

# **SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety**



**Contemporary  
Issues in Risk  
Assessment**

**June 17, 2015**



# SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

## Problem Formulation and Scoping for Human Health Assessments

Juleen Lam, PhD MHS MS

*Associate Research Scientist*

*Program on Reproductive Health and the Environment*

*Department of OB/GYN and Reproductive Sciences*

*University of California, San Francisco*

*San Francisco, CA*



# Conflict of Interest Statement

I declare that I neither myself nor any of my coauthors, including members of our immediate families, have any financial interest with a commercial organization that has a direct or indirect interest in the subject matter of my presentation.



# Outline

## RISK ASSESSMENT

1. Tool for decision-making
2. Scoping & Problem Formulation
3. Systematic Review Methods
4. Challenges & Opportunities



# Exposure to chemicals: everywhere, everyday



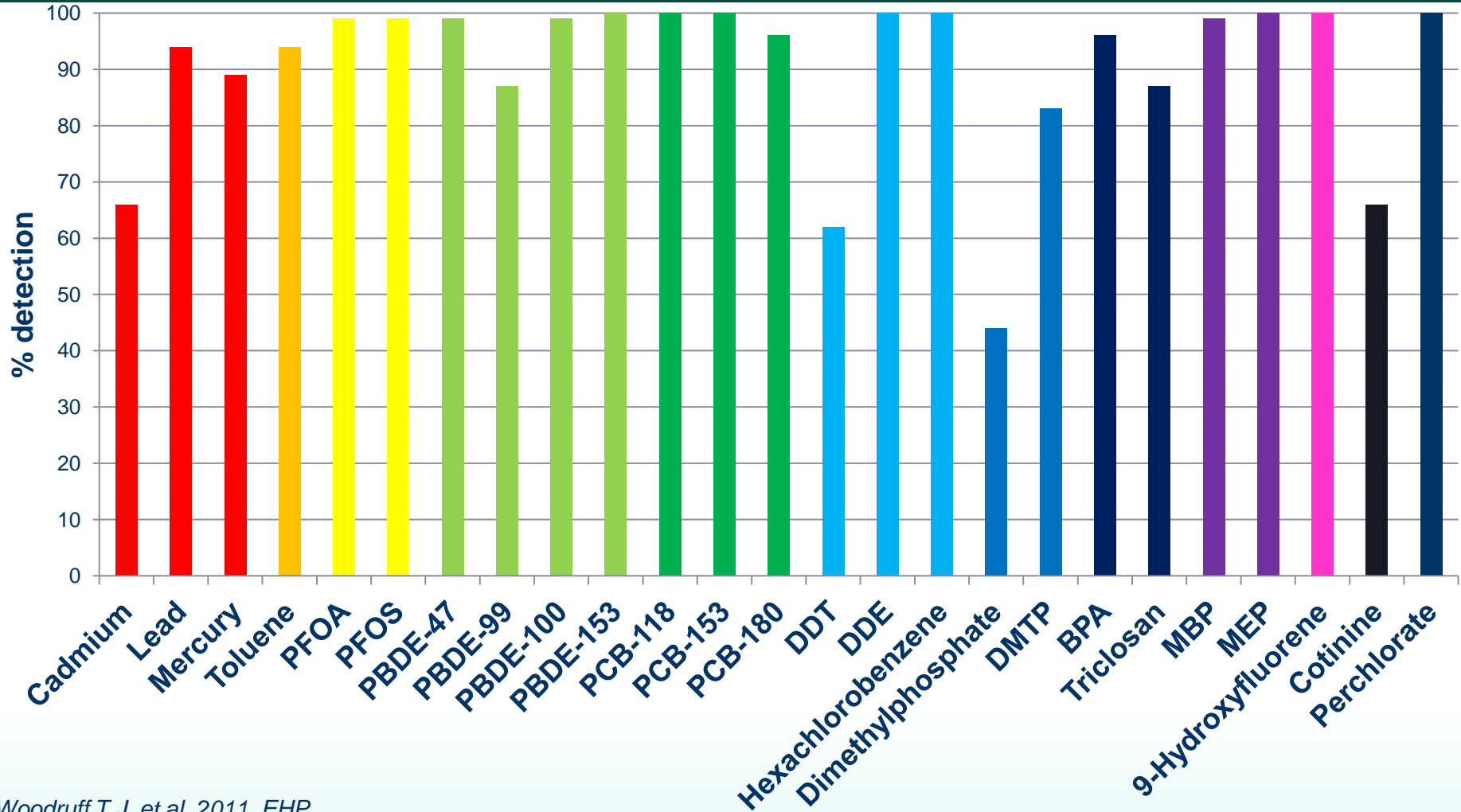
# Exposure to chemicals: every meal



Fish	Shellfish	Poultry	Fruits & vegetables	Canned/Packaged
PCBs	Methyl mercury	Arsenic	Organophosphate pesticides	BPA
Methyl mercury	Arsenic		Perchlorate	PBDEs
				Phthalates
				Vinyl chloride
Chemical additives to preserve, flavor, color, or otherwise alter food products				



