



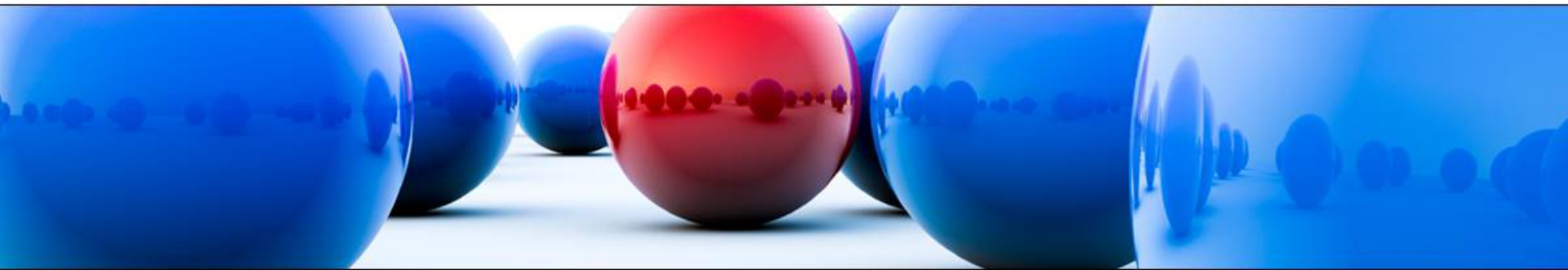
Claire L. Kruger, Ph.D., D.A.B.T.

**Overview of Regulatory Approval for
Ingredients in the US and EU**

**THE PATH TO FUNCTIONAL FOOD INGREDIENT APPROVAL:
DEVELOPMENTS IN THE SCIENTIFIC AND REGULATORY PROCESSES**

**American College of Nutrition
November 18, 2011**

Overview of Regulatory Approval for Ingredients in the US And EU; Discussion of the Science Involved in Evaluating Functional Ingredients and the Strategy for Effectively Communicating the Process to Consumers



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- **Regulatory Paths for Food and Dietary Ingredients**
- **The science drives the decision!**
- **Did you read that article in the paper? The role of the “Outrage” factor.**
- **How do we know what to believe when “science” is fueling the outrage?**
- **Recent news items – what is the evidence?:**
 - **Non-nutritive sweeteners (NNS) and carcinogenicity**
 - **The role of NNS in weight management**

From Beginning of Civilization

- **Man in quest for food learned certain foods produced varying degrees of illness or death**
- **Soon recognized harmful and beneficial consequences associated with taking materials into his body**
- **Concept involving division of chemicals into two categories has persisted to the present day**
 - **Not possible, however, to describe a strict line of demarcation**
 - **Beneficial chemicals**
 - **Harmful chemicals**
 - **Degrees of harmfulness and degrees of safeness for any chemical (the dose makes the poison)**
 - **All chemicals can cause toxic effects in large enough amounts**

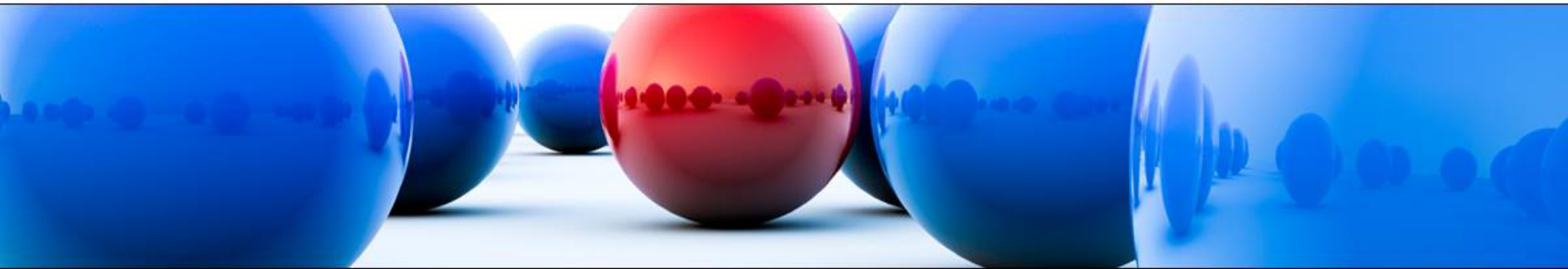
- **The goal of toxicology is to ensure the safety of products for human consumption**

