# Recap of March 2012 Workshop & Introduction to SAR Speaker

Ivan J. Boyer, Ph.D., D.A.B.T.

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Cosmetic Ingredient Review

# CIR Expert Panel 5 March 2012 SAR Workshop Recap

Speakers:

- **Chihae Yang, Ph.D.**, Chief Scientific Officer of Altamira LLC & Work package leader for the European COSMOS project
- **Andrew Worth, Ph.D.,** Leader of the Computational Toxicology group at the European Union (EU) Joint Research Centre (JRC)
- **Kirk Arvidson, Ph.D**., Review chemist & leader of the Structure Activity Relationship (SAR) Team in the U.S. FDA Office for Food Additive Safety (OFAS).
- **Karen Blackburn, Ph.D**., Research Fellow at P&G

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# SAR Workshop Recap: Chihae Yang, Ph.D.

- History, development, prospects of Computational Toxicology
  - Paradigm shift for toxicity assessments (Toxicology for the 21st Century)
    - From: primarily *in vivo* animal studies
    - To: *in vitro* assays, *in vivo* assays with lower organisms, & computational modeling
  - Premise: Computational methods can be used effectively to derive knowledge from theory & results of past experiments
- Central problem: (Q)SAR technologies cannot predict biological activities directly from molecular structures
  - They predict biological activity indirectly, based on molecular descriptors (i.e., electronic & steric/size effects & hydrophobicity) that represent molecular structures
  - Results need additional transformation & translation to use in risk assessments (adds more complexity to an already complex paradigm)

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# SAR Workshop Recap: Chihae Yang, Ph.D. (Continued)

- Specific Challenges
  - Develop formal, quantitative, weight-of-evidence approach to synthesize & present results of structural alert, SAR & read-across analyses
  - Define mode-of-action (MoA) categories of chemicals & incorporate mechanistic descriptors & biological assay descriptors to improve interpretability & biological relevance of (Q)SAR results
  - Develop chemical & biological space profiles based on (Q)SAR results for chemicals with sufficient data
    - Support reliable read-across for evaluating chemicals with suitable analogs
    - Facilitate application of knowledge about metabolic pathways, structural alerts, & structure activity relationships to predict toxicological endpoints & potencies for chemicals without adequate data or analogs

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# SAR Workshop Recap: Andrew Worth, Ph.D.

- EU cosmetic legislation driving development of alternatives to whole animal testing of cosmetic ingredients
  - Ultimate goal: Develop alternative predictive toxicology tools based on complete understanding of how chemicals can cause adverse effects in humans
  - COMOS Project: Develop integrated *in silico* models for predicting toxicity & informing safety assessment of cosmetic ingredients
    - (Q)SAR analyses can replace whole animal testing in principle
    - (Q)SAR more likely to be one of many elements used in integrated toxicology testing strategies
- Key acceptance barrier: Lack of guidance on how to use (Q)SAR methods to inform regulatory decisions
  - Key elements of adequate (Q)SAR predictions for regulatory purposes
    - (Q)SAR model scientifically valid, applicable to chemical, & yielding sufficiently reliable results
    - Prediction relevant for regulatory purpose
    - Adequacy of (Q)SAR modeling, in the regulatory context, explained & documented
  - JRC standardized templates for reporting validity of (Q)SAR models & adequacy of predictions

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# SAR Workshop Recap: Andrew Worth, Ph.D. (Continued)

- Projections
  - Acceptable alternatives achievable in short term for well-understood endpoints (skin irritation, sensitization & penetration, genotoxicity)
  - Full replacement of whole-animal skin-sensitization tests at least 7 years away
  - No timelines estimated for more challenging areas (toxicokinetics, repeated-dose systemic toxicity, carcinogenicity, reproductive toxicity)
- Limited use of *in vitro*, (Q)SAR, & read-across methods under the REACH regulation to date
  - Focus has been on evaluating the more dangerous chemicals, which have much data
  - Addressing lower tonnage chemicals with less information more likely to involve alternative methods, such as (Q)SAR, grouping & read-across, in accordance with SCCS guidance for testing & safety assessment of cosmetic ingredients

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# SAR Workshop Recap: Kirk Arvidson, Ph.D.

- Office of Food Additive Safety (OFAS)
  - Multiple (Q)SAR tools & databases used in concert, to maximize chemical space (i.e., domain of applicability)
  - Weight-of-evidence, consensus approach used to develop predictions & recommendations for food contact notification (FCN) review process
  - Conservative approach to interpreting & making decisions based on output
- Development of the Chemical Evaluation & Risk Estimation System (CERES) knowledgebase
  - Capture & consolidate institutional knowledge & information: structures, properties, toxicities, modes of action, metabolism, regulatory decisions…
  - Identify suitable analogs for (Q)SAR analysis & read-across, & discover relationships between new & existing data
  - Procter & Gamble donated ~40,000 high quality chemical structures
  - U.S. FDA to share CERES with COSMOS Group
  - CERES freely available online when JRC hosts the system on their Website

# SAR Workshop Recap: Karen Blackburn, Ph.D.

- Framework for identifying & evaluating the suitability of analogs for read-across assessments (requires expertise, discipline; provides actionable strategy, transparency, consistency)
  - Chemistry review
  - Toxicity review
  - Metabolism review
  - Uncertainty rating
- P&G published blinded case studies
  - Applied framework successfully to predict genetic, repeat dose, developmental or reproductive toxicity of 14 structures of interest (SOIs)
  - Yielded consistently reasonable, conservative NOAEL estimates for (SOIs)
  - Gained confidence in the "high quality" analogs identified
- PEG-Cocamine case study
  - Illustrated application of the framework for read-across over large, complex cosmetic ingredient group
  - Identified analogs that could adequately cover the chemical space of all ingredients in the group