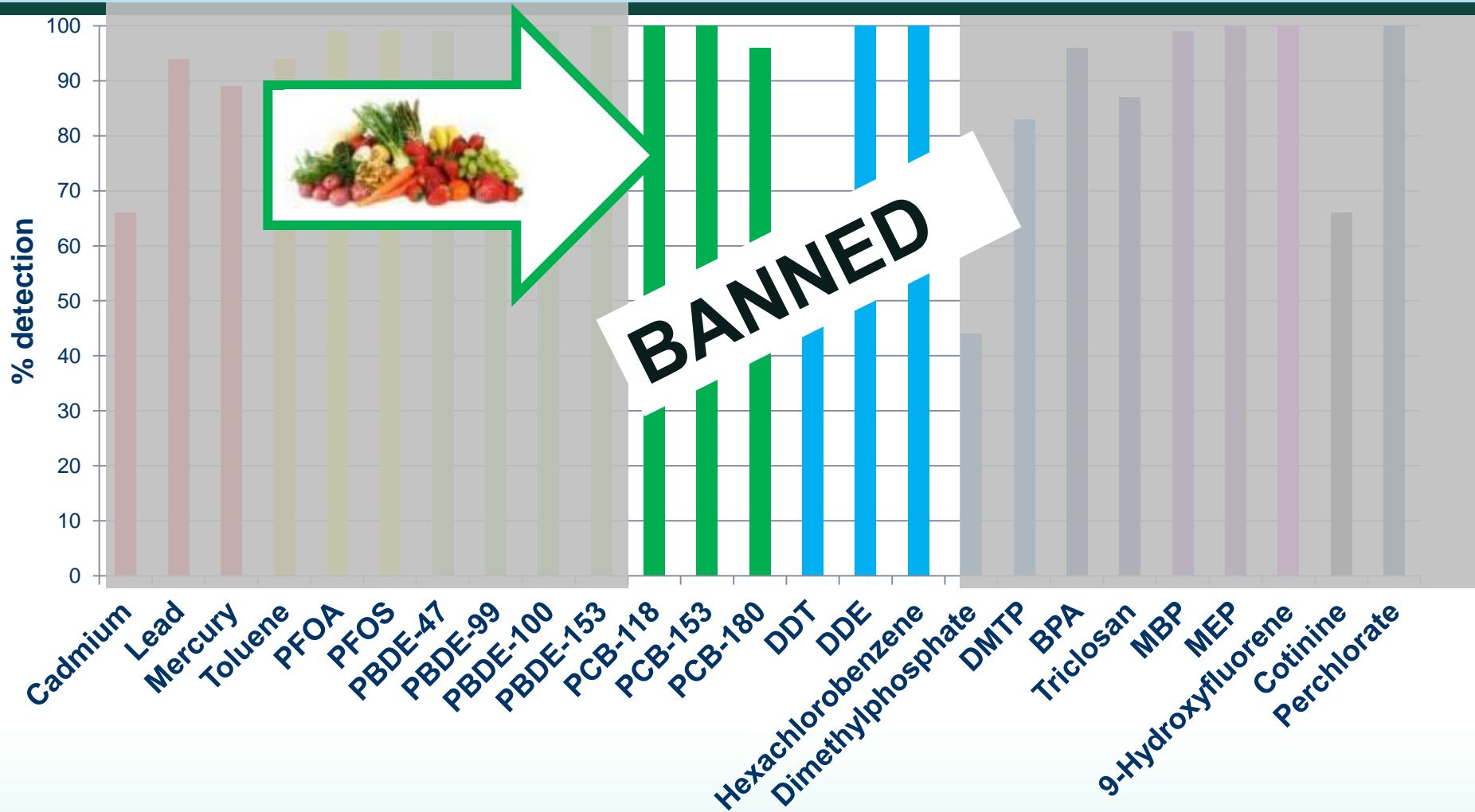
# Exposure to chemicals: everyone



Woodruff T.J. et al. 2011. EHP.



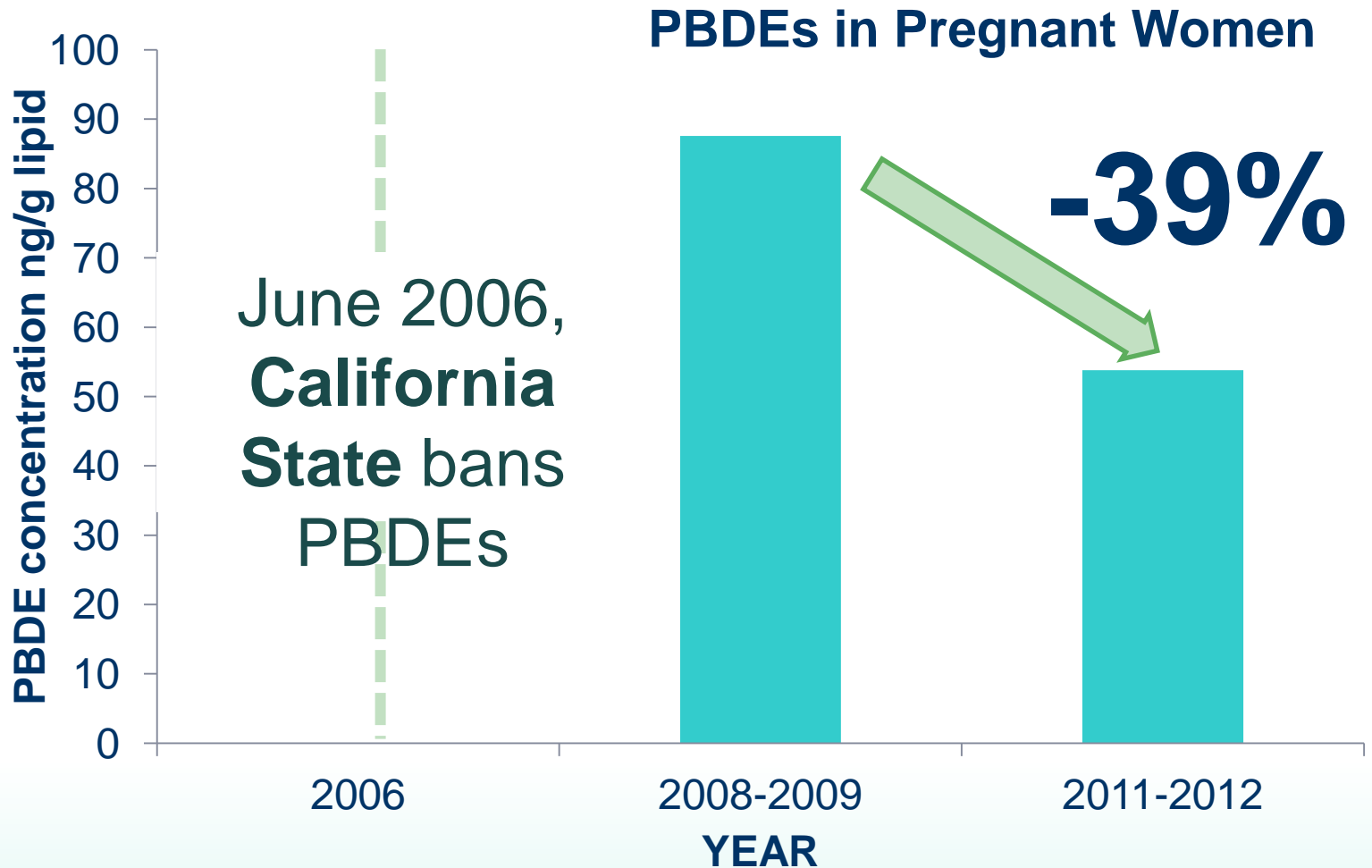
# Exposure to chemicals: everyone



Woodruff T.J. et al. 2011. EHP.



