Advancing the Use of New Approach Methods in the FDA Human Foods Program

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US Food and Drug Administration

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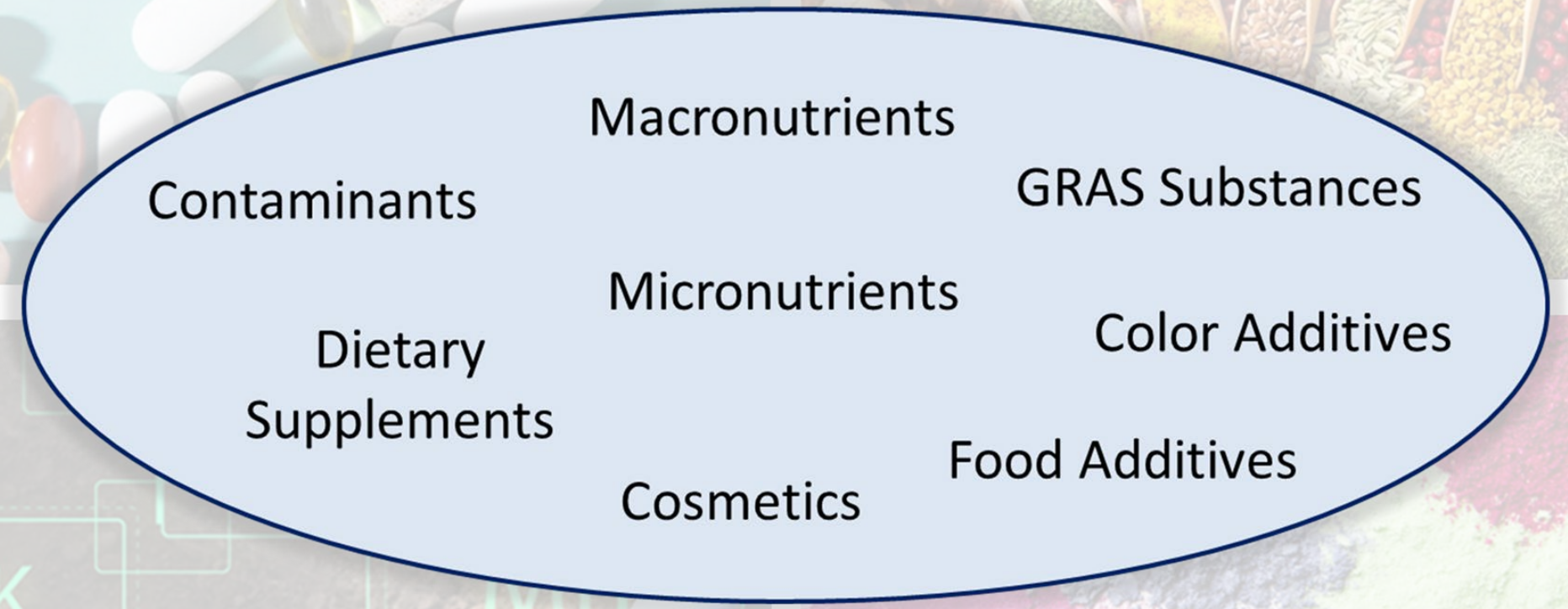
Center for Food Safety and Applied Nutrition (CFSAN) Regulatory Space

Safety is paramount and requires high-quality, reliable toxicology data



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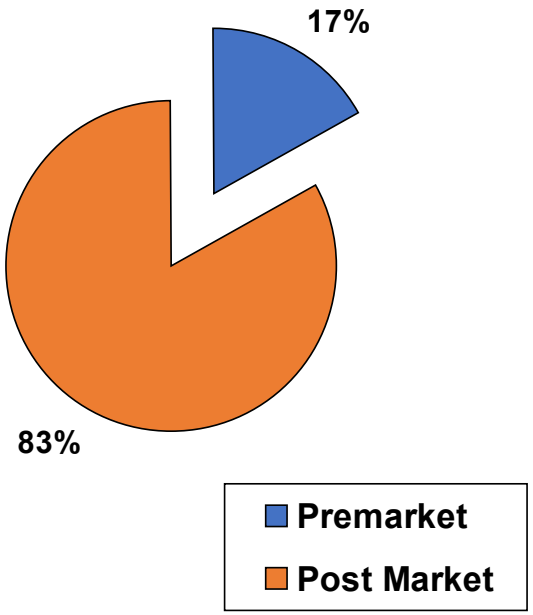
Center for Food Safety and Applied Nutrition (CFSAN) Regulatory Space

