



# **Chemical Safety for Sustainability Research Program**

**Supplemental Information Requested by SAB/BoSC  
Members following July 3, 2014 Introductory Call**

**Tina Bahadori, Sc.D.**  
National Program Director



## Action Items from July 3<sup>rd</sup> Call

- Committed to providing additional information, including references, for mixtures of chemicals and nano particles. (slide 3)
- Agreed to provide a list of themes and projects supporting the statistics on Slide 13 showing that “8 themes reduced to 4 Research Topics” and “21 Projects reduced to 9 project areas” showing what was dropped, what was saved, and what was consolidated. (slides 4-5)
- Agreed to provide additional, more specific examples of how different programs are using outputs from the CSS program (slides 6-11)
- Agreed to identify two or three areas that ORD considers as top challenges to increasing confidence in CSS outputs. (slide 12)

### Examples of translation, fit for purpose application, and stakeholder engagement (slides 13-26)

- Agreed to provide a more detailed slide than Figure 2 in the StRAP which shows the process of translation of fit-for-purpose research to its use. A member asked for an example of such a translation at a greater level of detail. (also slides 6-11)
- Agreed to provide more specific information on who ORD engages as stakeholders and how representative the stakeholders are.
- Agreed to provide more specific information about the training provided to EPA staff to upgrade their ability to use outputs from the CSS program.

- Requested references for how complexity, including multiple chemical interactions and other complex factors (time, spatial) might be addressed.
  - **Challenge: Understand and predict complex environmental exposures and subsequent effects to human health and the environment through computational models simulating effects in humans, endangered species, other individuals, populations and lifestages.**
  - **Approach: Apply tools of complex systems science to develop models and data required to simulate the linked human-environment system.**

### Example References:

- Exploring Complex Networks by Steven Stogatz
  - <http://www.nature.com/nature/journal/v410/n6825/abs/410268a0.html>
- Pattern-Oriented Modeling of Agent-Based Complex Systems: Lessons from Ecology by Grimm *et. al.*
  - <http://www.sciencemag.org/content/310/5750/987.short>
- Intake to Production Ratio: A Measure of Exposure Intimacy for Manufactured Chemicals by Nazaroff *et. al.*
  - <http://ehp.niehs.nih.gov/1204992/>



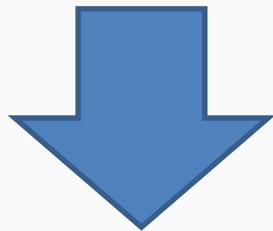
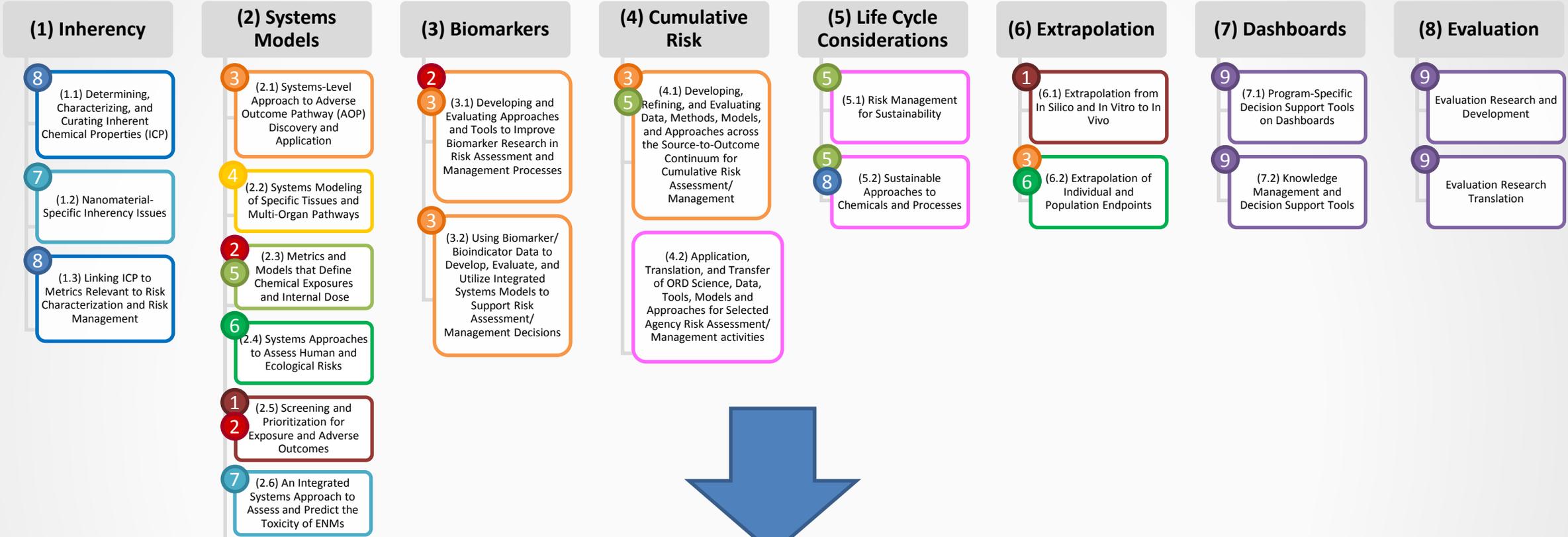
## Major Research Areas Being Reframed and/or Integrated

- Agreed to provide a list of themes and projects supporting the statistics on Slide 13 [CSS 101] showing that “8 themes reduced to 4 Research Topics” and “21 Projects reduced to 9 project areas” showing what was dropped, what was saved, and what was consolidated.
  - **Major areas being reframed/integrated – see mapping on Slide 5:**
    - Inherency and Green Chemistry will be integrated into Sustainable Chemistry Project Area (Lifecycle Analytics Research Topic)
    - Biomarker/bioindicator research will be redirected to address high-priority problems and will be integrated into Adverse Outcome Pathway Discovery & Development and Rapid Exposure & Dosimetry Project Areas
    - Cumulative risk will be integrated into Complex Systems Science Research Topic
    - Lifecycle assessment expertise will be directed toward developing sustainability indicators of impacts associated with chemical/material manufacture and use in Lifecycle Analytics Research Topic
    - Extrapolation, Dashboards, and Evaluation will be integrated into the Solutions-Based Translation & Knowledge Delivery Research Topic