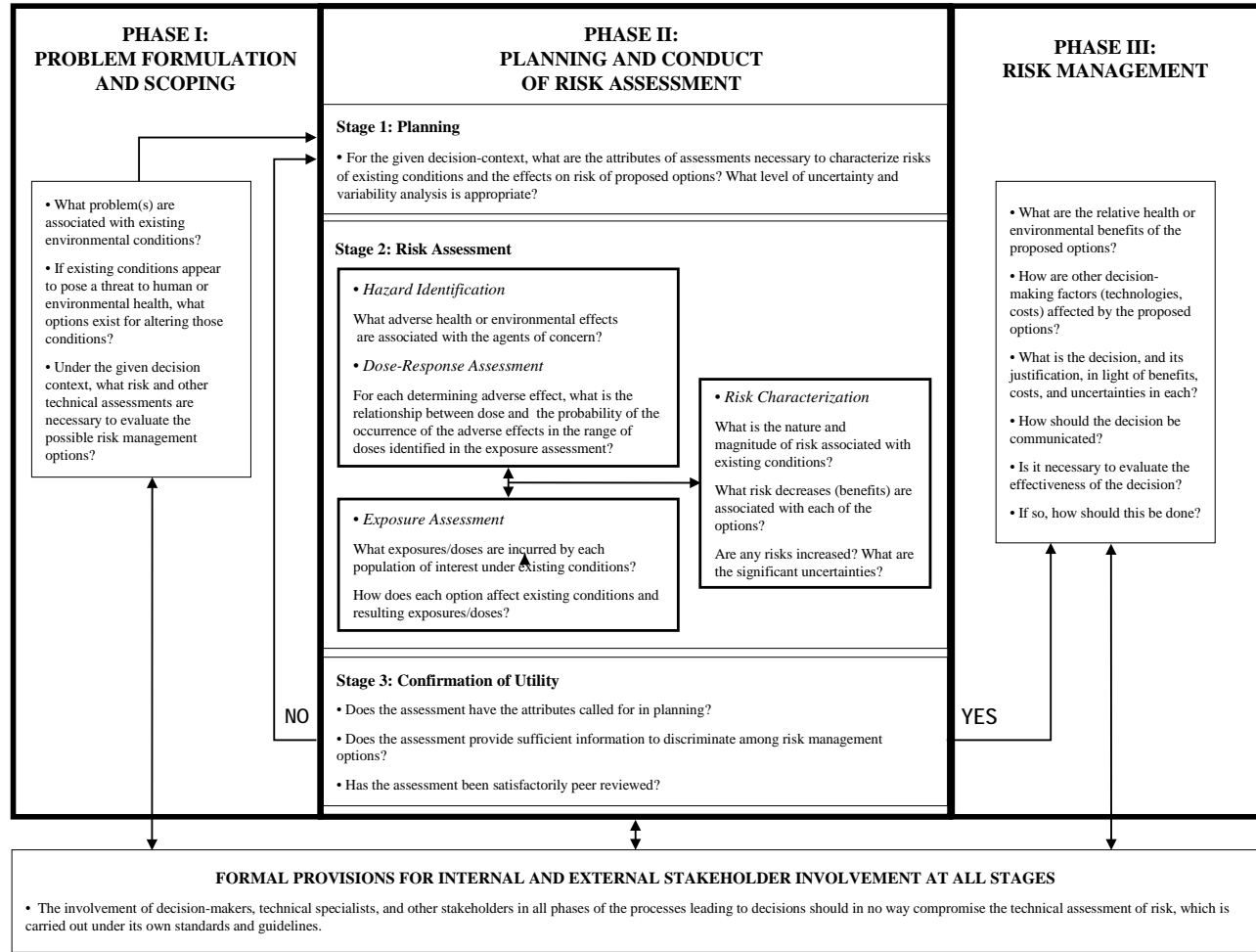
# Exposure to chemicals: Policy matters



Zota A.R., et al. 2013 ES&T.



# Risk Assessment Framework



National Research Council. Science and Decisions. 2009.



# Risk Assessment: A tool for decision-making

- Asking the right question
- Getting the science right
- Getting the right science
- Getting the participation right
- Getting the right participation
- Developing an accurate, balanced, and informative synthesis

*National Research Council. Understanding Risk. 1996; National Research Council. Science and Decisions. 2009.*



# Importance

“There is little evidence that the *scientific information* that the agencies are currently using and disseminating is unreliable. Virtually all of the challenges that have been filed so far under the [2004 Information Quality Act] have involved disputes over interpretations, inferences, models and similar policy issues, and not the “soundness” of the underlying data.”

McGarity, TO. *Kansas Law Review*. 2004.



# Risk Assessment Framework



NATIONAL ACADEMY OF SCIENCES

*Review of EPA's  
Integrated Risk  
Information System  
(IRIS) Process*

NATIONAL RESEARCH COUNCIL  
OF THE NATIONAL ACADEMIES

“EPA should consistently use a more **systematic approach** to evaluating the literature...” NAS 2014

“ ...**systematic-review standards** provide an approach that would substantially strengthen the IRIS process...” NAS 2014

REVIEW OF THE ENVIRONMENTAL PROTECTION  
AGENCY'S STATE-OF-THE-SCIENCE EVALUATION OF  
**NONMONOTONIC  
DOSE-RESPONSE  
RELATIONSHIPS**  
AS THEY APPLY TO  
**ENDOCRINE DISRUPTORS**

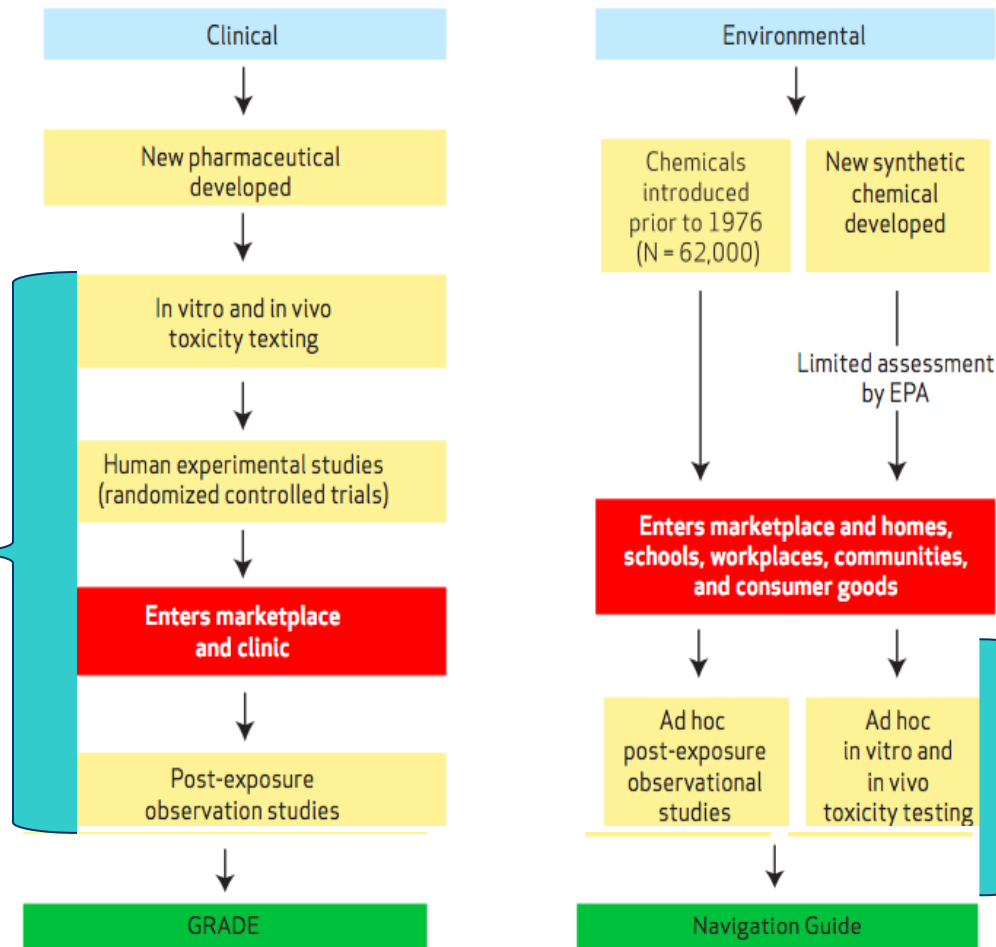
NATIONAL RESEARCH COUNCIL  
OF THE NATIONAL ACADEMIES

National Research Council. 2014.



**SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety**

# Systematic review in health assessment



>25 years

- Directly informs clinical and health care decisions
- Informs billions of dollars in healthcare spending annually

~6 years

- Tool to inform policy and decisions
- Has the potential to protect the health of billions

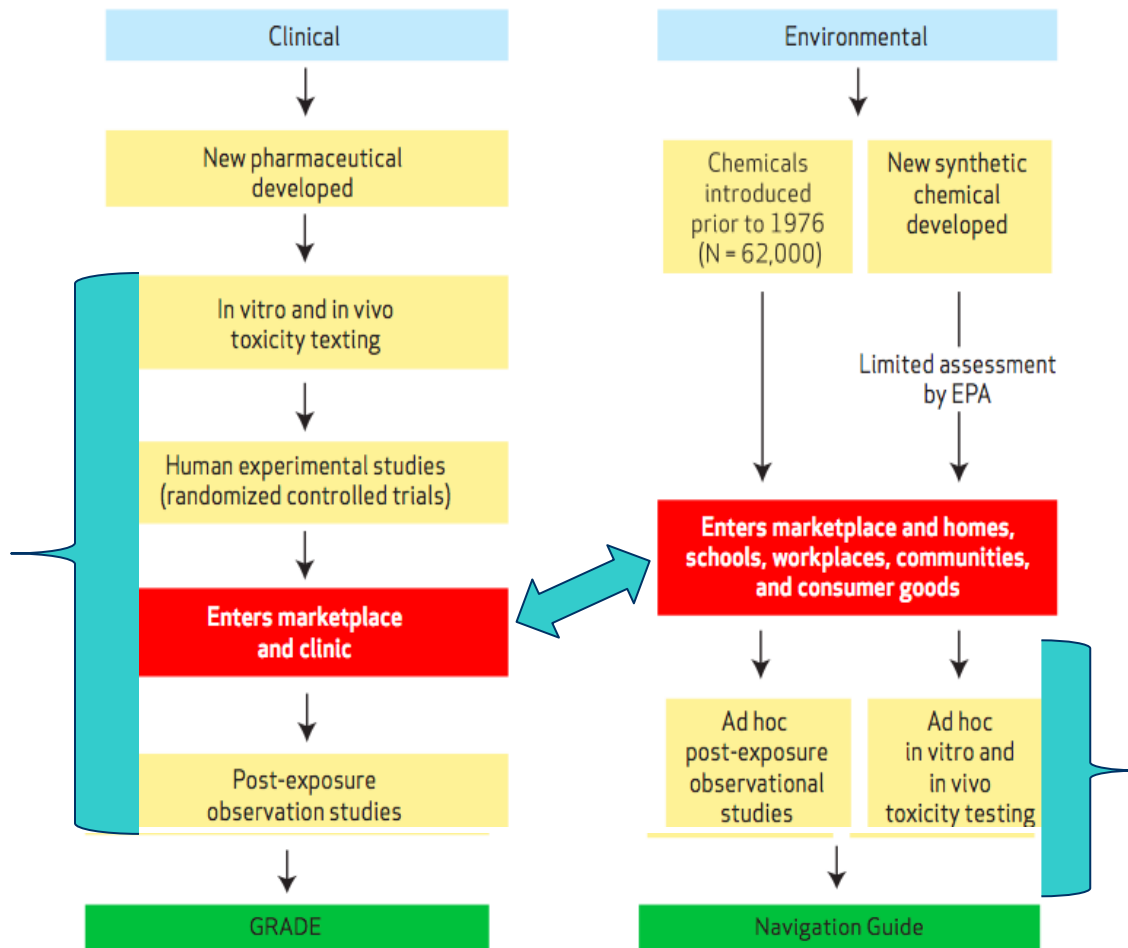
SOURCE University of California, San Francisco, Program on Reproductive Health and the Environment, Navigation Guide Work Group.



# Systematic review in health assessment

>25 years

- Directly informs clinical and health care decisions
- Informs billions of dollars in healthcare spending annually



~6 years

- Tool to inform policy and decisions
- Has the potential to protect the health of billions

SOURCE University of California, San Francisco, Program on Reproductive Health and the Environment, Navigation Guide Work Group.



# Phase I, part 1: Planning and Scoping

- Definition:
  - Discussion between decision-makers (risk managers) and stakeholders, with assessors supporting
  - Determination of hazards, mitigation options, and scope

Planning and Scoping
Sources of exposure
Source-mitigation options
Exposure pathways
Exposure-mitigation options
Direct hazards and stressors
Mitigation-related hazards and stressors
At-risk populations
Populations at mitigation-related risk
Individual intake pathways
Individual intake mitigations

Table adapted from: National Research Council. *Science and Decisions*. 2009.



# Phase I, part 2: Problem Formulation

- Definition:
  - Discussion between decision-makers and assessors (& technical stakeholders) to develop a detailed plan for the assessment that reflects results from planning & scoping
  - Linked to regulation/policy
  - Sources, environmental stressors, exposed populations

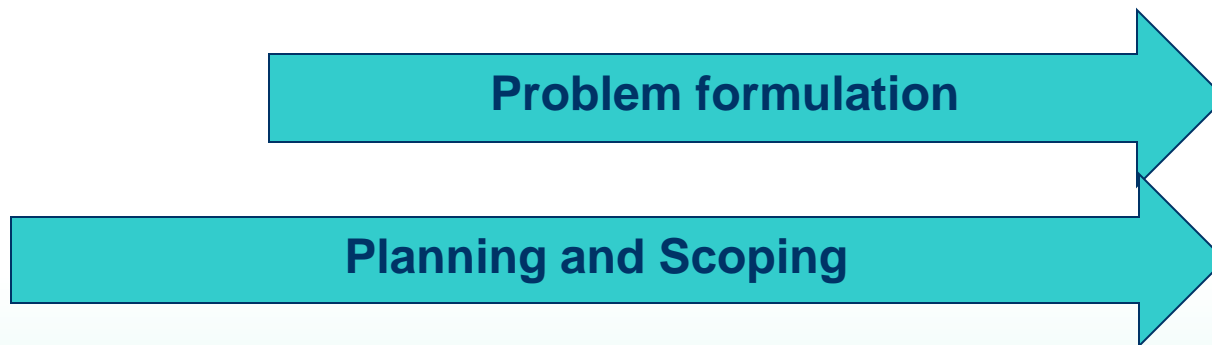


Table adapted from: National Research Council. *Science and Decisions*. 2009.



# Asking the right question

Systematic review PECO statement



**P**opulation

**E**xposures

**C**omparator group

**O**utcomes



*Images licensed under Public Domain via Wikimedia Commons*



# PECO statement

## Study question:

*Does fetal developmental exposure to PFOA or its salts affect fetal growth?*

**Population:** Humans who are studied during the reproductive/developmental time period (before and/or during pregnancy or development)

**Exposure:** Exposure to PFOA (CAS# 335-67-1) or its salts during the time before pregnancy and/or during pregnancy for females or directly to fetuses

**Comparator:** Humans exposed to lower levels of PFOA than the more highly exposed humans (i.e., a comparison across a range of exposures)

**Outcome:** Effects on fetal growth, birth weight, and/or other measures of size, such as length.

*Johnson PI et al. EHP. 2014.*



# PECO statement

Study question:

*Does fetal developmental exposure to PFOA or its salts affect fetal growth?*

**Findings:**

“PFOA is ‘known to be toxic’ to human reproduction and development based on sufficient evidence of decreased fetal growth in both humans and nonhuman mammalian species.”

*These findings were cited in a recent regulatory rule-making proposal by the European Chemicals Agency which would restrict exposure to PFOA*



# Narrative expert-based reviews

There **were inconsistent associations** reported for several different birth outcomes, including birth weight, birth length, head circumference, and ponderal index, among the five general population studies that measured PFOS and PFOA in the study subjects.

Cumulatively, the studies provide **inconsistent suggestions** of a possible decrement in birth weight associated with PFOA exposure, with studies varying in whether the association with PFOS is **similar** (Apelberg et al. 2007), **stronger** (Stein et al. 2009; Washino et al. 2009), or **weaker** (Fei et al. 2009; Hamm et al. 2009) than that reported for PFOA.

