

Research:

The Navigation Guide Systematic Review Methodology

4 articles are published in Environmental Health Perspectives on the Navigation Guide Systematic Review Methodology

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The Navigation Guide: The Theory and Practice of Systematic Reviews in Environmental Health Sciences

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California Department of Toxic Substances Control
ELC Seminar Series
April 22, 2015



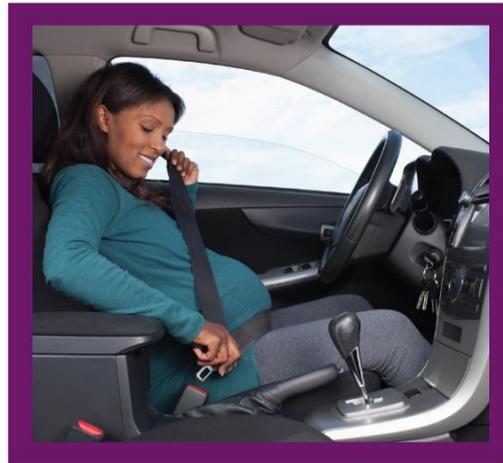
NO CONFLICT TO DECLARE



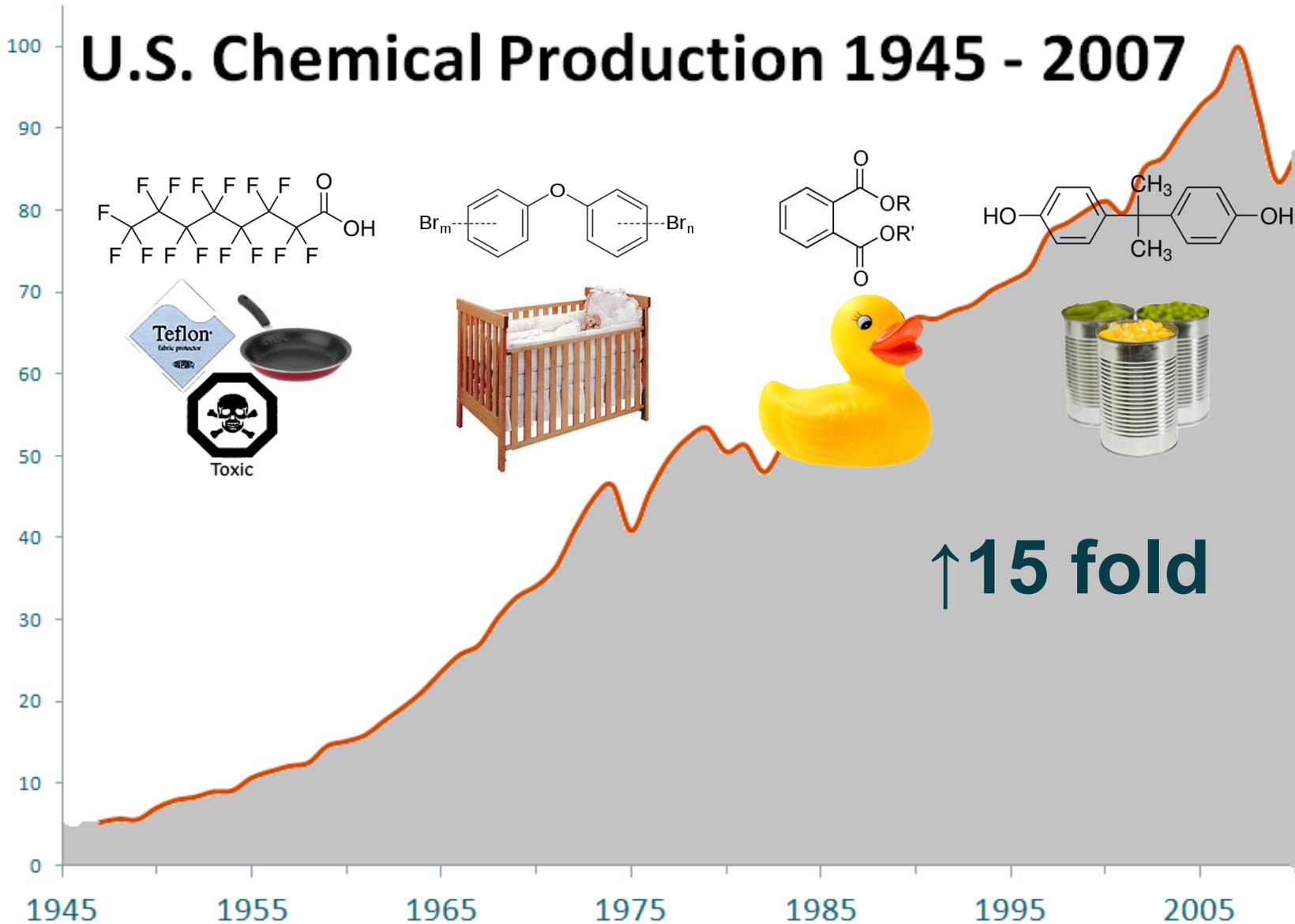
UCSF PROGRAM ON REPRODUCTIVE HEALTH AND THE ENVIRONMENT



Exposure Is Everywhere Everyday



U.S. Chemical Production 1945 - 2007



↑ 15 fold

Federal reserve data on chemical production is only offered as relative production, which is unit-less. A specific reference year is chosen and values are calculated relative to that years production. In this particular data set 2007 is the reference year and is assigned a value of 100.



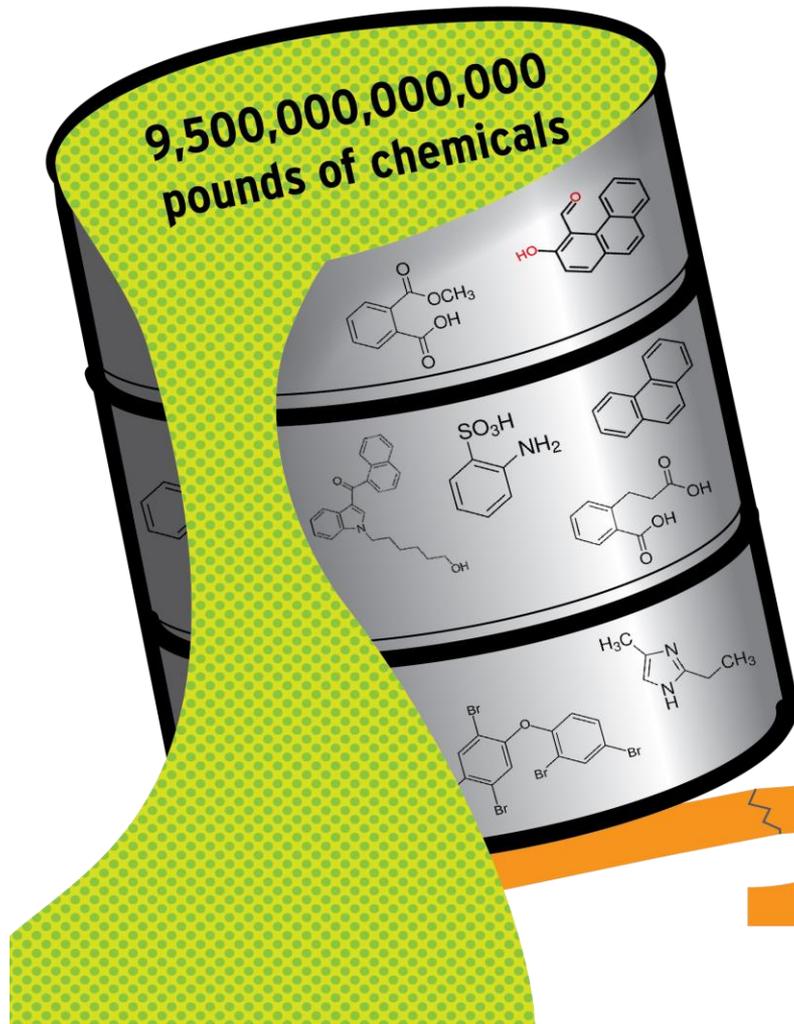
University of California
San Francisco

Data from: U.S. Federal Reserve Board, Division of Research and Statistics

Program on Reproductive
Health and the Environment



U.S. Chemical Production Volume Compared to Population



- 30,000 pounds of chemicals per person 

U.S. POPULATION:
313,000,000



US EPA CDR Fact Sheet: Chemical Snapshot, June 2014. The total reported (domestically manufactured and imported) for 2012.



Industrial Chemicals in Virtually Every U.S. Pregnant Woman





World Health
Organization



UNEP
United Nations
Environment Programme

State of the Science of Endocrine Disrupting Chemicals - 2012

Edited by
Åke Bergman, Jerrold J. Heindel, Susan Jobling,
Karen A. Kidd and R. Thomas Zoeller



University of California
San Francisco



INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Program on Reproductive
Health and the Environment



The status quo

... “to a disturbing extent, babies are born pre-polluted.”

