



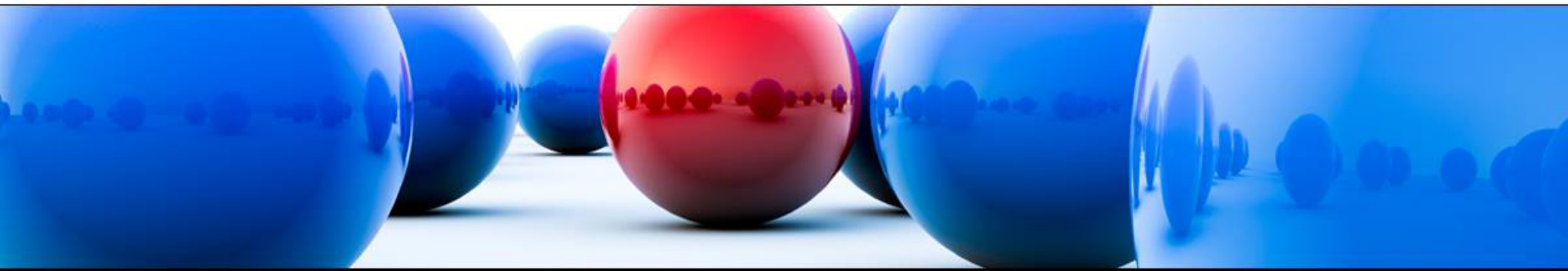
Nancy L. Booth, Ph.D.

Principles of Safety Assessment

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

**American College of Nutrition
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Principles of Safety Assessment: Integrating the Sciences of Nutrition, Chemistry, Toxicology and Pharmacognosy into Food Ingredient Evaluations



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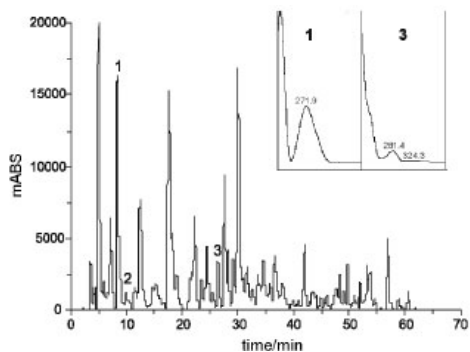
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Evaluating Safety of Complex Food Ingredients

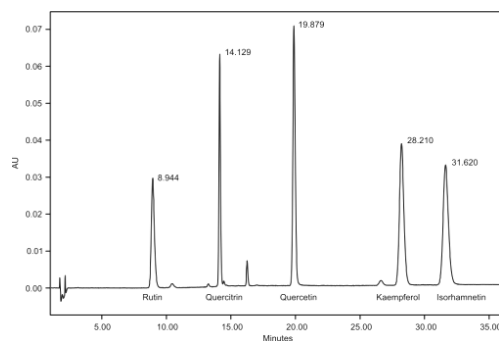
- Increasing focus on food ingredients with health and functional benefits
- Many of these ingredients are chemically complex
- Some are of natural origin, but...
 - **Natural does not necessarily = safe**
- How to evaluate safety of these ingredients?

- **What are “natural products?”**
 - **Naturally-occurring substances or molecules that are useful for their medicinal, ecological, gustatory, or other functional properties.**
 - **The species that are the source of the compounds include, but are not limited to, plants, fungi, marine invertebrates, and bacteria.**

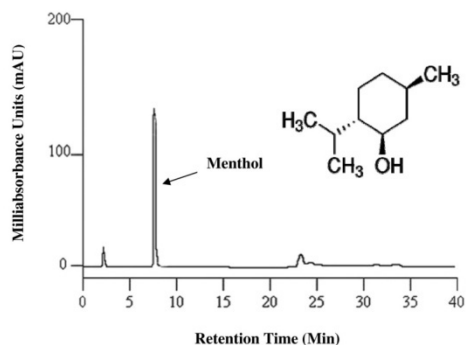
Natural Products Range in Chemical Complexity



◀ Extract



◀ Semi-purified fraction



◀ Purified compound



More complex

Less complex

Focus: Natural Product-Based Food Ingredients

- **As food ingredients, natural products are useful for their gustatory, nutritive and/or functional properties.**
 - **Examples:**
 - ❖ **Rosemary extract as a preservative;**
 - ❖ **Stevia semi-purified extract as a sweetener;**
 - ❖ **Docosahexaenoic acid (DHA)/arachidonic acid (ARA) for eye, brain development; and**
 - ❖ **Phytosterols for blood lipid management.**

Safety Evaluation of Natural Product-Based Food Ingredients

- What areas of science are utilized?
 - Chemistry
 - Botany (plants, fungi), Microbiology (bacteria, microbes)
 - Pharmacognosy – the study of natural products
 - Toxicology
 - Others (food safety, immunology, pharmacology, process engineering)

Safety Evaluation of Natural Product-Based Food Ingredients

- **What are the goals of the safety evaluation?**
 - 1. Confirm the (botanical/microbial) identity of the source material & chemical composition of the ingredient (“positive” criteria)**
 - 2. Demonstrate the absence of toxins, contaminants and/or adulterants (“negative” criteria)**
 - 3. Understand natural compositional variation**
 - 4. Establish safe levels of consumption**

Confirming Identity of the Source Material

- **Why does this matter?**
 - **Many species have similar or identical common names**
 - **Causes confusion**
 - **May be a safety concern in some cases**

Confirming Identity of the Source Material

- Example: What is “Ginseng?”

