NTP
National Toxicology Program

# Update on NICEATM Activities

**Warren Casey, PhD, DABT**

**Director, NICEATM**

**NIEHS / NTP**

**SACATM Meeting, September 2, 2015**

**Research Triangle Park, NC**

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), organized as an office under the NTP Division, part of NIEHS

National Toxicology Program
NTP

## Focus Areas

- Reference Data
- Fit for Purpose Validation
- Integrated Analysis of Data
- In Vitro to In Vivo Extrapolation (IVIVE)

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- **Fit for Purpose Validation**
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  - **Equivalent performance**
  - **Superior performance / predictive of toxicity in humans**

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## Using data from animal studies as the gold standard

- What is the objective of using a non-animal method?
  - **Equivalent performance**– Why use human-based alternative methods? Should use system that most closely matches the gold-standard (i.e., rat cell lines to predict rat toxicity).
  - **Superior performance / predictive of toxicity in humans**

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## Using data from animal studies as the gold standard

- What is the objective of using a non-animal method?
  - **Equivalent performance**– Why use human-based alternative methods? Should use system that most closely matches the gold-standard (i.e., rat cell lines to predict rat toxicity).
  - **Superior performance / predictive of toxicity in humans** – How is it possible to get better results than the gold standard?
    - Reference data derived from animal studies is, by definition, always correct.

We need more **human data** in order to develop/validate systems that are more predictive of human toxicity than animal-models.

# Reference Data: What is "Truth"?

## Using data from animal studies as the gold standard

- Skin Sensitization
  - Reference data from both human and mouse (Local Lymph Node Assay, LLNA) available.
  - LLNA is generally the preferred animal-based test

**Human**

| LLNA | NEG | POS |
|---|---|---|
| **NEG** | 20 | 5 |
| **POS** | 10 | 61 |

Predictivity of LLNA

Accuracy : 84%
Sensitivity : 92%
Specificity : 67%

**If validating a non-animal alternative, which is gold standard; LLNA or Human?**

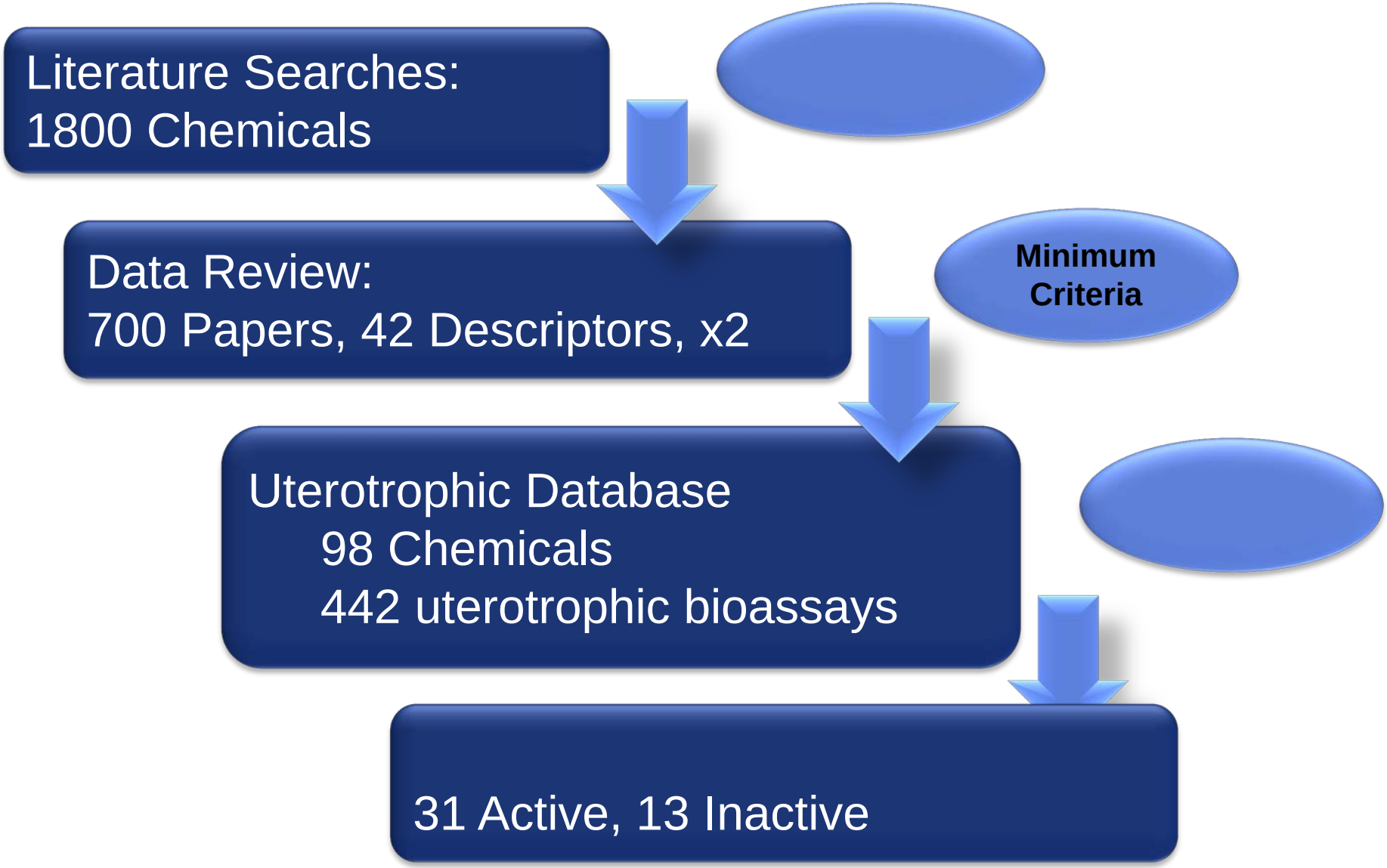
**What is the objective: predicting human toxicity or replacing the LLNA?**

