



Botanical Safety

Discovering Common Struggles, Needs, and Solutions

29th May 2020

Daniel S. Marsman, DVM PhD



Broad consumer demand for natural health and nutritional products

- U.S. dietary supplement industry: **\$46 billion** in annual **sales**.¹
- More than **170 million** Americans take **dietary supplements** annually, including vitamins, minerals, botanicals, and specialty products.
- **Half** of dietary supplement users take at least one **botanical** product.
- Most popular **Botanicals** in dietary supplements include²:
 - Horehound (*Marrubium vulgare*)
 - Echinacea (*Echinacea* spp.)
 - Turmeric (*Curcuma longa*)
 - Elderberry (*Sambucus nigra*)
 - Green Tea (*Camellia sinensis*)
 - Ginger (*Zingiber officinale*)
 - Ivy Leaf (*Hedera helix*)
 - Garlic (*Allium sativum*)
 - Fenugreek (*Trigonella foenum-graecum*)
 - Black Cohosh (*Actaea racemosa*)
 - Saw Palmetto (*Serenoa repens*)
 - Flax Seed (*Linum usitatissimum*)

Botanicals with recognized pharmacologic and toxicologic properties

- In addition to plants as an essential part of the diet, plants are creative chemical factories, for good or harm.



Safety concerns

- Adulteration continues as a problematic reality
- Complexity and uncertainty also drive the Safety concerns.

HEALTH

This stimulant is banned in sports but found in dietary supplements. A doctor asks why

