state of the individual;
- Dietary load, source, and food matrix;
- General health and state of gastrointestinal tract (e.g. rate of gastric emptying, motility status, time of day, and lifestyle factors);
  - Acute or chronic illness of the individual (e.g. hepatic insufficiency and impaired renal function);
  - Pregnancy status;
- If hospitalized (e.g. critical care unit);
  - Postoperative status (e.g. active recovery from surgical intervention and wound healing stage);
- Athletic status (e.g. ongoing athletic training or weekend athlete);
- Nutritive status (e.g. malnutrition or nutrient insufficiency);
- Age extremes (e.g. in general, drugs are metabolized more slowly in fetal, neonatal, and geriatric populations); and
- Genetic makeup of the individual.

Pressman, Clemens & Hayes. Toxicol Res Appl 2017

Red Palm Oil - Bioactives

- Predominant bioactives
  - free fatty acids, carotenoids, tocotrienols, tocopherols, sterols, phospholipids, squalene, coenzyme Q10

The Protective Effect of Red Palm Oil and the Mechanisms Involved in Different Models of Oxidative Stress

Red palm oil: physiological effect	Mechanism	Period of protection	Reference
Increased left ventricular developed pressure (LVDP)	PKB/Akt	Reperfusion	Engelbrecht et al. (2009)
Increased aortic output	PKB/Akt	Reperfusion	Engelbrecht et al. (2006)
	Antiapoptosis	Reperfusion	Engelbrecht et al. (2006)
	NO-cGMP	Ischemia	Esterhuyse et al. (2006)
Decreased infarct size	LDH	Reperfusion	Bester et al. (2010)
	MMP-2	Reperfusion	Bester et al. (2010)
	MMP-2	Preischemic	Szucs et al. (2011)
	PKB/Akt	Reperfusion	Bester et al. (2010)

van Rooyan. Bioactive Compounds in Red Palm Oil Can Modulate Mechanisms of Actions in In Vitro Anoxic Perfused Rat Hearts. 2013; doi: 10.1016/B978-0-12-396485-4.00020-7

What About Refining Conditions?

- Objective: evaluate palm oil refining conditions and their impact on free fatty acid (FFA), neutral oil loss, and possible bioactives (tocotrienols, squalene, phytosterols)
- Conditions:
  - Temperature: 200-260°C
  - Steam percentage: 0.5% to 3.5%
  - Initial FFA: 2.2% to 6.0%
- Results:
  - Increased processing temperature → significant reduction in bioactives
  - Retention best at lower temperature (200°C): 88% tocotrienols; 84% squalene; 98% phytosterols

Sampaio et al., J Food Sci 2017; doi: 10.1111/1750-3841.13805

Lycopene

- **Qualified Health Claims: Letter Regarding Tomatoes and Prostate Cancer (Lycopene Health Claim Coalition) (Docket No. 2004Q-0201) – November 2005**
  - The petition cited 177 publications and or websites as evidence to substantiate the relationship for the claims. These publications consisted of 38 review articles; three abstracts; 13 *in vitro* studies; ten animal studies; ***63 articles that did not measure lycopene***, tomatoes or tomato products and/or a type of cancer.
  - FDA concluded that there is no credible evidence to support a qualified health claim for tomato lycopene.
  - FDA concluded that there is very limited credible evidence for qualified health claims for tomatoes and/or tomato sauce.
  - QHC – Prostate Cancer (enforcement discretion)
    - Very limited and preliminary scientific research suggests that eating one-half to one cup of tomatoes and/or tomato sauce a week may reduce the risk of prostate cancer. FDA concludes that there is little scientific evidence supporting this claim

https://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072767.htm
Accessed July 1, 2017

Tocotrienols

- FDA – no health claim

- GRAS –
  - GRN 307 (2009): Palm Tocotrienol Rich Fractions (TRF) as Ingredients in Food
    - No questions (2010); may require color additive listing
    - Broad spectrum of food uses
  - GRN 471 (2013): Tocotrienol-rich extract derived from the seeds of *Bixa orellana*
    - No questions (2014): may require color additive listing
    - Broad spectrum of food uses, except for infant formula and foods with standard of identity
- Safety
  - Doses up to 1,000 mg/day (1,500 IU/day of the natural form or 1,100 IU/day of the synthetic form) in adults appear to be safe

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-foods-gen/documents/document/ucm269421.pdf
https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm359902.pdf

CoQ 10 (ubiquinone)

- FDA – No health claim
- EFSA 2010
  - No data have been provided supporting an effect of coenzyme Q 10 consumption on energy-yielding metabolism
  - The evidence provided does not establish that interactions between coenzyme Q10 and antihypertensive treatment (1 study)
  - A cause and effect relationship has not been established between the consumption of coenzyme Q 10 (ubiquinone) and the protection of DNA, proteins or lipids from oxidative damage.
  - Insufficient data on the relationship of coenzyme Q10 and normal cognitive function

Significant Scientific Agreement
Bradford Hill Viewpoints (7)

- Strength of association
- Consistency of the observed association
- Specificity of the association
- Temporal relationship of the observed association
- Dose response relationship
- Biological plausibility
- Coherence of the evidence

Hill AB, Proc R Soc Med. 1965; 58:295-300

Significant Scientific Agreement
Augmentation of Bradford Hill Viewpoints (4)

- Amount and type of evidence
- Quality of evidence
- Totality of evidence
- Relevance of evidence

…cause-effect decisions cannot be based on a set of rules.

Sir Austin Bradford Hill, 1965

Key Takeaways

- Safety is primary
- Single *in vitro* studies are insufficient to justify marketing statements
- Bioactives are subject to key elements of GRAS, including classic ADME and ADI for intended populations
- Consumers seek clean labels; Where do "bioactives" fit?
- Health claims are evidence-based; quality and quantity of that evidence are critical components of health claim development