SOT RASS Webinar
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# Natural Product Health Risk Assessment:
## Weaknesses and potential improvements

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# Some General Misconceptions

- Natural products are inherently safe
  - Botanical supplements & natural remedies are safer than conventional pharmaceuticals
  - Natural pest deterrents are safer than synthetic pesticides
  - Organic & GMO-free products are more healthful than conventional foods
- Synthetic food additives and pesticide residues are a significant health risk
- Natural plant foods are chemical free

# Safety Regulations often Reflect Similar Thinking

- Botanical supplements & herbal remedies are a prime example
  - DSHEA preamble states products are generally safe
- Disease resistant organic food crops don't require special testing (unless toxic constituents known)
  - Even though disease resistance is due to endogenous pest deterrents
- Conventionally bred food crops don't require same testing as genetically engineered plants

# Botanical Supplements & Herbal Remedies are a Special Risk

Regulated by DSHEA[a]

- Pre-1994 botanicals require no safety testing
- NDIs require notification but not specific testing
  - "History of safe use" commonly used as safety standard
- Health claims can be made without regulatory review
- Burden of proof to show harm is on FDA
  - FDA under-resourced
- Composition complex & variable (Identity standards unclear)
- 77% of U.S. adults take dietary supplements

[a]the Dietary Supplement Health & Education Act (DSHEA)

# Testing Required Before Sale Allowed

| Required Testing | Food Additive | Drug | Pesticide | Botanical Pre-1994 | Supplement NDI |
|---|---|---|---|---|---|
| General Toxicity | X | X | X | | Notify FDA |
| Cancer Induction | X | X | X | | History of Safe Use Accepted |
| Reproductive Effects | X | X | X | | |
| Neurotoxicity | X | X | X | | |
| Effectiveness | X | X | X | | |
| Identity Standards | X | X | X | | |
| Interactions & Susceptibility | | X | | | |

# A “history of safe use” doesn’t guarantee safety:

- **Without testing, toxicities & safety margins unknown**
  - **Testing to limit of toxicity necessary to determine safety margins**
- **It is difficult to demonstrate causality once a product is in widespread use**
  - **Cancer may take 15-20 years to develop**
  - **Genetic sensitivity or resistance can confound conclusions**
  - **Chemical interactions may determine outcomes**

# Smoking: A prime example of the limitations of epidemiology

Cigarette smoking causes 9 out of 10 fatal lung cancers in men in the U.S.

- In late 1880s lung cancer was ~1% of cancers
- Increased lung cancer deaths first noted before 1900
- Appx. 60 years of research required to establish smoking as the main cause of lung cancer
  - 15+ year lag to cancer development—Many factors to consider
  - Lung cancer became common, so doctors began to think it was just a natural occurrence
- Both laboratory and human studies are necessary to establish causation

# Aristolochia: Another example

Balkan endemic nephropathy

- Kidney disease-known before 1950s
- Found in some small farming areas-not others

Brussels Poisoning—1990s

- Chinese herb caused same disease in >100 people taking weight loss product
- Urothelial cancer in >40% patients w severe nephropathy
- Toxic chemical identified (Aristolochic Acid, AA)—very potent carcinogen in lab animals and humans
- Aristolochia seeds responsible for Balkan disease

Current major health risk: AA in many traditional Chinese herbs--past & present exposures → toxicity & cancer risk

# Plants are not Benign

They make >100,000 chemicals for defense & communication

They are unique to plants & foreign chemicals to predators, & pathogens

Many are toxic and have caused illness or death

Photo courtesy of Robert Belliveau; *Science* photo of the year recognition

# Plant products have caused serious toxicities

- Kidney failure & urothelial cancer from *Aristolochia*
- Stroke, heart attack, hypertension from ephedra alkaloids in weight-loss & athletic performance products (long delay in removal)
- Liver injury (steroids & uncertain ingredients)
- Lychee & Ackee (MCPG children deaths & brain damage India, Vietnam, Bangladesh)

# Interactions Are Another Issue

- Botanicals, foods, drugs can modify protective enzymes & cause serious interactions with prescription drugs


# Some Plants and Chemicals are Toxic only in People with Individual Sensitivities

Fava beans are toxic to people with genetic predisposition  (G6PD deficiency)