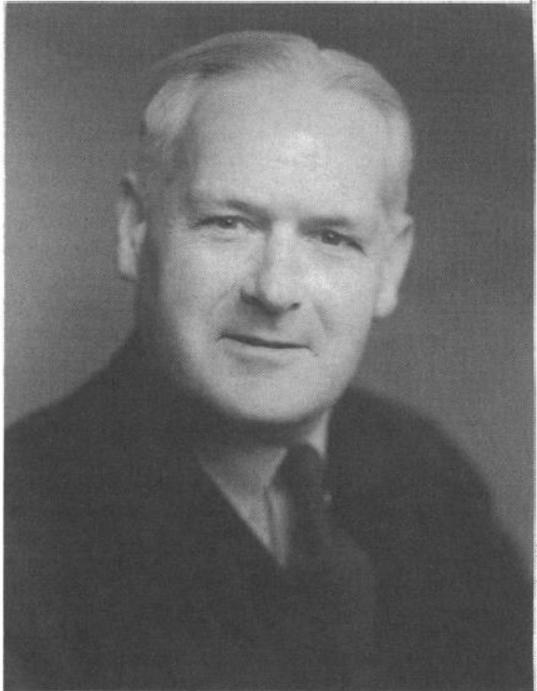
2008–2009 Annual Report  President's Cancer Panel

REDUCING ENVIRONMENTAL CANCER RISK

What We Can Do Now







GODFREY ARGENT

Sir Austin Bradford Hill, described as the greatest medical statistician of the twentieth century. He held no degree in either medicine or statistics

Sir Austin Bradford Hill

incompleteness of science ...

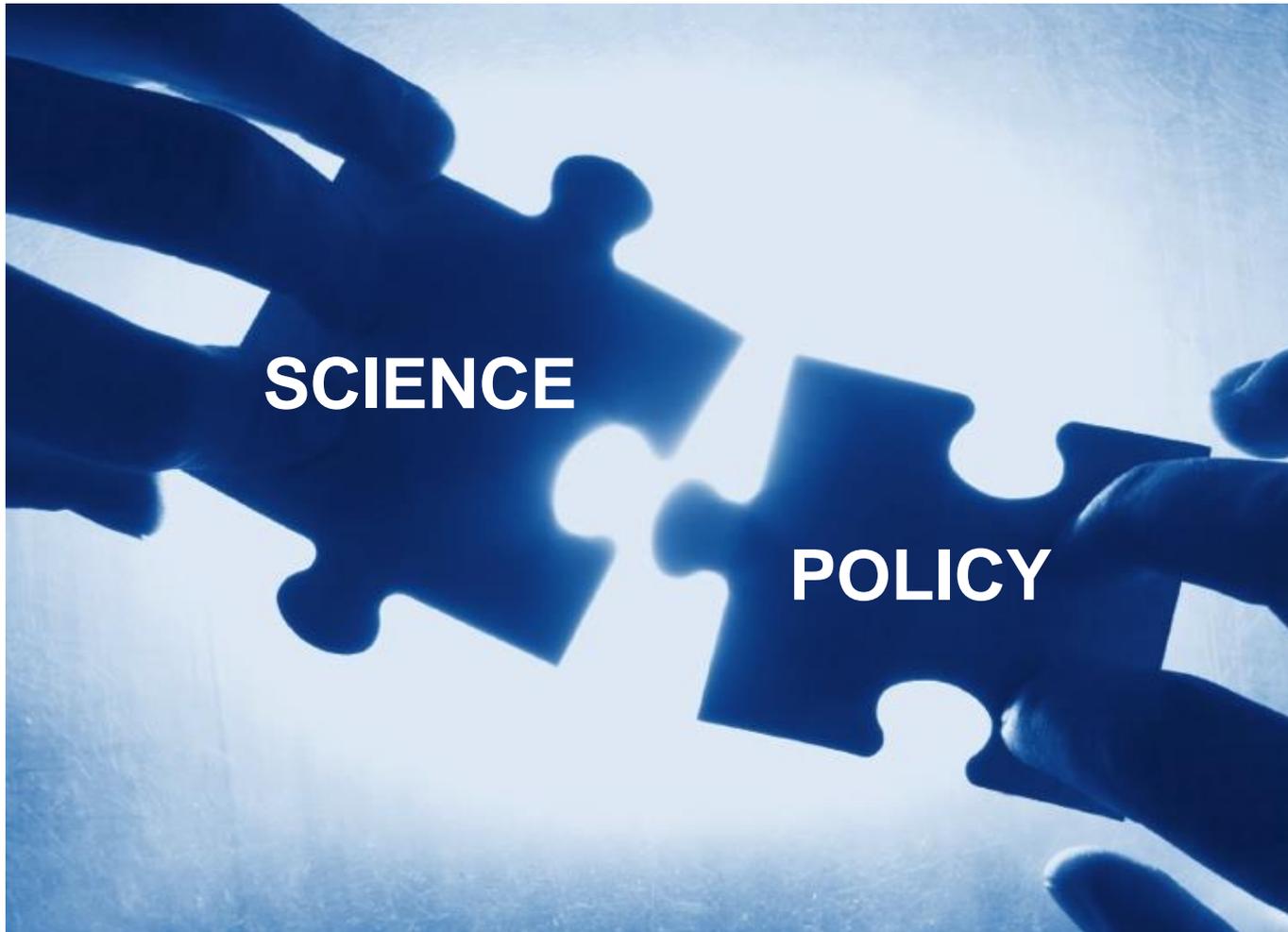
“does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time”

Hill AB. 1965. The environment and disease: association or causation? *Proc R Soc Med* 58:295–300.

<http://www.bmj.com/content/bmj/305/6868/1521.full.pdf>



Acting on the science to prevent harm



Reflection on Theoretical Approaches

Psychoanalytic:

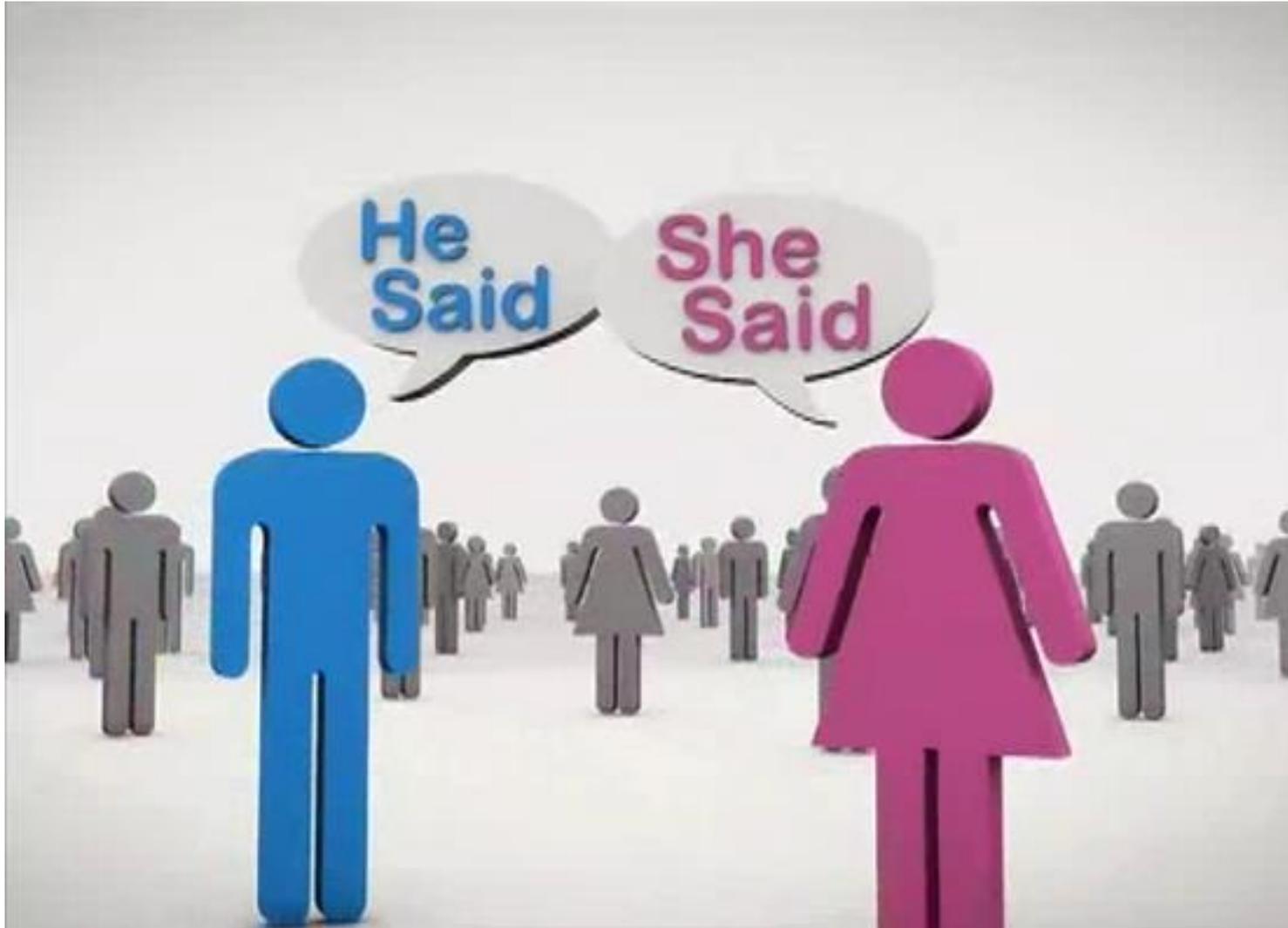
Psychoanalytic theory maintains a foundational belief in the unconscious, which consists of thoughts, feelings, and past events that are kept out of awareness. The unconscious experience significantly impacts daily functioning, especially in regard to a person's character and personality. Psychoanalytic group therapy aims to restructure members' character by making unconscious conflicts conscious through analyzing the transference and defenses.