# Restructuring of CSS Research Themes and Projects

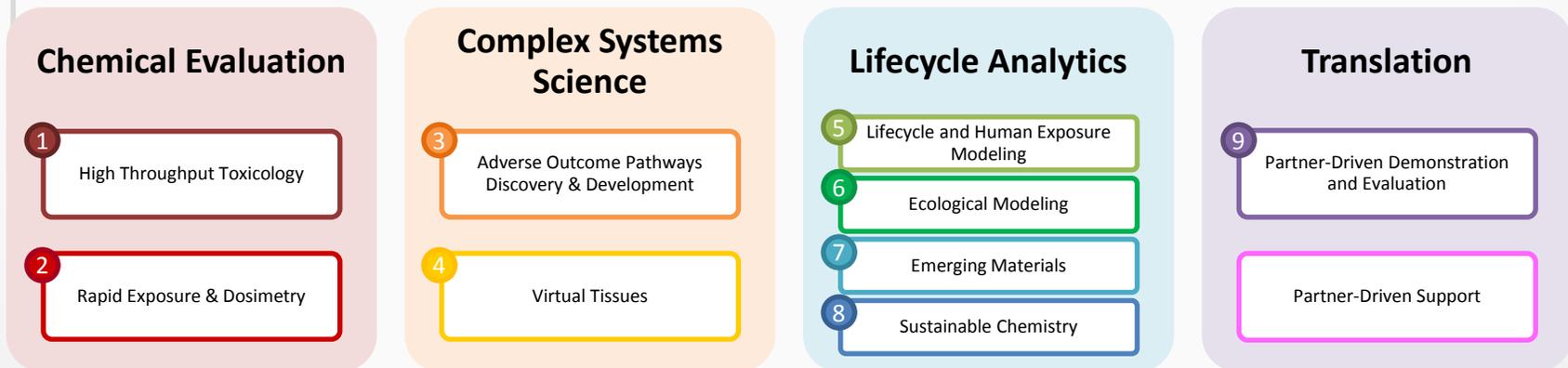
FY14 Research Themes

FY14 Research Projects



FY15+ Themes

FY15+ Research Project Areas





## Examples of EPA Using Outputs of CSS

- **Agreed to provide additional, more specific examples of how different programs are using outputs from the CSS program**
  - **OCSPD EDSP Program (slides 7-9, courtesy of OCSPD)**
  - **DfE for evaluating flame retardants (slide 10)**
  - **EPA Regions collaborating to translate and apply CSS research (slide 11)**



# Evolution of the EDSP

Courtesy of Office of Chemical Safety and Pollution Prevention

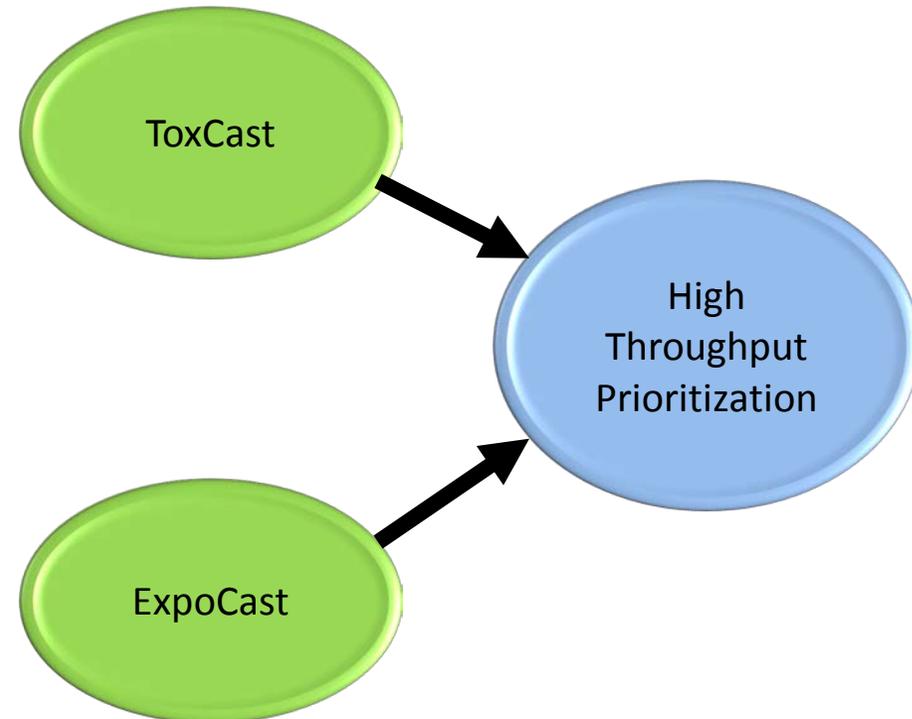
- Based on current pace it could take decades to screen all 10,000 chemicals for potential to interact with the endocrine system
- Recent advances in computational toxicology herald an important “evolutionary turning point” and an accelerated pace of screening and testing
- To address thousands of chemicals for potential to interact with the endocrine system, we must implement a more strategic approach to prioritize chemicals for targeted screening



# Screening and Prioritization

Courtesy of Office of Chemical Safety and Pollution Prevention

- **ToxCast**
  - Expanding use of CompTox (Phys-chem properties, QSARS, etc.) to support screening and prioritization
  - Transparent and collaborative
- **ExpoCast**
  - Rapid exposure estimation based on readily available chemical use and production data
  - Use toxicokinetics to bridge *in vitro*, concentration-based ToxCast data to *in vivo*, dose-based Exposures from ExpoCast