# Adulteration of Supplements with Bioactive Ingredients is a Serious Problem

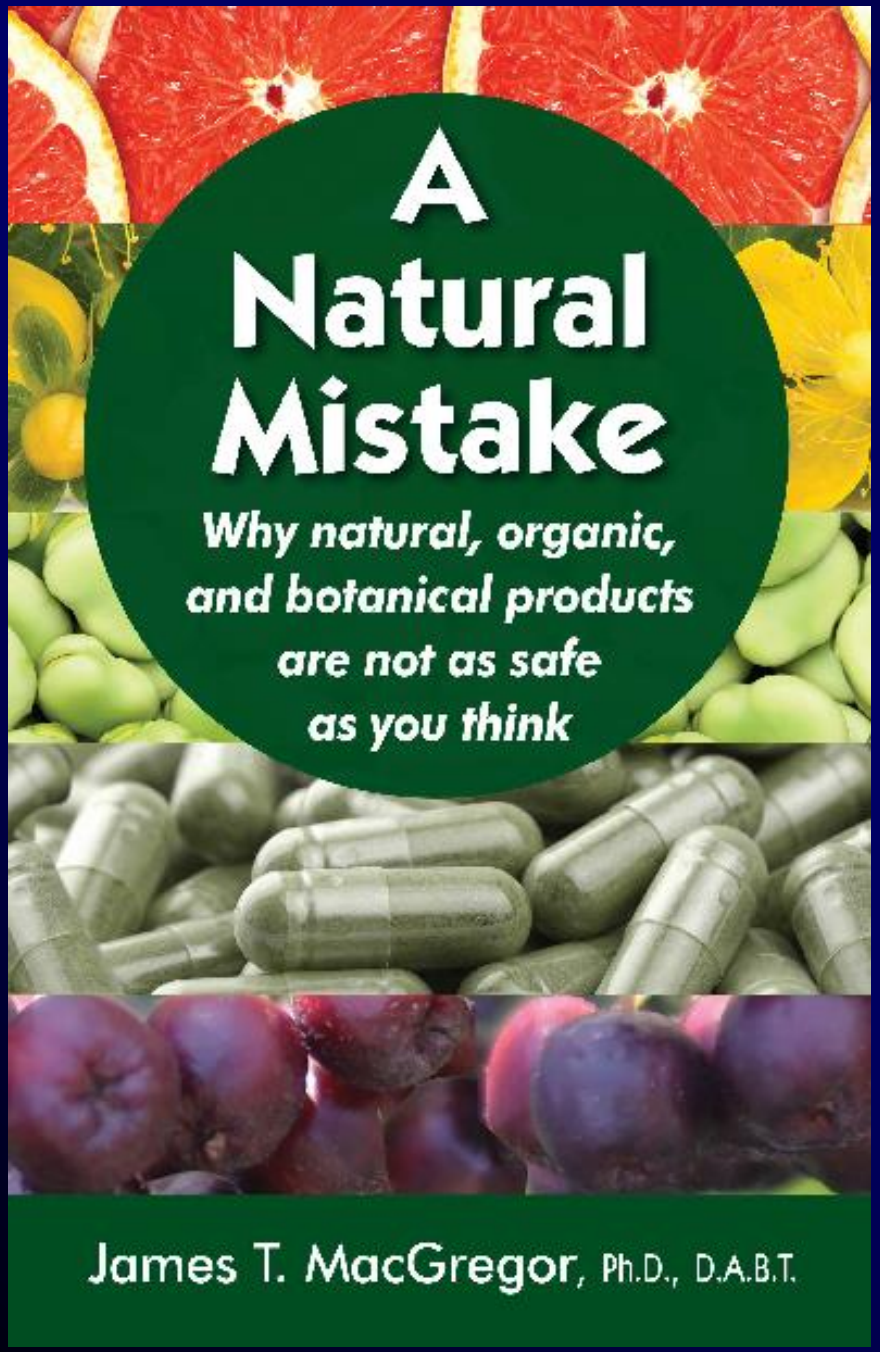
- Very common among weight loss, athletic performance, and sexual performance products
  - Vasoactive amines: Stroke, heart attacks
  - Appetite suppressants: Some have anxiety, depressant, suicidal effects
  - Steroids: sexual effects, liver toxicity
  - Sexual enhancement drugs: blood pressure effects, interactions