Unlike other approaches to group therapy, I will always retain Freud's foundational concepts such as the unconscious, the transference, and the ego. However, psychoanalysis is also a highly effective approach to group therapy and is not practical.

Group therapy is a highly effective approach to group therapy and is not practical.

Group therapy is a highly effective approach to group therapy and is not practical.

Group therapy is a highly effective approach to group therapy and is not practical.



Clinical sciences have faced and addressed these same challenges



A Comparison of Results of Meta-analyses of Randomized Control Trials and Recommendations of Clinical Experts

Treatments for Myocardial Infarction

Elliott M. Antman, MD; Joseph Lau, MD; Bruce Kupelnick; Frederick Mosteller, PhD; Thomas C. Chalmers, MD

Objective.—To examine the temporal relationship between accumulating data from randomized control trials of treatments for myocardial infarction and the recommendations of clinical experts writing review articles and textbook chapters.

Data Sources.—(1) MEDLINE search from 1966 to present; search terms used were *myocardial infarction*, *clinical trials*, *multicenter studies*, *double-blind method*, *meta-analysis*, and the text word “random.”; (2) references from pertinent articles and books; and (3) all editions of English-language general medical texts and manuals and review articles on treatment of myocardial infarction.

Study Selection.—Randomized control trials of therapies for reducing the risk

SHORTENING the time between medical research discoveries and clinical implementation of new technologies by practicing physicians has been a concern of the American public since Congress established the Heart, Cancer, and Stroke Program over 25 years ago.¹ An undesirable lag still exists, and overcoming it is one of the goals of the newly formed Agency for Health Care Policy



Evidence Based Medicine

Aims to apply the best available evidence gained from the scientific method to clinical decision making



**THE COCHRANE
COLLABORATION®**

GRADE



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The Convergence of

SCIENCE AND

GOVERNANCE

Research, Health Policy, and American States

Daniel M. Fox

Copyrighted Material



**But Evidence Based
Medicine Methodologies Are
Not Directly Transferable to
Environmental Science!**

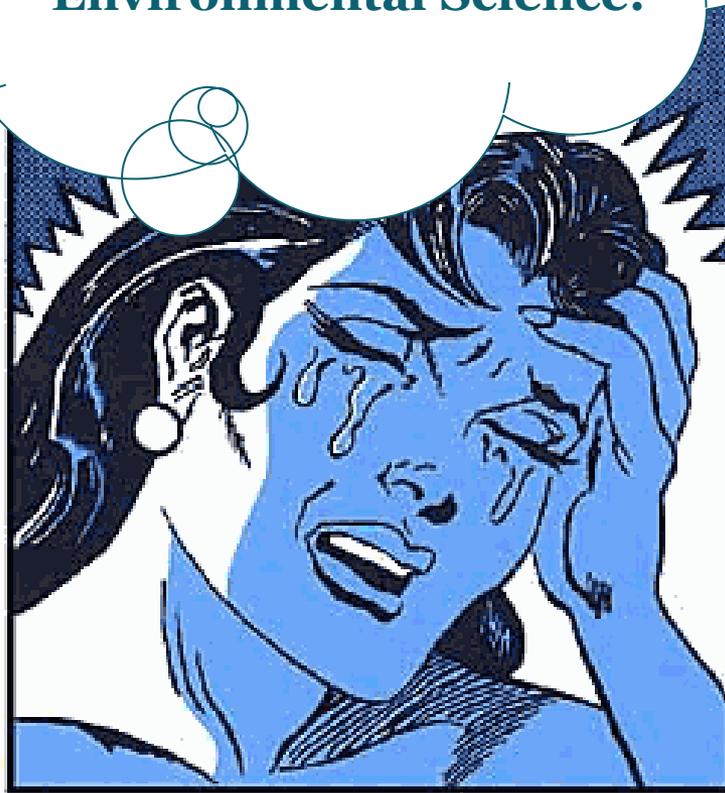
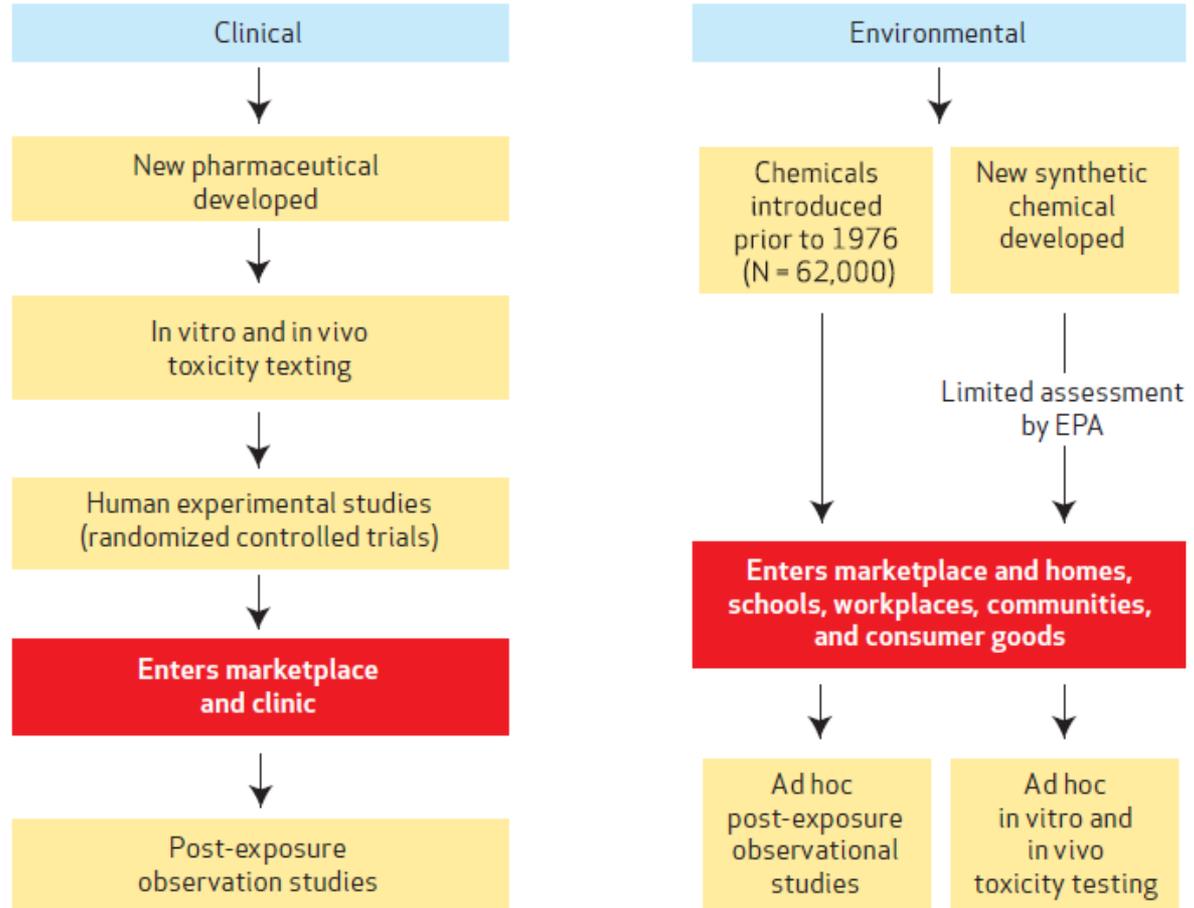


EXHIBIT 1

Streams Of Evidence For Chemical Toxicity Assessment In Clinical And Environmental Health Sciences