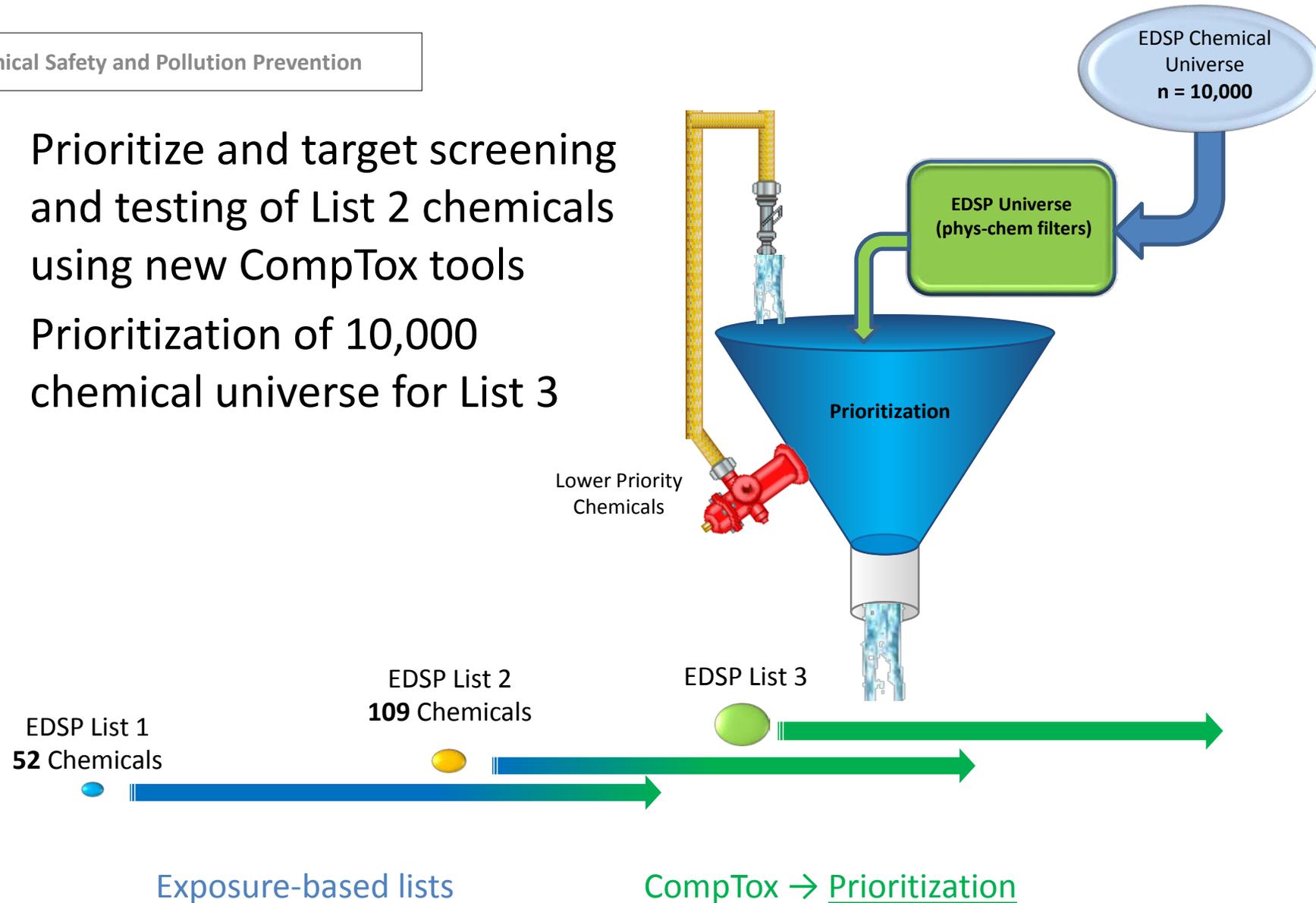




# Prioritization

Courtesy of Office of Chemical Safety and Pollution Prevention

- Prioritize and target screening and testing of List 2 chemicals using new CompTox tools
- Prioritization of 10,000 chemical universe for List 3





## EPA Programs Using CSS: Design for the Environment and Evaluating Flame Retardants and Alternatives

- **Working with OCSPP on alternatives analyses and applications to brominated flame retardants to enhance predictive capabilities for new chemicals and ability to target testing needs by supplementing current methods.**
  - **Goals are:**
    - Enable and facilitate use of high-throughput screening and exposure modeling
    - Build predictive signatures (reproductive, developmental, chronic/cancer endpoints) in chemical prioritization and hazard classifications.
  - **8 flame retardants tested in ToxCast HTS Phase II**
  - **45 retardants will be tested in Tox21/ToxCast Phase III and the data should be available over the coming year**
- **EPA funded NAS Study *Design and Evaluation of Safer Chemical Substitutions* due Fall 2014, will provide guidance on how “high throughput and high content data streams could inform assessment of potentially safer substitutes early in the chemical development process.”**



## Examples of EPA Regions Collaborating to Translate and Apply CSS Research

- **Region 1:** Exploring ways to use CSS Sustainable Chemistry and LifeCycle Analytistics tools to inform design of safer new products. R1 is working with business and industry, entrepreneurs, venture capitalists, non-profit groups, and others involved in the application of “green chemistry principles” to bring high value products to the market that are safer, healthier and more sustainable.
- **Region 5:** Pollution Prevention Program training academic and industry partners on using CSS developed tool Program to Assist the Replacement of Industrial Solvents (PARIS III) to inform decisions about safer solvent substitutions.
- **Region 5** (through Great Lakes National Program with OW): Collaborating to develop AOP-informed biological effects–based tools for monitoring impacted surface waters in the great lakes
- **Region 8:** Collaborating in the development of ‘high throughput toxicity values’ through application of CSS tools/models to data poor chemicals
- **Region 1, 2 and 9: Polychlorinated Biphenyls**
  - In response to concerns about PCBs in schools, CSS scientists identified and evaluated potential sources of PCBs in schools to better understand exposures to children, teachers, and other school workers.
  - CSS scientists investigated methods to reduce or eliminate PCB emissions in a school setting.
  - Research provided to Regions and CSS scientists present to other groups including the NY school board, parent groups, etc.



# Increasing Confidence In CSS Outputs

**Agreed to identify two or three areas that ORD considers as top challenges to increasing confidence in CSS computational toxicology outputs**

- **Increasing awareness, understanding, and comfort with high/medium throughput data among scientific and non-scientific audiences**
  - Increased transparency, access and training through enhanced focus on bi- (or multi-) directional engagement and training (Solutions-Based Translation & Knowledge Delivery Research Topic)
- **Developing and building consensus on an evaluation framework for high-throughput toxicity (HTT) testing schemes to inform specific chemical evaluation objectives**
  - CSS proposed FY16 output
- **Developing and building consensus around 'fit for purpose' applications of CSS data**
  - CSS proposed project Partner-Driven Demonstration & Evaluation will collaboratively develop a portfolio of tailored products in FY 15-19.

**Planning multi-agency funded NAS Study as a follow up to NRC's Toxicity Testing in the 21<sup>st</sup> Century that incorporates Exposure Science in the 21<sup>st</sup> Century. Seeking advice on whether the types of data CSS generates are ready to be applied; if so, under what circumstances; and what other steps are needed to increase confidence in the data and models that are being generated.**



## CSS Stakeholder Engagement Approach - I

- **Implement proactive communications and outreach plans**
- **Focus on three strategically selected audience groups**
  - **External stakeholder community (states, industry, academia, other government entities and non-governmental organizations)**
  - **EPA's Program Offices and Regions**
  - **General Public (increase general awareness)**
- **Focus on increasing awareness, interest and usage of CSS research to inform chemical safety decisions.**



## CSS Stakeholder Engagement Approach - 2

- **Promote application and integrate the use of CSS science and science products in chemical safety decisions, policies, voluntary efforts, and other actions**
- **Increase meaningful involvement in the development of research and tools**
- **Encourage two-way dialogue between stakeholders and EPA about CSS research products and research planning efforts**
- **Provide regular updates about research progress and plans for the future research direction of CSS**



## Engagement, Outreach, and Training

- **Webinars/training**
- **Workshop Participation and Stakeholder Feedback**
- **Database and Tools Usage Statistics**
- **CSS research presented and promoted at conferences and events**
- **Other scientists using or citing CSS research**



## CSS Webinars/Training: External

Webinars/Training for External Stakeholders	Date	Participant No.
Computational Tool for Defining Conservation of Molecular Initiating Events Across Species (Communities of Practice)	8/22/2013	67
FDA ToxCast Data and Dashboard Overview	9/11/2013	27
Overview of ToxCast Data and Dashboard Before Public Release (partners with signed research agreement)	9/19/2013	64
Adverse Outcome Pathway Wiki (Communities of Practice)	9/26/2013	52
iCSS Dashboard and ToxCast Data Overview (Communities of Practice)	12/12/2013	78
Office of Management and Budget Dashboard Briefing	12/20/2013	7
California EPA Webinar: ToxCast Data & Dashboard Demo	1/10/2014	6
Chemical Product Categories Database (Communities of Practice)	1/23/2014	103
Targeted Analysis of House Dust Samples Using Time Flight of Mass Spectrometry	4/24/2014	39



