Update on CFSAN Toxicology Activities

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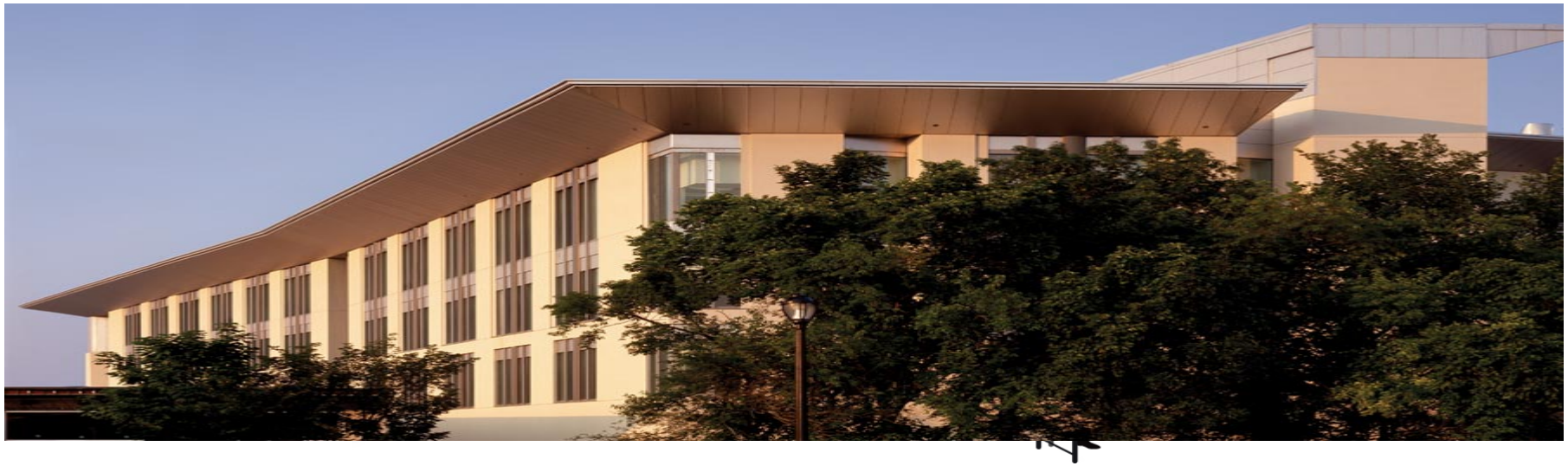
December 5, 2018



FDA-DARPA-NIH Microphysiological Systems Program

- Started in 2011 to support the development of human microsystems, or organ “chips,” to screen for safe and effective drugs swiftly and efficiently (before human testing)
- Collaboration through coordination of independent programs

Engineering platforms and biological proof-of-concept (DARPA-BAA-11-73: Microphysiological Systems)

Underlying biology/pathology and mechanistic understanding (RFA-RM-12-001 and RFA RM-11-022)

Advise on regulatory requirements, validation and qualification

This was a unique partnership because it involved regulatory scientists at the very beginning- was able to address identified gaps in knowledge need to regulate FDA products

NATURE | NEWS

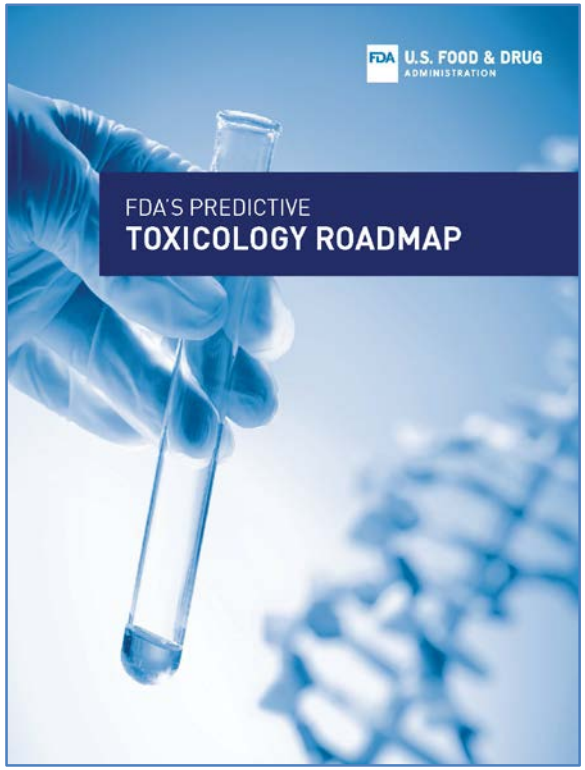
Miniature liver on a chip could boost US food safety