Panax ginseng C. A. Mey. (Araliaceae) (“Asian ginseng”)

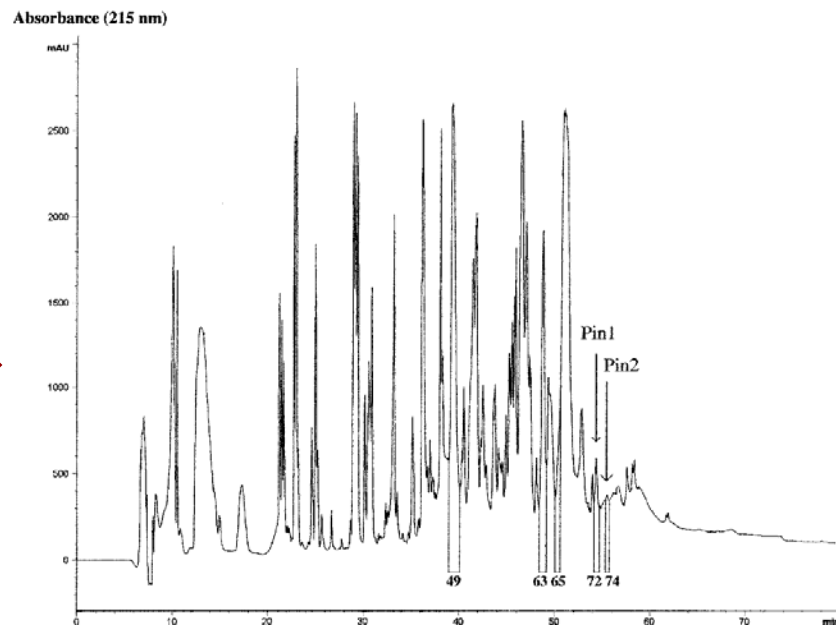
P. notoginseng (Burkill) F.H. Chen ex C.H. Chow
(Araliaceae) (“Sanchi ginseng”)

P. quinquefolius L. (Araliaceae) (“American ginseng”)

Eleutherococcus senticosus (Rupr. ex Maxim.) Maxim.
(Araliaceae) (“Siberian ginseng”)

Pfaffia paniculata (Mart.) Kuntze (Amaranthaceae)
(“Brazilian ginseng”)