Contrast to Medical Product Centers

- Authorities
- Postmarket vs Premarket
- Chronic vs. Acute toxicity issues

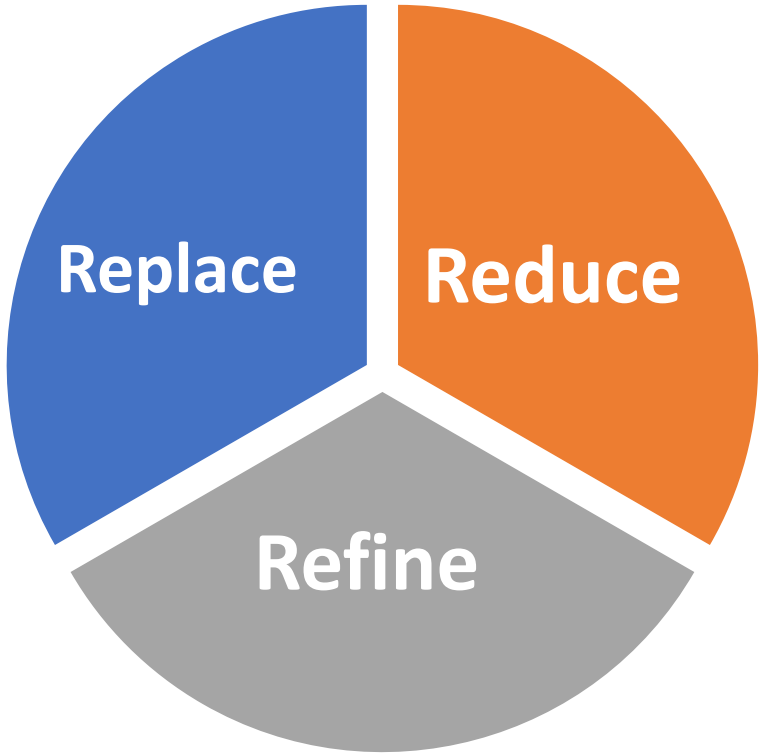


Why NAMs are Needed at CFSAN?

- CFSAN must react quickly and decisively to any potential threat to the food supply.

- Animal studies take months to years to complete before safety information is known about a compound.
  - No longer acceptable in a global marketplace
  - Need faster and more efficient identification of toxicity and associated pathways

- Alternative methods would provide both more timely and more detailed information (e.g., mechanistic data) to predict safety.
  - Better modeling of human toxicity
  - Potentially lower overall cost compared to animal studies



CFSAN Activities on NAMS

- CFSAN has been very involved in developing NAMs for use in its different programs.
- CFSAN activities can be divided into four areas:
  - Center activities and partnerships
  - Agency activities and partnerships
  - Cross federal agency activities and partnerships
  - Global activities and partnerships

Use of Dogs as a Second Species in Toxicology Testing

- CFSAN recently published a paper on the retrospective analysis of dog study data from food and color additive petitions.
- The paper concluded that future research should investigate the use and value of alternative animal models as replacements for the use of a second species in food and color additive safety assessments.
- Using alternative methods that are potentially less time consuming, less expensive, and perhaps more predictive of human health risk compared to animal models is a goal that is important for stakeholders and regulatory agencies alike.
- Retrospective analysis of dog study data from food and color additive petitions https://www.sciencedirect.com/science/article/pii/S0273230023001915?via%3Dihub

Center activities and partnerships

CFSAN has formed a NAMs Working Group with representatives from SSAS, OFAS, ODSP, OAO, ORS, and OARSA

CFSAN NAMs WG has conducted a survey of the food industry to determine NAMS currently in use- Mainly in silico methods

CFSAN NAMs Group has conducted a gap analysis where new tools are needed by CFSAN programs office to answer outstanding questions- OFAS, ODSP, OAO and ORS participated