**(emphasis added)**

*Olsen et al. 2009. Reproductive Toxicology; Steenland K, et al. 2010. Environ Health Perspect.*



# PECO statement

***Is exposure to PFOA or PFOS associated with changes in immune-related measures in humans?***

**Population:** Humans without restriction based on sex or on life stage at exposure or outcome assessment

**Exposure:** Exposure to PFOA (CAS# 335-67-1) or PFOS (CAS# 1763-23-1) or their salts based on administered dose or concentration, biomonitoring data (e.g., urine, blood, or other specimens), environmental measures (e.g., air, water levels), or indirect measures such as job title

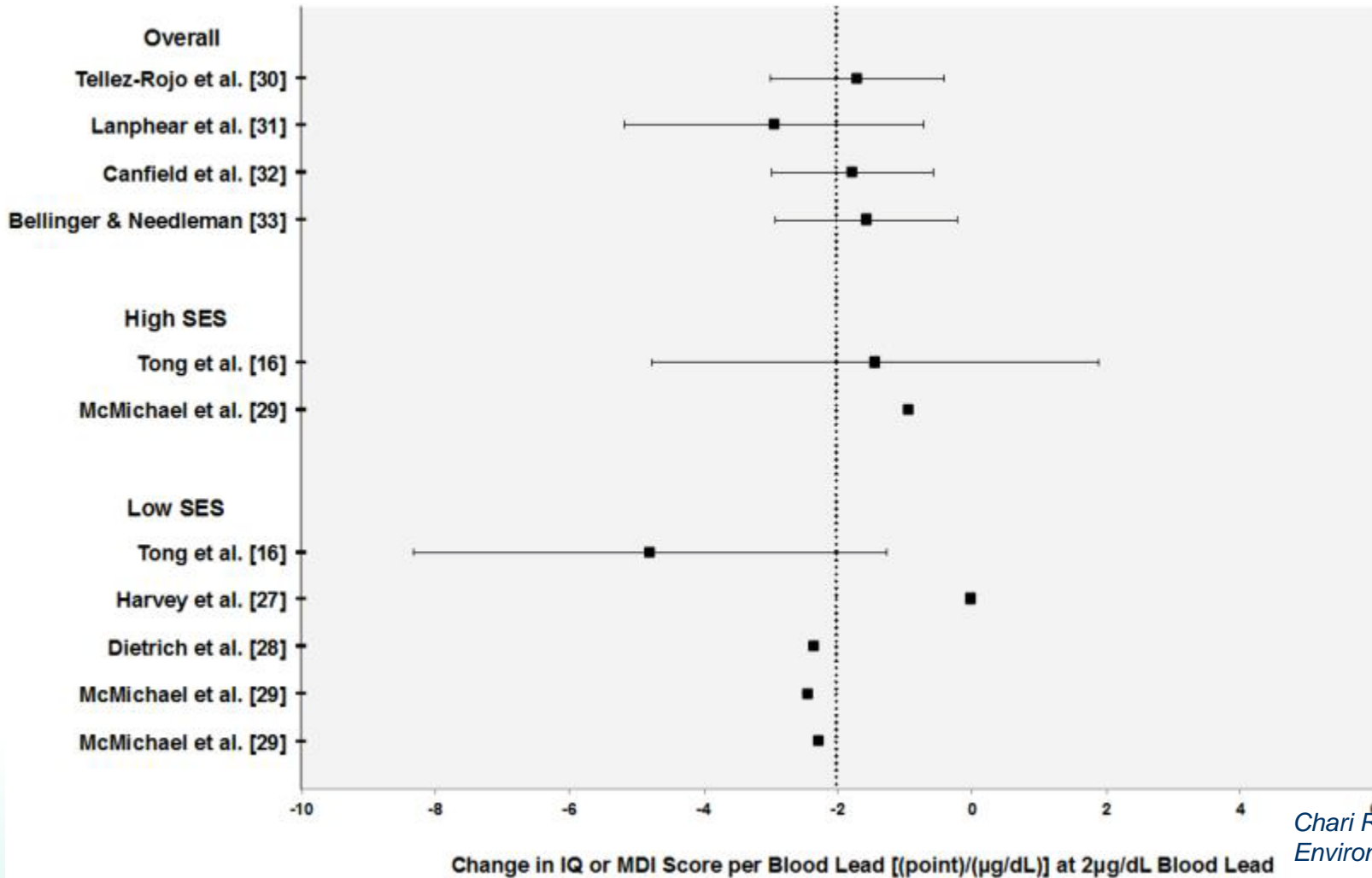
**Comparator:** Humans exposed to lower levels of PFOA or PFOS

**Outcome:** Primary outcomes: Immune-related diseases and measures of immune function: immunosuppression (e.g., otitis, infections, or decreased vaccine antibody response); sensitization and allergic response (e.g., atopic dermatitis or asthma); autoimmunity (e.g., thyroiditis or systemic lupus erythematosus)