## CSS Webinars/Training: EPA Programs & Regions

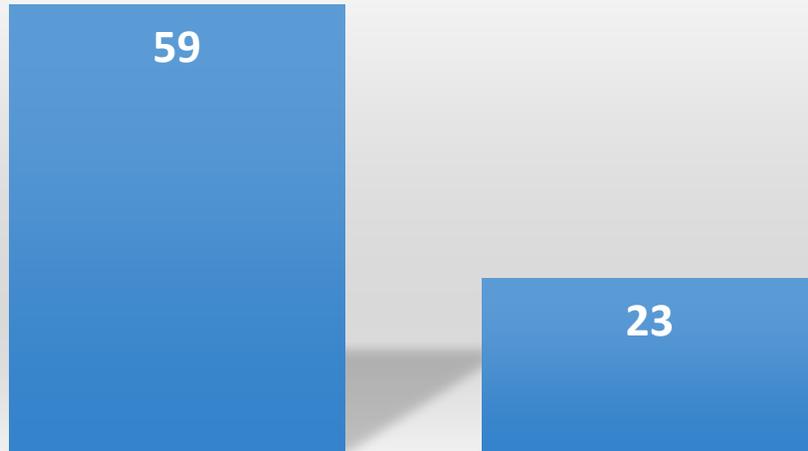
CSS Webinars/Training for EPA Program & Regional Offices	Date	Participant No.
Overview of CSS research efforts and discussion with Regions about research priorities	7/10/2013	41
Ecological Modeling Research: Web-Ice, MCnest	7/17/2013	53
Overview of iCSS Dashboard and Stakeholder Outreach Efforts for ACC	7/18/2013	~15
Nanomaterials Research Update	8/21/2013	98
Perchlorate Case Study	9/18/2013	100
Overview of ToxCast Data and Dashboard Before Public Release	9/19/2013	34
Mode of Action (MOA) Look Up Tool linking pesticides to Distributed Structure Searchable database	11/20/2013	108
Fiscal Year 2013 CSS Key Products Overview	2/19/2014	68
CSS FY15-17 Research Planning and Discussion with Regions	3/18/2014	20
Chemical and Product Categories database (CPCat DB)	6/11/2014	32



# CSS Stakeholder Workshops

Held two stakeholder workshops (January in RTP and April in DC area) to provide an overview of high-throughput screening data from ToxCast and how to access the data. Presentations described ToxCast data, provided early interpretation of data, demonstrated how to access ToxCast data through the iCSS dashboard and provided opportunity for stakeholders to provide feedback.