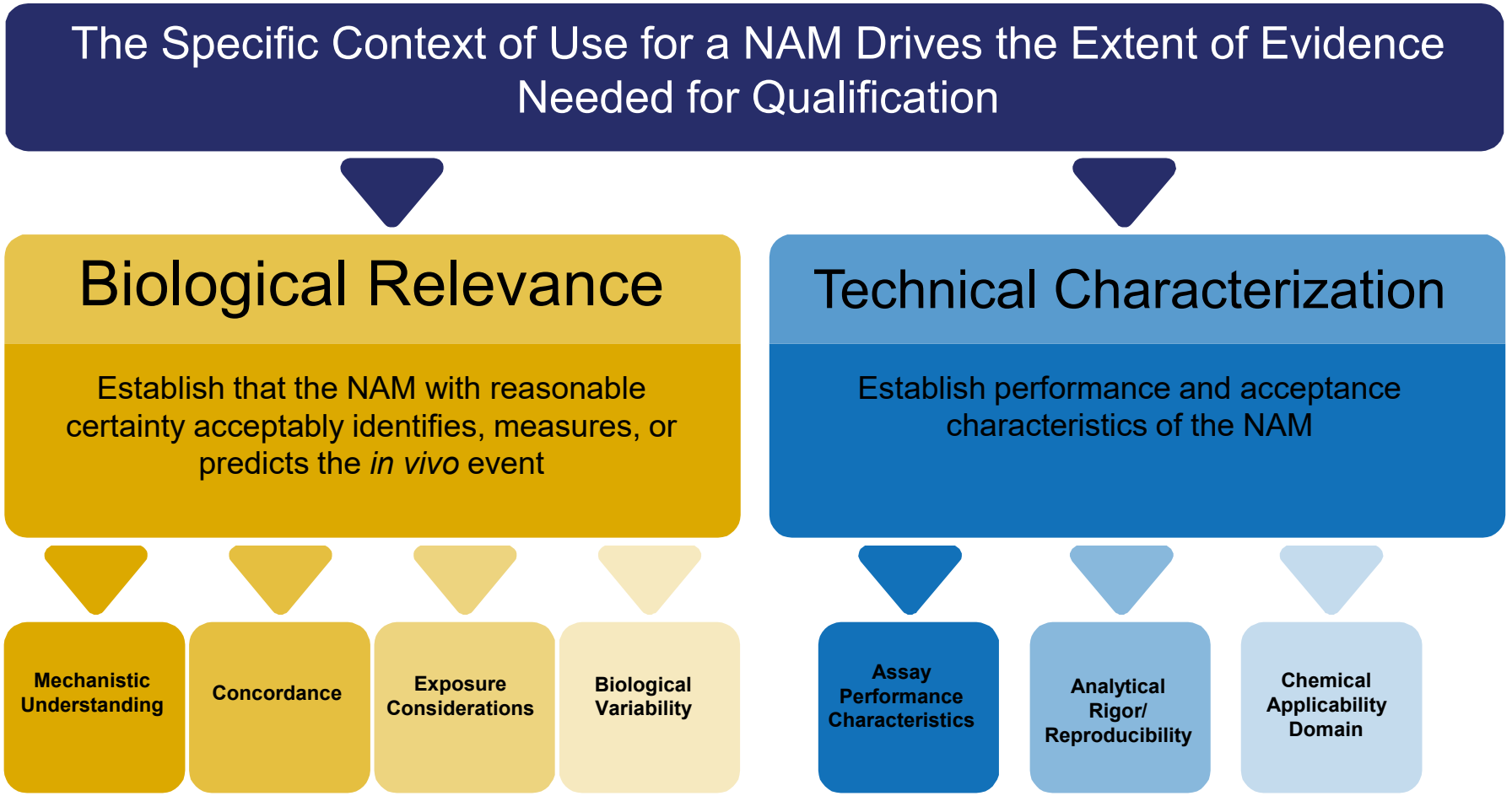
This gap analysis will help direct NAMs research with its stakeholders

Gap analysis and ways to partner with CFSAN will soon be posted on our public website.

CFSAN Plan For NAMs

- Accordingly, CFSAN has undertaken a leadership role in developing alternative methodologies to traditional animal testing that could provide timelier and more detailed information to predict safety, work that will only grow in importance if recent legislation proposing to ban animal testing in cosmetics products passes.
- One area of particular focus will be to evaluate new methodologies and technologies to ensure that they are ‘qualified’ and suitable for regulatory decision making.

Scientific and Analytical Criteria for Acceptance for New Approach Methods for Food Chemicals- Based upon the NICETAM Guidelines



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Training by Doing

Government agencies need to consider “succession plans” to ensure valuable scientific skills aren’t lost with retirements and transfers.

For NAMs, there are no training courses on regulatory issues, identifying gaps, determining data needed for confidence in new data, qualification, validation, or application to regulatory use.

Training by Doing is a program where promising younger scientists are included and given roles in NAMs Committees

CFSAN Biomarker Committee- includes younger scientists from across CFSAN

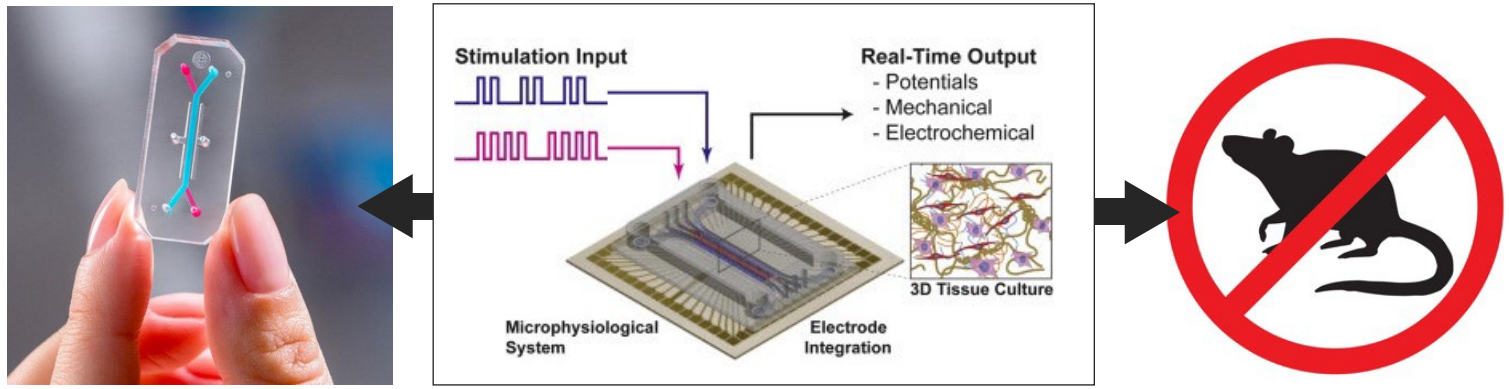
NAMs Group- given the opportunity to report directly to senior management on data needs for developing confidence in NAMs.