- CFSAN Researchers will be evaluating the effectiveness of this technology to better understand the effects of medicines, disease-causing bacteria in foods, chemicals, and other potentially harmful materials on the human body

FDA Using Platforms that Received DARPA/NCATS Funding

- CFSAN working with Emulate (spin-off from Wyss Institute)
- CDER working with CN Bio (spin-off from MIT) and Kevin Healy at UC Berkeley
- Both groups focusing first on liver
- FDA is working together across the
- Agency on this and other predictive toxicology tools

FDA's Predictive Toxicology Roadmap



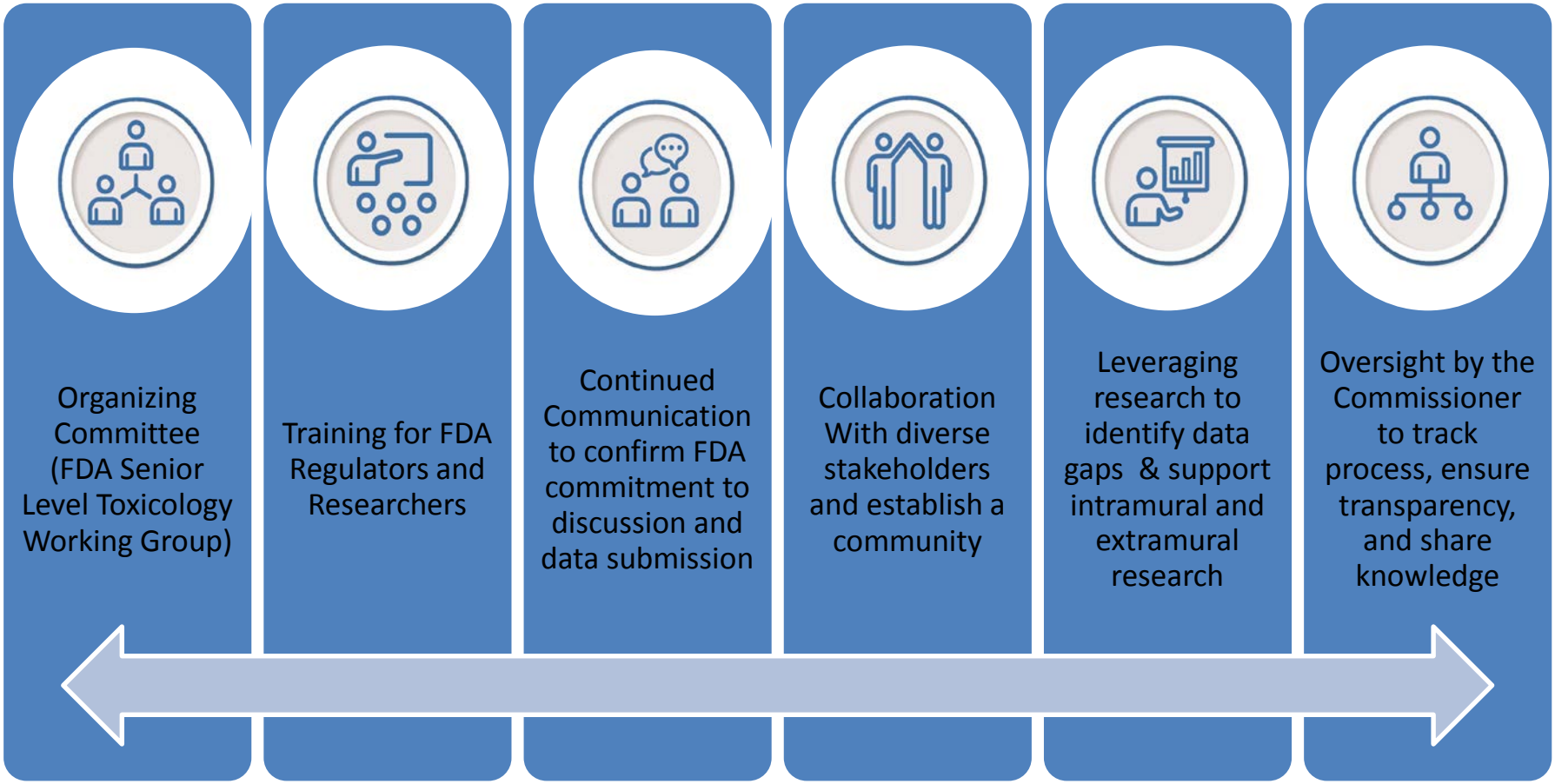
FDA thought on viable ways to:

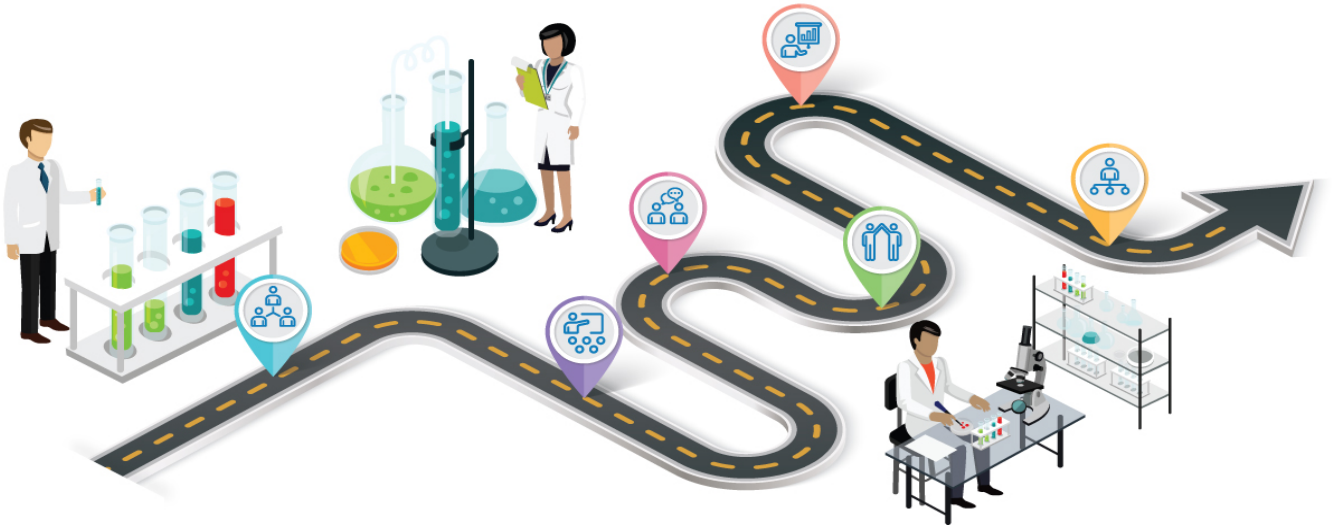
- Foster the development and evaluation of emerging toxicological methods and new technologies, and
- Incorporate these methods and technologies into regulatory review, as applicable.

December 6, 2017

https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM587831.pdf

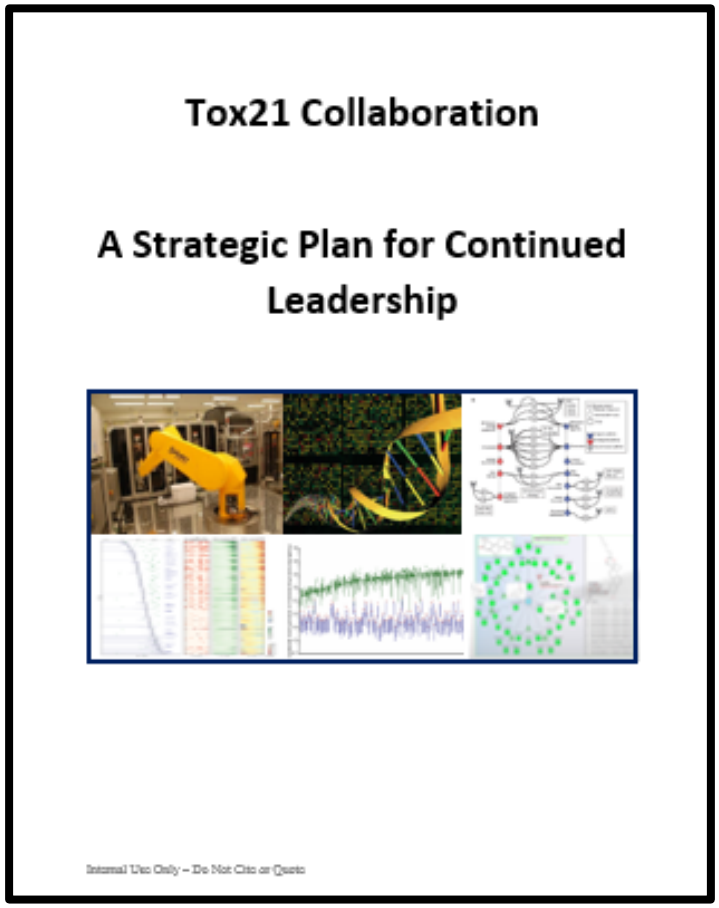
FDA's Roadmap: Framework for Incorporating Emerging Predictive Toxicology Methods in Regulatory Reviews