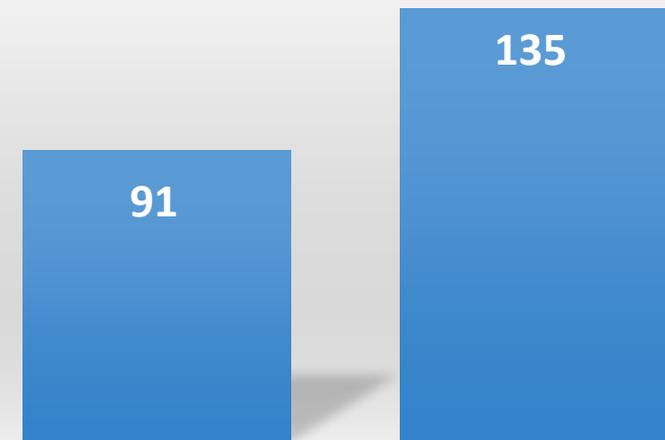
## January Participation



In Person

Webinar

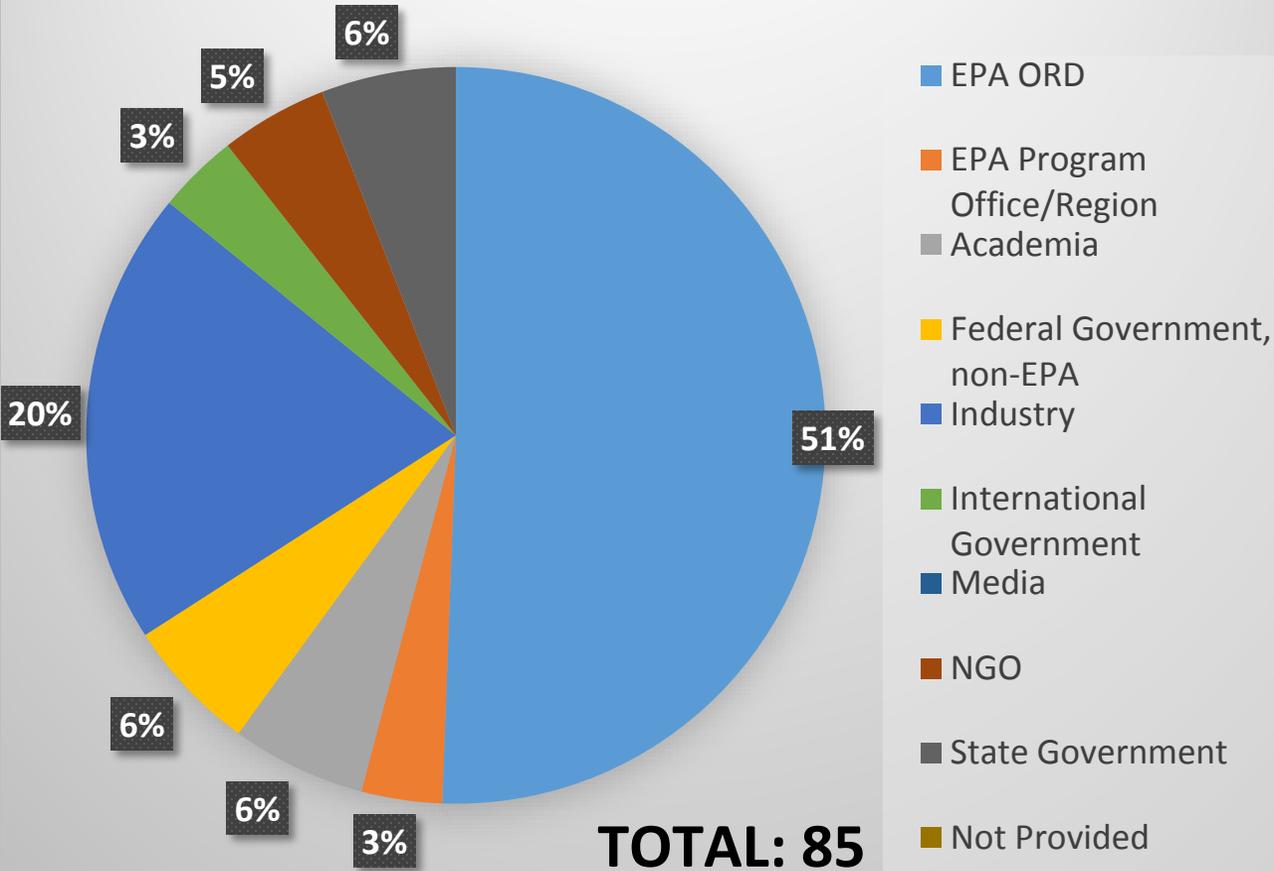
## April Participation



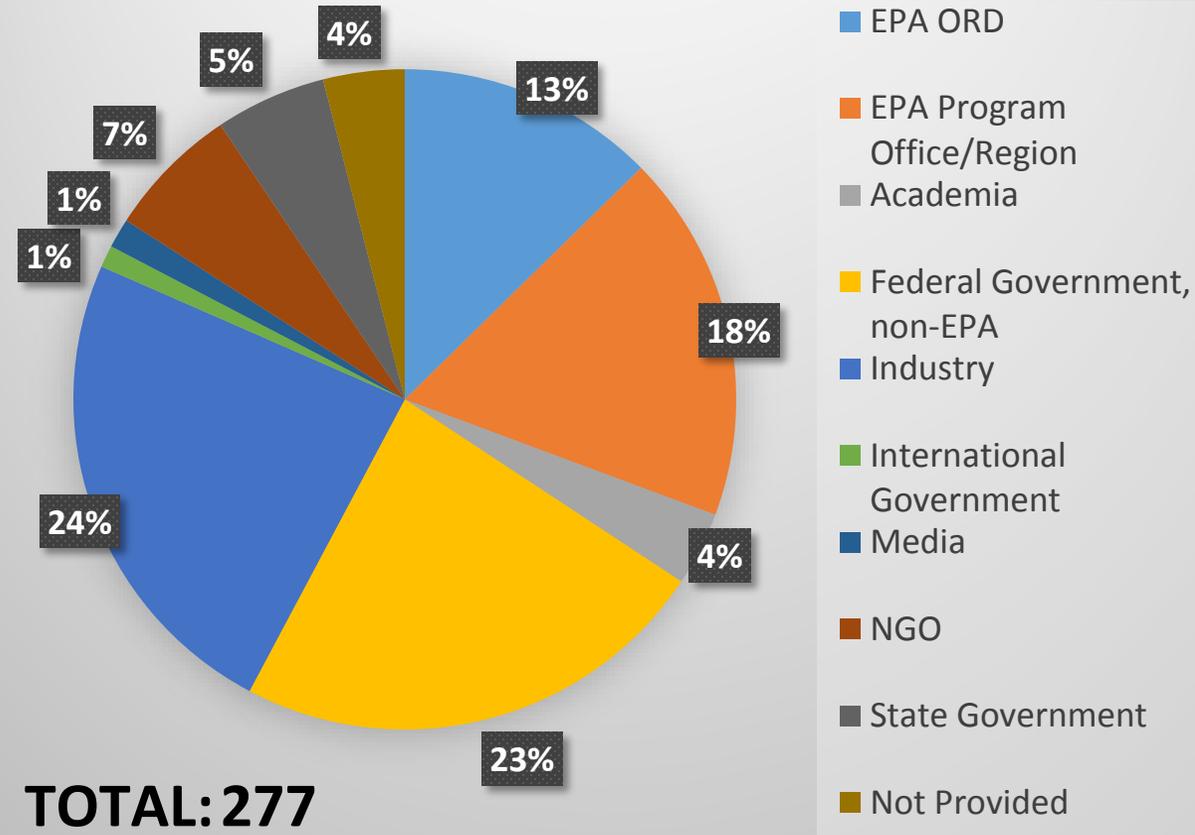
In Person

Webinar

## ToxCast Stakeholder Workshop Participation, January 14 2014



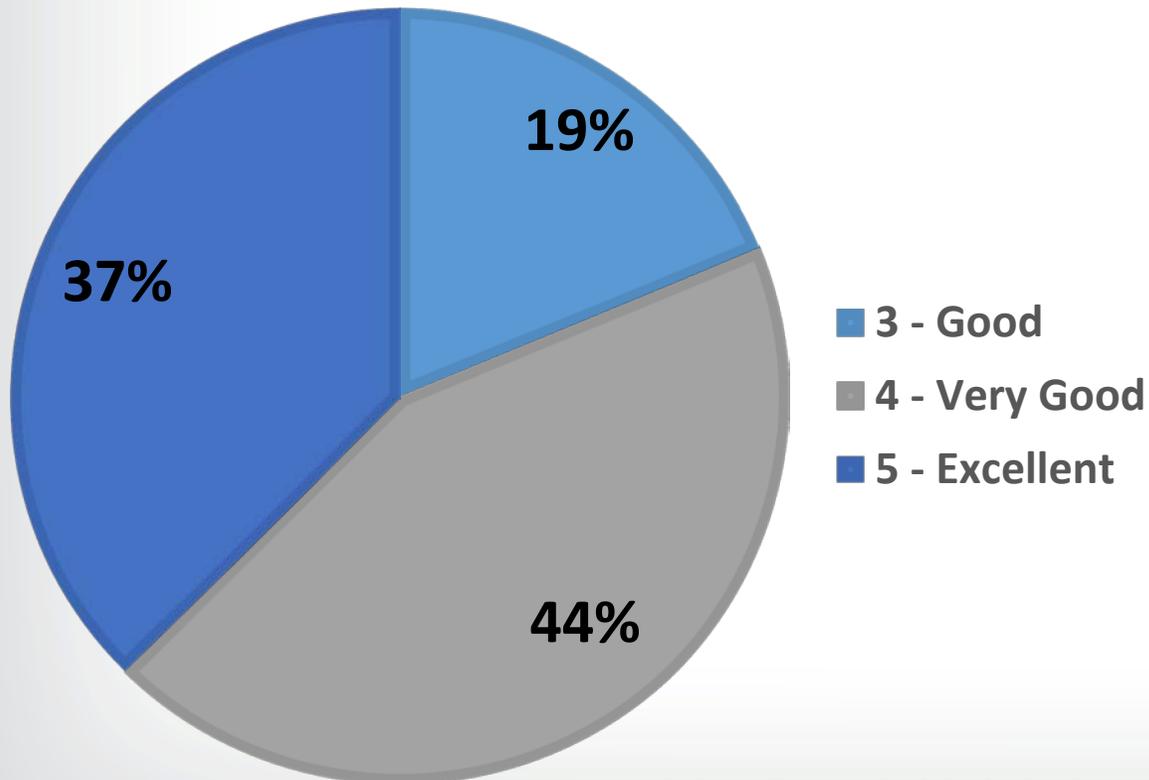
## ToxCast Stakeholder Workshop Participation, April 2-3 2014