Chemical Composition is Key to Evaluating Safety

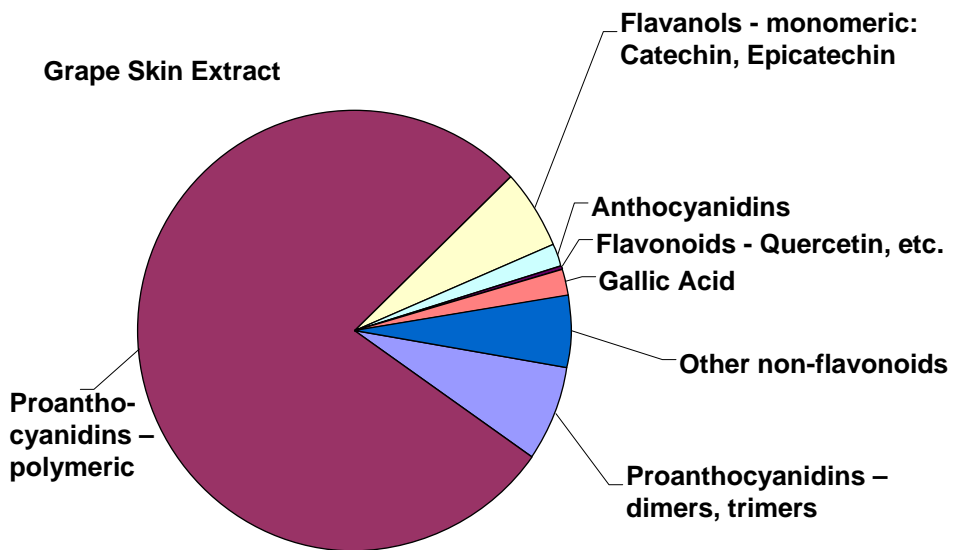


Extract compound profile

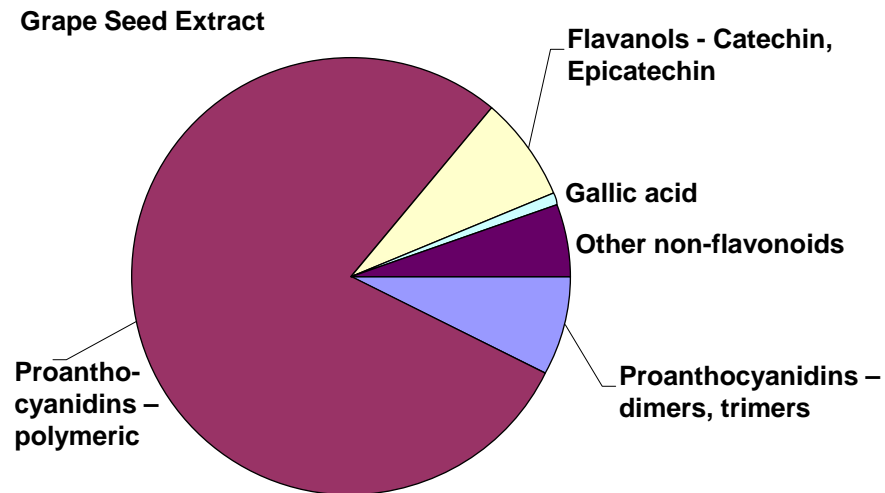
What Affects Chemical Composition of Natural Products?

- **Plant part**
- **Harvest time**
- **Extraction method**
- **Presence of natural toxins**
- **Presence of other contaminants**

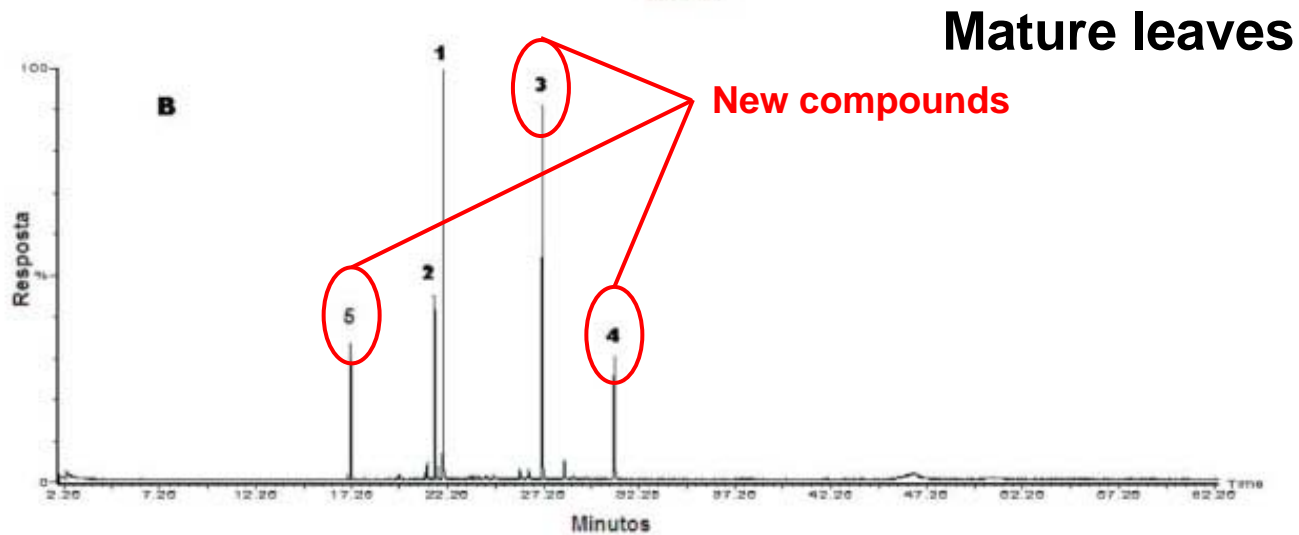
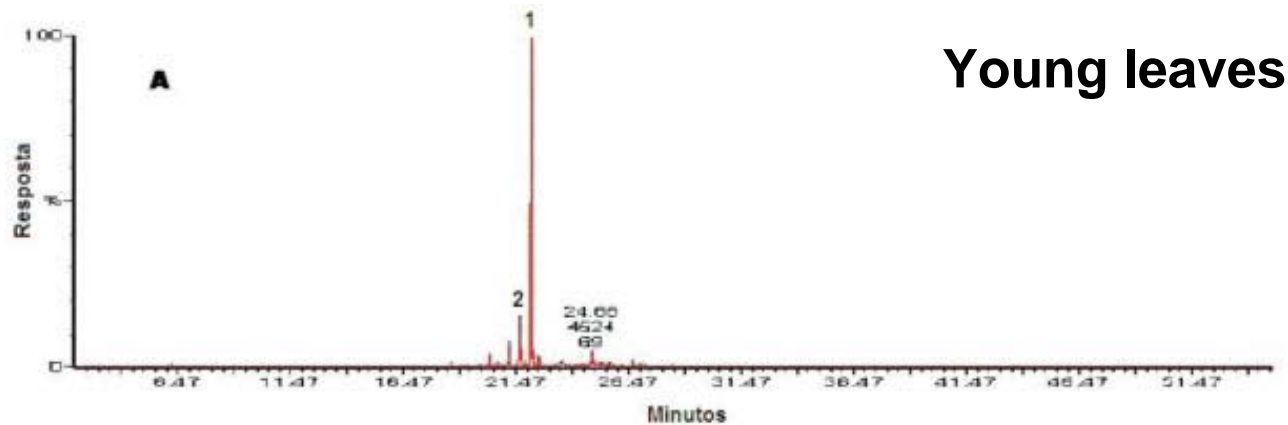
Polyphenols from Grape Skins