The Objective of Toxicology

- **To determine how an organism is affected by exposure to a substance**
 - **How the substance moves through the body**
 - **Metabolism of the substance**
 - **What organs or tissues are affected**
 - **The health outcomes of this exposure**
- **The more thorough this understanding, the more accurately we can predict what will happen when humans ingest the substance**

- **Hazard**
 - Types of toxic effects caused by the chemical
 - Manifestation depends on route, amount, duration and frequency of exposure
- **Risk**
 - Likelihood that the toxic properties of a chemical will be produced in populations of individuals under their actual conditions of exposure; exposure must precede adverse event
- **Safety**
 - Little or no harm will result from chemical under given set of exposure circumstances
 - It is not the absolute absence of risk; it is the inverse of risk

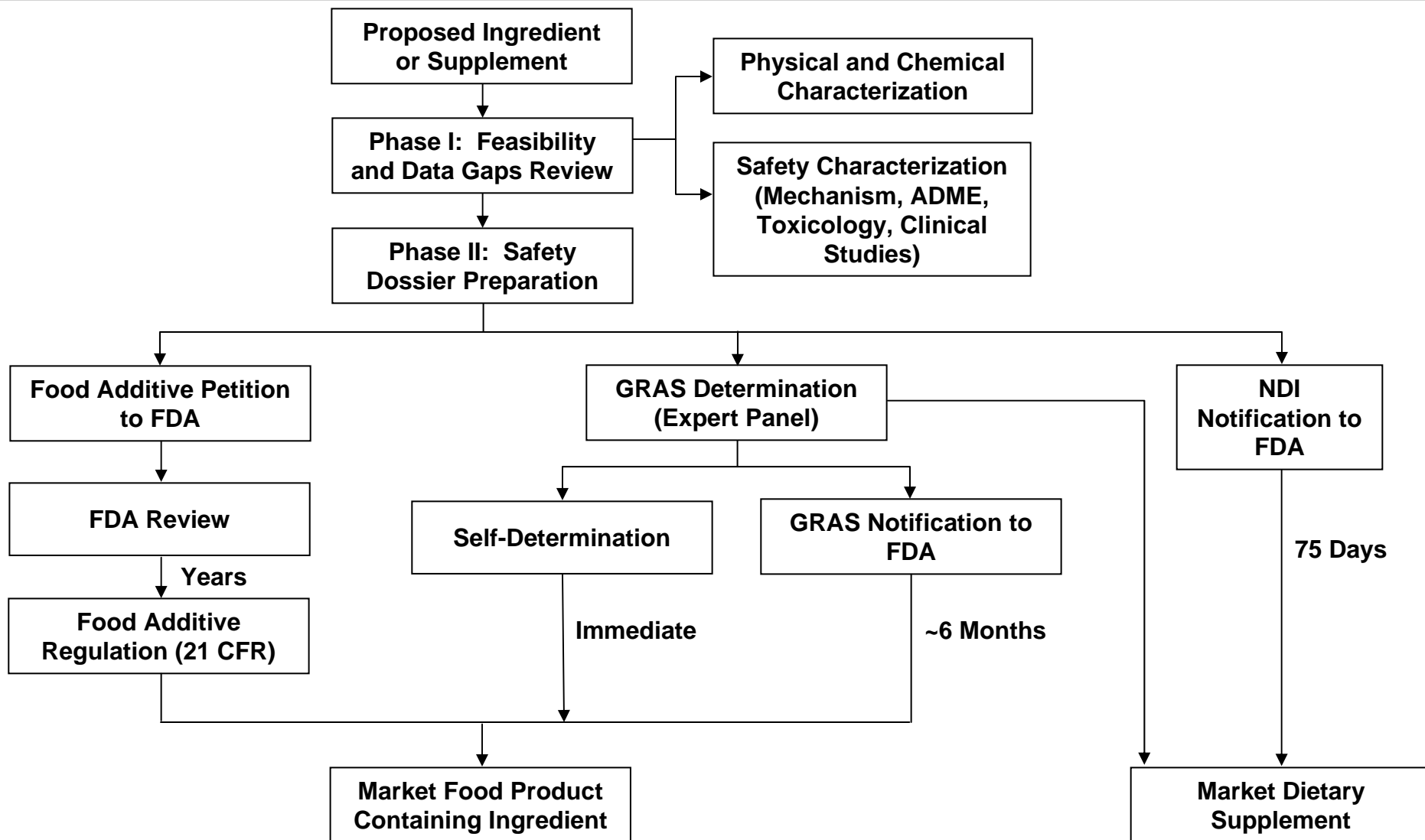
United States Regulatory Pathways: Compare and Contrast