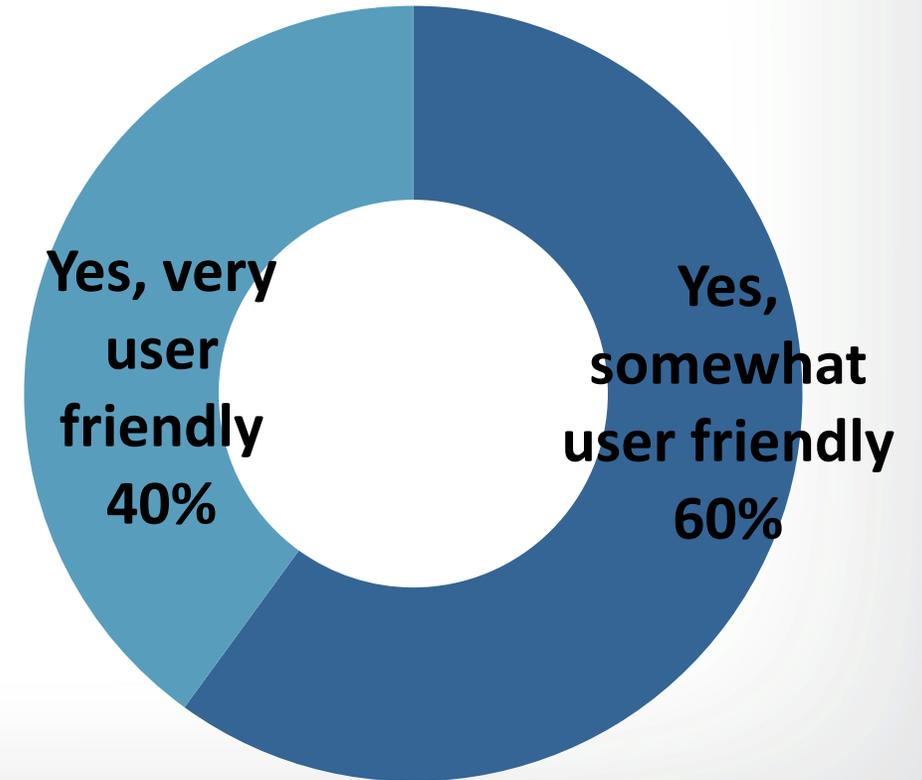
# CSS Stakeholder Workshop Feedback

## JANUARY WORKSHOP: ACHIEVEMENT OF OBJECTIVES



## Did you find the iCSS Dashboard user-friendly?

Scale: Very user friendly, somewhat user friendly, Non user-friendly

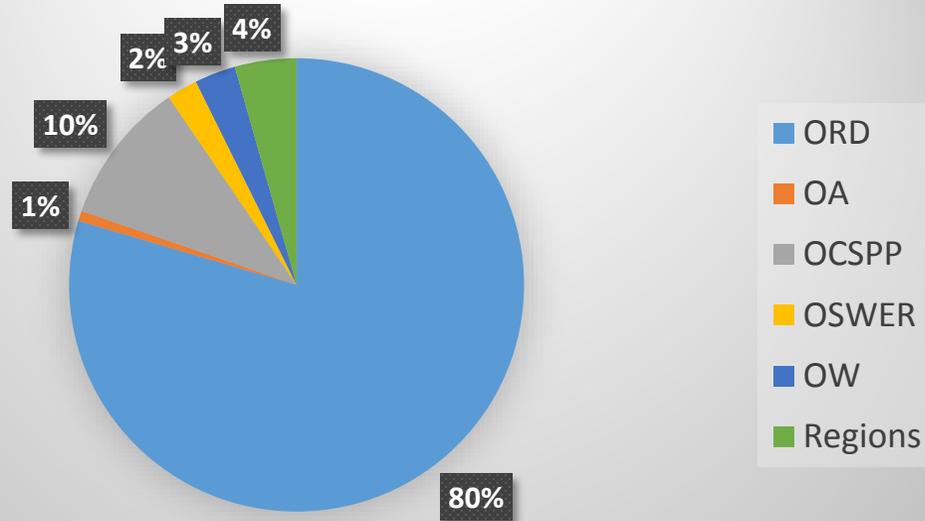




## Other Examples of CSS Stakeholder Meetings

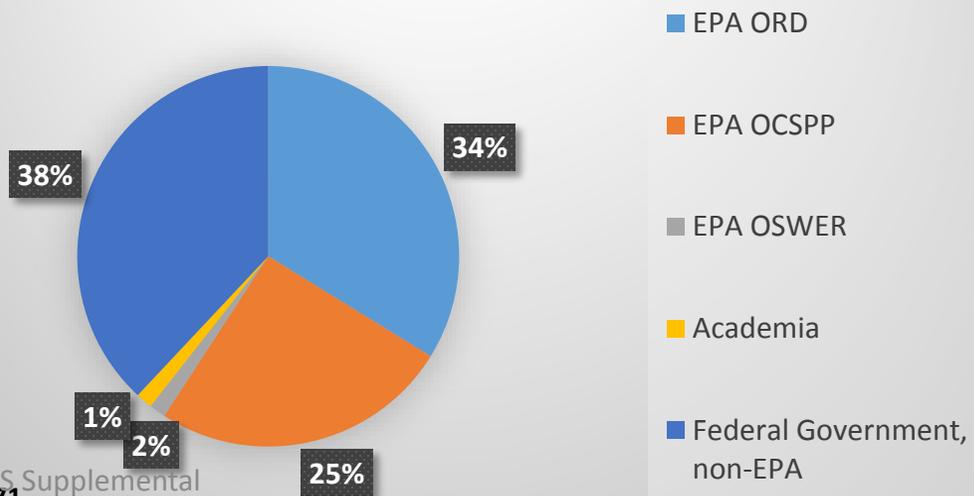
- **Flame Retardant Meeting:** Presented ongoing research, future research plans and had a panel discussion about the science direction and priorities across federal agencies. Focused on understanding potential impacts of flame retardant chemicals. 77 government agency staff participated including EPA OCSP, EPA ORD, NIEHS, CPSC, OSHA, ATSDR, DOD, Health Canada, Environment Canada and academic partners.
- **Nanomaterials Research Partner Meeting:** Facilitated development of long term research goals and plans regarding Engineered Nanomaterials (ENM) as a focal point for research on emerging materials. 66 participants including staff from EPA OCSP, EPA OSWER, EPA ORD, Duke/CEINT, UC/CEIN, U South Carolina/CENR, CPSC, NIEHS, NIOSH
- **Connectome for EPA Program Offices & Regions:** Representatives from EPA Program and Regional offices met with CSS to 1) provide an overview of the CSS research program through presentations and posters and 2) elicit stakeholder feedback through partner panel discussions and question and answer sessions. Over 138 EPA staff participated in the meeting.

### CSS Connectome Participation May 2014



TOTAL: 137

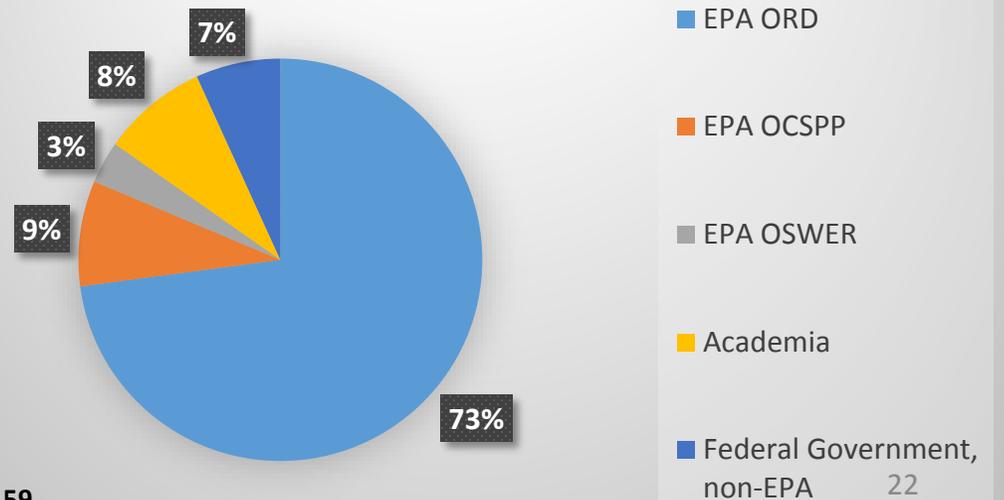
### U.S Cross-Federal Agency Flame Retardant Meeting, May 8 2014