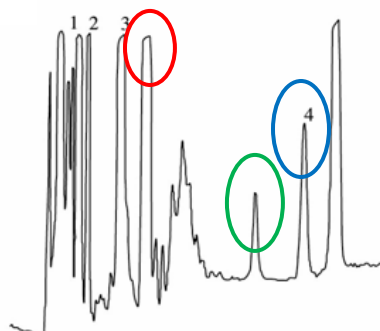
Polyphenols from Grape Seeds



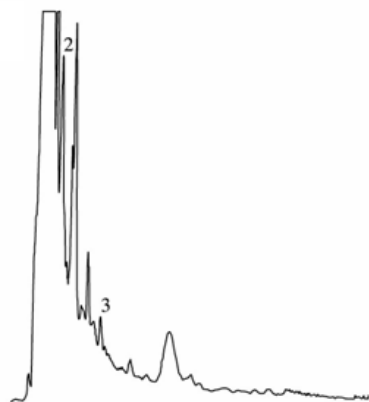
Harvest Time Affects Composition: Young vs. Old Leaves



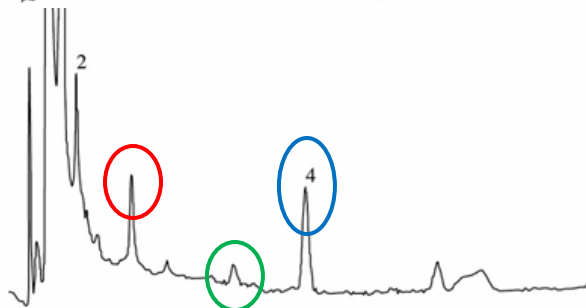
Different Extraction Methods Affect Composition



Fresh garlic

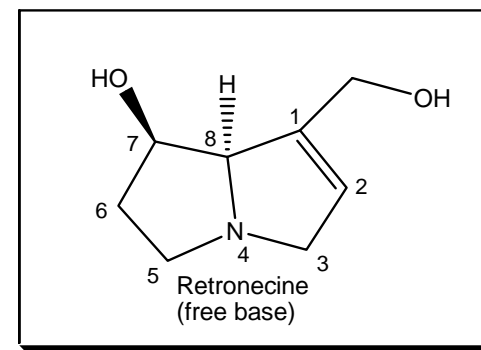
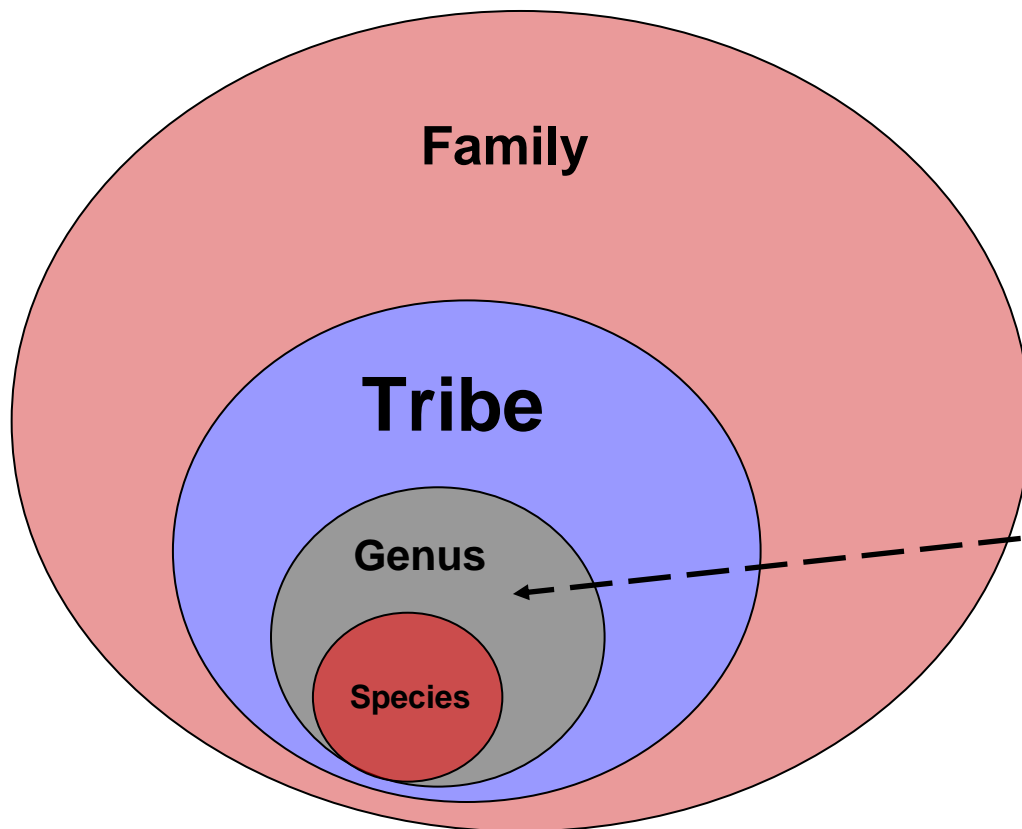