# Reference Data: What is “Truth”?

## Regardless of source, need quality and context

- Estrogen signaling: uterotrophic bioassays
- Androgen signaling: in vitro studies
- Acute Toxicity: Oral and Dermal $LD_{50}$ Studies
- Developmental toxicity

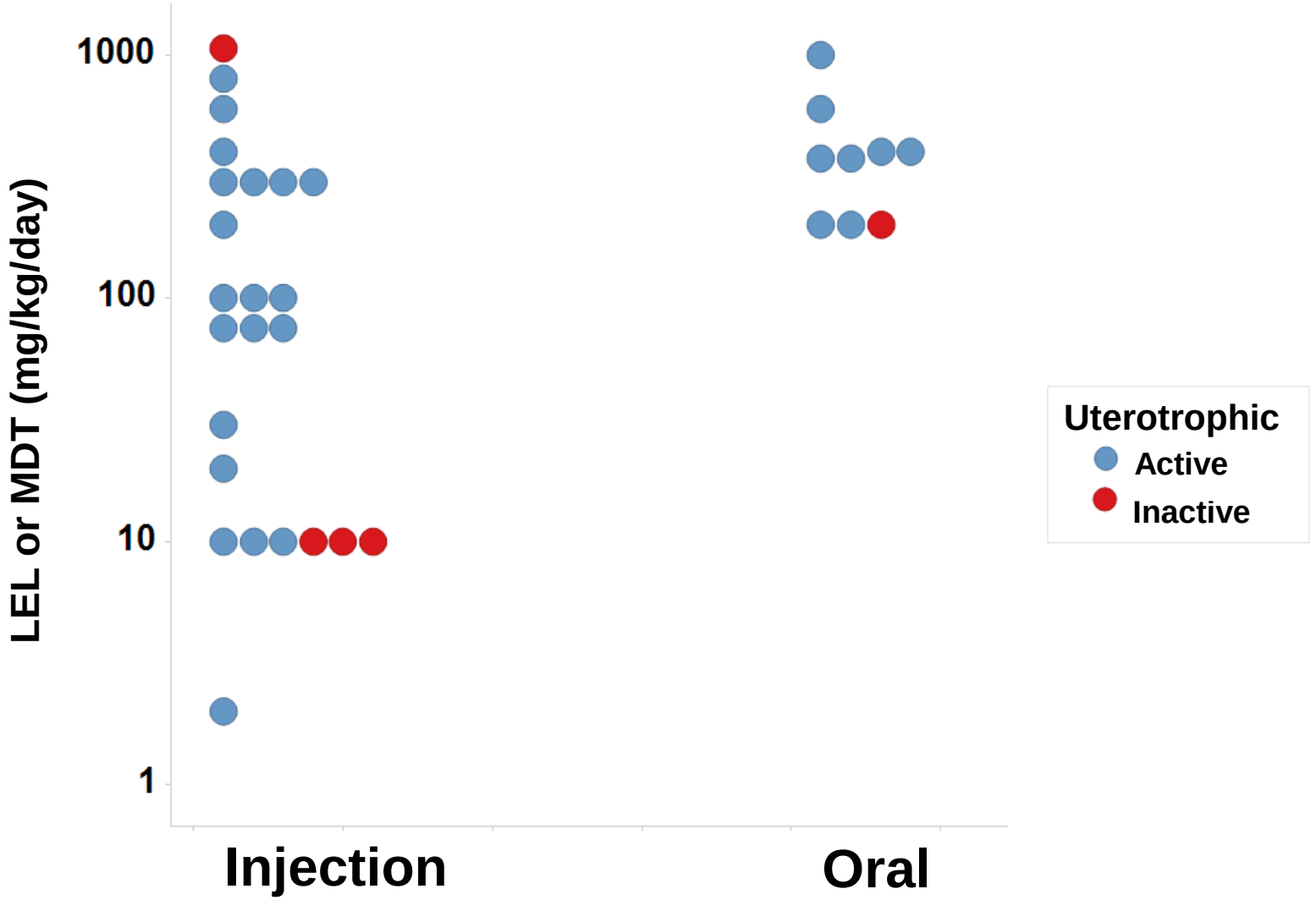
# Identifying Uterotrophic Reference Chemicals




