

# Applying Modern Toxicology to Botanical Dietary Supplements



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SAFETY CONSORTIUM

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SOT Webinar  
23 April 2020

# Outline

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- Background on the Botanical Safety Consortium (BSC)
- Goals and Objectives
- Structure and management
- Next steps and opportunities



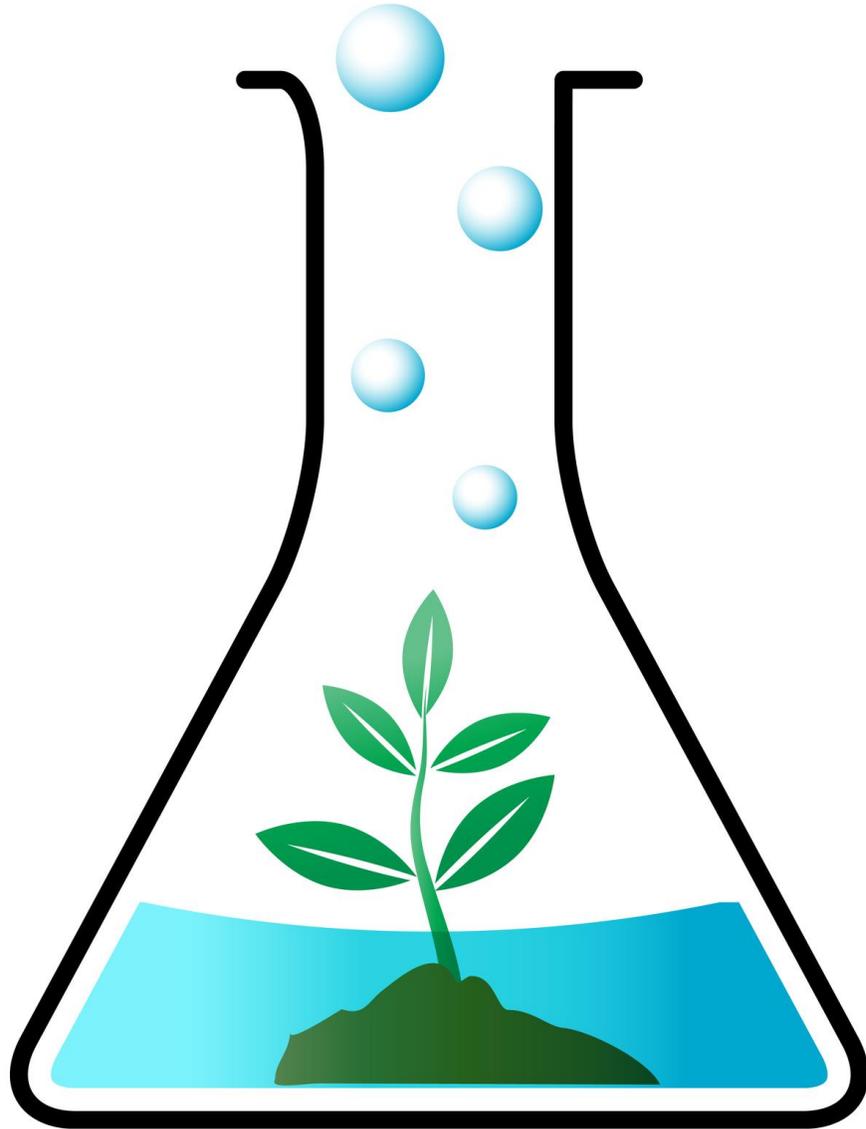
# Conflict of interest

No conflicts of interest to declare

# Botanicals are complex

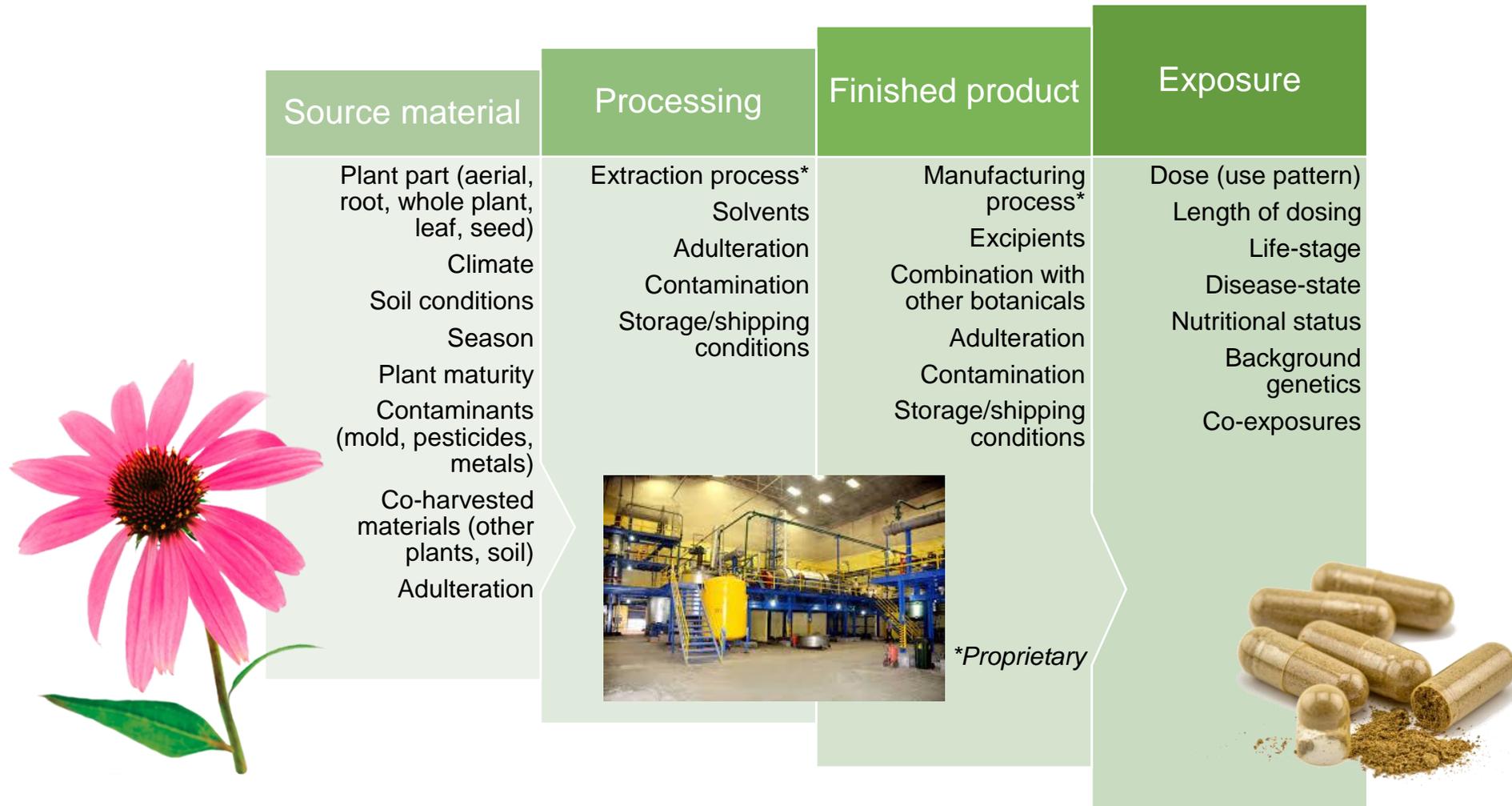
- **Plants are chemical factories**

- *28,187 plant species recorded 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, or consumer products*



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

# Botanical products are variable



# Consumption is widespread\*

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- *~18% of adults in the U.S. used non-vitamin, non-mineral dietary supplements in the past 12 months according to the 2012 National Health Interview Survey*
- *U.S. sales of botanicals topped 8 billion dollars in 2017*
- *Recommended doses can be in the range of 100s - 1000s mg per day*



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\*Clarke et al., 2015. Trends in the Use of Complementary Health Approaches Among Adults: United States, 2002-2012. Smith et al., 2018. Herbal Supplement Sales in US Increased 8.5% in 2017, Topping \$8 Billion. HerbalGram, 119, 62-71



# A System Built for Single Chemicals



- Drugs and pesticides are the most highly regulated industries
- Our toxicity testing, safety evaluation, and risk assessment processes were built around and optimized for single chemicals
- How do botanicals compare to drugs and pesticides?