Ethanolic extract



Supercritical CO₂
(More like fresh garlic)

- Consider the chemical content and pharmacological activity of closely-related species compared with the species in question.



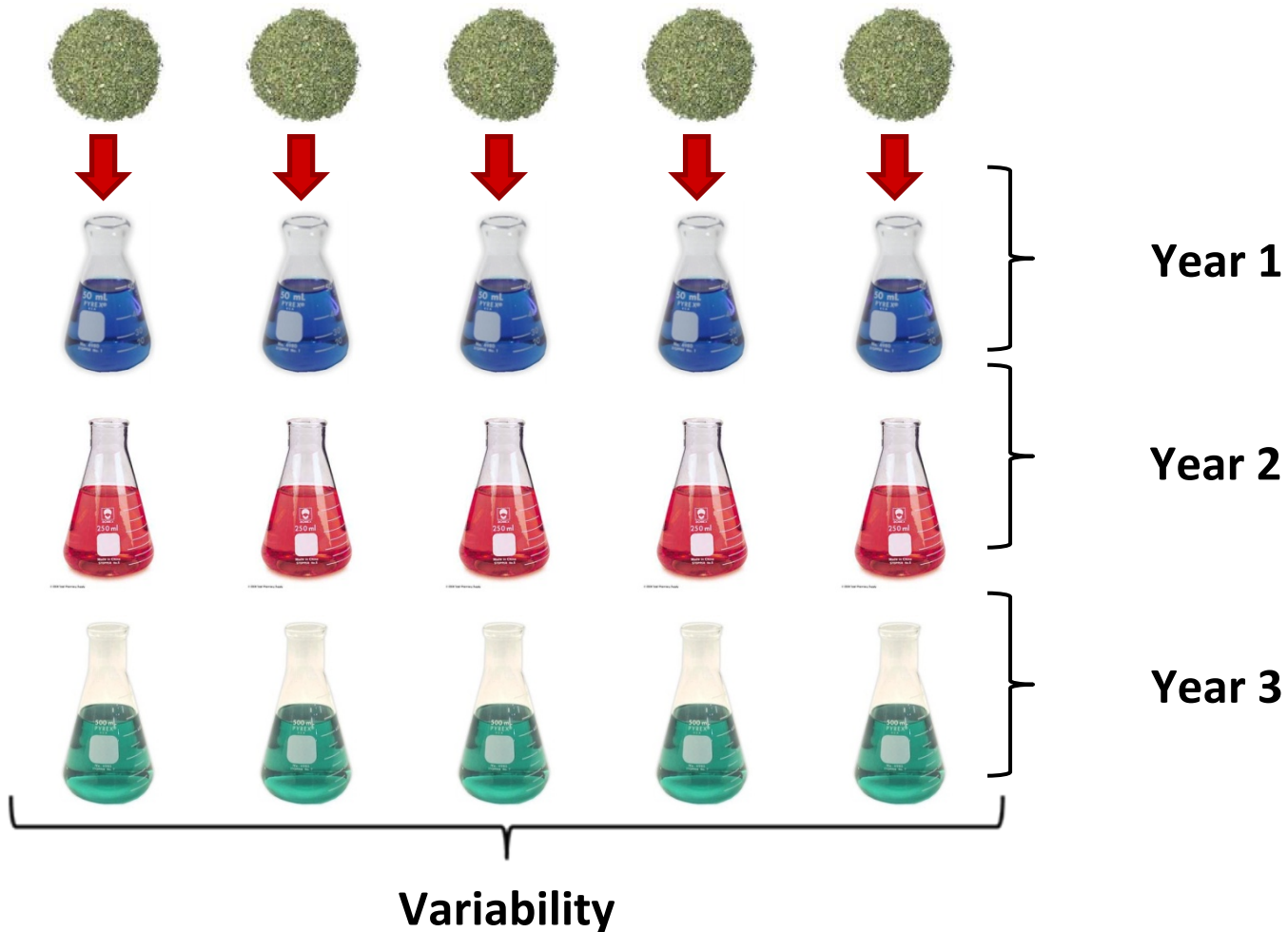
E.g., 1,2-unsaturated pyrrolizidine alkaloids (PAs) occurring in *Symphytum* and *Senecio* spp.