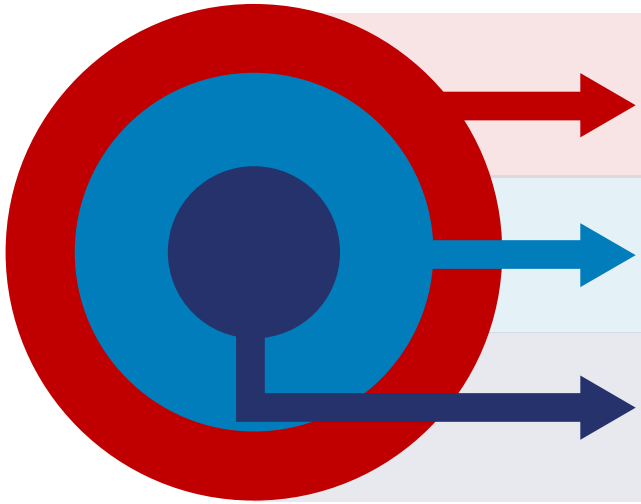
Recent NAMs Workshops Co-Chaired by CFSAN

- Along with NCATS and Harvard, co-chaired the first MPS World Forum (New Orleans, May 2022)
- In collaboration with EFSA co-chaired the ILMERAC Global Meeting in (Italy, Sept. 2023)
- Working with NIEHS and JHU, co-chaired a workshop on establishing confidence in gastrointestinal models (Bethesda, Oct. 2023)
- Sponsored a workshop on assessing developmental neurotoxicity (DNT) using NAMs (College Park, Nov. 2023) – Series?
- CFSAN, JHU, IMPSS, ILMERAC, Singapore will co-chair a global workshop on the use of MPS for food chemicals (Spring 2024)
- CFSAN and JHU will co-chair a global meeting on the use of MPS to evaluate chemicals (Fall 2024)

State of the Science on Assessing Developmental Neurotoxicity (DNT) Using New Approach Methods (NAMs)

CFSAN Neuromuscular Junction (NMJ): Clostridium botulinum





Develop Qualification Standards to evaluate microscale NMJ performance and fitness for its intended use

Conduct Regulatory Evaluation of Neuromuscular Junction (NMJ) Models for BoNTs (OnGoing)

Support FDA's Regulatory Review Programs and transfer of technology and testing methodologies across FDA-wide

CFSAN Strategic Partnerships Under SSAS

CFSAN recognizes need to increase our scientific programs and has or is developing strategic partnerships with other stakeholders.

CFSAN and EPA will form a WG to look at translating NAMs data into PODs for regulatory use. SSAS and ORD have a MOU to work on mutual science issues.

CFSAN and NCATS have a partnership to develop and qualify a neuromuscular junction on a chip for bot tox testing-to replace the mouse lethality test

CFSAN signed an RCA with JHU CAAT to increase our science base on NAMs, AI, exposome and other science issues.