## Drugs



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

## Botanicals



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



# Safety concerns

- **The label may not reflect the content!**
  - *Efficacy-driven adulteration*
  - *Economic adulteration*

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.

# The Problem...



- Limited botanical safety assessment toolkit and framework
  - 1) Compile history-of-use data.
  - 2) Are there significant safety gaps?
  - 3) If no, safety substantiation is complete.
  - 4) If yes, proceed with traditional *in vivo* toxicity testing (cost, time, and ethical concerns)
- Lack of global consensus regarding what constitutes sufficient safety substantiation for a botanical
- Global botanical safety requirements are diverse and varied
- Very little toxicity data on most botanicals currently on the market

# The Botanical Safety Consortium

Applied In Vitro Toxicology, Vol. 5, No. 1 | Roundtable

 Full Access

## The Botanical Safety Consortium

Moderator: Amy L. Roe Participants: Joseph T. Dever, Stefan Gafner, Daniel S. Marsman, Cynthia V. Rider  and Sibyl Swift

Published Online: 13 Mar 2019 | <https://doi.org/10.1089/aivt.2018.29018.rtl>

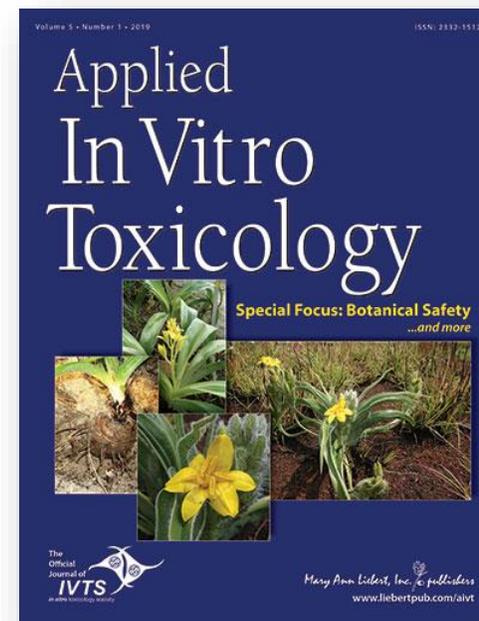
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 Tools  Share

FDA STATEMENT

### Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's new efforts to strengthen regulation of dietary supplements by modernizing and reforming FDA's oversight

*"...as with other commodities that the agency regulates, it's critical that FDA continue to work closely with our partners in industry to achieve our primary goal of protecting public health and safety. As the dietary supplement industry develops new products and ingredients, advances new delivery systems and innovates in other ways, the FDA must do more to leverage its existing resources and authorities to evaluate these products. This requires collaborative research and a shared understanding. I'm pleased to announce that we've recently created the Botanical Safety Consortium, a public-private partnership that will gather leading scientific minds from industry, academia and government to promote scientific advances in evaluating the safety of botanical ingredients and mixtures in dietary supplements. This group will look at novel ways to use cutting-edge toxicology tools, including alternatives to animal testing, to promote the goals of safety and effectiveness we share with consumers and other stakeholders."*



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# The Botanical Safety Consortium

19 Nov 2019

## FDA Announces Convening of the Botanical Safety Consortium

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### Constituent Update

November 14, 2019

The U.S. Food and Drug Administration (FDA) announced today that the Botanical Safety Consortium (BSC) has formally been convened. This milestone is the result of a [Memorandum of Understanding \(MOU\)](#) that was recently signed between the FDA, the [National Institutes of Health's National Institute of Environmental Health Sciences](#), and the [Health and Environmental Sciences Institute \(HESI\)](#) [↗](#). This MOU establishes the framework for the BSC.

The BSC was originally announced in the FDA's [February 2019 statement](#) on the agency's new efforts to strengthen regulation of dietary supplements through modernization and reform. The Consortium's mission is to provide a forum for scientists from government, academia, consumer health groups, industry, and non-profit organizations to work collaboratively to generate a sound scientific basis for integrating existing safety data and the latest toxicology tools to evaluate botanical safety in dietary supplements. With the execution of the MOU, specific guidelines for membership and participation in the BSC will be established by early 2020.