**Kleinstreuer NC, Ceger P, Allen D, Strickland J, Chang X, Hamm J, Casey W.** 2015. A Curated Database of Rodent Uterotrophic Bioactivity. Environmental Health Perspectives: Cond. Accepted

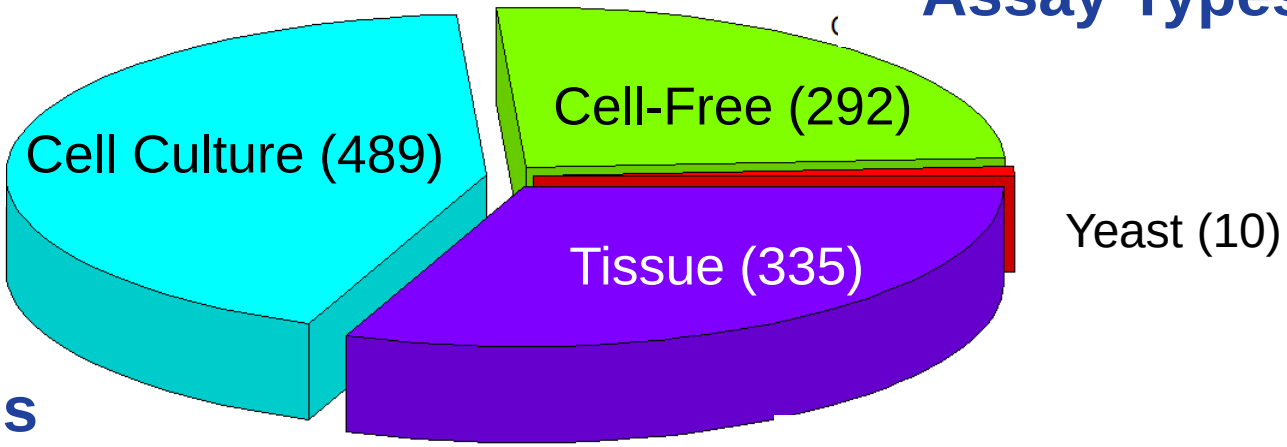
# Uterotrophic Reproducibility

## Immature Rat: BPA



# Identifying AR Reference Chemicals

## Assay Types

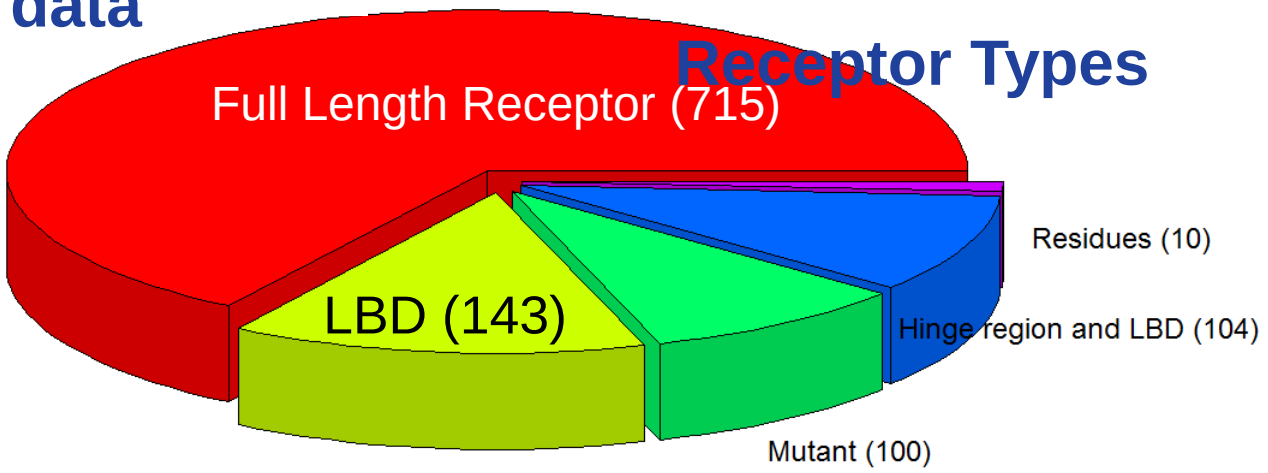



**158 Chemicals**

**443 Papers**

**5611 Rows of data**

## Receptor Types



# Database of Developmental Toxicants

- **Identify a database of prenatal developmental toxicants supported by sufficient publicly available data from animal models/humans.**
- **Focus on identifying agents that produce subtle developmental effects**
  - Fetal weight changes, ossification alternations, axial skeleton shifts, metabolic changes, developmental delays, gestation length changes, etc.
- **TK and windows of susceptibility are critical**
- **Includes both positives and negatives**

# Fit for Purpose Validation

## One Size Does Not Fit All

# Fit for Purpose Validation

## Agency Specific: EPA

-Endocrine Disruptor Screening Program