By ELIZABETH COONEY @cooney_liz / SEPTEMBER 6, 2018



Few essential oils met label spec in recent test

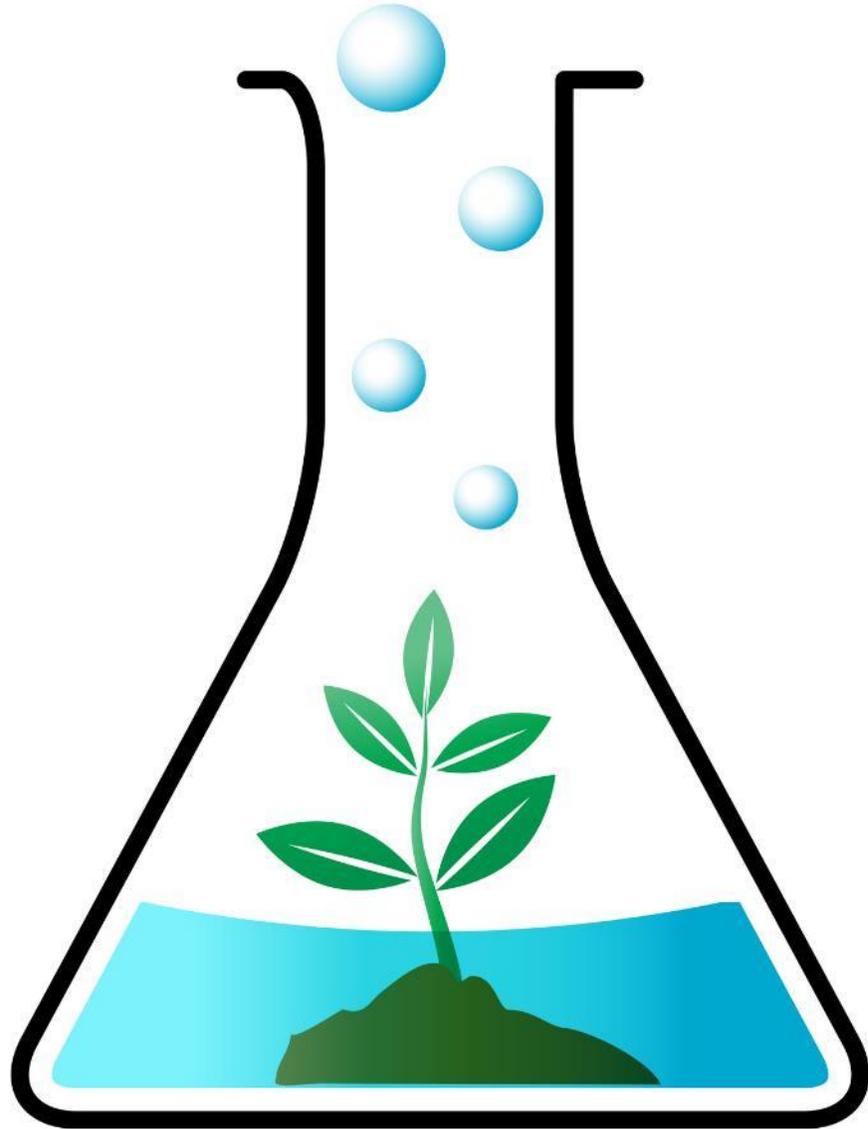
By Hank Schultz

21-Feb-2019 - Last updated on 22-Feb-2019 at 13:27 GMT



Essential oil adulteration continues to be an issue in the marketplace, according to testing results revealed by a major dietary supplement manufacturer.

Botanicals are complex



- **Plants are chemical factories**

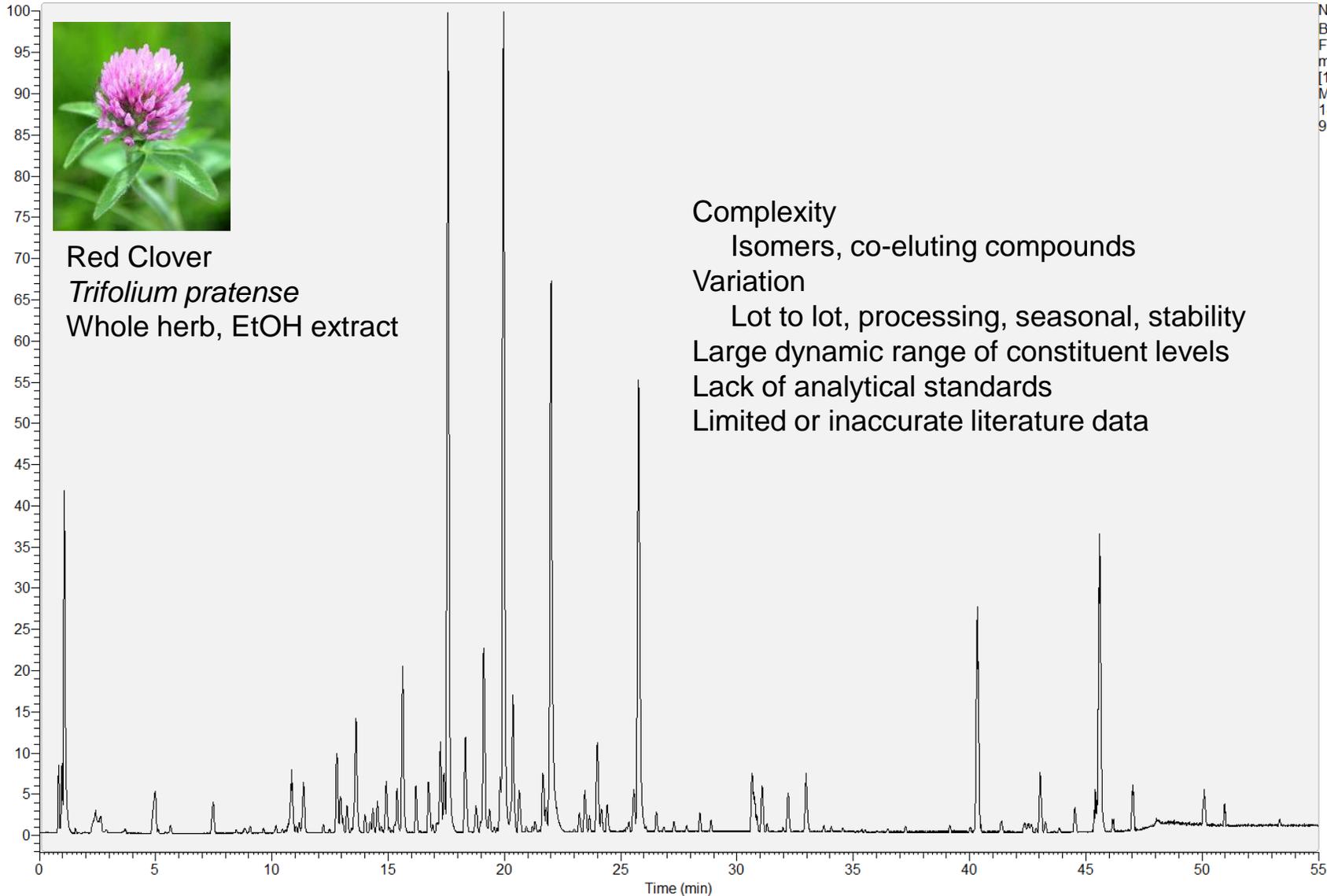
- *28,187 plant species recording as being of medicinal use**
 - *Very few (16%) cited in regulatory publications*
- *Secondary metabolites exhibit a broad range of bioactivities*
- *Many bioactive constituents from plants have been exploited by humans for use as pesticides, pharmaceuticals, poisons, or other consumer products*