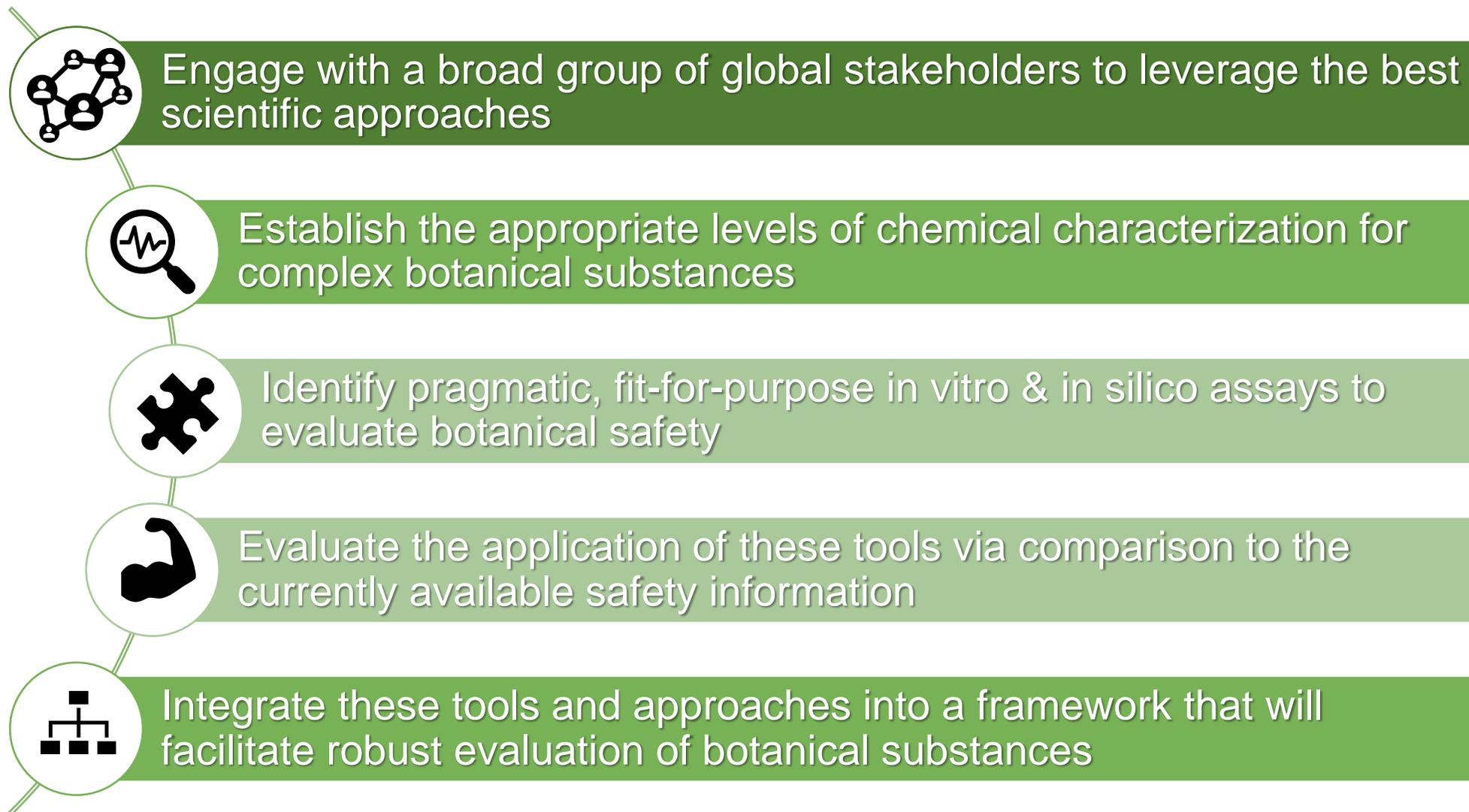
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# Mission of the Botanical Safety Consortium