- Acute Oral / Dermal $LD_{50}$

## Agency Specific: Skin Sensitization

| Agency | Reg. Products | Information Needed |
|---|---|---|
| EPA | Chemicals/Pesticides | Nonsensitizer<br>Sensitizer |
| CPSC | Consumer Products | Nonsensitizer<br>Sensitizer<br>Strong Sensitizer |
| FDA | Drugs / Cosmetics | Ask FDA |

## Single Laboratory Validation

- How important is transferability?

# Validation: OECD GD34

**OECD SERIES ON TESTING AND ASSESSMENT**
**Number 34**

**GUIDANCE DOCUMENT ON THE VALIDATION AND INTERNATIONAL ACCEPTANCE OF NEW OR UPDATED TEST METHODS FOR HAZARD ASSESSMENT**

- Rationale / relationship to endpoint is described
- Protocol is made available
- Variability is characterized
  - Within-Lab
  - Between-Lab (transferability); Ring Trials
- Performances is characterized with established reference chemicals
- Validation data are peer reviewed

# In Vitro to In Vivo Extrapolation (IVIVE)

- How do results from in vitro assays relate to bioactivity and toxicity seen in animals and humans?
- NICEATM is sponsoring a Best Practices Workshop at EPA (RTP), NC  February 17-18 2016