BOTANICAL
SAFETY CONSORTIUM

*[Kew Royal Botanic Gardens State of the Worlds Plants Report, 2017.](#)

Analytical Challenge



Red Clover
Trifolium pratense
Whole herb, EtOH extract

NL: 1.15E7
Base Peak F:
FTMS + p ESI Full
ms
[100.00-1800.00]
MS
140206_RC-
98_Org

Complexity

Isomers, co-eluting compounds

Variation

Lot to lot, processing, seasonal, stability
Large dynamic range of constituent levels
Lack of analytical standards
Limited or inaccurate literature data

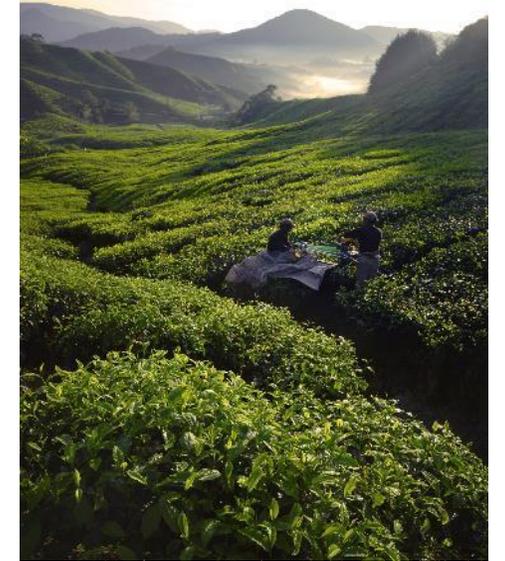
Identify all of these
components...
...and quantify them.