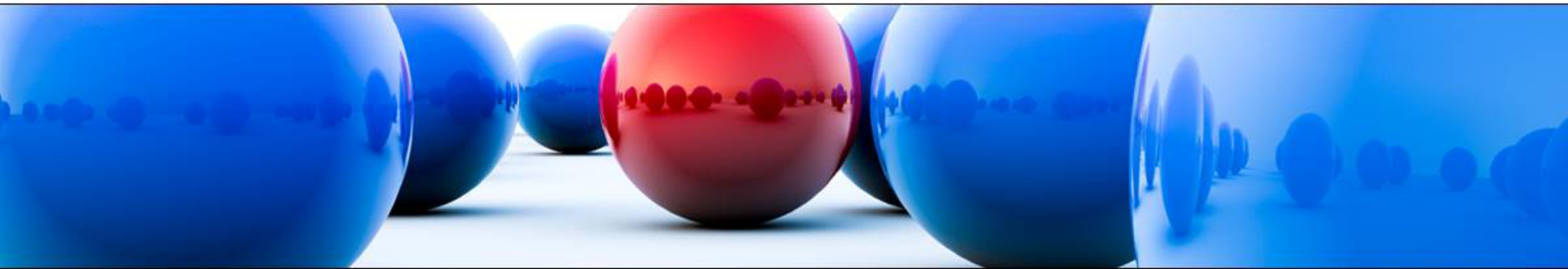
Foods: Comparison of U.S. Regulatory Paths

FOOD ADDITIVE	GRAS	Dietary Supplement
Federal Food, Drug, and Cosmetic Act 1938	Exemption to Food Additives Amendment 1958 Notification Process Promulgated 1997	DSHEA 1994 Draft Guidance for Industry 2011
Food Additive Petition	General Recognition of Safety by Expert Panel: GRAS dossier (self-GRAS or Notification)	Pre-1994: No FDA Notification Post-1994: NDI Notification to FDA
Information and data may be unpublished	Pivotal Information and data must be published	Information and data may be unpublished
Assumes lifetime exposure	Assumes lifetime exposure	Duration and frequency of exposure dictated on label
FDA makes the determination of safety based on data provided by submitter.	General Recognition of Safety based on publicly available data and consensus of expert panel opinion	Burden is on the submitter to establish safety for NDI under the conditions of use defined in the labeling.

Food Regulatory Paths



EU Regulation for Food



- **Novel Foods (not consumed to a significant degree in the EU before 1997) (Regulation 258/97)**
- **Food additives (e.g. preservatives, flavorings, colors, sweeteners)**
- **Special and medical food (Parnuts, i.e. foods for babies, weight reduction, drip-feed etc.)**
- **Food supplements (only vitamins and minerals)**