CFSAN signed an RCA with Robyn Tanguay zebra fish lab at Oregon State University

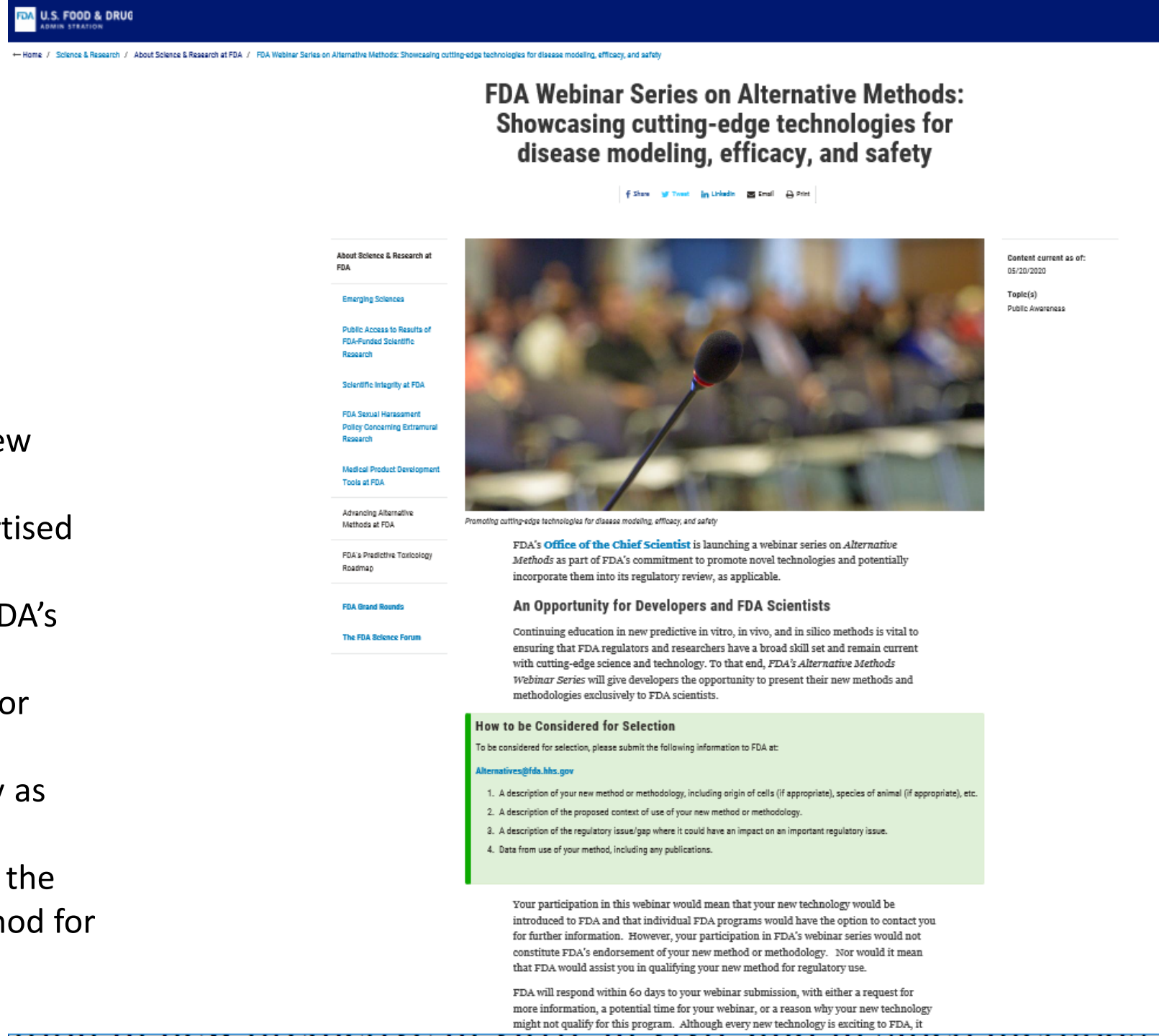
CFSAN signed an RCA with to support the development and application of NAMs

Alternative Methods Working Group (AMWG)

- Under Office of Chief Scientist, Office of Commissioner
  - Chaired by Drs. Fitzpatrick (CFSAN) and Qiang Shi(NCTR), includes regulatory and research members from each Center NCTR and OCS
- Discuss alternative activities across FDA
- Provide external representation of FDA alternative activities.
- The activities of FDA's Alternative Methods Group are informational and do not serve as official regulatory guidance.

FDA Office of the Chief Scientist Webinar Series on Alternative Methods

- Opportunity for developers to present new methods and methodologies to FDA.
- Webinars will be held monthly and advertised to all FDA scientists exclusively.
- If selected, developers' participation in FDA's webinar series would not constitute the agency's endorsement of a new method or methodology.
- Emphasized developmental neurotoxicity as area of interest to FDA
- Nor would it mean that FDA would assist the developer in qualifying his/her new method for regulatory use.



U.S. FOOD & DRUG ADMINISTRATION

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FDA Webinar Series on Alternative Methods: Showcasing cutting-edge technologies for disease modeling, efficacy, and safety

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- Advancing Alternative Methods at FDA
- FDA's Predictive Toxicology Roadmap
- FDA Grand Rounds
- The FDA Science Forum

Promoting cutting-edge technologies for disease modeling, efficacy, and safety

Content current as of: 05/20/2020

Topic(s) Public Awareness

FDA's **Office of the Chief Scientist** is launching a webinar series on *Alternative Methods* as part of FDA's commitment to promote novel technologies and potentially incorporate them into its regulatory review, as applicable.

An Opportunity for Developers and FDA Scientists

Continuing education in new predictive in vitro, in vivo, and in silico methods is vital to ensuring that FDA regulators and researchers have a broad skill set and remain current with cutting-edge science and technology. To that end, *FDA's Alternative Methods Webinar Series* will give developers the opportunity to present their new methods and methodologies exclusively to FDA scientists.

How to be Considered for Selection

To be considered for selection, please submit the following information to FDA at:

Alternatives@fda.hhs.gov

1. A description of your new method or methodology, including origin of cells (if appropriate), species of animal (if appropriate), etc.
2. A description of the proposed context of use of your new method or methodology.
3. A description of the regulatory issue/gap where it could have an impact on an important regulatory issue.
4. Data from use of your method, including any publications.

Your participation in this webinar would mean that your new technology would be introduced to FDA and that individual FDA programs would have the option to contact you for further information. However, your participation in FDA's webinar series would not constitute FDA's endorsement of your new method or methodology. Nor would it mean that FDA would assist you in qualifying your new method for regulatory use.