TOTAL: 71

CSS Supplemental

### EPA Nanomaterials Research Meeting, February 2014

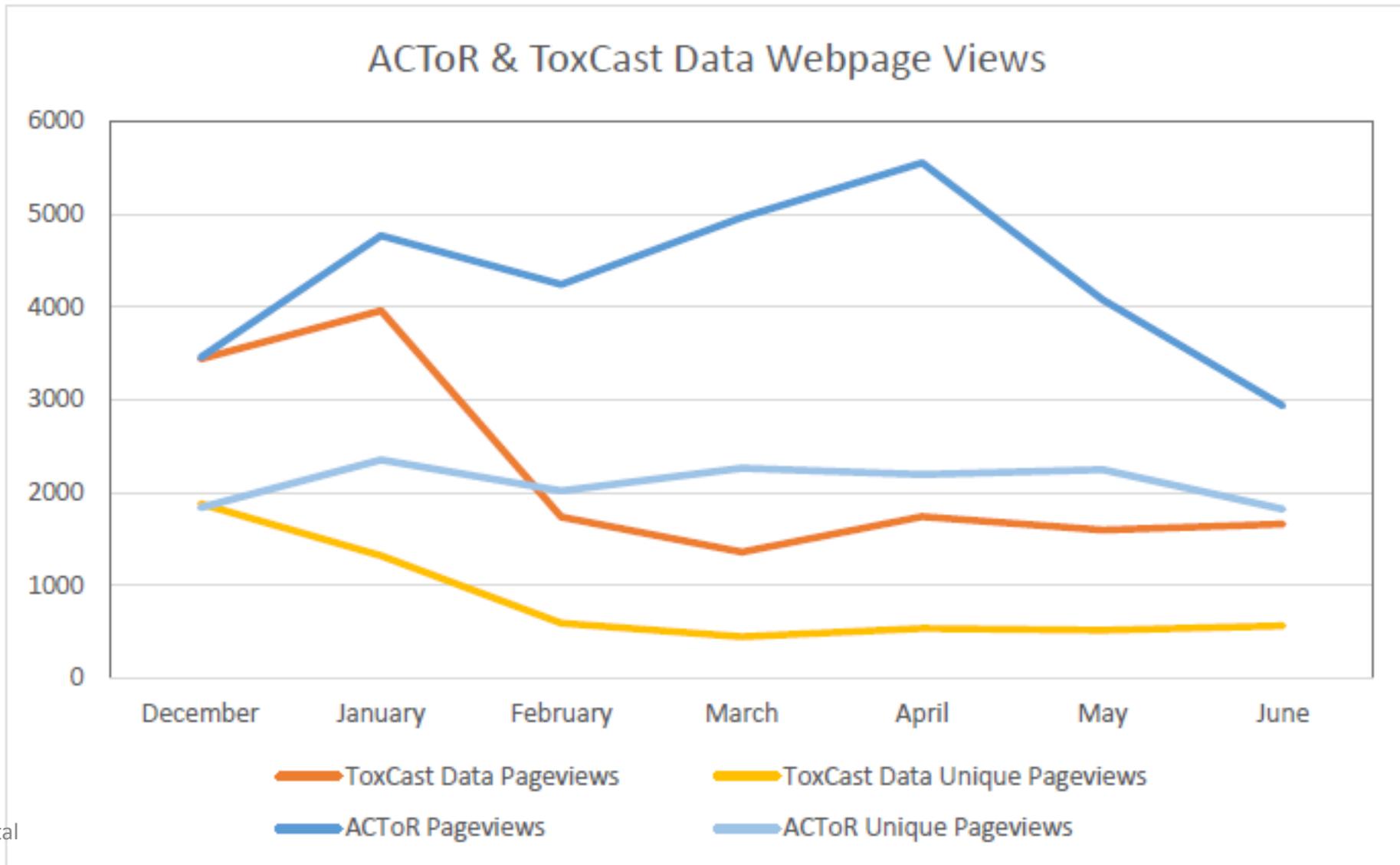


TOTAL: 59

22

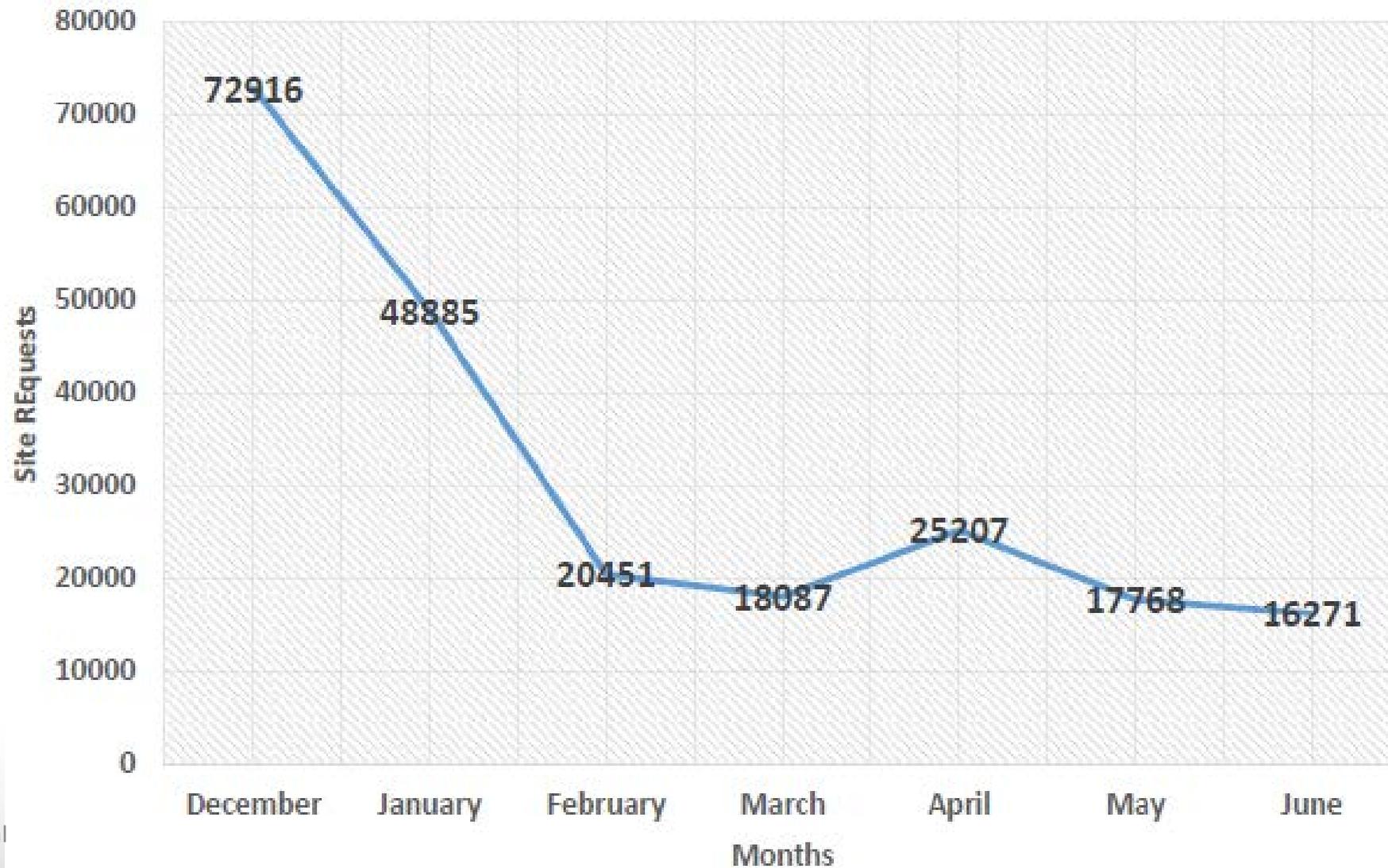


# ToxCast Data & AcTOR Webpage



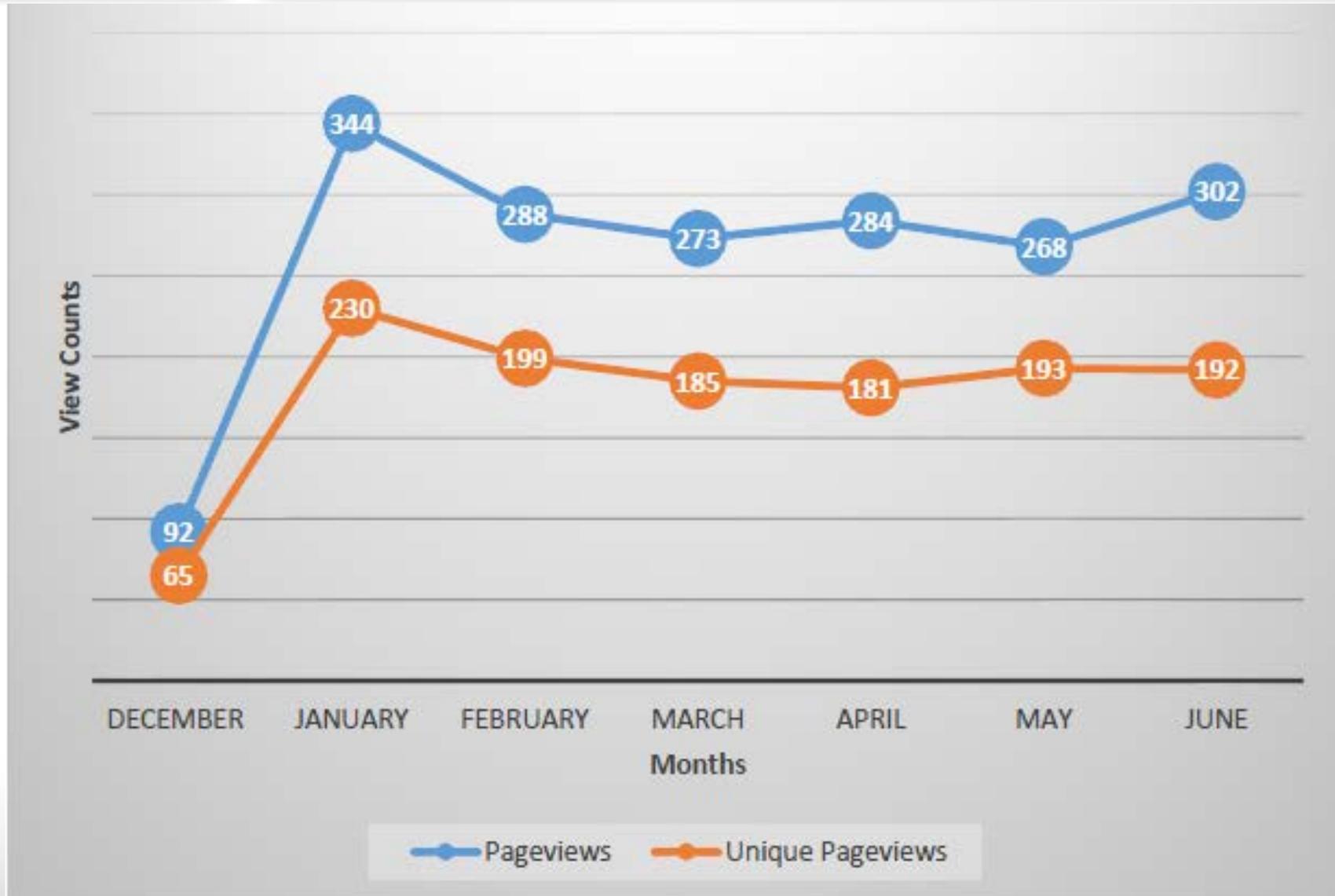


# iCSS Dashboard





# Chemical Product Category (CPCat) Database Usage





## Highlighted Conferences & Events Featuring CSS

- **SOT Future Tox II (January 2014) *In Vitro* Data and *In Silico* Models for Predictive Toxicology:** EPA scientist co-chair of organizing committee and featured presentations and posters about CSS research.
- **ACS Green Chemistry Institute's Annual Green Chemistry & Engineering Conference (June 2014):** CSS NPD conference co-chair, CSS Deputy part of organizing committee, featured presentations and posters about CSS research. EPA booth promoting research.
- **American Chemistry Council briefings about AOP Wiki (September 2013) and iCSS Dashboard (July 2013):** Briefed American Chemistry Council about AOP Wiki and iCSS Dashboard.
- **Society for Environmental Toxicology and Chemistry Conference (November 2013 and 2014 planned):** Feature presentations and posters about CSS research.
- Booth and hands-on demonstrations of CSS database, models and tools at several scientific meetings, including SOT, ISES, and SETAC.
- **Society of Toxicology (March 2014):** Featured presentations and posters about CSS research. EPA booth and demonstrations of CSS databases, models and tools.



## Examples of Scientific Community Referencing & Using CSS Research

### Citation of CSS research products

- **Adverse Outcome Pathways: A Conceptual Framework to Support Ecotoxicology Research (Ankley et al, Environmental Toxicology and Chemistry): Cited 239 times**