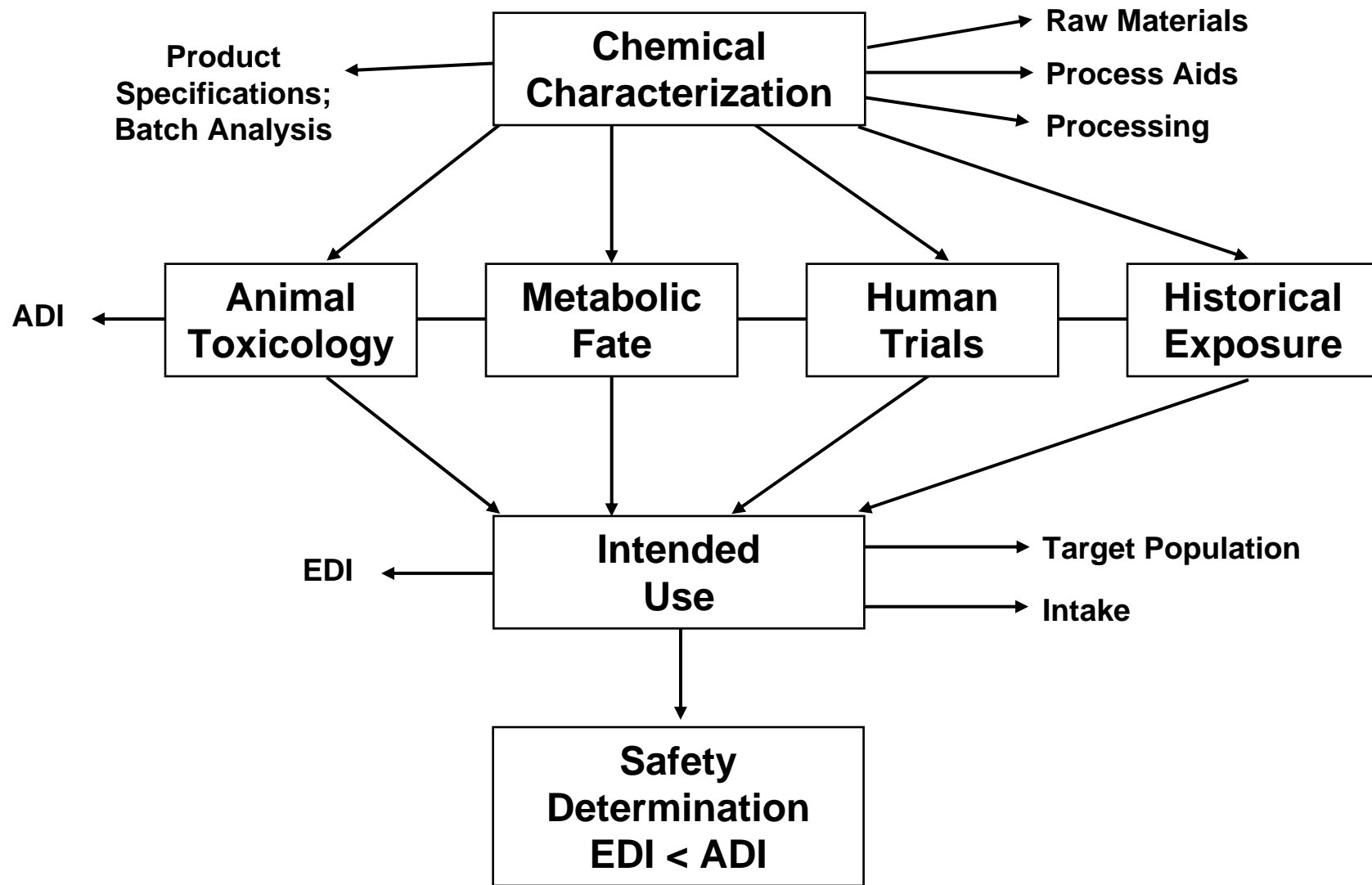
- **Novel Food Petition**
- **Novel Food Notification**

- **Novel foods or novel food ingredients may follow a simplified procedure, only requiring notifications, when they are considered by a national food assessment body as "substantially equivalent" to existing foods or food ingredients**
 - **as regards their composition, nutritional value, metabolism, intended use and the level of undesirable substances contained therein**
 - **when a novel food qualifies for a substantial equivalence application, safety studies are not required because the assessment for the novel food product is based on the history of safe use and/or the safety evaluation of the food counterpart**

Elements of the Novel Food Petition

- **Specification**
- **Production Process, Equipment, Processing Aids, and Production Facility**
- **History of the Production Organism**
- **Anticipated Intake and Extent of Use**
- **Information from Previous Human Exposure**
- **Nutritional Information**
- **Microbial Information**
- **Toxicological Information**

How Is Safe Use Determined?