FDA will respond within 60 days to your webinar submission, with either a request for more information, a potential time for your webinar, or a reason why your new technology might not qualify for this program. Although every new technology is exciting to FDA, it

Leveraging human brain organoids for mixture neurotoxicity and the understanding of individual susceptibilities – BrainMixTox

- Human mini brains are micro-scale physiological systems consisting of mixed populations of neural progenitor cells, glial cells, and neurons that may represent key features of human brain anatomy and function.
- The FDA Alternative Methods Group in partnership with the FDA Johns Hopkins University CAAT developed an FDA CERSI (Center for Emerging Research and Science Innovation) to jointly study whether the JHU minibrain models the effects of metals- arsenic, cadmium, lead – on developmental toxicity.
- JHU and the FDA Foods Program are considering whether this model can be used as a test case for our developing qualification program.

CFSAN Led Cross-Agency Activities and Partnerships

- Represents FDA on the Tox 21 partnership with EPA, NCATS, and NIEHS.
- Lead Agency representative to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
- Co-chair the ICCVAM Metric Committee
  - Drafted a report explaining how federal agencies will track their progress on developing NAMs (report requested by Congress).
- Co-chaired the recent ICCVAM Validation WG
  - Published the “Report on Qualification, Validation and regulatory Acceptance of New Approach Methods”

Update on 6PPD-Quinone Interagency Working Group

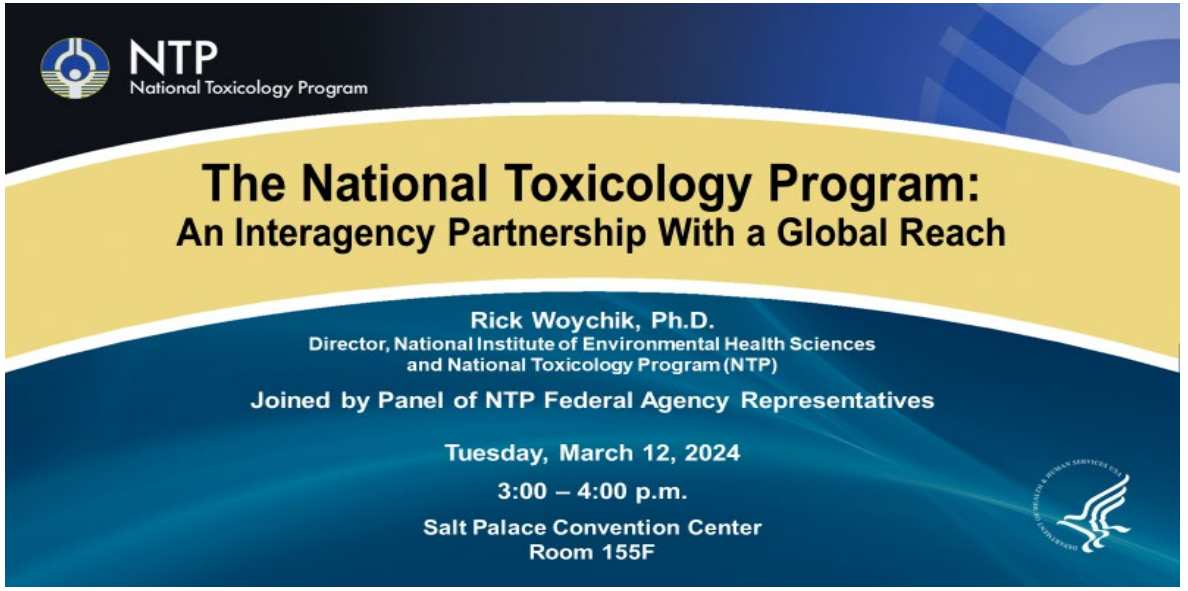
- ***Cross-Governmental Workgroup***
  - National Science and Technology Council's (NSTC's) Joint Subcommittee on Environment, Innovation and Public Health along with the National Toxicology Program (NTP)
  - Update provided at the ***NTP session on "An Interagency Partnership with Global Reach" on March 12, 2024, Society of Toxicology, SLC, Utah.***

NTP National Toxicology Program

6PPD-Quinone Interagency Working Group

Annette Guiseppi-Elie, Ph.D., FAIMBE

National Program Director, Chemical Safety for Sustainability, Office of



Global Partnerships Can Advance New Methods for Chemical Risk Assessment

- ***Improved confidence*** of consumers and stakeholders in RA methods, approaches and data come thru through international harmonization and collaboration
- CFSAN represents FDA on the ASPIS International Regulatory Board
- CFSAN represents FDA on the PARC International Regulatory Board
- In partnership with EFSA, CFSAN helped create the International Liaison Group on MEthods for Risk Assessment of Chemicals (ILMERAC)