The Cochrane Collaboration

International Agency for Research on Cancer

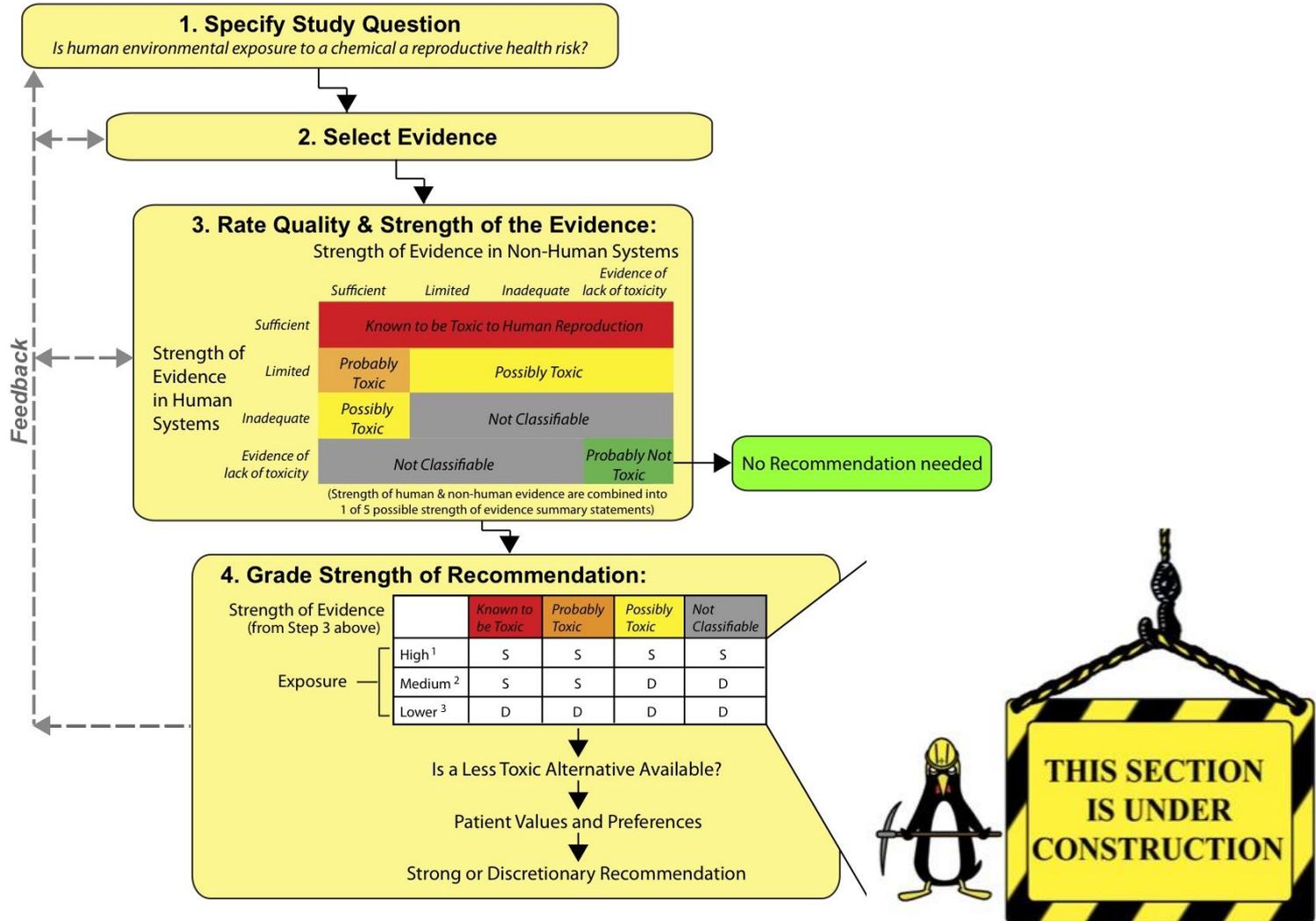


World Health Organization

Navigation Guide Work Group



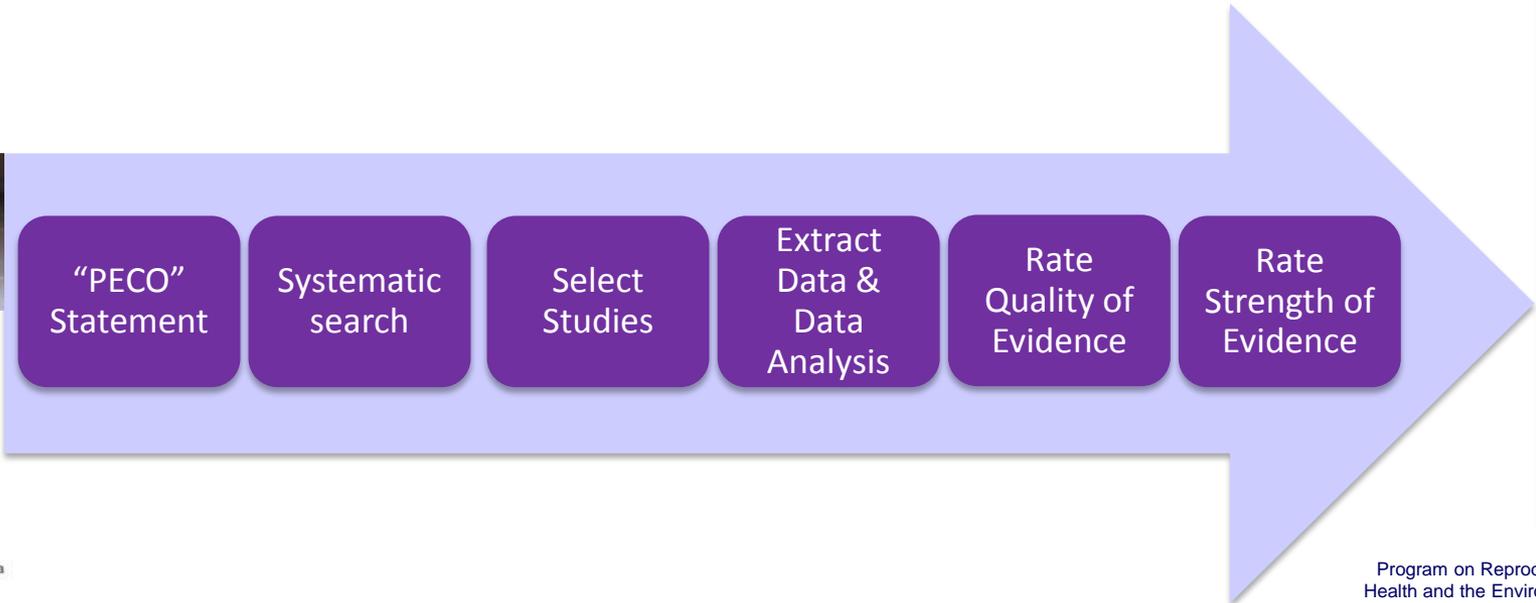
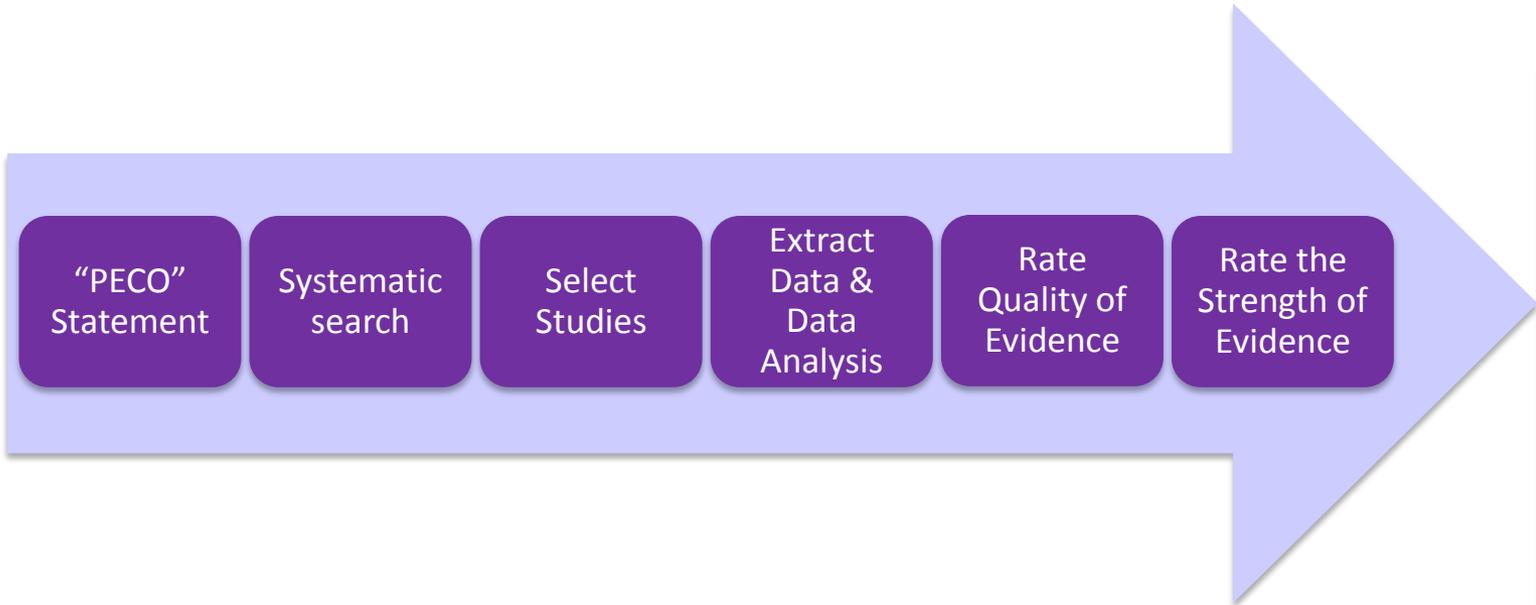
Overview of Navigation Guide Systematic Review Methodology



Systematic review approach for each evidence stream



Human
Data



Overall Conclusion



Non
Human
Data

UCSF

University of California
San Francisco



The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes

Tracey J. Woodruff and Patrice Sutton

Program on Reproductive Health and the Environment, University of California, San Francisco, Oakland, California, USA

BACKGROUND: Synthesizing what is known about the environmental drivers of health is instrumental to taking prevention-oriented action. Methods of research synthesis commonly used in environmental health lag behind systematic review methods developed in the clinical sciences over the past 20 years.