- Key publications:
  - Browne P, Judson R, **Casey W, Kleinstreuer N,** Thomas R. 2015. Screening chemicals for estrogen receptor bioactivity using a computational model. Environ Sci Technol 49(14):8804-8814.
  - **Kleinstreuer NC, Ceger P, Allen D, Strickland J, Chang X, Hamm J, Casey W.** 2015. A Curated Database of Rodent Uterotrophic Bioactivity. Environmental Health Perspectives: (accepted-pending)
  - Goodson WH, Lowe L, Carpenter DO, (107 other authors), **Kleinstreuer N,** (60 other authors), Luqmani Y, Chen Z, Hu Z. 2015. Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: the challenge ahead. Carcinogenesis 36(Suppl 1):S254-S296.
  - Hu Z, Brooks SA, Dormoy V, (24 other authors), Lowe L, Jensen L, Bisson WH, **Kleinstreuer N**. 2015. Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: focus on the cancer hallmark of tumor angiogenesis. Carcinogenesis 36(Suppl 1):S184-S202.

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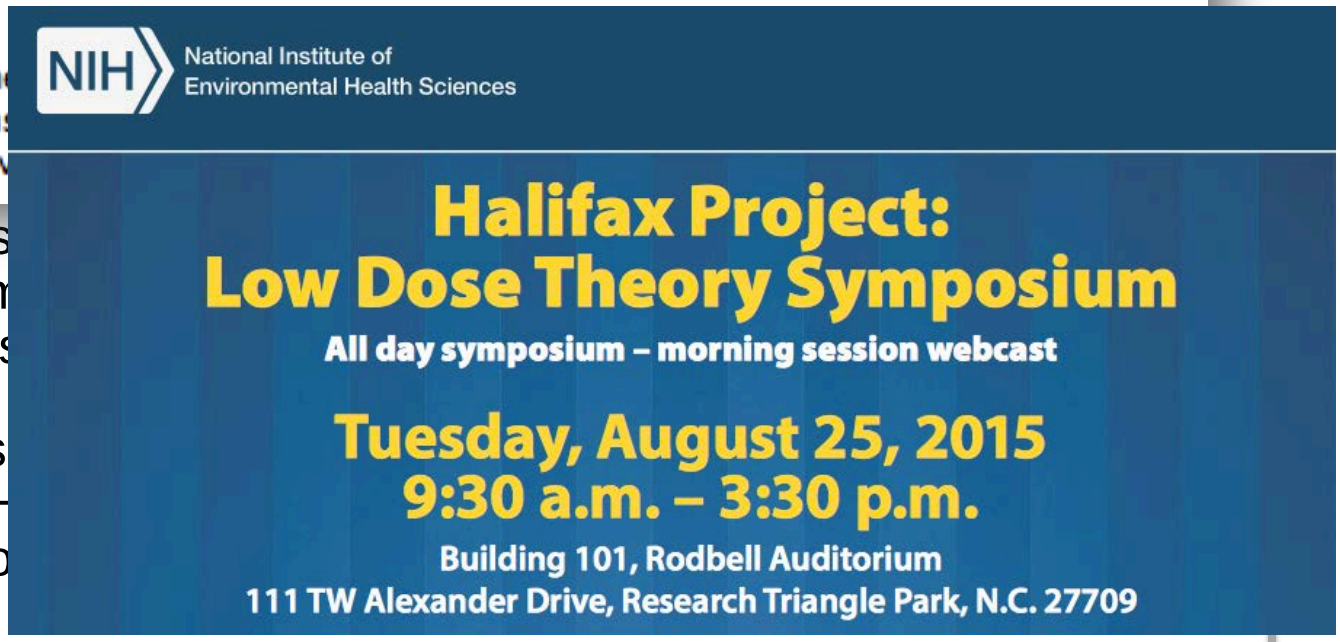
**The Halifax Project**

Hundreds of cancer researchers and physicians from around the globe have now been formed into two large task forces that will each be tackling a very important and very challenging problem. One task force is focused on an advanced therapeutic design that will be aimed at a broad-spectrum of targets (in an attempt to tackle the problem of therapeutic resistance and disease relapse). While the second task force will be focused on the carcinogenic potential of low dose exposures to mixtures of chemicals in the environment.

In August of 2013 many of th
workshops to collaborate. Plea
the many scientists who are inv

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Carcinogenes

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# Questions for SACATM

Please provide suggestions for future scientific workshops, symposia, research opportunities, or other activities related to moving towards ‘fit for purpose’ validation approaches.