- **ToxCast Project: In vitro screening of environmental chemicals for targeted testing prioritization (Judson et al, Environmental Health Perspectives): Cited 159 times**
- **Impact of Environmental Chemicals on Key Transcription Regulators and Correlation to Toxicity Endpoints within ToxCast (Martin et al, Chemical Research in Toxicology): Cited 62 times**
- **Predictive models of prenatal developmental toxicity from ToxCast (Sipes et al): Cited 48 times**

CSS Supplemental

### Non-EPA researchers publishing using CSS research

- [Developing scientific confidence in HTS-derived prediction models: Lessons learned from an endocrine case study.](#) (Cox et al, Regulatory Toxicology and Pharmacology)
- [Analysis of Pfizer compounds in EPA's ToxCast chemicals-assay space.](#) (Shah et al, Chem Res Toxicol)
- [ToxCast on target: in vitro assays and computer modeling show promise for screening chemicals.](#) (Haynes et al, Environ Health Perspect)
- [Evaluation of computational docking to identify pregnane X receptor agonists in the ToxCast database.](#) (Kortagere et al, Environ Health Perspect)
- [Consideration of dosimetry in evaluation of ToxCast™ data.](#) (Aylward LL et al, Journal of Applied Toxicology)
- [Predicting the carcinogenicity of chemicals with alternative approaches: recent advances.](#) (Benigni R et al., Expert Opin Drug Metab Toxicol.)
- [Building predictive models for mechanism-of-action classification from phenotypic assay data sets.](#) (Berg EL et al, J Biomol Screen)