FDA held a public hearing on Wednesday, September 12, 2018. to solicit comments on its Predictive Toxicology Roadmap.
The Agency sought comments on how to foster the development and evaluation of emerging toxicological methods and new technologies and incorporate them into regulatory review, as applicable.
https://www.fda.gov/ScienceResearch/AboutScienceResearchatFDA/ucm601090.htm

New Tox21 Strategic and Operational Plan

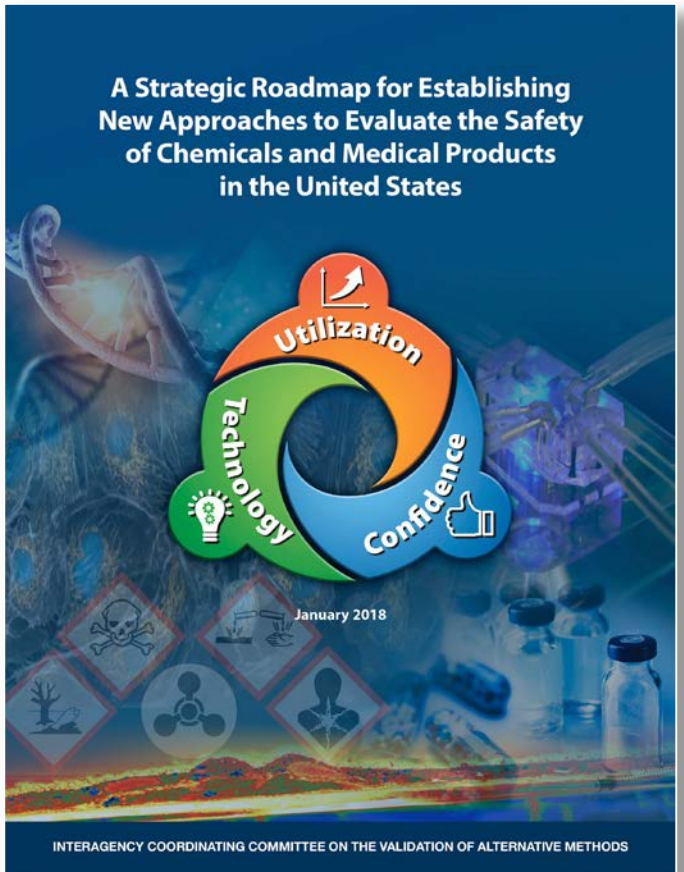


Areas of Focus

1. Develop and deploy alternative test systems that are predictive of human toxicity and dose response
2. Address key technical limitations of current *in vitro* test systems
3. Curate and characterize legacy *in vivo* toxicity studies to serve as a resource for interpreting Tox21 data
4. Develop framework for efficient validation of Tox21 approaches
5. Refine and deploy *in vitro* methods for characterizing pharmacokinetics to increase predictivity and reduce uncertainty

ICCVAM Road Map

- **Published Jan 30, 2018**
- https://ntp.niehs.nih.gov/go/natl-strategy



"Federal agencies and stakeholders will work together to build a new framework to develop, establish confidence in, and encourage use of new approaches to toxicity testing that improve human health relevance and reduce or eliminate the need for testing in animals."

“The 3Cs” Themes that Run Thru All These Roadmaps

Communication

Collaboration

Commitment

Considering Traditional Tests

- Toxicity Studies in Dogs
  - *Use of Dog Studies in FDA's Safety Assessments for Food Additives and Color Additives*, Anyangwe et al., abstract submitted to the 2019 SOT Annual Meeting.
- Rodent Bioassays
  - SOT-FDA Colloquium Series, February 20, 2019.

