Entrance Criteria for Bioactive DRI Value Considerations

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Bioactives: Qualitative Nutrient Reference Values for Lifestage Groups?
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Goal of the Presentation

- 1. Why is it important to have a DRI-like process for the evaluation of "Bioactives"?
- 2. What are the advantages of having a DRI-like value for "bioactives"?
- 3. What are the challenges to establishing such a process and how can they be dealt with?
  - Challenge: A "Flood" of "Bioactives" to evaluate
  - Solution: Set the bar high for entrance into the system

What are Bioactives?

- "Constituents in foods or dietary supplements, other than those needed to meet basic human nutritional needs, which are responsible for changes in health status."
  - US National Institutes of Health (NIH) in a working definition.

What are Dietary Reference Intake Values (DRIs)

- DRIS are
  - A set of values by age, and gender, as to how much of a specific nutrient we should be consuming on a daily basis.
  - They originated with the Institute of Medicine, in the US, but today most countries have their own DRI values.
  - DRIS = NRVs (nutrient reference values).

- They are based on a single endpoint, which has the strongest science in support of setting an intake value.
  - Usually for a vitamin or mineral this is a blood or tissue value that describes sufficiency of intake for that nutrient.
  - For fiber it was decreased risk of CHD
  - At this time in the US DRI values are only for traditional nutrients

Why is it important to have a DRI-like process for Bioactives?

- They are important to human health. There is a substantial scientific database on beneficial physiological effects of certain classes of bioactives.
- Cesar G. Fraga "Flavanols: Do the data support a nutrient reference value?"
- Mark Messina "Soybean isoflavones: Do the data support a nutrient reference value?"
- Joseph Levy "NRV for lycopene and other tomato carotenoids based on intervention and population studies?"

Why is it important to have a DRI-like process for Bioactives?

- The study of bioactives is a significant part of Government, University, and Corporate research programs.
- If there were a process to evaluate the strength of the science behind the intake of a bioactive and decreased risk of disease (or other health condition)
  - Standards would be set for this research
  - Studies could be compared across laboratories
  - The field could move forward more quickly

Why is it important to have a DRI-like process for Bioactives?

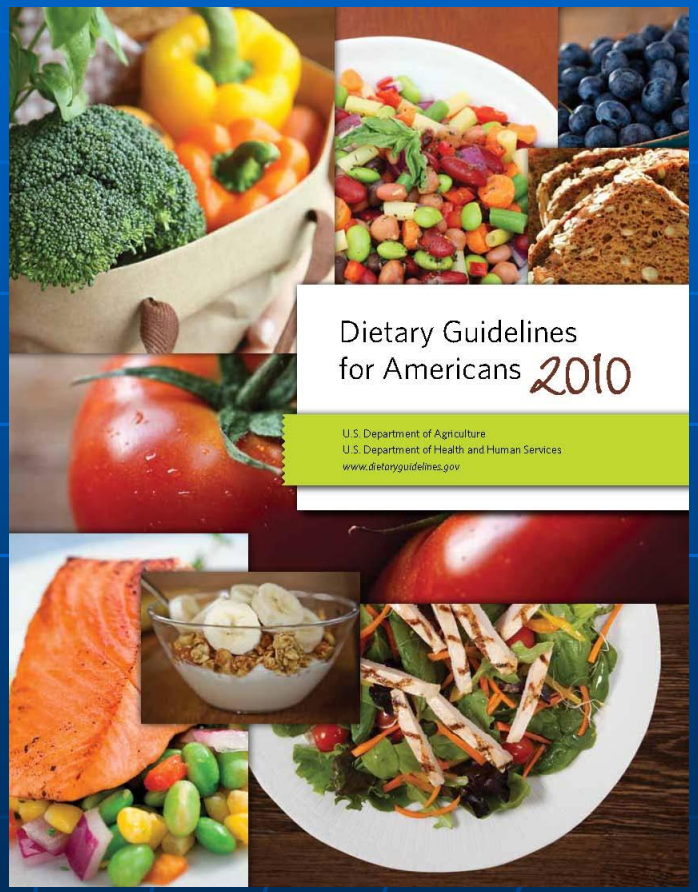
- Consumers are interested in bioactives and are purchasing foods containing them
- Food is now viewed as a source of substances to provide optimal health rather than just to protect against nutrient deficiency diseases
- It's important to provide consumers with information as to
  - How strong the science is behind purported benefits
  - How much they would need to eat to achieve these benefits

Advantages of having a DRI value for Bioactives

- Would set a goal for intake
  - Potential incorporation into food intake surveys (such as NHANES) to see if we are meeting the DRI value.
  - If considered a “short fall” nutrient potential for Government sponsored programs to encourage higher intake.
  - Health professionals would be comfortable in promoting intake.