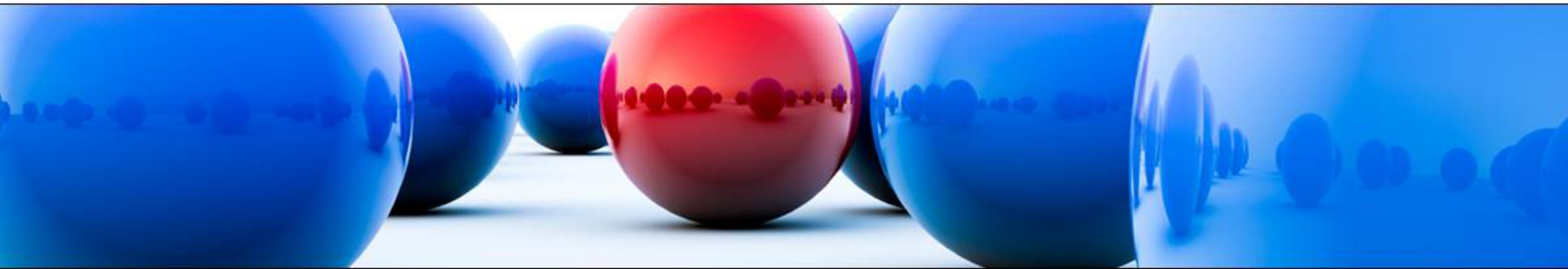


Studies Address these Endpoints:

- **ADME/Pharmacokinetics**
- **Acute Toxicity**
- **Subchronic and Chronic Toxicity**
- **Carcinogenicity**
- **Reproductive Toxicity/Teratology**
- **Neurotoxicity**
- **Immunotoxicity/Allergenicity**
- **Weight Management**

CASE STUDY:

Non-nutritive Sweeteners



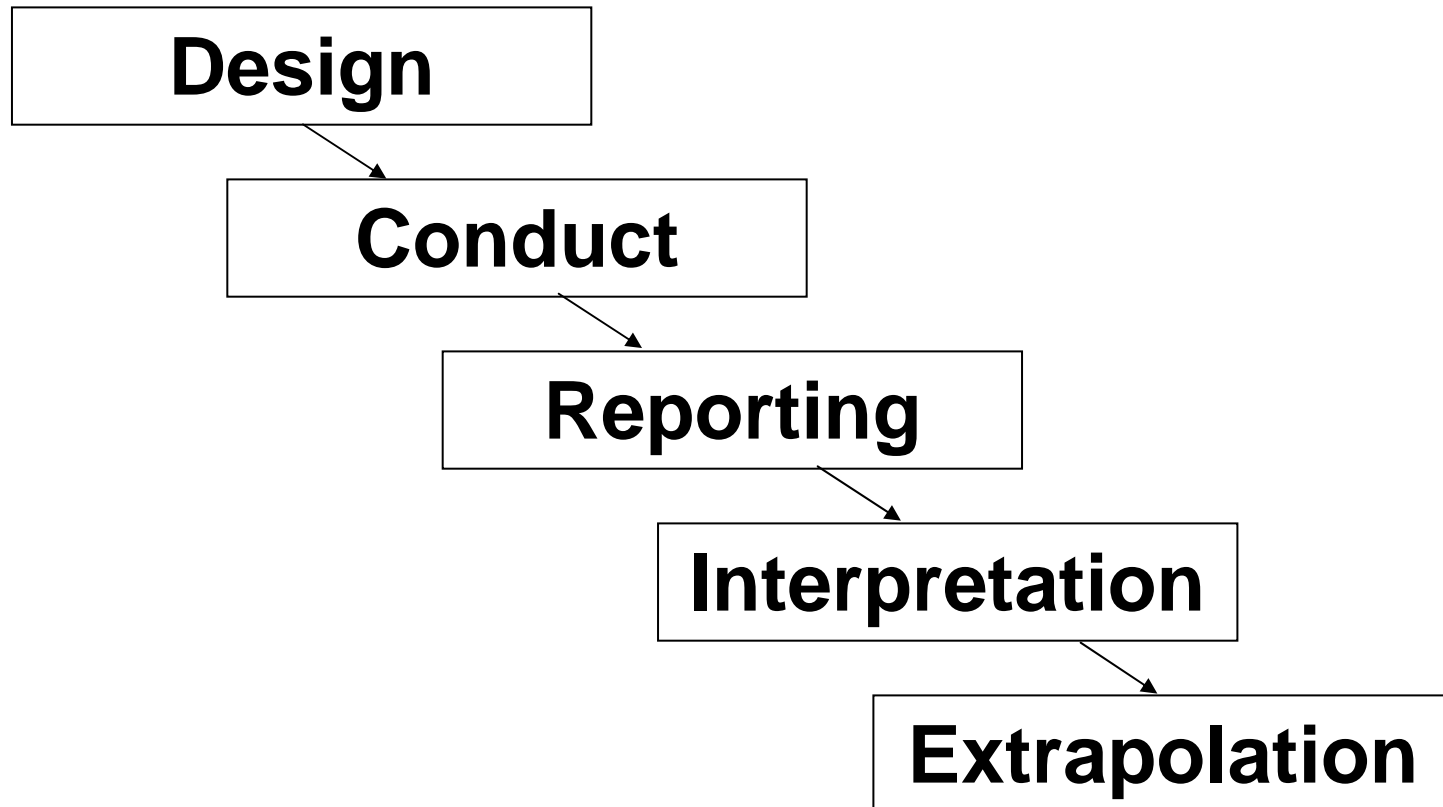
- **Current intake of added sugars greatly exceeds discretionary calorie allowances (2005 US Dietary Guidelines)**
- **The American Heart Association cites 300 calories per day consumed by the average American in added sugar intake**
- **Leading experts are recommending lower sugar intakes, in light of the global pandemic of obesity**
 - **About 65% of adults in the US are overweight or obese**
 - **Significant increase in the risk for several disabling medical and psychological conditions**