Testing in C. Elegans for Mixtures of Metals

- CFSAN is concerned about mixtures of metals in children's food
- Developed test using C. Elegans to look at impact of metals on developmental neurotoxicity
- Test measures developmental delays and effects on motor activity
- Preliminary data shows effects on from exposure to arsenic, cadmium, lead and mercury alone and in mixtures

Chemical Evaluation and Risk Estimation System (CERES)

- Created to address technical challenges in food ingredient evaluation processes in the Office of Food Additive Safety (OFAS) by consolidating all data into one place and bringing them under a standardized vocabulary
- Designed to be a knowledgebase of chemicals regulated by CFSAN
  - Most CFSAN compounds in CERES are food chemicals
    - Priority-Based Assessment of Food Additives (PAFA) Database
    - Food Application Regulatory Management (FARM) System
  - Incorporation of other CFSAN's chemicals of interest (e.g. cosmetics) in the future
- Designed to provide cheminformatics capabilities
- Releases: 1.0 (2012), 1.1 (2014), 2.0 (2015), 2.1-2.3 (2016), 2.4-2.6 (2017), 2.7-2.9 (2018)

Cheminformatics in CERES

- Predictive models (through collaborations with Altamira LLC and Molecular Networks GmbH)
  - Cleft Palate
  - Bacterial reverse mutagenicity
  - *In vitro* chromosome aberration
  - *In vivo* micronucleus
  - Mouse tumor
  - Rat tumor
  - Skin sensitization hazard
  - Skin sensitization potency
- Chemical structure similarity calculation
- Chemical structure and data export
  - Portable document format (PDF)
  - Structure data file (SDF) can be processed by other software

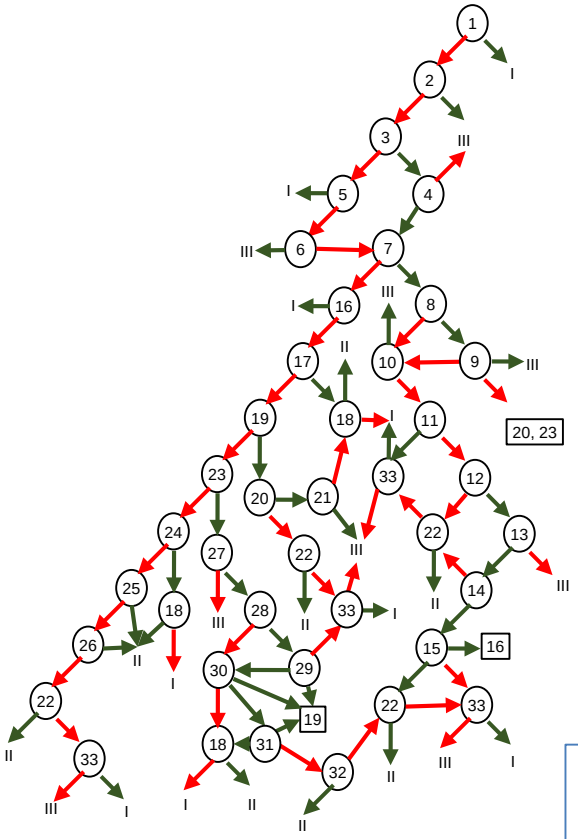
Read-Across

- According to FDA's Predictive Toxicology Roadmap read across is a methodology that "uses data from a data-rich substance for a data-poor substance that is considered similar enough to use the same data as a basis for assessing safety."
- Technology Transfer Agreement with Underwriter's Lab on REACH Across
- Expanded Decision Uses Tree Read-Across.