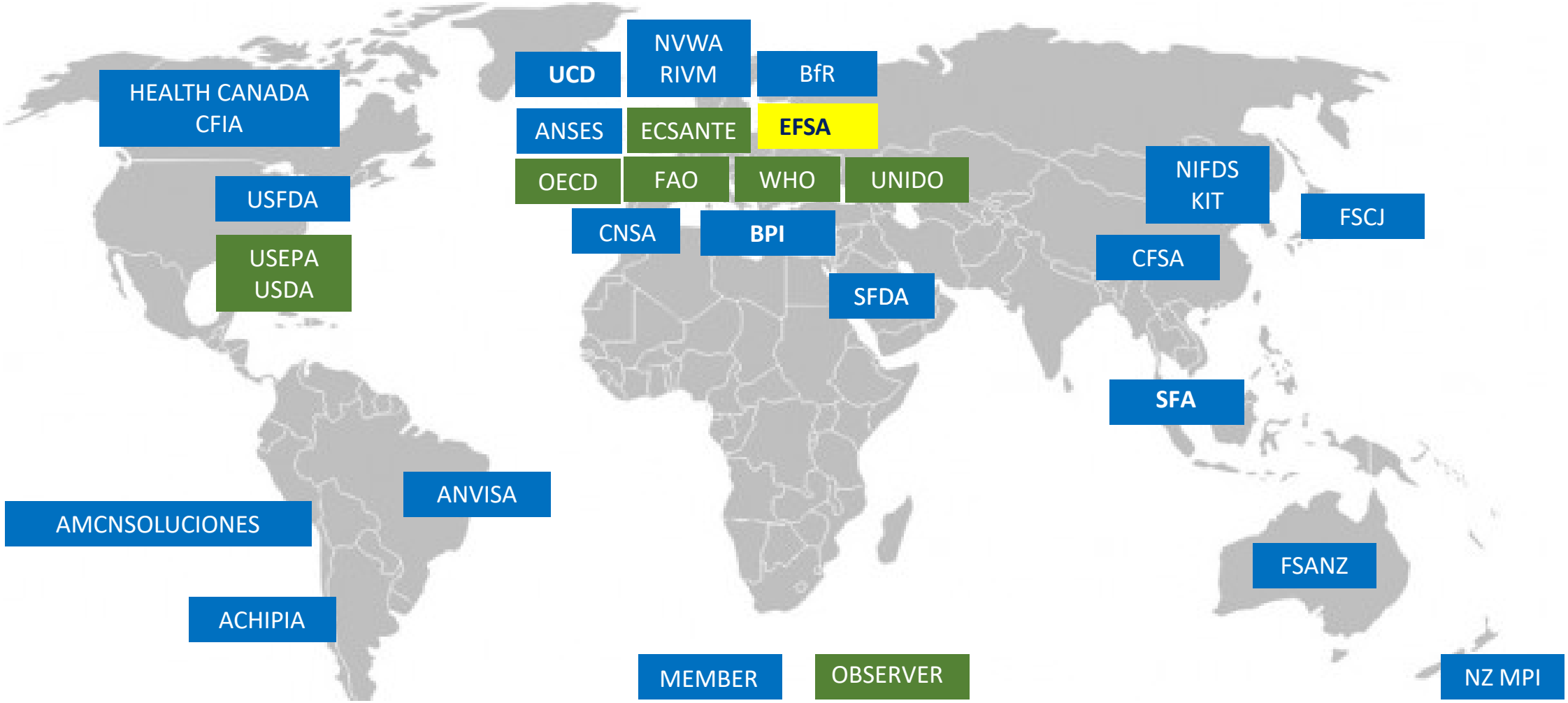
Global Activities and Partnerships

In partnership with EFSA, created the International Liaison Group on MEthods for Risk Assessment of Chemicals (ILMERAC)