Advantages of having a DRI value for Bioactives

- Potential for incorporation into Dietary Guidance Documents
- Although Dietary Guidance is for foods rather than nutrients it is based on meeting nutrient needs



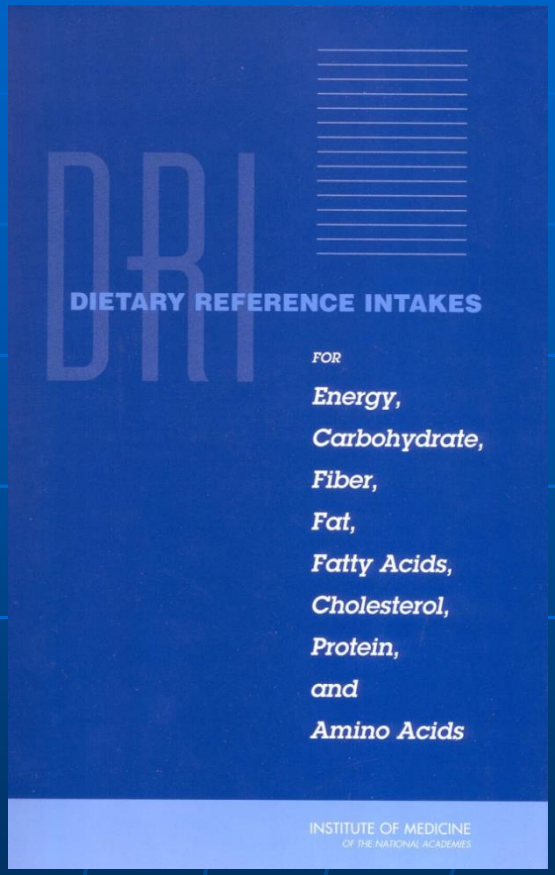
Dietary Guidance is based on Dietary Reference Intakes

- Philosophy is: If you follow the Dietary Guidelines you will meet your DRI values.

- Bioactive compounds could be mentioned in Dietary Guidance but they would not have specific recommendations or be mandated without a DRI value

Fiber as an example of a bioactive that has achieved DRI status

- Dietary Fiber is a non-essential nutrient but it does have an intake value.
- It is on most fact based food labels.
- It is promoted in Dietary Guidance.



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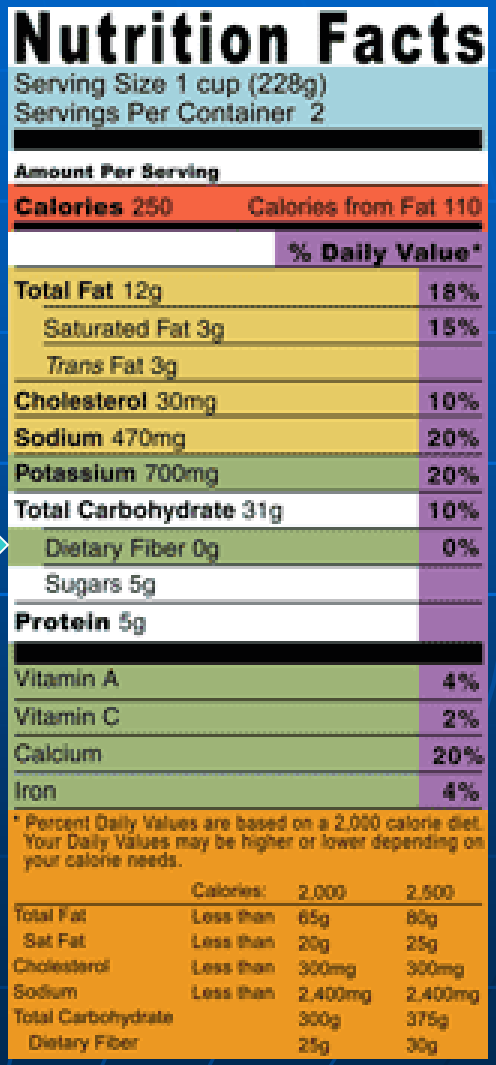
Fiber



Nutrition Facts

Serving Size 1 cup (228g)
Servings Per Container 2

Amount Per Serving

Calories 250	Calories from Fat 110
	% Daily Value*
Total Fat 12g	18%
Saturated Fat 3g	15%
Trans Fat 3g	
Cholesterol 30mg	10%
Sodium 470mg	20%
Potassium 700mg	20%
Total Carbohydrate 31g	10%
Dietary Fiber 0g	0%
Sugars 5g	
Protein 5g	
Vitamin A	4%
Vitamin C	2%
Calcium	20%
Iron	4%

* Percent Daily Values are based on a 2,000 calorie diet. Your Daily Values may be higher or lower depending on your calorie needs.