► Avoid these genera of plants, or take steps to ensure they are not present in the product.

Other Contaminants that May Be Present in Natural Products

- **Economic adulterants (use of cheaper species or materials; substitution is profit-motivated)**
- **Nuisance species (co-collected during harvest; weeds, impure seed lots)**
- **Inadvertent substitution with (incorrect) species having similar botanical characteristics**
- **Pesticide/herbicide/insecticide residues**
- **Heavy metals content**
- **Mycotoxin content, mold, microbes, moisture (due to improper harvesting and handling practices)**
- **Contaminants introduced during processing or extraction procedures (e.g., solvent residues)**

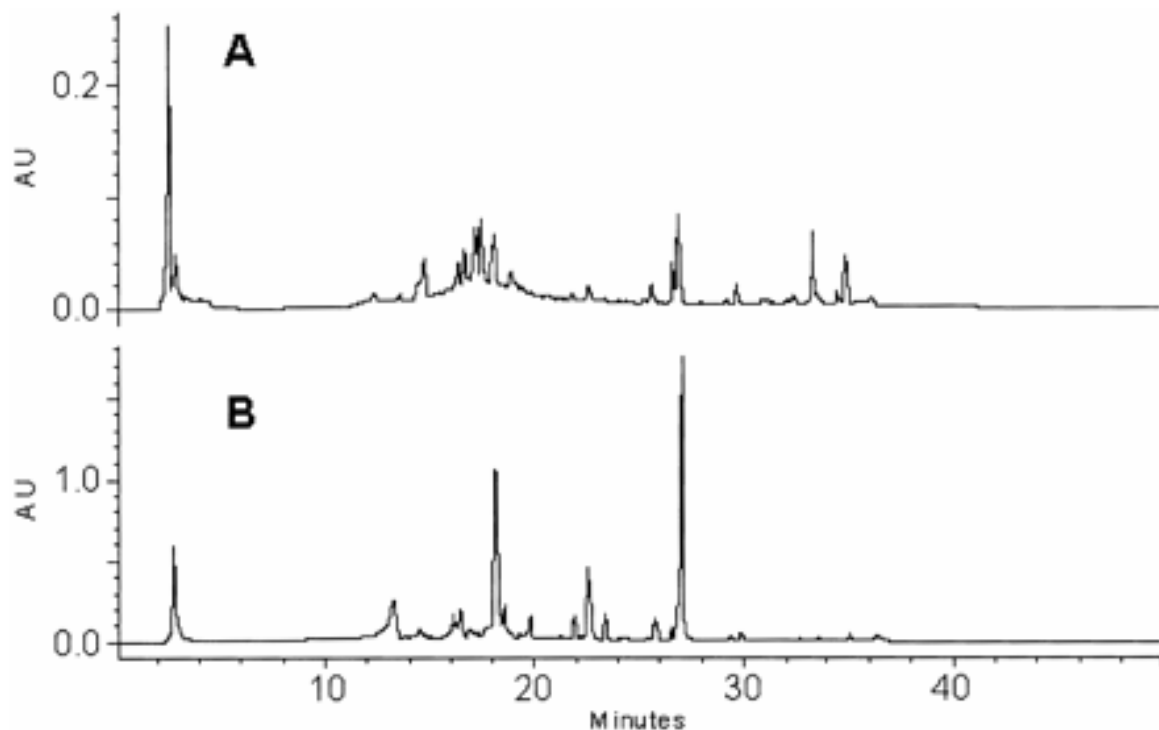
Composition Consistency Over Time



Natural Compositional Variability May or May Not Be Toxicologically Relevant

Questions:

- 1) Are extracts A & B *qualitatively* similar?
- 2) Are extracts A & B *quantitatively* similar?



Answers:

- 1) Yes.
- 2) No.

Is there a toxicological significance of the differences?