# Enforcement of Adulteration is Problematic

- Two Cohen *et al*. studies[a,b] illustrate problem:
  1. Of 27 supplements returned to market after recall for illegal addition of chemical agents, **66.7% again contained one or more bioactive adulterants!!**
  2. 9 prohibited stimulants found in 17 brands of sports & weight-loss supplements

[a]JAMA 312:1691-1693, 2014
[b]Clinical Toxicology, March 23, 2021 Pre-Publ. Online

FDA has burden to demonstrate health risk but resources insufficient




# For more information

- Why product risks often misunderstood
- Differences in safety standards across food & drug products
- Examples of unanticipated toxicities & barriers to enforcement of botanical safety
- Recommendations for improved natural product risk assessment

https://amazon.com/author/jtmacgregor

# Can natural product safety assurance be improved?

- Prospective testing is needed because epidemiology and even well-structured post-market adverse event reporting don't reliably predict:
  - delayed effects
  - individual susceptibilities
  - chemical interactions
- Natural products usually contain large numbers of chemicals, making comprehensive animal studies of individual agents impractical

# Fen-Phen: Case of failure of post-market reporting

- Fenfluramine-Phentermine for obesity 1990s
  - Each drug approved but not combination
  - 18 million prescriptions in 1996
- 1997 Clinician group in Minnesota recognized 24 cases of heart valve defect in middle-aged women
  - No history of cardiac disease; all had leaky valves
  - Drugs withdrawn
- Follow-up studies of asymptomic women receiving Fen-Phen showed 30-38% with heart valve defects !!
  - Extensive medical damage, but not detected by surveillance system !

# How can natural product safety assurance be improved?

- Strategies will require “next-generation” screening (SAR, AI, and HT in vitro studies), with escalation strategy to animal and/or human studies
- More effective epidemiological studies
- Consolidating responsibility for regulation of similar products would increase efficiency and more uniform decisions across product classes
- Some controlling legislation and regulatory policies require modification

# Some Specific Ideas to Improve the Safety Assessment of Natural Products

and

# Enhance Consumer Safety

(For Discussion)

# Develop New Paradigms for Early Risk Categorization

- Computational predictions, HT screening, and *in vitro* studies in metabolically competent cells might help categorize:
  1) Constituents of complex botanicals requiring detailed evaluation
  2) Food additives, drugs, & pesticides that could have reduced testing (*e.g.*, one species)
- *In Vitro* to *In Vivo* extrapolation of metabolism and exposure will be necessary

# Legislative and Regulatory Actions

- Repeal DSHEA
- Create single food agency to regulate all food products under a single set of testing and evaluation standards
- Bring therapeutic drugs, botanical health supplements, dietary supplements (including vitamins and minerals) under the authority of the Food, Drug, and Cosmetics Act
  - Develop uniform testing standards that ensure efficacy, safety, and product quality (incl. manufacturing, confirmation of identity, lack of impurities, etc.)

# Legislative and Regulatory Actions (cont'd)

- Place more attention & resources on food and botanical supplement products
- Make dietary supplements & cosmetics subject to pre-market testing that assures their safety and the accuracy of health and beauty claims

(Move burden of proof to manufacturer or vendor)

# Improved human epidemiology and after-market studies

- A national health records system would reduce medical costs and greatly facilitate correlational analysis of exposure factors with health outcomes
  - Eliminate unnecessary repetition of medical tests
  - Great savings for epidemiological analysis as byproduct
- Use existing clinical testing facilities to support human epidemiological studies
  - *E.g.*, Quest Diagnostics recent support of clinical trials by soliciting patient authorization to use samples already being tested

# Support consumer education

Support education about risk assessment & product safety

- Teach basics of hazard and risk in elementary school (Risk = Hazard Potency x Exposure)
- Avoid adverse effects through better-informed consumer choices

Ideas best developed by an interagency committee with outside experts to plan for increased uniformity of safety assurance across product classes

- The FDA-NIEHS-HESI Botanical Safety Consortium is an example being implemented

  (https://botanicalsafetyconsortium.org)

# Reserve Slides

# Required labeling of health claims under DSHEA