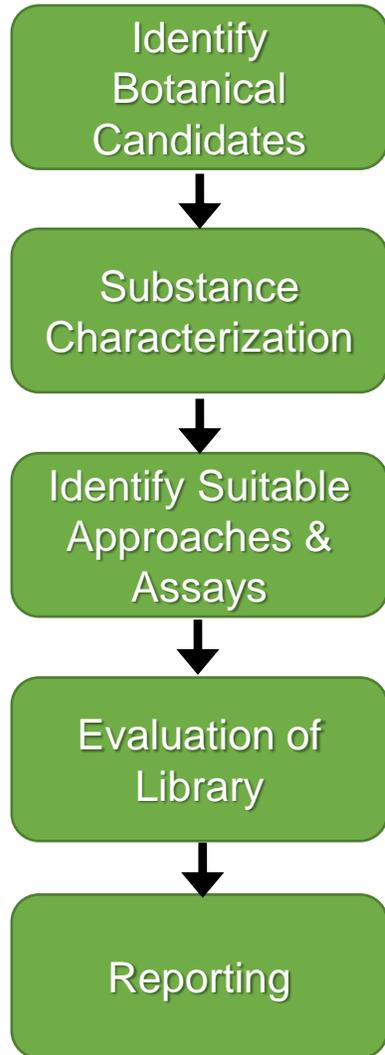
To enhance the botanical safety toolkit and bring clarity to botanical dietary ingredient assessments for manufacturers and regulators.