BOTANICAL
SAFETY CONSORTIUM

Agricultural practices drive additional complexity

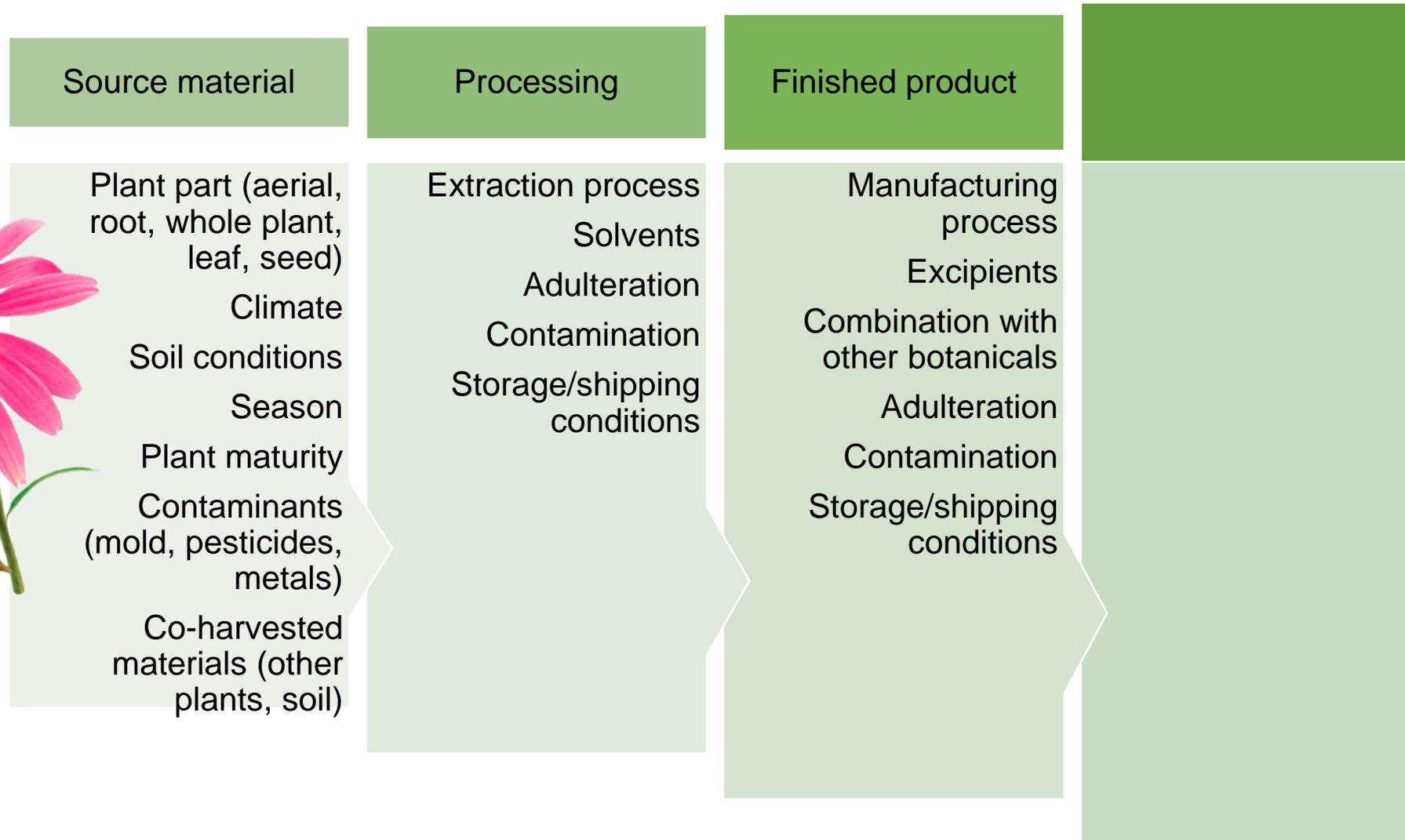
- Good Agricultural Practice
- Harvest Conditions
- Botanical Parts



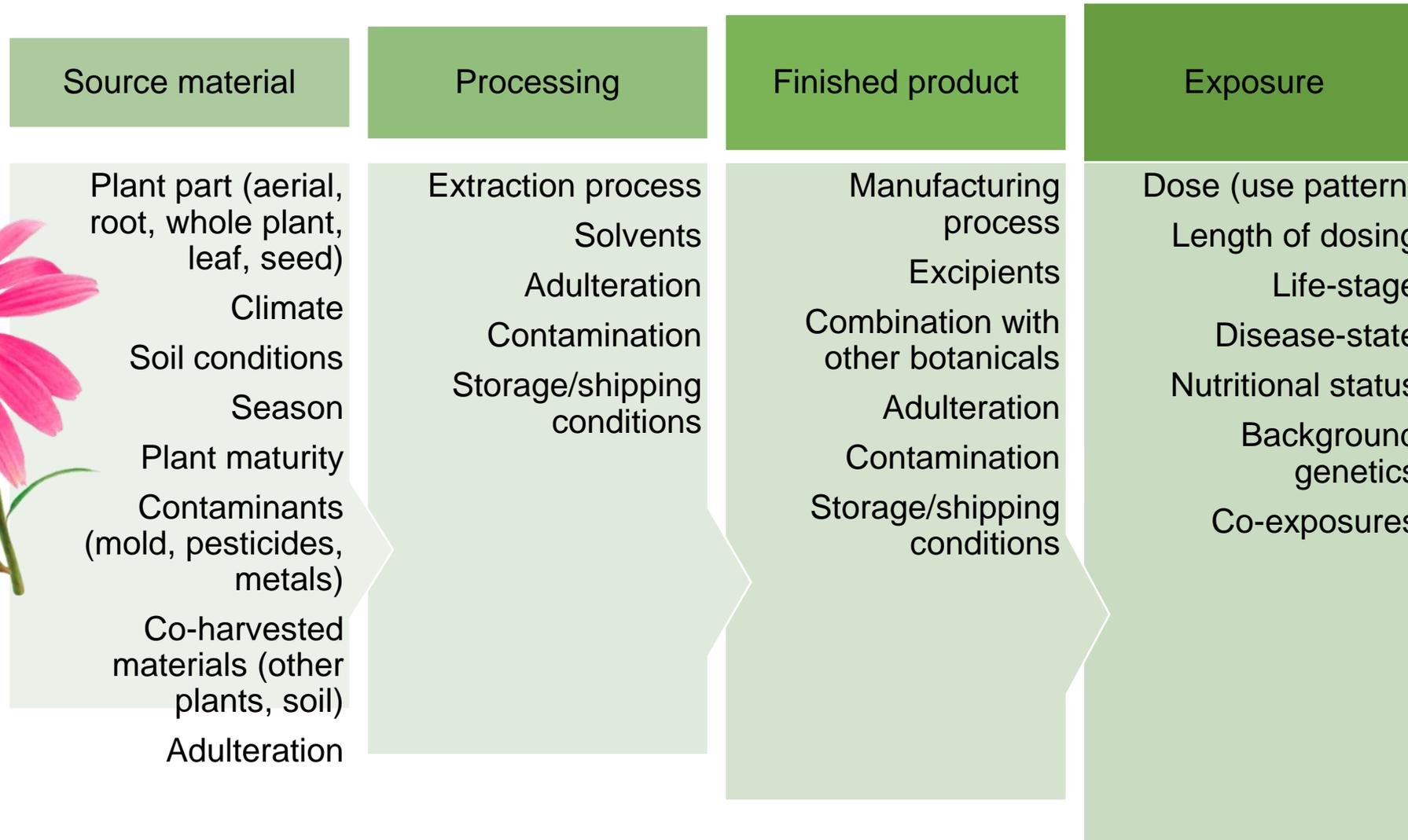
Botanical raw material processing adds additional complexity