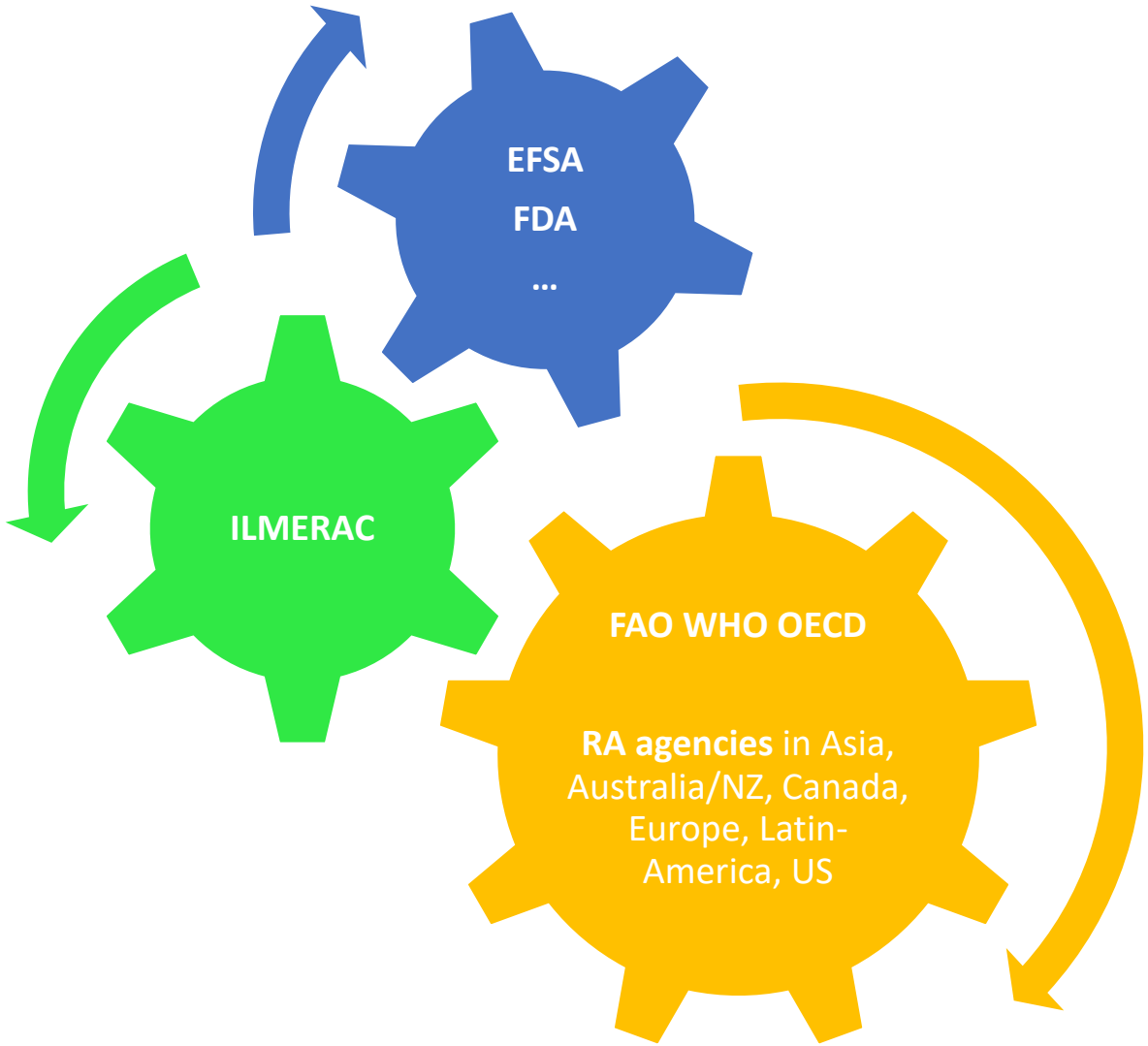
- Supports the development of new risk assessment methods for chemicals in food
- Includes food regulators from around the world working together on NAMs.
- Specifically:
  - Propose action plans for implementing global harmonization of methods
  - Assist in identification of research needs
  - Promote application of new science in risk assessment practice
  - Facilitate global harmonization through joint events and projects and exchange of staff
  - Provide recommendations to WHO, FAO, and OECD
- **ILMERAC represents FDA's largest global coalition**

CFSAN Global Activities and Partnerships

29 ILMERAC Members and Observers



Benefits for a scientific RA Agency



Possible Topics for consideration by ILMERAC

Draft mandates
Draft guidance
Draft opinions
New challenges
New themes
New methods/approaches
New models & tools
Chemical databases
Emerging topics
Discussion of priorities (roadmaps)
Identifying RA partners
Launching joint activities
International harmonisation
and standardisation

Working Arrangements

- Governmental and intergovernmental food safety organizations
- Technical Secretariat (rotating every three years)
- Technical Secretariat coordinates, plans, organizes meetings, drafts agenda and reports, tracks actions, etc.
- Type of contributions: exchange info on ongoing & planned activities, new guidance documents, invite experts, ILMERAC activities, ad-hoc working groups
- Meetings: conference calls (2-3/year), physical meeting every 1- 2 years
- Confidentiality arrangements

WHAT'S NEXT FOR ILMERAC

- BfR has taken over Executive Secretariat- in partnership with FDA
- Criteria for additional members adopted- UK, Switzerland, Norway are interested
- Priorities for 2024-5- Mixtures, Human Relevance, MPS for Chemical Risk Assessment
- Planning a "Ring Trial" with TissUse GmBH, BfR, EFSA, CFSAN/NCTR, and Singapore to study use of MPS in chemical risk assessment
- Included in the next face to face meeting of ILMERAC in Berlin 12/2024.
- Including discussions/partnering with PARC on advancing risk assessment criteria for chemical risk assessment

Keep Moving Forward…

- Investments in regulatory science can enable us to better protect and promote the health of people throughout the world.
- Moving from current to newer methods is challenging and we need to work together to define needed pathways and catalyze change.
- Roadblocks to change can only be overcome through collaboration between all who make up the complex system of discovery and product development.
- FDA Foods Program is working collaboratively to move research into regulatory use and then global acceptance.