# Botanical Safety Consortium Objectives



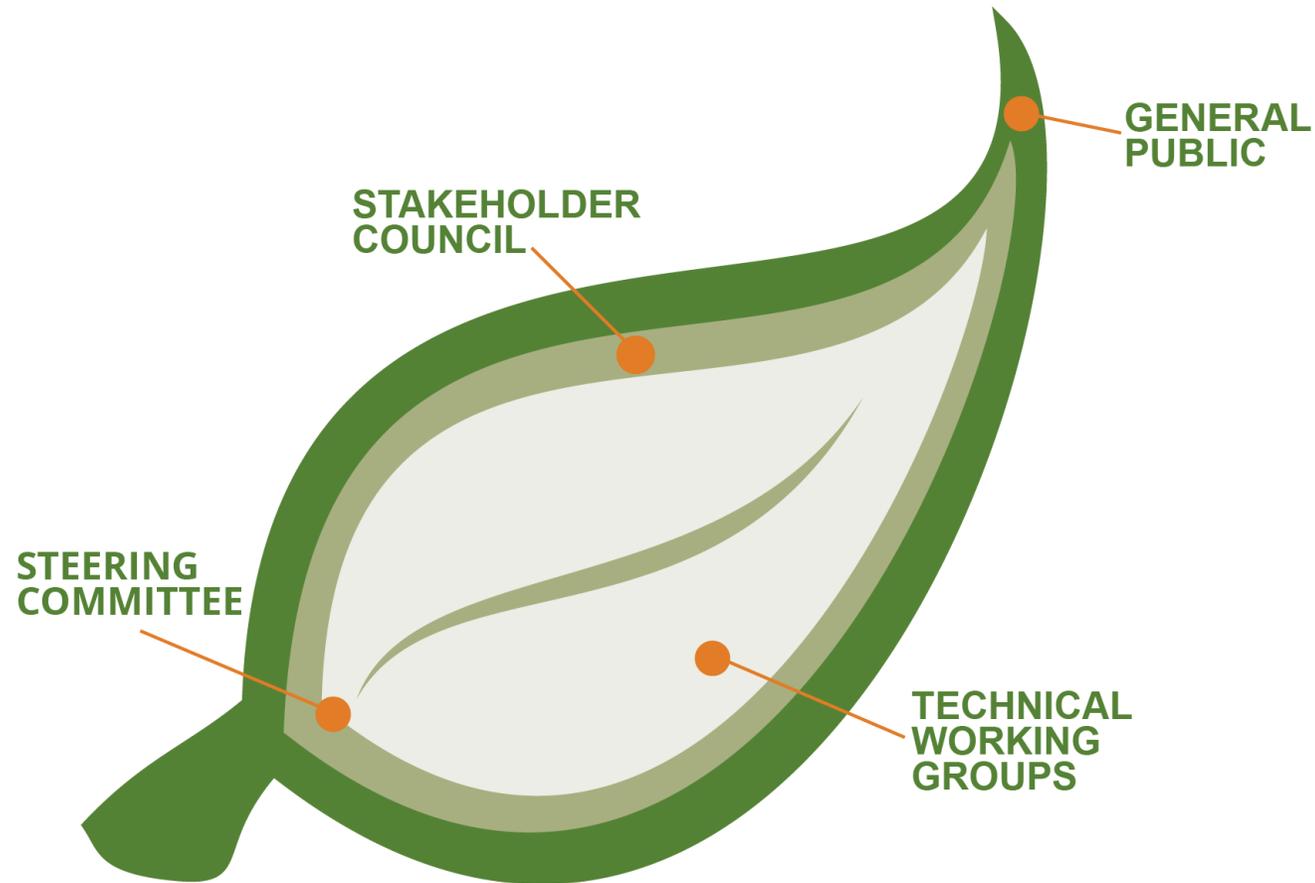
# Strategy



- Develop a list of botanical reference substances that have available safety information
- Create a reference substance library
- Utilize non-targeted and targeted analytical approaches and chemometrics for adequate characterization
- Develop strategies to address variability between botanical substances for safety assessment
- Identify suitable in vitro/in silico assays that are within the identified domain of applicability for botanicals
- Evaluate the botanical reference substances in a battery of selected in vitro/in silico assays
- Perform suitable data analysis
- Compare the results from the testing battery to existing animal and human safety data
- Make data publicly available
- Provide recommendations based on learnings



# Botanical Safety Consortium Structure



# Botanical Safety Consortium Structure

**Steering Committee:** This group is comprised of the overall consortium chairs, liaisons from the Technical Working Groups, and two at-large members from the Stakeholder Council.



**General Public:** Open to all. Access to materials via the website and the opportunity to attend the Annual Meeting.

**Stakeholder Council:** Comprised of interested parties that provide a justification statement (private sector must provide a financial contribution.) Members receive an invitation to the Annual Meeting and will be placed on a distribution list for quarterly newsletters and webinars. Members will also be able to submit feedback and project ideas.

**Technical Working Groups:** These members are selected from the Stakeholder Council via an application process reviewed by the Steering Committee and appropriate existing Technical Working Group members.