OBJECTIVES: We sought to develop a proof of concept of the “Navigation Guide,” a systematic and transparent method of research synthesis in environmental health.

DISCUSSION: The Navigation Guide methodology builds on best practices in research synthesis in evidence-based medicine and environmental health. Key points of departure from current methods of expert-based narrative review prevalent in environmental health include a prespecified protocol, standardized and transparent documentation including expert judgment, a comprehensive search strategy, assessment of “risk of bias,” and separation of the science from values and preferences. Key points of departure from evidence-based medicine include assigning a “moderate” quality rating to human observational studies and combining diverse evidence streams.

CONCLUSIONS: The Navigation Guide methodology is a systematic and rigorous approach to research synthesis that has been developed to reduce bias and maximize transparency in the evaluation of environmental health information. Although novel aspects of the method will require further development and validation, our findings demonstrated that improved methods of research synthesis under development at the National Toxicology Program and under consideration by the U.S. Environmental Protection Agency are fully achievable. The institutionalization of robust methods of systematic and transparent review would provide a concrete mechanism for linking science to timely action to prevent harm.

CITATION: Woodruff TJ, Sutton P. 2014. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. *Environ Health Perspect* 122:1007–1014; <http://dx.doi.org/10.1289/ehp.1307175>

about how environmental health science is translated into strength of evidence conclusions have been lacking [Beronius et al. 2010; Gee 2008; National Research Council (NRC) 2009, 2011].

Today, methods of research synthesis prevalent in environmental health mirror that of clinical medicine > 40 years ago when the clinical sciences largely relied on a system of expert-based narrative reviews on which to recommend treatment decisions (Rennie and Chalmers 2009). In a landmark paper published in 1992 in the *Journal of the American Medical Association*, Antman et al. (1992) showed the superiority of systematic review methods by comparing

Address correspondence to T.J. Woodruff, UCSF Program on Reproductive Health and the Environment, 1330 Broadway, Suite 1135, Oakland, CA 94612 USA. Telephone: (510) 350-1241. E-mail: woodrufft@obgyn.ucsf.edu

We are indebted to D. Atchley, D. Axelrad, L. Bero, P. Johnson, E. Koustas, and J. Lam for providing invaluable comments and suggestions on this com-



Protocol

UCSF Program on Reproductive Health
and the Environment

Navigation Guide Protocol for Rating
the Quality and Strength of
Human and Non-Human Evidence
December 5, 2012

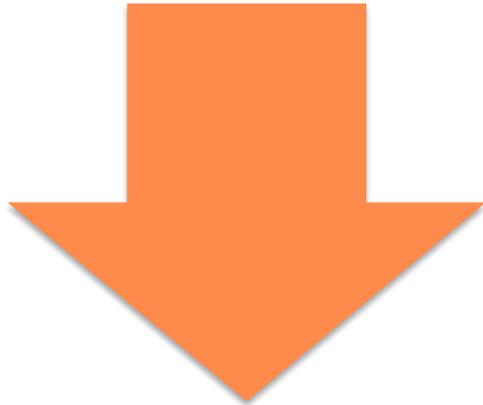




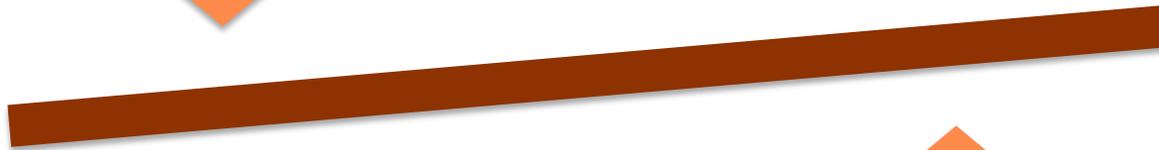
Photo credit: http://water.usgs.gov/nasqan/sample_collection_methods.html



Risk of Bias



Characteristics of a study that can introduce systematic errors in the magnitude or direction of the results



Higgins and Green 2011



Rate Risk of Bias for Each Individual Study



Domains

- Recruitment strategy
- Blinding
- Exposure assessment
- Confounding
- Incomplete outcome data
- Selective reporting
- Conflict of interest
- Other bias

Determinations

(for each risk of bias domain)

- Low risk
- Probably low risk
- Probably high risk
- High risk



Pharmaceutical industry sponsorship and research outcome and quality: systematic review

Joel Lexchin, Lisa A Bero, Benjamin Djulbegovic, Otavio Clark

Abstract

Objective To investigate whether funding of drug studies by the pharmaceutical industry is associated with outcomes that are favourable to the funder and whether the methods of trials funded by pharmaceutical companies differ from the methods in trials with other sources of support.

Methods Medline (January 1966 to December 2002) and Embase (January 1980 to December 2002) searches were supplemented with material identified in the references and in the authors' personal files. Data were independently abstracted by three of the authors and disagreements were resolved by consensus.

Results 30 studies were included. Research funded by drug companies was less likely to be published than research funded by other sources. Studies sponsored by pharmaceutical companies were more likely to have outcomes favouring the sponsor than were studies with other sponsors (odds ratio 4.05; 95% confidence interval 2.98 to 5.51; 18 comparisons). None of the 13 studies that analysed methods reported that studies funded by industry was of

Conclusion Systematic bias favours products which are made by the company funding the research. Explanations include the selection of an inappropriate comparator to the product being investigated and publication bias.

favourable outcome may result in biases in design, outcome, and reporting of industry sponsored research.⁷ We reviewed the relation between the source of funding of the research and the reported outcomes and investigated the quality of the methods in trials funded by pharmaceutical companies compared with other studies.

Methods

Study selection

We included only studies that specifically stated that they analysed research sponsored by a pharmaceutical company, compared methodological quality or outcomes with studies with other sources of funding, and reported the results in quantitative terms. Outcomes of interest were conclusions about differences in drug effectiveness, adverse effects, cost outcomes, or publication status between industry funded trials and other trials. Work published in any language was eligible for inclusion.

Search strategy

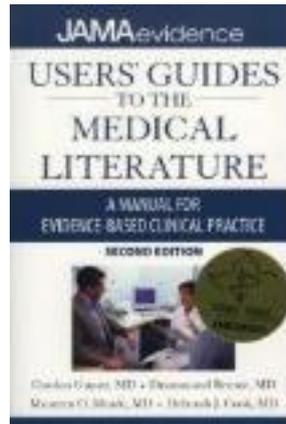
We searched Medline from January 1966 to December 2002 and Embase from January 1980 to December 2002 using a combination of terms as both MESH subject headings and key words (see bmj.com). We scanned the reference lists from each of the articles and searched the Cochrane methodology register. We placed messages on two email drug discussion groups, contacted content experts, and searched our libraries.



“... the biggest threat to [scientific] integrity [is] financial conflict of interest”

Drummond Rennie

Deputy Editor (West), JAMA



Rate the Quality of the Body of Evidence



High

Animal evidence

Moderate

Human evidence

Low



Rate the Quality of the Body of Evidence



Quality of Evidence *across all studies.*

Downgrade Criteria

- Risk of bias across studies
- Indirectness
- Inconsistency
- Imprecision
- Publication bias

Upgrade Criteria

- Large magnitude of effect
- Dose response
- All possible confounding accounted for

Rating

(based on all quality criteria)

- High quality
- Moderate quality
- Low quality

Factors for downgrading/upgrading evidence were derived directly from factors used in GRADE and Cochrane



Rating Strength of Evidence

CONSIDERATIONS

1. What is the quality of the data?
2. What is the direction of the effect?
3. What is our confidence in the effect?
4. Are there other compelling attributes of the data that may influence certainty?

Sufficient

Limited

Inadequate

Evidence of lack of toxicity



Integration of each evidence stream



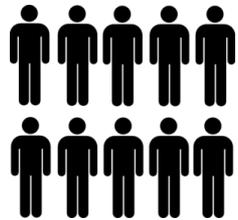
Sufficient

Limited

Inadequate

Sufficient

Known to be toxic



Limited

Probably toxic

Possibly toxic

Inadequate

Possibly toxic

Not classifiable





NTP

National Toxicology Program
U.S. Department of Health and Human Services

Implementing Systematic Review at the National Toxicology Program: Status and Next Steps

Linda S. Birnbaum, Kristina A. Thayer, John R. Bucher, Mary S. Wolfe

National Institute of Environmental Health Sciences, National Institutes of Health,
Department of Health and Human Services, Research Triangle Park, North Carolina,
E-mail: bucher@niehs.nih.gov

Environ Health Perspect 121:a108-a109 (2013).