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

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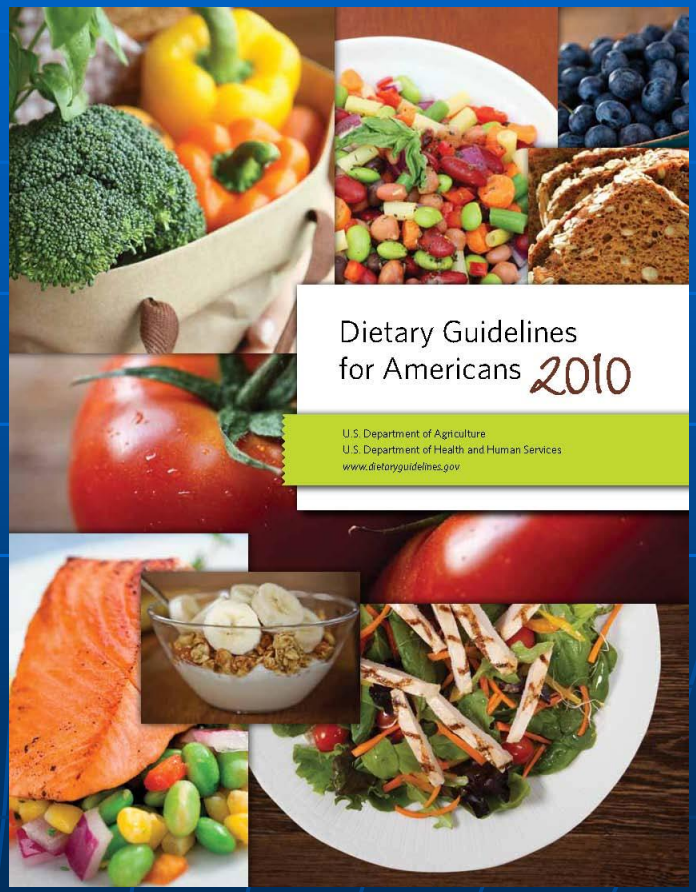

What are the challenges to establishing such a system and how can they be dealt with?

- 1. The absence of a specific bioactive in the diet does not result in a deficiency disease
- The absence of an essential nutrient does result in a deficiency disease
  - Vitamin C – scurvy
  - Calcium – osteopenia
  - Thiamin – beriberi
  - Niacin – pellagra
  - Iron - anemia

What are the challenges to establishing such a system and how can they be dealt with?

- Need different types of endpoints
  - Decreased risk of disease
  - Optimal Health
- Moving from deficiency endpoints to the relationship to disease risk is a paradigm shift that has yet to happen.
- Moving from decreased risk of disease to optimal health is an even larger paradigm shift.
- Ben van Ommen "Role of biomarkers in studying the health effects of bioactives."

What are the challenges to establishing such a system and how can they be dealt with?

2. Setting specific reference intake values.
   - Do we need both genders, all life stages and specific values?
   - Should ranges be considered?

- Stephanie Atkinson. "Bioactive status assessment and recommendations: Dilemmas for infants, children and youth."

What are the challenges to establishing such a system and how can they be dealt with?

3. Safety. Particularly for fortified foods.
   - If the bioactive is intrinsic to the food there is not as much concern.
   - If concentrated and put in new foods there is more concern.

- Even if the bioactive is considered GRAS (generally regarded as safe) it still means safe "for intended use").

- David P. Richardson "risk analysis approaches for establishing maximum levels of essential nutrients and other bioactive substances in fortified foods and food supplements."

What are the challenges to establishing such a system and how can they be dealt with?

4. Who has "ownership" of the system and how are decisions made.
   - Namsoo Chang "Setting nutrient reference values for bioactives in South Korea".
   - Yuexin Yang "Setting specific proposed levels for bioactive compounds: Recent experiences in China."

What are the challenges to establishing such a system and how can they be dealt with?

5. The Challenge: Having to evaluate multiple potential "bioactives" with little science behind them.

- A potential solution: Set a high standard that has to be met before being considered for a DRI value.
  - Entrance criteria for bioactive DRI value considerations.