# Inaugural Steering Committee



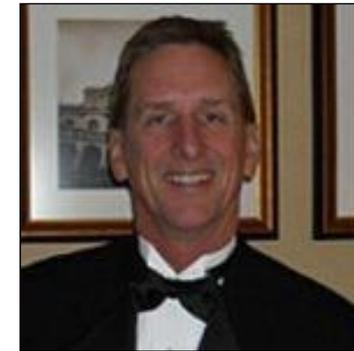
Cynthia Rider  
NIEHS / NTP



Cara Welch  
FDA/ODSP



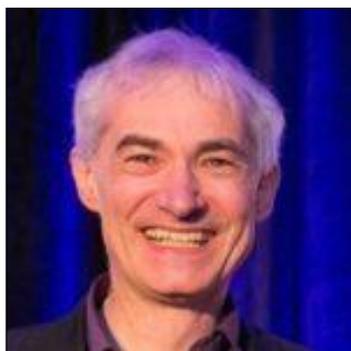
Joe Dever  
Amway



Dan Marsman  
Procter & Gamble



James Griffiths  
CRN



Stefan Gafner  
ABC



Michelle Embry  
HESI



Connie Mitchell  
HESI

# Technical Working Groups

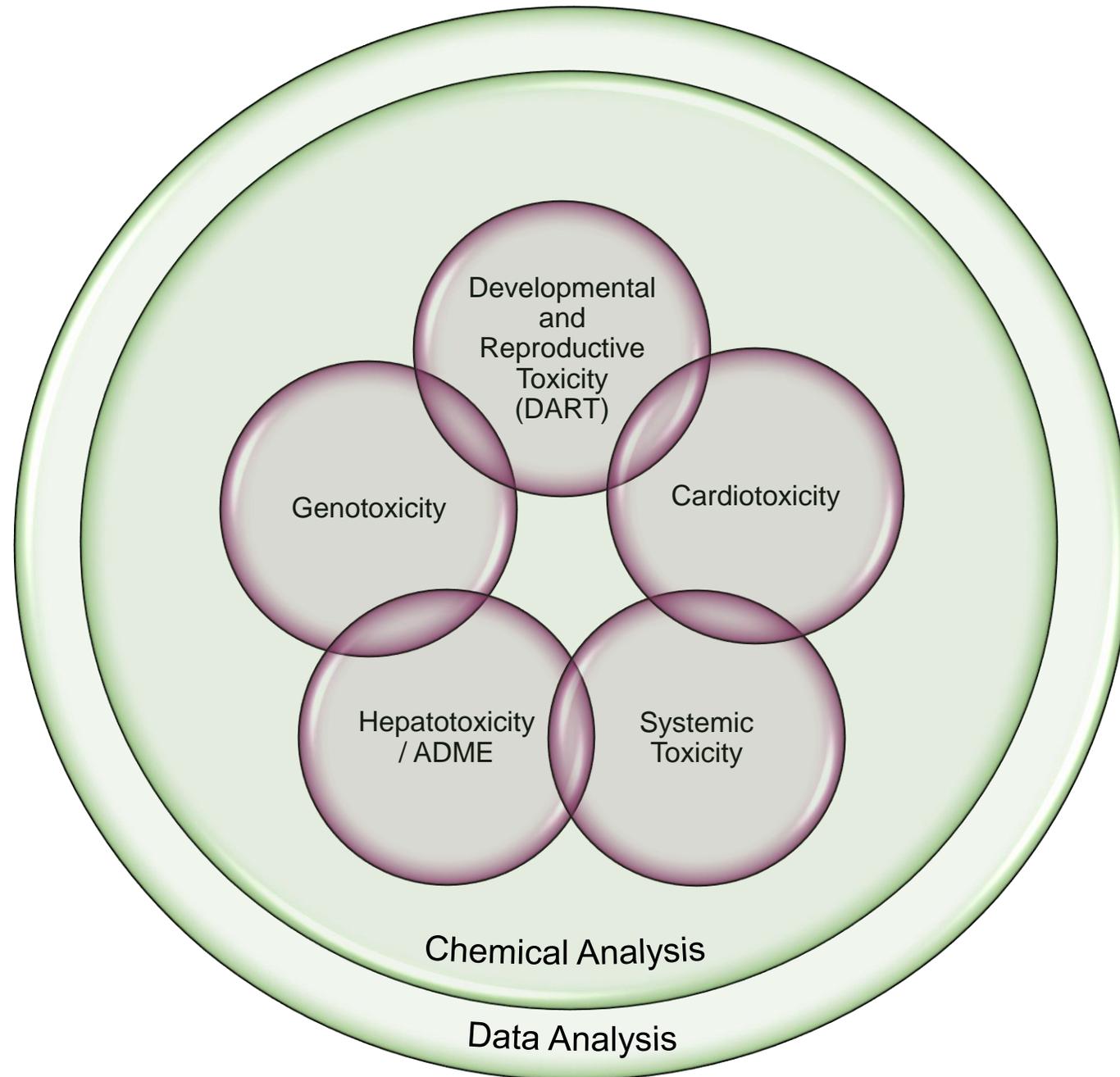
- Chemical analysis
- Priority endpoints/systems to evaluate
  - Genotoxicity
  - Hepatotoxicity
  - Developmental and reproductive toxicity
  - Systemic toxicity
  - Cardiotoxicity\*
- Data analysis

Selected based on:

- Severity of associated disease (e.g., genotoxicity and cancer, cardiotoxicity and heart disease)
- Adverse event reporting and research on botanicals (e.g., hepatotoxicity)
- Building bridges with current gold standard - animal safety data (e.g., *in vitro* systemic toxicity vs repeat dose *in vivo*)
- Availability of alternative assays to measure effects in that system



# Technical Working Groups



# Technical Working Groups – Current status

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- Formation of teams of experts for each of the focus areas
  - Balance of industry, government, and academic scientists
  - Global representation, where possible
- Refining goals and objectives
- Reviewing the state of the science on botanicals research in each of the key areas



# What the BSC is.....and is not.....



- Focused on *in vitro* and *in silico* approaches
- Dedicated to advancing the science of botanical safety evaluation
- Aimed at providing recommendations for tools and technologies that are useful in evaluating botanical safety



- Focused on generating new *in vivo* toxicity data
- Involved in regulatory decisions or guidance
- Aimed at developing additional testing requirements for botanical products



# 1<sup>st</sup> BSC (virtual) Annual Meeting

*29 May 2020*

*9:00 – 12:45 (US Eastern)*

## Meeting Objectives:

- Provide information on the structure, mission, objectives, and strategy of the BSC
- Share an overview of the current Technical Working Group (TWG) plans
- Recruit new BSC members
- Solicit input into current scientific challenges and opportunities related to botanical dietary supplement safety

Visit [www.botanicalsafetyconsortium.org](http://www.botanicalsafetyconsortium.org) to register!