<http://dx.doi.org/10.1289/ehp.1306711> [online 01 April 2013]

Systematic Review and Evidence Integration for Literature-Based Environmental Health Science Assessments

Andrew A. Rooney, Abee L. Boyles, Mary S. Wolfe, John R. Bucher, and Kristina A. Thayer



National Toxicology Program
U.S. Department of Health and Human Services

Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration

January 9, 2015

Office of Health Assessment and Translation (OHAT)

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

http://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf

Comparison of Narrative reviews and Navigation Guide/OHAT

Narrative Review

Reference	Specify study question	Specify inclusion/exclusion criteria	Conduct reproducible search	Assess Risk of Bias	Data analysis and/or meta-analyses	Summary of findings table	Assess quality of body of evidence	Integrate evidence streams
Post et al 2012	Green	Pink	Pink	Pink	Pink	Green	Pink	Pink
Lindstrom et al 2011	Green	Pink	Pink	Pink	Pink	Pink	Pink	Pink
Stahl et al 2011	Green	Pink	Pink	Pink	Pink	Green	Pink	Pink
White et al 2011	Green	Pink	Pink	Pink	Pink	Green	Pink	Pink
Steenland et al 2010	Green	Pink	Pink	Pink	Pink	Pink	Pink	Pink
DeWitt et al 2009	Green	Pink	Pink	Pink	Pink	Pink	Pink	Pink
Olsen et al 2009	Green	Pink	Pink	Pink	Pink	Yellow	Pink	Pink
Jensen and Leffers 2008	Pink	Pink	Pink	Pink	Pink	Pink	Pink	Pink
Lau et al 2007	Green	Pink	Pink	Pink	Pink	Pink	Pink	Pink
Butenhoff et al 2004	Green	Green	Pink	Pink	Yellow	Green	Pink	Pink
Kennedy et al 2004	Green	Pink	Pink	Pink	Pink	Green	Pink	Pink
Lau et al 2004	Green	Pink	Yellow	Pink	Pink	Pink	Pink	Pink
Hekster et al 2003	Green	Yellow	Yellow	Pink	Pink	Green	Pink	Pink
Kudo and Kawashima 2003	Green	Pink	Pink	Pink	Pink	Pink	Pink	Pink
Navigation, OHAT/NTP	Green	Green	Green	Green	Green	Green	Green	Green



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

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

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

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

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



UCSF: Proof of Concept Documented in 5 Case Studies of Applying the Navigation Guide

1. PFOA and fetal growth (*published*)
2. Maternal glomerular filtration rate (GFR) and fetal growth (*published*)
3. Triclosan and reproductive & developmental health outcomes (*in preparation*)
4. Air pollution and Autism Spectrum Disorder (*in progress*)
5. PBDEs and Attention Deficit Disorder and IQ (*in progress*)



Strengths

- Permits action on available data
- Systematic and transparent
- Based on empirically-proven methods
- Can identify evidence gaps for future work
- Can support identification of safer alternatives
- Separates science from values and preferences

Limitations

- Analysis limited to available data
- Novel parts of methodology need validation
- Further definition of moving from quality of evidence to strength of evidence
- Does not address non-scientific barriers to prevention-oriented action



Case Study: Triclosan and DART



Drug Facts

Active ingredient
Triclosan 0.15 %

Uses ■ For hand washing to

Warnings
For external use only.

When using this product ■ Avo
rs, rinse thoroughly with water

Using this product and ask
out of reach of children ■

Source: fda.gov

Navigation Guide systematic review methodology



- Draft protocol with PECO (Population, Exposure, Comparator, Outcome)
- Review protocol
- Define inclusion/exclusion criteria
- Define quality and strength criteria

- Formulate search terms
- Conduct literature search

- Set up forms for screening
- Conduct title/abstract , then full text screening according to criteria
- Reconcile any differences between screeners
- Conduct search of reference and citation lists

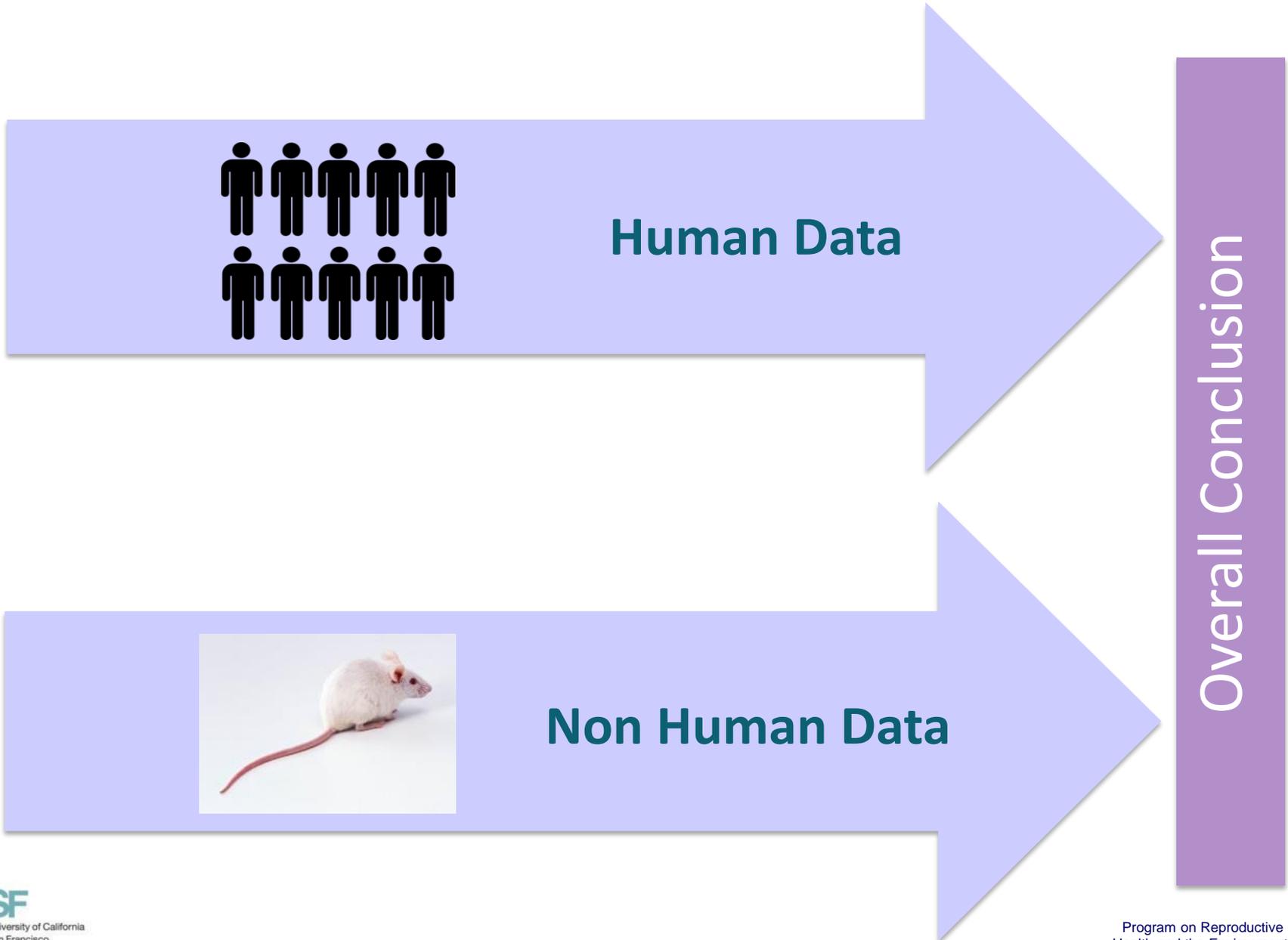
- Extract data from included studies
- Contact study authors for any additional data or info.
- Rate risk of bias of individual studies
- Summarize data for group
- Devise data analysis plan
- Conduct data analysis

- Review data summaries
- Rate overall quality across studies according to criteria
- Reconcile any differences between coauthors
- Summarize responses of coauthors

- Review data summaries
- Rate overall strength of evidence according to criteria
- Reconcile any differences between coauthors
- Summarize responses of coauthors



Integration of each evidence stream



Specify the Study Question

Does exposure to triclosan have adverse effects on human development or reproduction?



PECO

Participants

Exposure

Comparator

Outcome



PECO

Participants:

Humans or animals (whole organism studied during the reproductive or developmental time period, tissue, organ, cell line or components), or computer models of humans or animals.



PECO

Participants:

Humans or animals (whole organism studied during the reproductive or developmental time period, tissue, organ, cell line or components), or computer models of humans or animals.

Exposure:

Developmental - Pre-conception (exposure of either or both parents or, if relevant, preceding generations), prenatal (exposure of pregnant female and/or directly of fetus), or postnatal (until the time of sexual maturation) exposure, by any route, to triclosan.

Reproductive - Exposure to triclosan at any time preceding assessment of reproductive outcome.



PECO

Participants:

Humans or animals (whole organism studied during the reproductive or developmental time period, tissue, organ, cell line or components), or computer models of humans or animals.

Exposure:

Developmental - Pre-conception (exposure of either or both parents or, if relevant, preceding generations), prenatal (exposure of pregnant female and/or directly of fetus), or postnatal (until the time of sexual maturation) exposure, by any route, to triclosan.

Reproductive - Exposure to triclosan at any time preceding assessment of reproductive outcome.

Comparator:

Comparable populations or subjects (humans, non-human, tissues, organs, cell lines or components) exposed to vehicle-only treatment or lower levels of triclosan than the more highly exposed subjects.