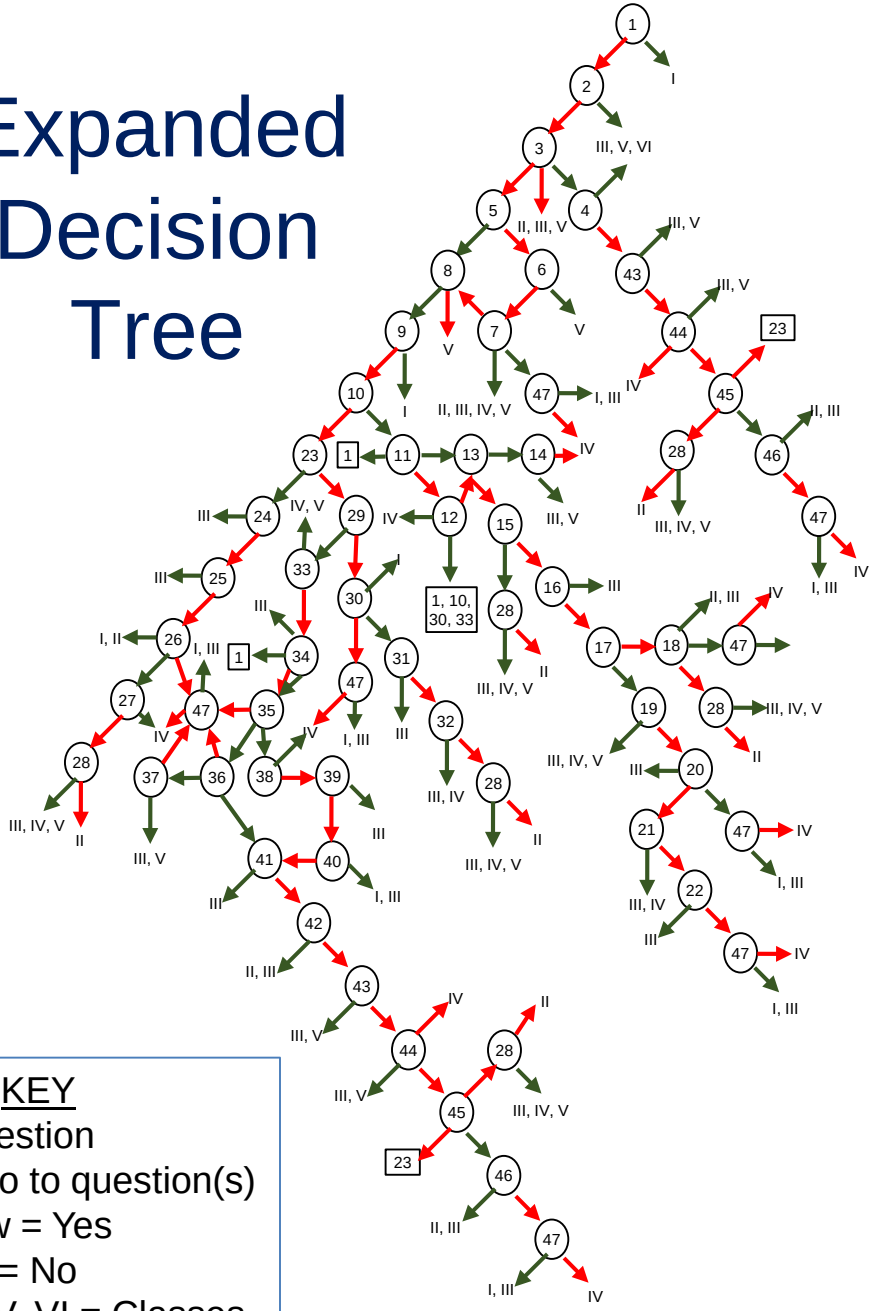
Expanded Decision Tree (EDT)

- Comprehensive revision of the DT to update scientific data underpinning Cramer et al. DT questions
- Remove non-structure-based questions in old DT
- Increase scope of EDT to address majority of substances in food (six vs. three classes)
  - Increase elements and functional moieties
- EDT incorporates “mode of action”/species differences
  - Address alpha-2u-globulin, peroxisome proliferation, progressive renal nephropathy, etc.
- Increase scope and size of EDT database (~2000)

Cramer et al. Decision Tree



Expanded Decision Tree



KEY

Circle = question
Square = go to question(s)
Black arrow = Yes
Red arrow = No
I, II, III, IV, V, VI = Classes

Risk and Exposure Analytical Software

- FDA-iRisk 4.0
  - This is a web-based system designed to estimate the risk associated with microbial and chemical hazards in food. It returns an estimate of the resulting health burden on a population.
  - Find it at: https://irisk.foodrisk.org/
- @Risk @RISK is an add-in to Microsoft Excel that lets you analyze risk using Monte Carlo simulation. @RISK shows you virtually all possible outcomes for any situation—and tells you how likely they are to occur. This means you can judge which risks to take on and which ones to avoid—critical insight in today's uncertain world.
- FARE-NET
  - Food Analysis and Residue Evaluation program: It is a software tool for assessing dietary exposure to nutrients, food ingredients and contaminants.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