Botanical products are variable



Botanical products are variable



Testing scheme built on single chemicals

- Toxicity testing, safety evaluation, and risk assessment processes was built around and optimized for single chemicals (drug, pesticides...)

Drugs

- Regulatory structure aimed at ensuring safety and efficacy
- Assumed to be harmful until proven safe
- Simple and consistent
- Biological activity is associated with the constituent



Botanicals

- Regulatory structure aimed at ensuring access
- Assumed to be safe until proven harmful
- Complex and variable
- Biological activity is associated with the whole mixture



Safe History of Documented Use: Hallmark of a botanical risk assessment

- Dietary use patterns provide essential bridge to safe human use
- Accurate historical records establish:
 - dose, duration, population size & diversity;
 - botanical part, species identity,
 - harvest conditions, extraction conditions, solvents...
- What if not identical?

Food & Function

[View Online / Journal Homepage / Table of Contents for this issue](#)
[Dynamic Article Links](#)

Cite this: *Food Funct.*, 2011, **2**, 760

www.rsc.org/foodfunction

REVIEW

Safety assessment of plant food supplements (PFS)†

Suzanne J. P. L. van den Berg,^{*,a} Lluís Serra-Majem,^{b,c} Patrick Coppens^d and Ivonne M. C. M. Rietjens^e

Received 13th May 2011, Accepted 20th June 2011

DOI: 10.1039/c1fo10067j



Plant food supplements (PFS), are widely used in an increasing concern in the market. Regulatory bodies assess the safety of PFS. The presence of botanical compounds, including botanical compounds, in food supplements (PFS) is a concern for the European Food Safety Authority (EFSA). The concept of Margin of Exposure (MOE) is used to assess the safety of PFS. More research is needed to discuss the safety of PFS. Altogether, it is a concern at levels far above the amount as a herb or tea.

Quality of Botanical Preparations

Specific Recommendations for the Manufacturing of Botanical Preparations, Including Extracts as Food Supplements