PECO

Outcome:

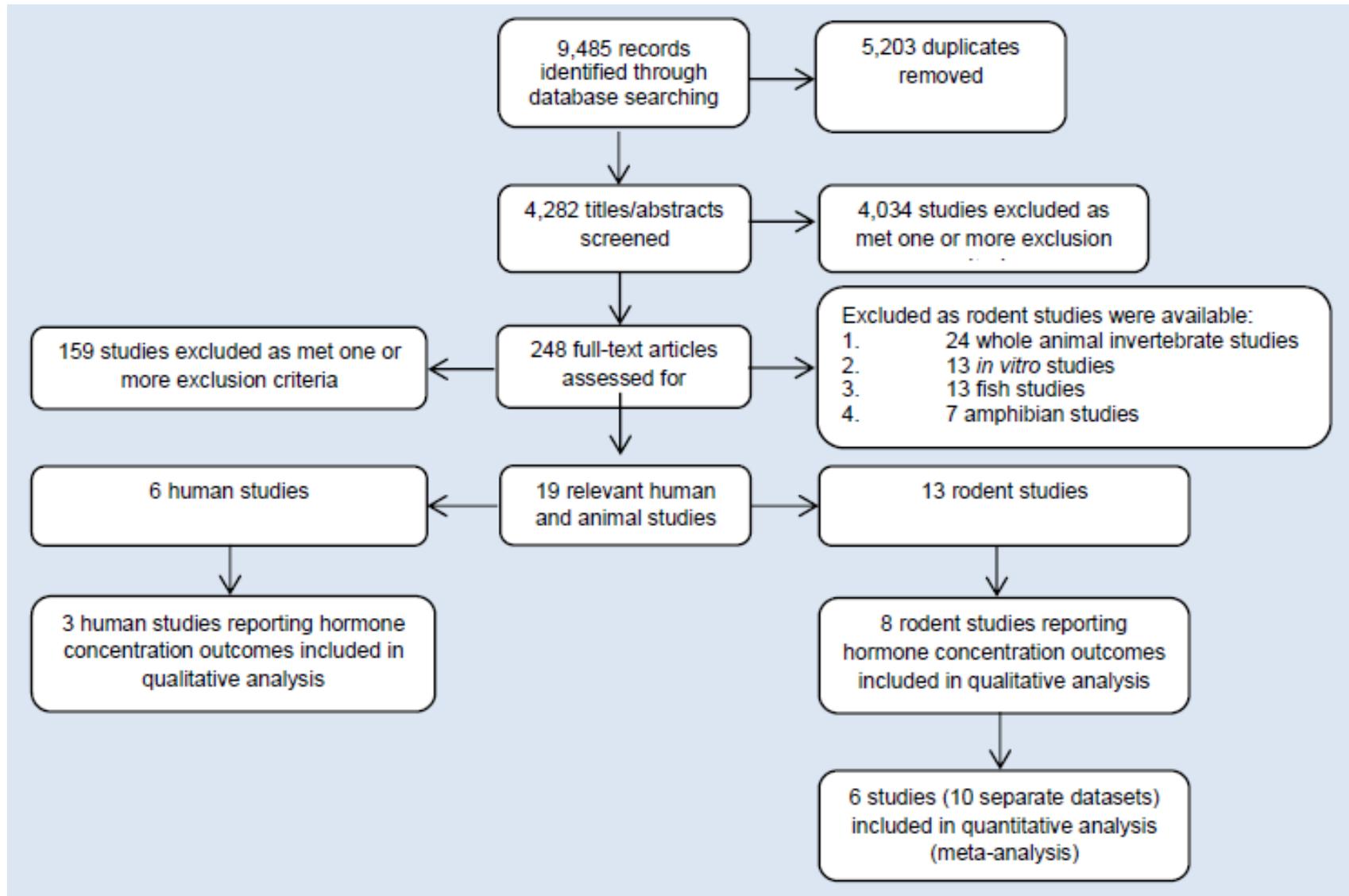
Reproductive effects: alterations in hormone levels; effects on male or female gametes (production, maturation, or transport), fertility, fecundity, estrous cycles, menstrual cycles, endocrine function, sexual behavior, gestation, parturition, lactation, age at puberty or reproductive senescence or menopause; pregnancy complications; increased pregnancy wastage; or alterations in size, morphology, or function of reproductive organs.

Developmental effects: fetal loss or resorption, stillbirth, neonatal or subsequent mortality, alterations in sex ratio, altered fetal or postnatal growth, structural malformations and variations, altered gestation length, functional deficits such as alterations in behavior, and morbidity. In addition to effects of prenatal exposure during all or any part of gestation, developmental toxicity can result from:

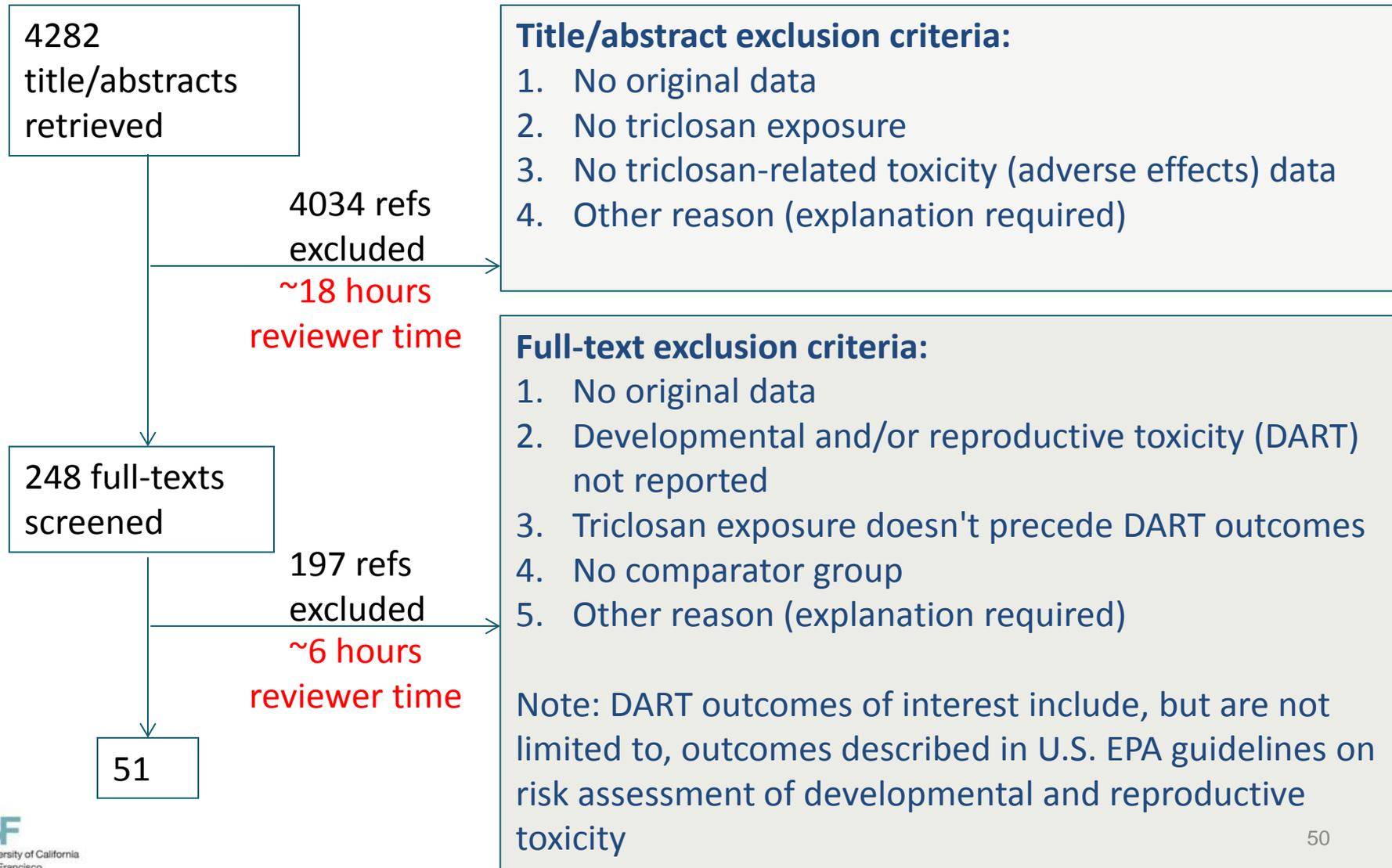
- Pre-conception exposure of parental or previous generations causing genetic mutation or epigenetic changes, which in turn affect development of unexposed offspring.
- Postnatal exposure when the developing offspring is more susceptible to adverse effects of the toxic agent than is the mature animal:
 - Qualitatively: Effect not seen in similarly-exposed adults
 - Quantitatively: Effect seen at lower doses, or to a greater extent, in immature organisms than in adults



Select the Evidence



Reference Screening



Refid: 46, Association of exposure to phenols and idiopathic male infertility

M. Chen, R. Tang, G. Fu, P. Zhu, S. Qiao, X. Chen, B. Xu, Y. Qin, C. Lu, B. Hang, Y. Xia and X. Wang

Attachments

46 Chen et al.pdf

Widespread human exposure to phenols has been documented recently, and some phenols which are potential endocrine disruptors have demonstrated adverse effects on male reproduction in animal and in vitro studies. However, implications about exposure to phenols and male infertility are scarce in humans. Case-control study of 877 idiopathic infertile men and 713 fertile controls was conducted. Urinary levels of bisphenol A, benzophenone-3, pentachlorophenol, triclosan, 4-tert-octylphenol (4- t-OP), 4- n-octylphenol (4- n-OP) and 4- n-nonylphenol (4- n-NP) and semen parameters were measured. After multivariate adjustment, we found 4- t-OP, 4- n-OP and 4- n-NP exposure was associated with idiopathic male infertility (p-value for trend: <0.0001, 0.014 and 0.001, respectively). Aside from these associations, 4- t-OP and 4- n-NP exposure was also associated with idiopathic male infertility with abnormal semen parameters. Moreover, we observed significant associations between sum alkylphenols (APs) exposure and idiopathic male infertility. There were no relationships between exposure to other phenols and idiopathic male infertility in the present study. Our study provides the first evidence that exposure to APs (4- t-OP, 4- n-OP and 4- n-NP) is associated with idiopathic male infertility. 2013 Elsevier B.V.