*National Toxicology Program. DRAFT protocol. 2013.*



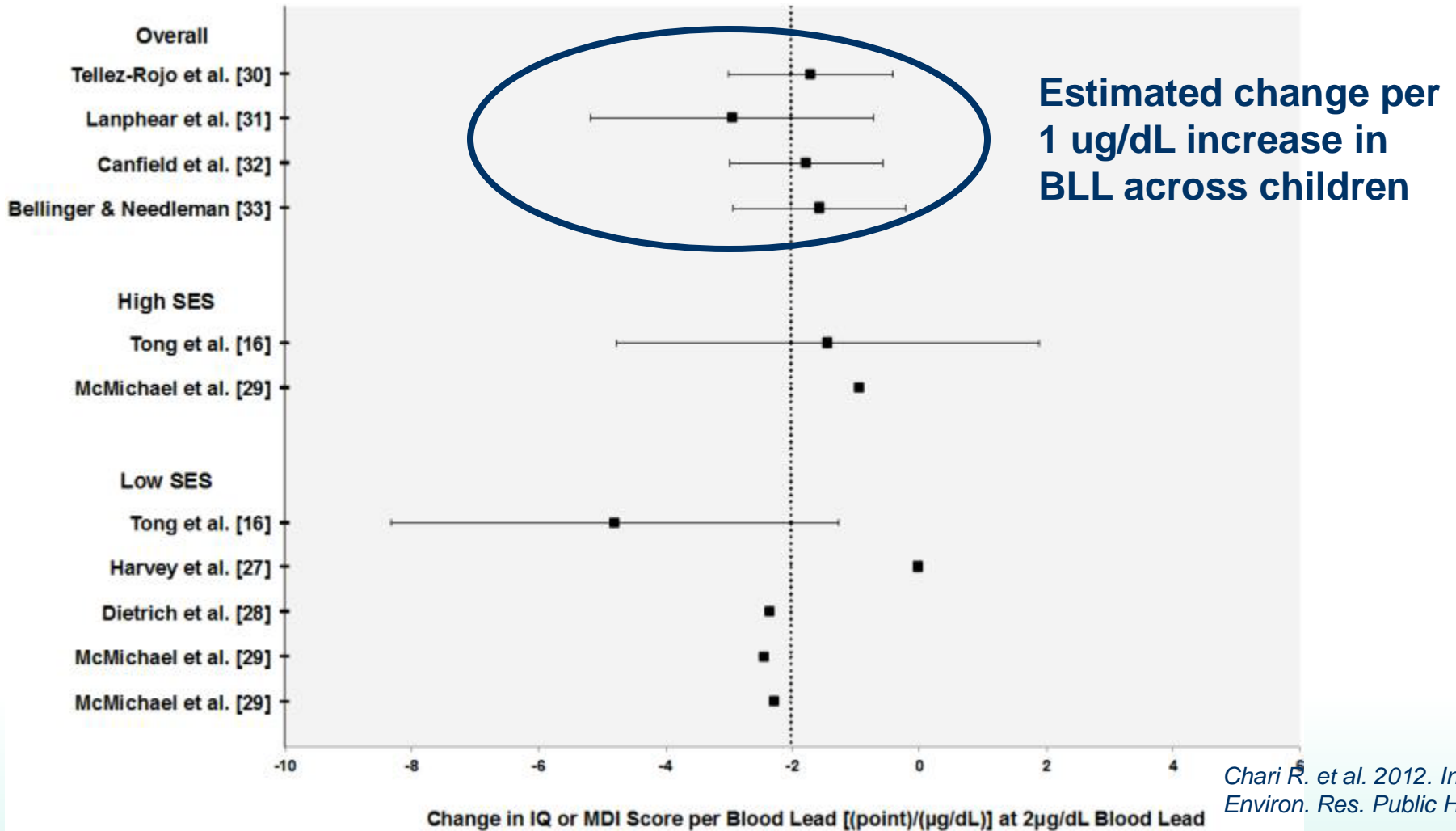
# Asking the right question



Chari R. et al. 2012. *Int. J. Environ. Res. Public Health*



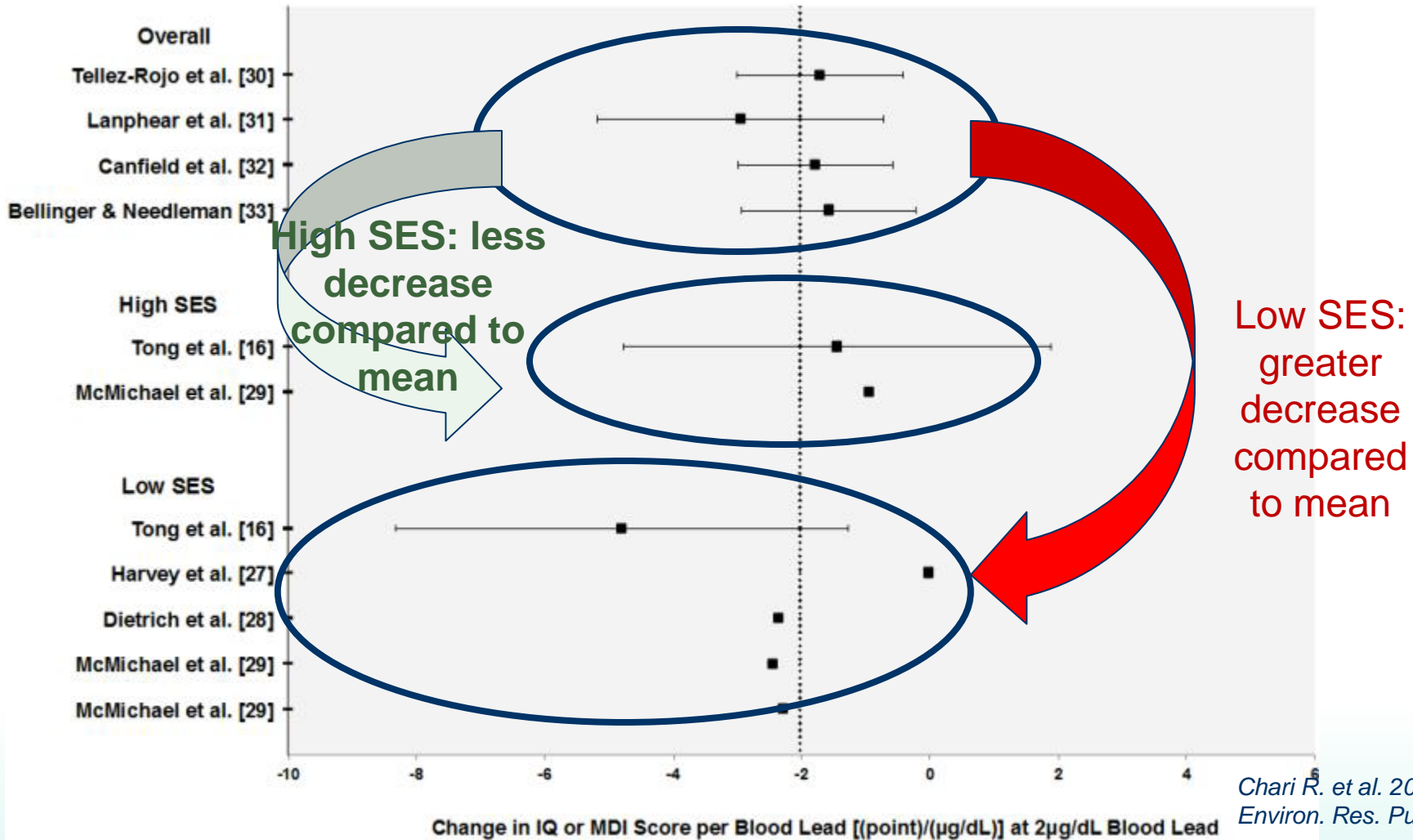
# Asking the right question



Chari R. et al. 2012. *Int. J. Environ. Res. Public Health*



# Asking the right question

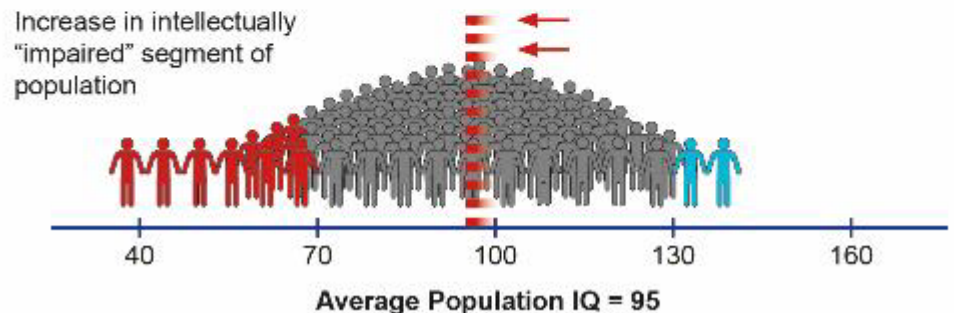
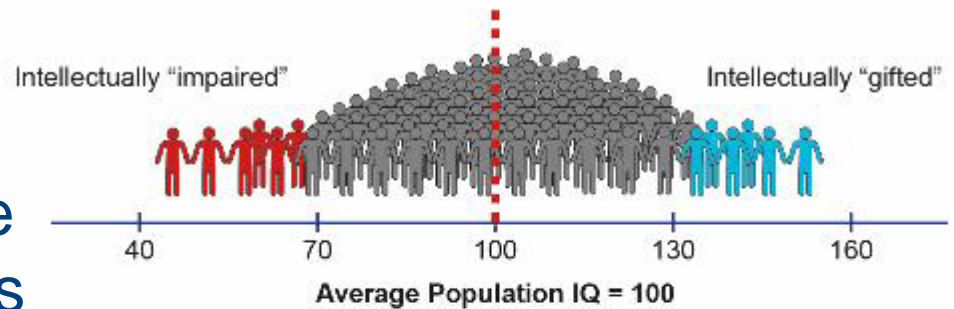