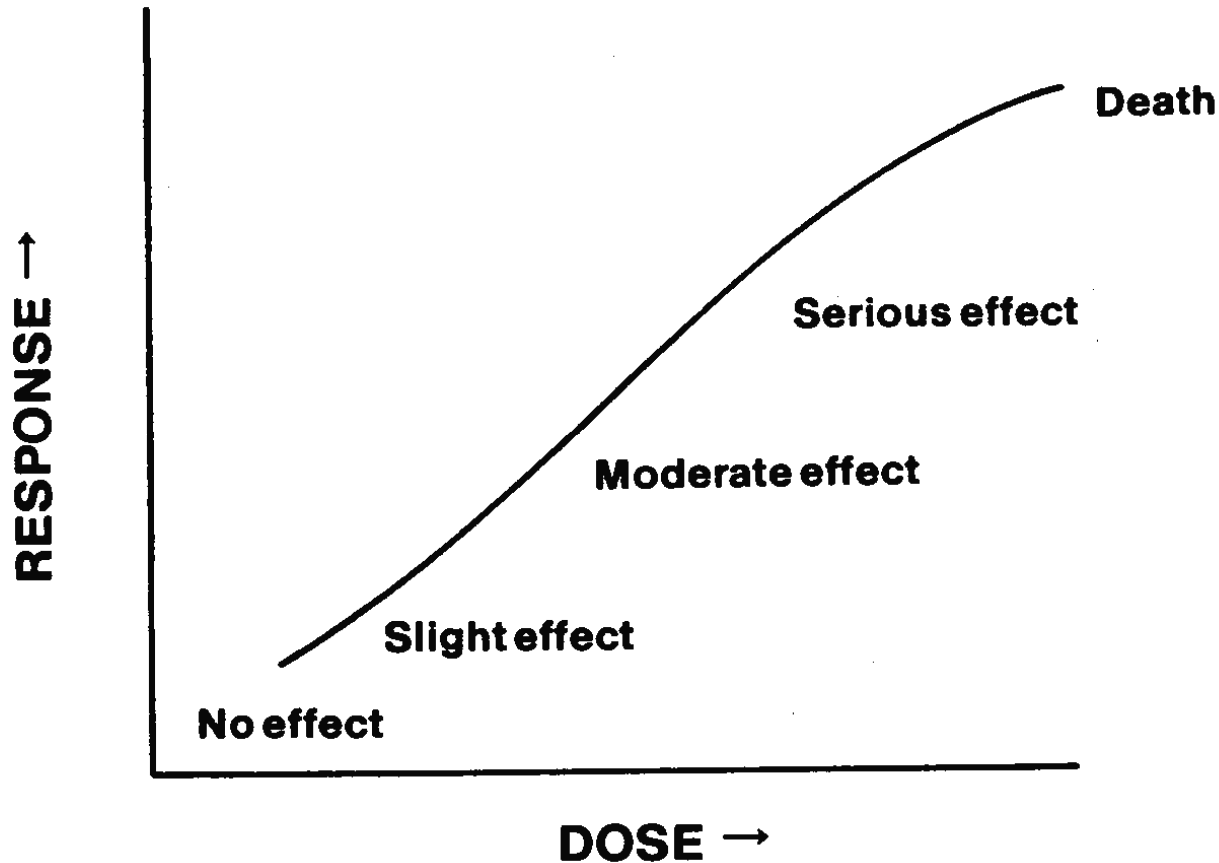
Spectrum of Toxic Effects

- **Local and systemic effects**
 - At site of first contact (gastrointestinal)
 - At site(s) distal to point absorbed (internal organ damage)
- **Reversible and irreversible effects**
 - Disappear following cessation of exposure (enzyme changes, respiratory depression)
 - Persist or even progress after exposure is discontinued (cancer, genetic alterations, birth defects, death)
- **Immediate and delayed effects**
 - Develop shortly after single exposure (cyanide poisoning)
 - Occur after a lapse of time (10-20 years for cancer)

Understanding the Toxicology of Natural Product Food Ingredients

- **Chemical composition**
- **Dose or amount ingested**
- **Duration of administration**
- **Frequency of administration**

Dose-Response is Important



Dose-response relationship for a typical chemical.

- **Efficiency of repair is an important determinant of the dose-response relationship**
 - **Amount, frequency and duration of exposure are involved**
 - **For example, repair processes may not be overwhelmed at a dose given over a short period of time but the same dose given over a longer period of time may overwhelm these repair processes, resulting in toxicity**
 - **Similarly, frequency of exposure of the same dose may affect the efficiency of the repair processes, producing more toxicity at greater frequencies of administration**

Toxicology is Used to Derive an Acceptable Daily Intake (ADI)

- **Acceptable Daily Intake (ADI) is defined as the daily intake of the ingredient that during the human lifetime appears to be without appreciable risk.**
- **Risk is the likelihood that toxicity will be produced under the conditions of exposure.**
- **Safety is the inverse of risk.**