Science required for “entrance into the system”

- A definition of the substance which is commonly accepted.
- A method of analyzing the substance that is consistent with the definition.
  - AOAC methodology

BOX 1

Codex Alimentarius Definition of Dietary Fiber

Dietary fiber consists of carbohydrate polymers with ten or more monomeric units, which are not hydrolyzed by the endogenous enzymes in the small intestine of humans and belong to the following categories: edible carbohydrate polymers naturally occurring in the food as consumed; carbohydrate polymers which have been obtained from food raw material by physical, enzymatic or chemical means and which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities, and; synthetic carbohydrate polymers which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities.

a. When derived from a plant origin, dietary fiber may include fractions of lignin and/or other compounds when associated with polysaccharides in the plant cell walls and if these compounds are quantified by the AOAC gravimetric analytical method for dietary fiber analysis: fractions of lignin and the other compounds (proteic fractions, phenolic compounds, waxes, saponins, phytates, cutin, phytosterols, etc.) intimately “associated” with plant polysaccharides in the AOAC 991.43 method.

b. Decision on whether to include carbohydrates of 3 to 9 monomeric units should be left up to national authorities.

Codex Alimentarius (2010)

Importance of having a single accepted definition and an approved method of measuring

- Research on the substance can be compared across studies.
- Need a definition and method to determine intake values.
- Need a definition and method to determine if populations are meeting recommended intake values.

Importance of a database with amounts of substance in foods

- Database needed to see how much of the substance is in the diet
- To compare intake to "recommendation"
  - Short fall nutrient?
- To determine amount that could be in food if foods were fortified to provide the efficacious amount
- To provide information for prospective epi studies and baseline data for clinical trials

Science required for a DRI value (Epidemiological Studies)

- Prospective cohort studies (men and women) showing ↓ risk of a disease such as CVD with increased intake of the bioactive
  - Must be able to isolate the specific bioactive vs other bioactives
  - Best if the bioactive is also measured in blood/urine in subset of population and supports food intake data
- Relationship to the disease should be consistent with clinical trials
- Dose response data or at least highest quintile vs lowest quintile for the bioactive

Science required for a DRI value (Clinical Trials on digestion, etc. and safety)

- Need information on the digestion, absorption, activation, transport, excretion of the substance which can then be used for efficacy studies.
- Need information on safety issues at the level of intake that might be anticipated
  - Even if the bioactive is GRAS (generally regarded as safe) GRAS means "safe for intended use"
  - Safety for special populations such as children, pregnant or lactating women

Science required for a DRI value (clinical trials on efficacy and dose)

- Healthy populations
- Bioactive must be measured
- Accepted endpoint linked to ↓ risk of the particular disease
  - Must be a significant disease, e.g. CHD, Type 2 diabetes
- If surrogate marker, must be "accepted"
  - e.g. for CVD ↓ blood pressure (FDA)
  - Flow Mediated Dilation (EFSA)
- Need a good body of evidence on a single endpoint, because values are based on a single endpoint
- Need dose response data to determine the efficacious level
  - Can it be ingested over the day in small amounts

Other important considerations (Systematic reviews and meta analyses)

- In the US, the Institute of Medicine now requires systematic reviews for DRI values
  - Most recent was Calcium and Vitamin D
- The US Dietary Guidelines now requires these
- Having a systematic review that shows efficacy is a *real plus* and *may* be necessary
  - e.g. Cochrane reviews
  - Reinforces the need to have major prospective epi studies and randomized clinical trials

Other important considerations (A Plausible Biological Explanation for Efficacy)

- This is not required but is a very large plus if it is available
- Scientists/evaluators of the research are more comfortable if there is an explanation
  - Particularly if that explanation is accepted by the scientific community

Summary of data needed

- Accepted definition and method of analysis
- Database of substance in foods and knowledge of intake from foods
- Epi cohort studies where the bioactive is measured
- Clinical information on digestion, absorption, metabolism, excretion
- Clinical information on safety
- Clinical trials with accepted surrogate endpoints
  - Dose response data
  - Knowledge of intake of the bioactive
  - "Healthy" individuals
- A systematic review for efficacy
- A biologically plausible mechanism of action

Conclusion

- Bioactive substances should be considered for DRI or DRI-like values and for Dietary Guidance
- The appropriate steps to achieve these goals should be established
  - Preferably on a global level
- Having a DRI like process to establish efficacy of bioactives would
  - Set standards that investigators would have to achieve
  - Help funders put resources into the most science-based programs
- Make a significant contribution to human health

Further Information

- For institute of Medicine Reports
  - Http://www.iom.edu/
- To contact me (Joanne Lupton)
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