Chari R. et al. 2012. *Int. J. Environ. Res. Public Health*



# Asking the right question

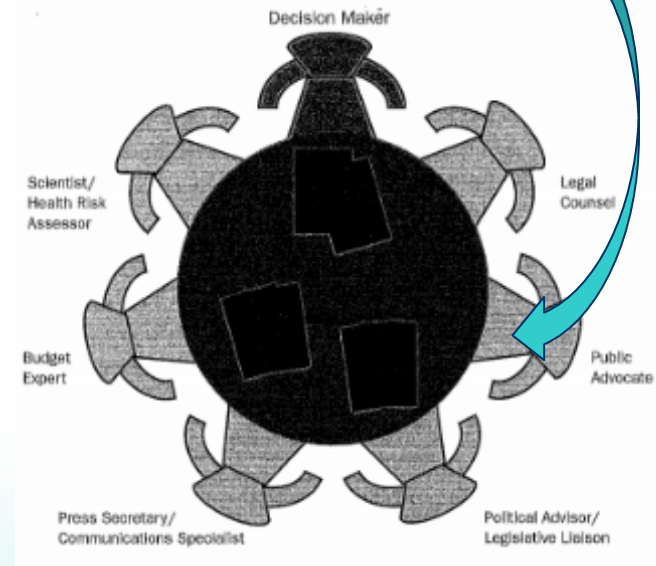
- Low-SES groups → greater susceptibility to lead's effects on IQ
- Setting regulatory exposure standards at the mean does not adequately protect all
- To protect against adverse health effects: consider the most vulnerable or susceptible



# Asking the right people

- **Stakeholder involvement**

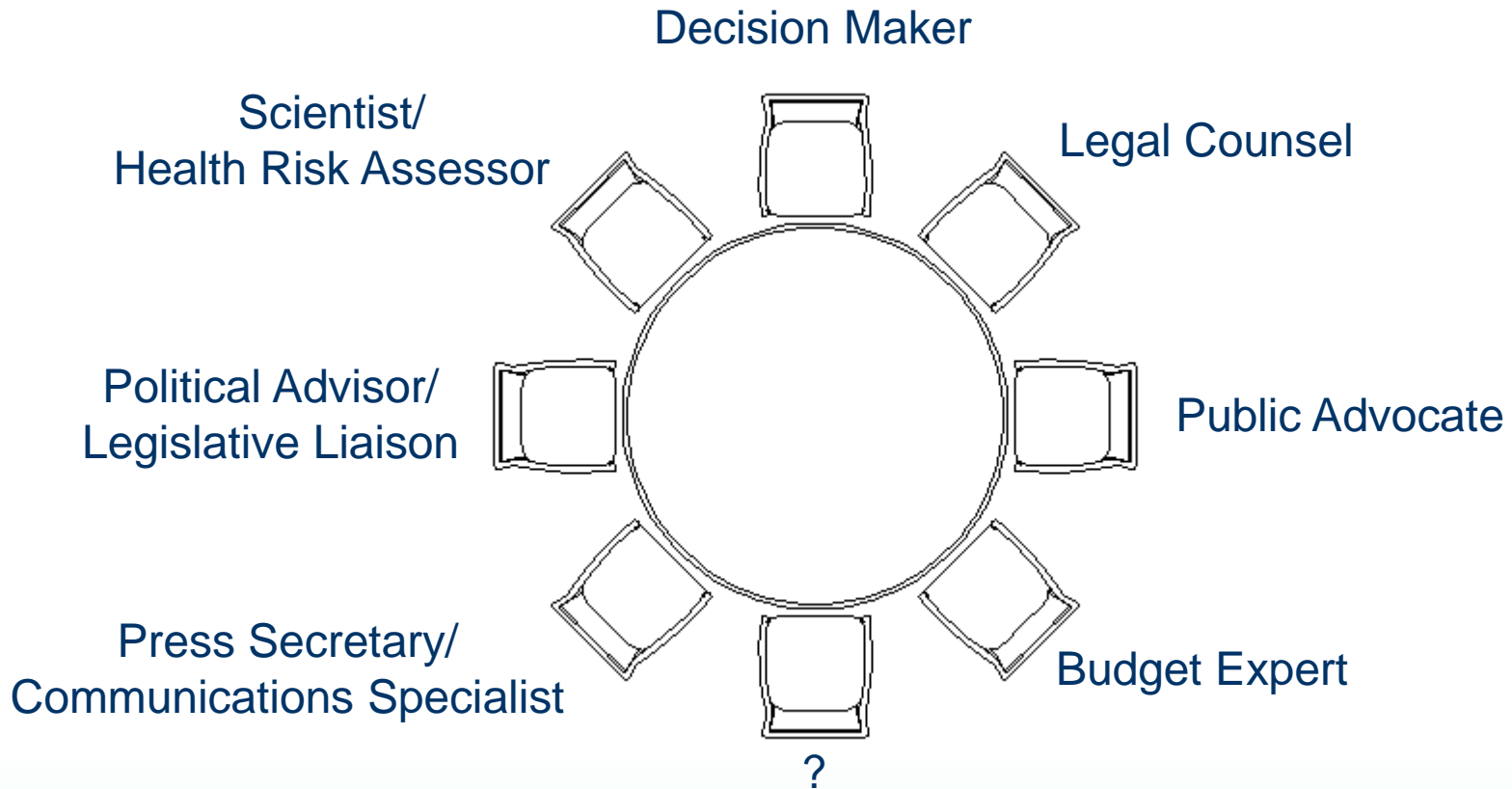
- Upfront, early, balanced, inclusive
- Increases transparency of process
- More effective, efficient, and credible risk-based decision-making
- In particular for cumulative risk assessment, affected communities have not been adequately involved



*Images licensed under Public Domain via Wikimedia Commons  
Burke TA, et al. Regulating Risk: The Science and Politics of Risk. 1993..*



# Asking the right people



Adapted from: Burke TA, et al. *Regulating Risk: The Science and Politics of Risk*. 1993.



# Asking the right people

- **Stakeholder involvement**

- Not all stakeholders have scientific/financial resources to provide timely comments
- NAS review of EPA IRIS process: expand opportunities (e.g., technical-assistance programs) to under-resourced stakeholders to balance public input
  - EPA IRIS bimonthly meeting (February 2015): NAS agreement to arrange for independent scientific experts to attend and participate
  - Continuing for EPA IRIS bimonthly meeting in June 2015
- Time limits to ensure timely decision-making



# Protocol: a guide to communicate

- **Essential component of systematic review**
  - Detailed plan/set of steps to be followed
- PECO statement and inclusion/exclusion criteria
- Methods to search, locate, and select relevant evidence
- Plans to extract data and analyze (before seeing data)
- Details on evaluating risk of bias, quality, and strength of evidence & integrating evidence across human, animal, or mechanistic data



# Protocol

- **Essential component of systematic review**
  - Minimizes bias in the inclusion/exclusion of studies, evaluation of data, rating of bias, ratings of quality and strength of evidence, and overall conclusions regarding the evidence
  - Increases transparency and reproducibility of the process
  - Allows for stakeholder input at the onset



# Protocol Registration

- PROSPERO: University of York's Center for Reviews and Dissemination.
  - International database of prospectively registered systematic reviews in health and social care
  - Creates permanent online record of protocols, and allows tracking of changes in the process