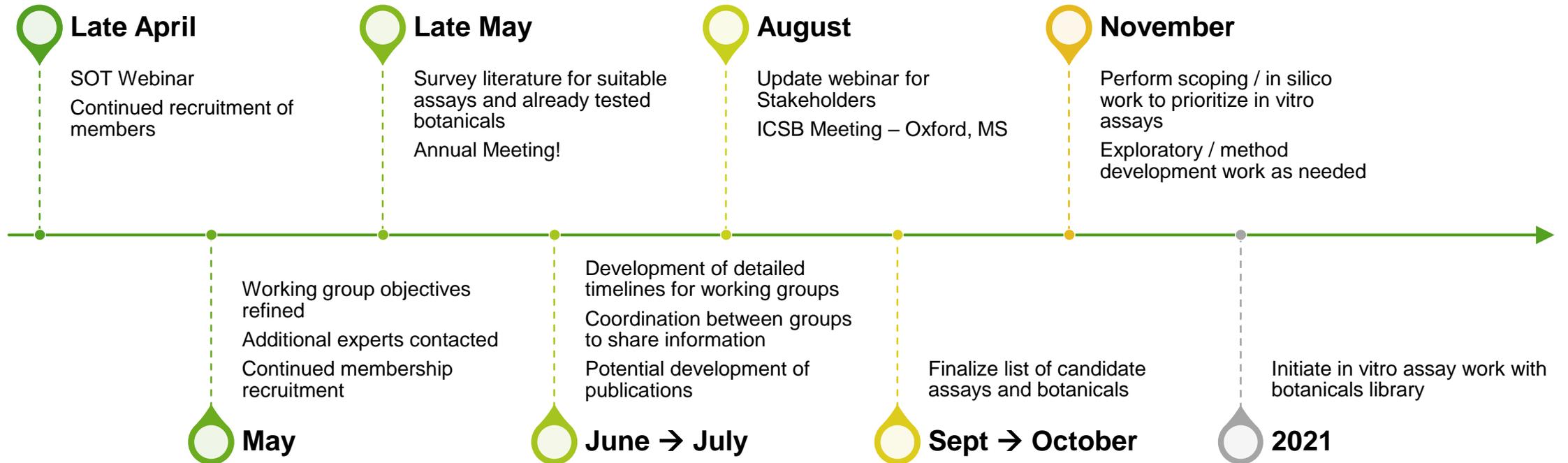


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# Agenda

- 9:00 **Introductions & Objectives**  
*Michelle Embry, HESI*
- 9:15 **Botanical Safety: Discovering Common Struggles, Needs, and Solutions**  
*Dan Marsman, Procter & Gamble*
- 9:35 **The BSC as a public-private partnership: HESI's involvement in the BSC**  
*Connie Mitchell & Michelle Embry, HESI*
- 10:05 **Research on Botanical Safety at the National Toxicology Program**  
*Cynthia Rider, NIEHS / NTP*
- 10:25 **The Modernization of FDA's Dietary Supplement Program: the Botanical Safety Consortium**  
*Cara Welch, USFDA CFSAN*
- 10:45 **What are the objectives of the BSC and how does it plan to meet them?**  
*Jim Griffiths, CRN*
- 11:00 **Botanical Ingredient Characterization; a tale of more than one thousand and one compounds**  
*Stefan Gafner, ABC*
- 11:30 **Avengers Assemble! A Day in the Life of the BSC Technical Working Groups**  
*Joe Dever, Amway*
- 12:00 **Conclusions**
- 12:15 **Open discussion / Q&A**
- 12:45 **Adjourn**

# BSC Timeline





- Website: [www.botanicalsafetyconsortium.org](http://www.botanicalsafetyconsortium.org)
- Email: [botanicalsafety@hesiglobal.org](mailto:botanicalsafety@hesiglobal.org)  
[membry@hesiglobal.org](mailto:membry@hesiglobal.org)

*Thanks to Cynthia Rider & Joe Dever for slides*