October 2014

FOOD SUPPLEMENTS CONTAINING BOTANICALS

IMPORTANT ISSUES TO CONSIDER IN THE DEVELOPMENT OF REGULATORY MEASURES

www.iadsa.org

IADSA
International Alliance of Dietary/
Food Supplement Associations

Traditional toxicology tools are generally not fit-for-purpose for botanicals

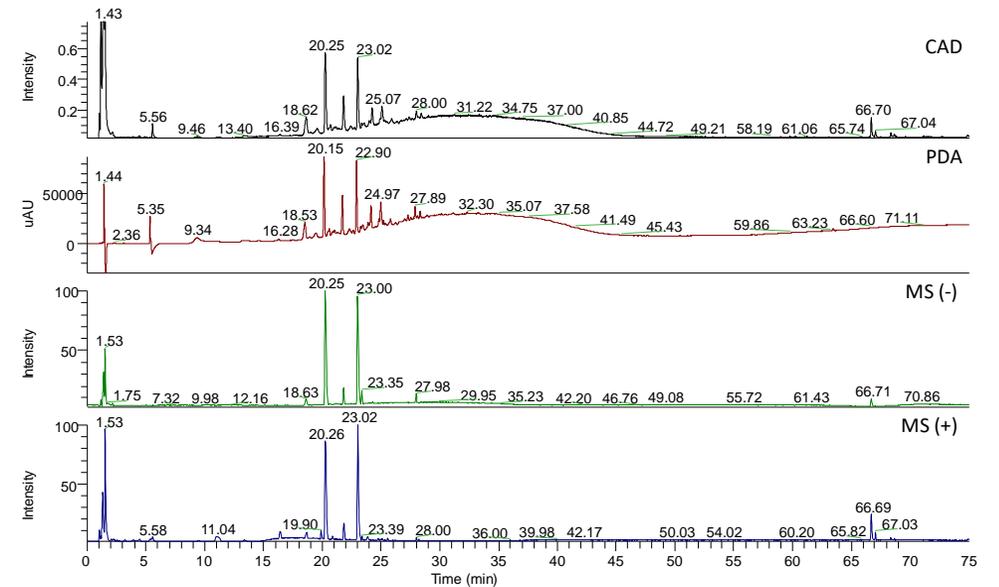
For a novel botanical, the current safety qualification process is highly dependent on animal testing:

- Often a high degree of variability when evaluating mixtures,
- An insensitive tool for discerning minor variations,
- Resource and time intensive,
- Moral/ethical considerations.



New 21st Century methodologies are providing an improved path forward

- Advances in chemical analysis provide clearer picture of raw material composition and variance
- Differential analysis provides framework to evaluate relevant differences

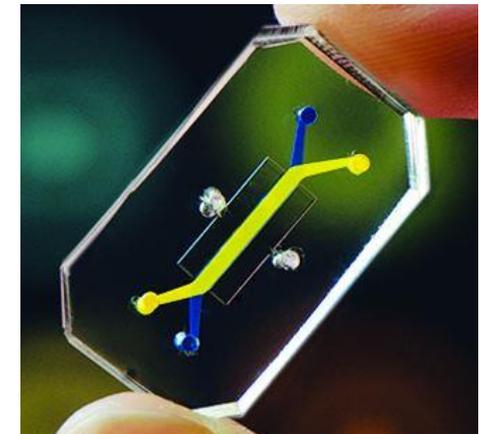
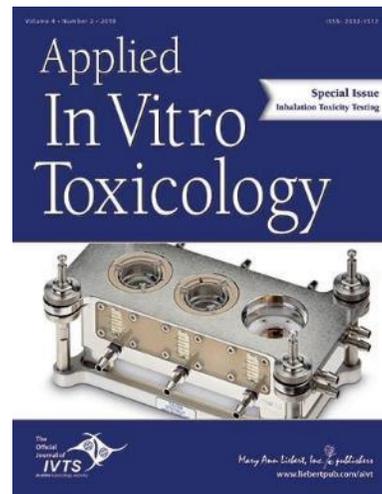