Derivation of the ADI to Support Safe Intake

$$\text{ADI} = \frac{\text{NOAEL (mg/kg/day)}}{\text{Safety Factors}}$$

**ADI = Acceptable Daily Intake, a fixed,
calculated value based on safety studies**

NOAEL = No Observed Adverse Effect Level

Calculation of the EDI to Support Safe Intake

EDI = Estimated Daily Intake

--A calculated value, can vary according to food use

Comparison of the EDI with the ADI

EDI \leq ADI: Safe consumption level

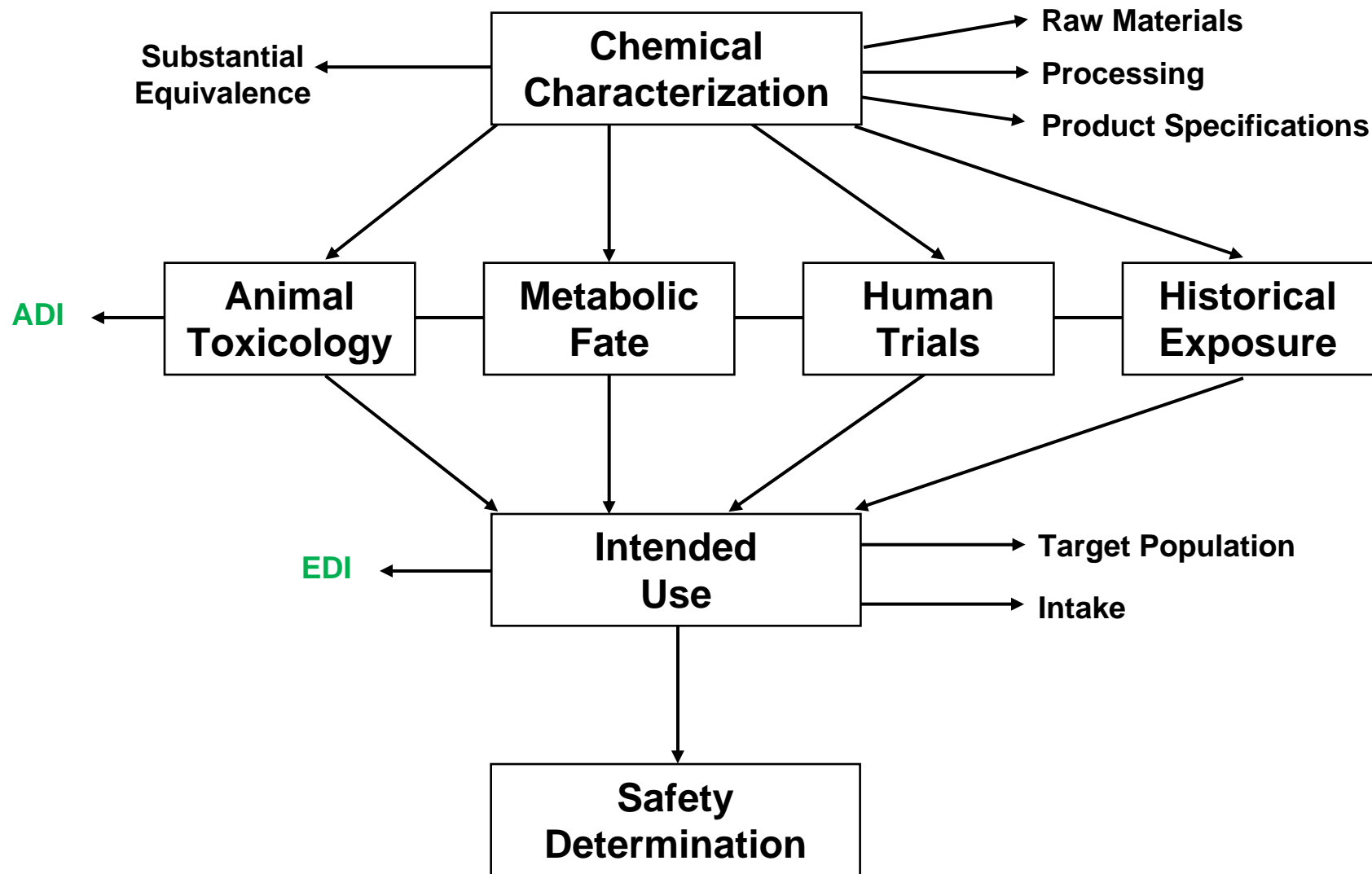
EDI $>$ ADI: Non-safe consumption level

Comparison of the EDI with the ADI

*EDI ≤ ADI: Safe consumption level

EDI > ADI: Non-safe consumption level

Safety Analysis



- **US Based:**

- Claire Kruger, PhD, DABT
- A. Wallace Hayes, PhD, DABT
- Nancy Booth, PhD
- Ronald Slesinski, PhD, DABT
- Susan Phillips, MS
- Yongming Lu, PhD
- Roger Clemens, PhD, CNS
- Dietrich Conze, PhD
- Robert Lodder, PhD
- Nathalie Chevreau, PhD, RD
- Susan Trimbo, PhD

- **International:**

- John Howlett, BSc – EU
- Nino Binns, PhD – EU
- Silvia Berlanga de Moraes Barros, PhD – Latin America
- Tetsuo Satoh, PhD – Japan
- S.K. Gupta, PhD, DSc – Asia
- Govinder Flora, PhD – Asia

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THANK YOU!

Questions?