- **There are six NNS currently approved in the US**
- **All provide no calories and have been extensively tested and determined to be safe for their intended use**
- **About 15% of Americans regularly consume beverages and foods that contain NNS**

- **Carefully designed and methodically conducted programs completed to evaluate NNS for potential safety concerns**
- **No adverse reactions including absence of carcinogenicity with lifetime daily intake in appropriate animal models**
 - **For example: Testing shows no carcinogenic potential in animal models using an intake of sucralose equivalent in sweetness to >40 lbs sugar/day**
- **These rigorous testing programs are completed to allow regulatory approval of non-nutritive sweeteners**

- **Appropriate protocols used for testing to evaluate carcinogenic potential are found in Guidelines promulgated by national and international regulatory agencies. For relevant extrapolation of results from these studies to humans, consideration of many factors are essential including:**
 - **Selection of the animal model;**
 - **Characterization of the test substance;**
 - **Choice of the number of doses, dose levels and durations of exposure used;**
 - **Appropriate numbers of animals per group; and**
 - **Execution of complete and peer reviewed histological evaluations and appropriate statistics.**

- **Shortcomings in any of the following parameters lead to compromised conclusions!**



Not All Studies Are Created Equal!

- **Conflicting views on results of different animal carcinogenicity test have arisen from:**
 - **Differences and deficiencies in the design of studies, rigorousness of test procedures, dose selection, histopathology, and statistical evaluations**

The result of shortcomings in study design/execution is an extension of the interpretation beyond the limits supported by the data obtained.



Rat Study Shows Cancer, Aspartame Link

Monday, November 21, 2005

By Salynn Boyles

“A study in rats links the popular **artificial** sweetener aspartame to a wide range of **cancers**, but **industry** officials charge that the research is badly flawed...” ***what is the takeaway?***

- Perception that a hazard has been identified but with no quantification of risk and uncertain potential for harm
- Application of Precautionary Principle

Uncertainty Underlying the Precautionary Principle Approach

Instead of → How much risk is allowable

Substitute → How much hazard is possible

Consumer fear is driven by Uncertainty

Carcinogenicity: What the Science Really Tells Us

- **NNS do NOT cause cancer in humans**
 - **Extensive, critical evaluation using studies with extremely intakes every day over all phases of life, including gestation**
- **Safety conclusion is affirmed by experts, world-wide**
 - **FDA, EFSA, JECFA (WHO/FAO), FSANZ**

Consumer Confidence Is Supported by Understanding the Process

“Does a weight problem prompt people to try to cut calories or does the consumption of artificial sweeteners lead to their weight problem?”