<http://www.crd.york.ac.uk/PROSPERO/>



# Protocol Registration

UNIVERSITY *of York*  
Centre for Reviews and Dissemination

  
National Institute for  
Health Research

**PROSPERO International prospective register of systematic reviews**

---

**Applying the navigation guide systematic review methodology. Case study #5:  
association between developmental exposures to PBDEs and human  
neurodevelopment**

*Juleen Lam, Patrice Sutton, Jennifer McPartland, Lisette Davidson, Natalyn Daniels, Saunak Sen, Daniel Axelrad,  
Bruce Lanphear, David Bellinger, Tracey Woodruff*

---

**Citation**

Juleen Lam, Patrice Sutton, Jennifer McPartland, Lisette Davidson, Natalyn Daniels, Saunak Sen, Daniel Axelrad, Bruce Lanphear, David Bellinger, Tracey Woodruff. Applying the navigation guide systematic review methodology. Case study #5: association between developmental exposures to PBDEs and human neurodevelopment. PROSPERO 2015:CRD42015019753 Available from [http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015019753](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015019753)

**Revision Notes**

Date	Revision Note
23/04/2015	Uploaded new version of review



# Handbook for Protocol

- Agencies are developing “Handbooks” that outline their approach to conducting systematic reviews and evidence integration
  - Defines key terms
  - Outlines problem formulation, scoping, and subsequent steps of the assessment
  - Consistency, transparency, sets expectations



## OHAT Handbook



*National Toxicology Program. 2015.*



# Challenges & opportunities

- Consensus among involved parties: requires a balance among competing values
- Broad scope to capture potential effects and affected populations → balance with time/resource constraints
  - Focus on sensitive and vulnerable populations
  - Higher chemical burdens & increased susceptibility to toxic effects



# Conclusions

- Systematic review processes can:
  - Increase transparency, consistency, and improve communication with stakeholders
  - Improve decision- and policy-making
  - Apply to environmental health questions
- Need to ask the right question
- Need to ask/involve the right people
- Public health protection from existing exposures



# Acknowledgments

- SOT FDA Food Safety Colloquia Organizing Committee
  - Ivan Rusyn
  - Betty Eidemiller
  - Suzanne Fitzpatrick
  
- UCSF colleagues
  - Tracey Woodruff
  - Patrice Sutton



# References

- Burger J, Stephens W, Boring CS, et al. Ethnicity and risk: fishing and consumption in people fishing along the Savannah River. *Risk Anal.* 1999;19:427–438
- Burger J, Kirk-Pflugh K, Lurig L, et al. Fishing in urban New Jersey: II. ethnicity affects information sources, perception and compliance. *Risk Anal.* 1999;19:217–229
- Burke TA, et al. *Regulating Risk: The Science and Politics of Risk.* Intl Life Sciences Inst. 1993.
- Chari, R, Burke, TA, White, RH, & Fox, MA. Integrating susceptibility into environmental policy: An analysis of the National Ambient Air Quality Standard for lead. *International journal of environmental research and public health.* 2012;9(4):1077-1096.
- Gilbert, SG & Weiss, B. A rationale for lowering the blood lead action level from 10 to 2 g/dL. *Neurotoxicology.* 2006;27, 693–701
- Johnson, PI, Sutton, P, Atchley, DS, Koustas, E, Lam, J, Sen, S, ... & Woodruff, TJ. The Navigation Guide—evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. *Environ Health Perspect.* 2014;122(10):1028-1039.
- Louisiana Sea Grant College Program Louisiana State University. *Morgan\_City\_Fishing\_2006.* Available from: [https://commons.wikimedia.org/wiki/File:Morgan\\_City\\_Fishing\\_2006.jpg](https://commons.wikimedia.org/wiki/File:Morgan_City_Fishing_2006.jpg)
- McGarity, TO. Our science is sound science and their science is junk science: Science-based strategies for avoiding accountability and responsibility for risk-producing products and activities. *Kansas Law Review.* 2004;52(4):897-937.
- National Research Council. *Understanding Risk: Informing Decisions in a Democratic Society.* National Academies Press. 1996.



# References

- National Research Council. Science and Decisions: Advancing Risk Assessment. National Academies Press. 2009.
- National Research Council. Review of EPA's Integrated Risk Information System (IRIS) Process. National Academies Press. 2014.
- National Research Council. Review of the EPA's State-of-the-Science Evaluation of Nonmonotonic Dose-Response Relationships as they Apply to Endocrine Disruptors. National Academies Press. 2014.
- National Toxicology Program. DRAFT protocol: Systematic review to evaluate the evidence for an association between PFOA or PFOS exposure and immunotoxicity. 2013. Available from: [http://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/pfos\\_pfoa\\_immuneprotocoldraft.pdf](http://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/pfos_pfoa_immuneprotocoldraft.pdf)
- National Toxicology Program. Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integrations. 2015. Available from: [http://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015\\_508.pdf](http://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf)
- Needham LL, Sexton K. Assessing children's exposure to hazardous environmental chemicals: an overview of selected research challenges and complexities. J Expo Anal Environ Epidemiol. 2000;10:611–629
- Neltner, TG, Alger, HM, Leonard, JE, & Maffini, MV. Data gaps in toxicity testing of chemicals allowed in food in the United States. Repro Tox. 2013;42, 85-94
- Olsen GW, Butenhoff JL, & Zobel LR Perfluoroalkyl chemicals and human fetal development: An epidemiologic review with clinical and toxicological perspectives. Reproduct Tox. 2009. 27(3–4):212-30.



# References

- Sheehan MC, Lam J, Burke TA. Environmental Health: From Global to Local. Chapter 27: Risk Assessment in Environmental Health. Published by Jossey-Bass, second edition. In Press.
- Steenland K, Fletcher T, & Savitz DA. Epidemiologic evidence on the health effects of perfluorooctanoic acid (PFOA). Environ Health Perspect. 2010;118(8):1100-8.
- US Environmental Protection Agency (EPA). Integrated Risk Information System (IRIS) glossary. 2011. Available from: [http://ofmpub.epa.gov/sor\\_internet/registry/termreg/searchandretrieve/home.do](http://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/home.do)
- Wilson, David. 19660412 08 Horse Drawn Fruit Cart, South Philadelphia. 2011. Available from: [https://commons.wikimedia.org/wiki/File:19660412\\_08\\_Horse\\_Drawn\\_Fruit\\_Cart,\\_South\\_Philadelphia\\_\(7404242372\).jpg](https://commons.wikimedia.org/wiki/File:19660412_08_Horse_Drawn_Fruit_Cart,_South_Philadelphia_(7404242372).jpg)
- Woodruff, TJ, Zota, AR, & Schwartz, JM. Research| Children's Health. Environ Health Perspect. 2011;119(6), 879.
- Woodruff, TJ, & Sutton, P. An evidence-based medicine methodology to bridge the gap between clinical and environmental health sciences. Health Affairs. 2011;30(5):931-937.
- Zota, AR, Linderholm, L, Park, JS, Petreas, M, Guo, T, Privalsky, ML, ... & Woodruff, TJ. Temporal comparison of PBDEs, OH-PBDEs, PCBs, and OH-PCBs in the serum of second trimester pregnant women recruited from San Francisco General Hospital, California. Environ Sci & Technol. 2013;47(20):11776-11784.



# Thank you!

## Contact Information:

Juleen Lam

University of California, San Francisco

Juleen.Lam@ucsf.edu