Analysis of Grape Seed Extract

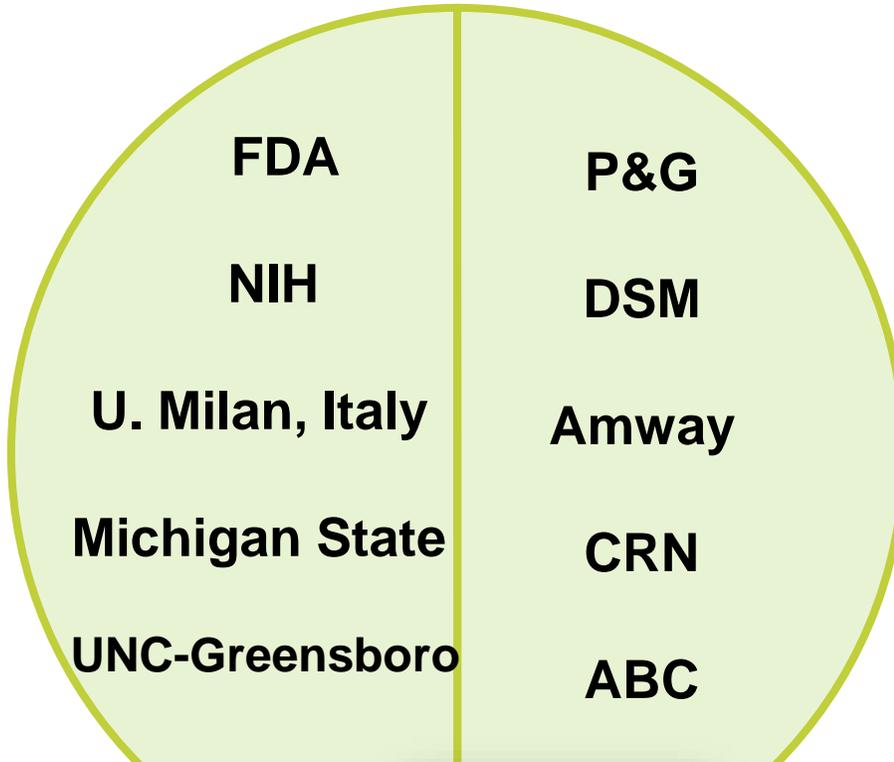
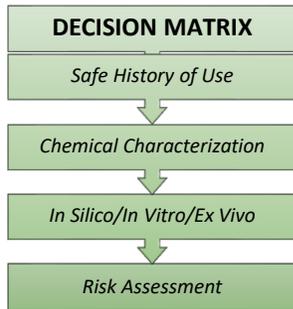
Sica, V.P.; Mahony, C.; Baker, T.R. "Multi-detector Characterization of Grape Seed Extract to Enable *In Silico* Safety Assessment" *Frontiers in Chemistry*, 2018, 6, 334.

New 21st Century methodologies are providing an improved path forward

- Current Safety Methods (*in vitro*, *ex vivo*, *in silico*) provide a suite of new options



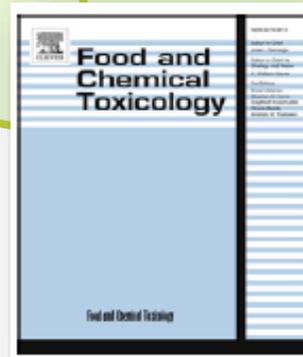
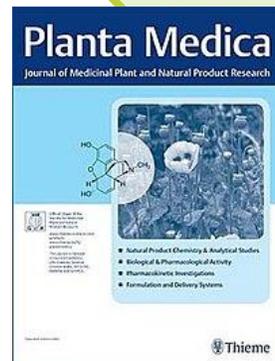
Finding Common Ground



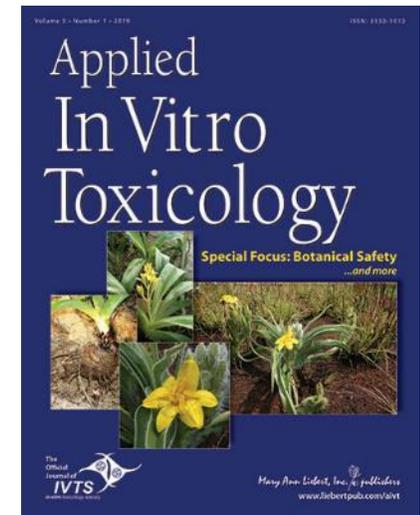
2018
2019



Development of a Consensus Approach for Botanical Safety Evaluation – A Roundtable Report.
C. L. Galli, et. al., *Tox. Lett.* 314:10-17, 2019



In silico approach to safety of botanical dietary supplement ingredients utilizing constituent-level characterization.
J. G. Little, et. al., *Food Chem. Tox.* 107:418-29, 2017



Common Struggles, Needs, and Solutions

- Growing demand for botanical products, and growing trend towards modified or specialty botanicals.
- Diverse botanical starting materials, coupled with variable agricultural and processing practices.
- Ongoing need for bridging to biosimilar materials, and a transparent discussion on qualification of new materials
- Desire to apply 21st Century (non-animal) methodologies



Mission of the Botanical Safety Consortium

To enhance the botanical safety toolkit and bring clarity to botanical dietary ingredient assessments for manufacturers and regulators.