- NY Times Feb 16, 2009

Coincidence or Causality?

- **Some HYPOTHESES for causality:**
 - **Does the use of NNS result in caloric overcompensation because sweetness, regardless of its source, produces an increased desire for sweet tasting foods?**
 - **Does the use of NNS fool the body, by divorcing sweet taste from calories, leading to an increased craving for *extra* calories?**
 - **Do NNS disrupt regulation of satiety by interacting with gut taste receptors leading to:**
 - **Disruption of normal regulatory gut hormones?**
 - **Increased absorption of glucose from the GIT?**

- **Activity**
 - Television, cars, desk-jobs, computers, work-saving appliances
- **Social norms**
 - Play outside? Walk to school/work?
 - Food choices and portion sizes
- **Food economy**
 - Energy dense, low-cost
- **Time economy**
 - Fast foods – out of home or in
- **Food palatability**
 - Easy to engage interest with wide range of choices

The Bottom Line:

Do NNS Affect Food Intake?

- Numerous studies in humans provide compelling evidence that NNS do not cause a long-term increase in food intake or body weight
- Chronic (lifetime), high-dose (orders of magnitude above actual intake levels) animal studies are strong evidence of no effect on body weight
- Possible mechanisms that would link all major NNS to produce body weight dys-regulation are ruled out by research
- Taken together, evidence suggests that NNS have the potential to aid in weight management

- **Dietary studies in animals need careful consideration:**
 - **Does taste impact results?**
 - **Does level of physical activity impact results?**
 - **Do other study design elements have any effect on signals that control post-ingestive modulation of feeding?**
 - **Have results been fairly juxtaposed against existing animal data?**

Fueling the Obesity Epidemic? Artificially Sweetened Beverage Use and Long Term Weight Gain

- **Human studies need careful consideration:**
 - **Is there actual evidence of causality? (dietary recall surveys)**
 - **Was the study double-blinded, randomized and done with appropriate controls?**
 - **Was the study of sufficient duration?**
 - **Are there biases?**
- **Be aware of the difference between association and causality:**
 - **The more firemen fighting a fire, the bigger the fire is going to be.**

More Points to Consider

- **No calorie sweeteners have no calories**
- **Possible mechanisms of action are refuted by science**
 - **No increased blood glucose/insulin**
 - **No effect on hormones involved in satiety regulation**
 - **No increased caloric intake in controlled clinical trials**
 - **DECREASED caloric intake in controlled clinical trials**
 - **No evidence of increased sweet intake**
- **Must consider effects on appetite, energy intake and finally body weight**
- **Weight outcome is a multi-factorial phenomena**

Fear does not equal truth
Information equals enlightenment

What Does the Science Say?

- **Influence of NNS on appetite, energy intake and body weight has been the subject of hundreds of human studies**
- **These studies provide compelling evidence that NNS do not cause a long-term increase in food intake or body weight in adults or children.**
- **Taken together, evidence suggests that NNS have the potential to aid in weight management**
- **Weight control is fundamentally a function of caloric balance**

CALORIES COUNT

- **“The bottom line on whether low-calorie sweeteners are beneficial in weight management comes down to how people choose to use them. Those who use foods and beverages with low-calorie sweeteners prudently, in place of higher calorie options in their diet, could find them beneficial in weight management. However, they clearly will not prevent weight gain among individuals who use them to rationalize over-consumption of high-calorie foods and beverages, or make little effort to otherwise keep their caloric intake on track.”**

Coca-Cola Company Bulletin

- **US Based:**

- Claire Kruger, PhD, DABT
- A. Wallace Hayes, PhD, DABT
- Nancy Booth, PhD
- Ronald Slesinski, PhD, DABT
- Susan Phillips, MS
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- Roger Clemens, PhD, CNS
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THANK YOU!

Questions?