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# Introduction: Chronology

- 2004-2006: U.S. National Toxicology Program (NTP)
  - Releases "*A National Toxicology Program for the 21st Century: A Roadmap for the Future*"
  - Establishes initiatives to integrate automated screening assays, including high-throughput screening (HTS) assays, into testing program
    - Begins collaboration with NIH Chemical Genomics Center (NCGC) to screen ~1400 NTP compounds in cell-viability assays, with results deposited into PubChem
- 2005: U.S. Environmental Protection Agency
  - Funds National Research Council (NRC) to develop long-range vision for toxicity testing & implementation strategy to:
    - Enable future testing & assessment paradigms to meet new regulatory needs
    - Incorporate advances in the sciences & information technology
  - Establishes National Center for Computational Toxicology (NCCT) to promote the evolution of Toxicology
    - From: predominantly observational science at the level of disease-specific models *in vivo*
    - To: predominantly predictive science focused on broad inclusion of target-specific, mechanism-based, biological observations *in vitro*

# Introduction: Chronology (Continued)

- 2007:
  - NRC publishes "*Toxicity Testing in the 21st Century: A Vision and a Strategy*" proposing:
    - *in vitro* testing as the principal approach, addressing uncertainties with:
      - Genetically engineered *in vitro* systems
      - Microchip-based genomic technologies
      - Computer-based predictive toxicology models
    - *Filing knowledge gaps with in vivo* assays, including tests on:
      - Non-mammalian species
      - Genetically engineered animal models
  - NCGC begins evaluating differential sensitivity of human cell lines from International Haplotype Map of the Human Genome (HapMap) Project
  - U.S. EPA NCCT launches ToxCast to evaluate use of computational chemistry, HTS assays & toxicogenomic technologies to predict toxicity & prioritize testing
    - Forecast toxicity based on bioactivity profiling
    - Identifying toxicity targets or pathways across hundreds of endpoints
      - Biochemical assays of protein function
      - Cell-based transcriptional reporter assays
      - Multicell interaction assays
      - Nematode & zebra fish embryo assays
      - Transcriptomics on primary cell cultures

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# Introduction: Chronology (Continued)

- 2008: Launch of Tox21 Project
  - Article in Science announces collaborative project among EPA, NTP, NCGC
  - FDA joins effort in 2009
- 2009: Release of ToxCast Phase I data sets for ~300 mainly pesticide actives across ~500 assays
- 2011: Tox21 Screening begins at NCGC
  - Robotic screening for potential toxicity begins on 10,000 chemicals & mixtures
  - Library includes all ToxCast compounds
- 2012: U.S. EPA & L'Oreal announce research collaboration
  - $1.2M to Compare ToxCast results to L'Oreal safety data for representative set of 20 cosmetic ingredients (including dyes & surfactants)
  - Evaluate reliability & relevance of ToxCast results for use in cosmetic ingredient safety assessments; rapid screening, lower costs, earlier safety predictions, without whole-animal testing
  - Expand chemical-use groups assessed by ToxCast

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# Introduction: ToxCast

- Goal: Bioactivity fingerprints, chemical groupings, & toxicity predictions from associations/correlations among multiple data domains (chemical structure, bioactivity profile, toxicity outcome) & across chemicals
  - Identify biological targets or pathways that lead to toxicity when perturbed
  - Develop assays that probe molecular initiating events or key events
  - Determine *in vitro* "signatures" of *in vivo* toxicity through predictive models
  - Use signatures to screen & prioritize data-poor chemicals for further testing
- Underlying hypothesis: Toxicological response is driven by interactions between chemicals & biomolecular targets
- Approach: Similar to that used in drug discovery by generating broad-based bioactivity profiles from coordinated biochemical & cellular assays
  - Drug discovery: targeted chemical space, interest in hits, false negatives ok
  - Toxicity screening: diverse chemical space, false negatives of greater concern

# Introduction: ToxCast (Continued)

- Data source: Matrix containing large number of potential targets with chemical interactions amenable to characterization by (listed in order of increasing biological relevance & cost):
  - *In silico* models
  - Biochemical assays
  - Cell-based *in vitro* assays
  - Nonmammalian animal models
- Public access: transparent, searchable, & freely downloadable online databases
- Partners
  - Pharmaceutical companies
  - L'Oreal
  - Others

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# Introduction:
# Dr. Ann Richard

- Ph.D., Theoretical Physical Chemistry, University of North Carolina Chapel Hill, 1983
- Principal Investigator at U.S. EPA's Office of Research & Development (ORD) for more than 20 years
  - Environmental Carcinogenesis Division
  - National Center for Computational Toxicology (NCCT) since 2005
- Range of research activities
  - Applying computational chemistry & SAR methods to environmental toxicology
  - Developing cheminformatics capabilities to support computational & predictive toxicology
- Currently
  - Leads the Distributed Structure-Searchable Toxicity (DSSTox) project
  - Leads chemical data management & cheminformatics components of ToxCast & Tox21 projects
- Discuss
  - Enabling *in vitro* toxicity testing strategies in Computational Toxicology
  - Latest developments in Tox21 & ToxCast projects

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