Submit Form and go to This Form - Next Reference or Skip to Next

<p>1. Include this study?</p> <ul style="list-style-type: none"><input checked="" type="radio"/> Yes - study is relevant<input type="radio"/> Whole animal study on invertebrates<input type="radio"/> Unclear<input type="radio"/> Useful information<input type="radio"/> No - exclude (see box for exclusions) ----><input type="radio"/> Relevant abstract	<p>Possible reasons for exclusion:</p> <ul style="list-style-type: none">• no original data• developmental and/or reproductive toxicity (DART) not reported• triclosan exposure doesn't precede DART outcomes• no comparator group• other <p>Note: DART outcomes of interest include, but are not limited to, outcomes described in U.S. EPA guidelines on risk assessment of developmental and reproductive toxicity.</p>
--	---

2. If you think this might be a duplicate study, explain why:

3. Language (if not English)

4. Comments:

Endpoints from 12 rodent studies

144 unique outcomes reported...

Hormone concentrations

Growth

Viability

Organ weight

Gestational length

Sex ratio

Feminization

Developmental landmarks

Birth defects

Histology and morphology



Postnatal Administration of Triclosan and Thyroxine (T4)

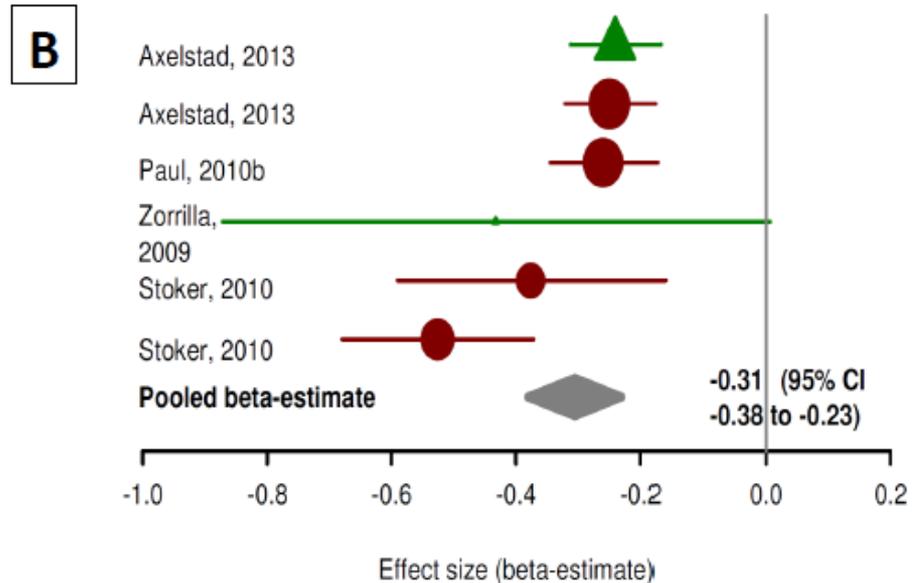
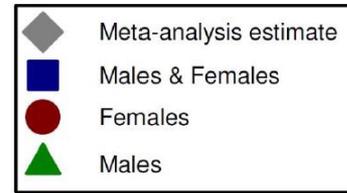
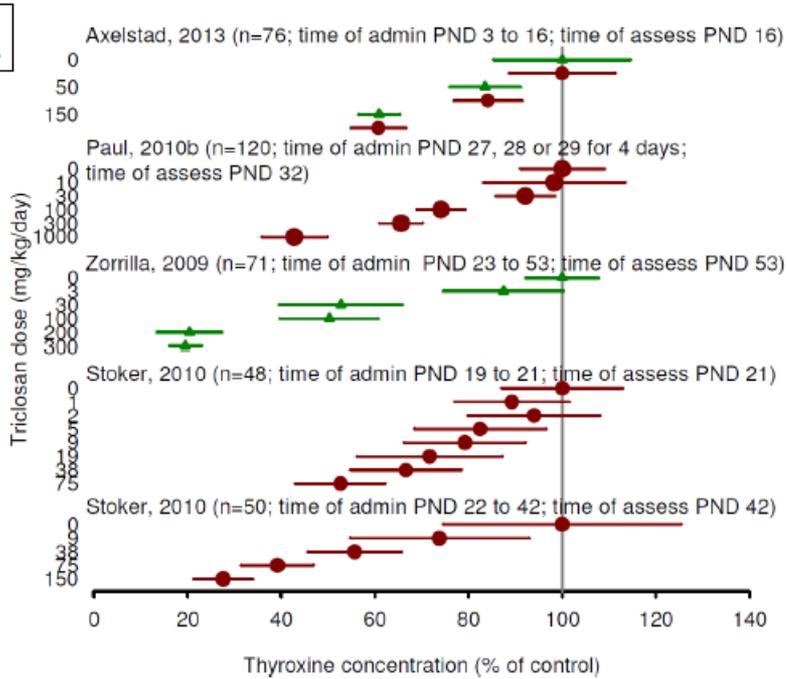


Figure 5. Postnatal Triclosan administration and thyroxine concentration.

A. Postnatal triclosan administration and thyroxine concentration as a percentage of the control group for doses up to 300mg/kg/day

B. Postnatal beta-estimates for dose response and the random effects meta-analysis estimate

Rating Quality

Risk of Bias for non-human experimental studies

1. *Sequence generation*

Was it appropriately randomized?



2. *Allocation concealment*

Was allocation adequately concealed?



3. *Blinding*

Were study personnel and outcome assessors blinded?



4. *Incomplete outcome data*

Did study authors report all incomplete outcome data?



5. *Selective outcome reporting*

Were outcomes reported selectively?



6. *Conflict of interest*

Was study supported by entity with financial interest?



7. *Other potential threats to validity*

Any other problems that could bias?

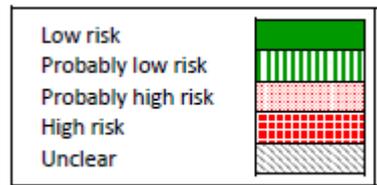


Rating Quality

Risk of Bias for non-human experimental studies

- Paul et al. 2012
- Stoker et al. 2010^a
- Stoker et al. 2010^b
- Paul et al. 2010a
- Rodriguez and Sanchez 2010
- Paul et al. 2010b
- Zorilla et al. 2009
- Kumar et al. 2009
- Axelstad et al. 2013

	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome data	Conflict of interest reporting	Other bias
Paul et al. 2012	Probably high risk	Probably high risk	Probably high risk	Probably high risk	Low risk	Probably high risk	Low risk
Stoker et al. 2010 ^a	Probably high risk	Probably high risk	Probably high risk	Probably low risk	Low risk	Probably high risk	Low risk
Stoker et al. 2010 ^b	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Low risk	Probably high risk	Low risk
Paul et al. 2010a	Probably low risk	Probably high risk	Probably high risk	High risk	Low risk	High risk	Low risk
Rodriguez and Sanchez 2010	Probably high risk	Probably high risk	Probably high risk	High risk	Low risk	Probably low risk	Low risk
Paul et al. 2010b	Probably low risk	Probably high risk	Probably high risk	Probably low risk	Low risk	Probably low risk	Low risk
Zorilla et al. 2009	Probably low risk	Probably high risk	Probably high risk	Probably high risk	Low risk	Probably low risk	Low risk
Kumar et al. 2009	Probably high risk	Probably high risk	Probably high risk	Probably low risk	Low risk	Low risk	Low risk
Axelstad et al. 2013	Probably high risk	Probably high risk	Probably high risk	Probably low risk	Low risk	Low risk	Low risk



Rating Quality

Risk of Bias for human studies

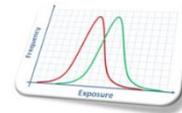
1. Are the study groups free from baseline differences?



2. Was knowledge of the exposure groups adequately prevented during the study?



3. Were exposure assessment methods robust?



4. Were outcome assessment methods robust?



5. Were confounding and effect modification adequately addressed?



6. Were incomplete outcome data adequately addressed?



7. Are reports of the study free of suggestion of selective outcome reporting?

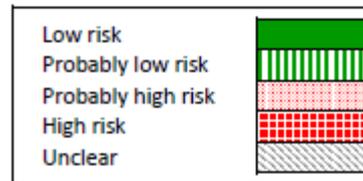
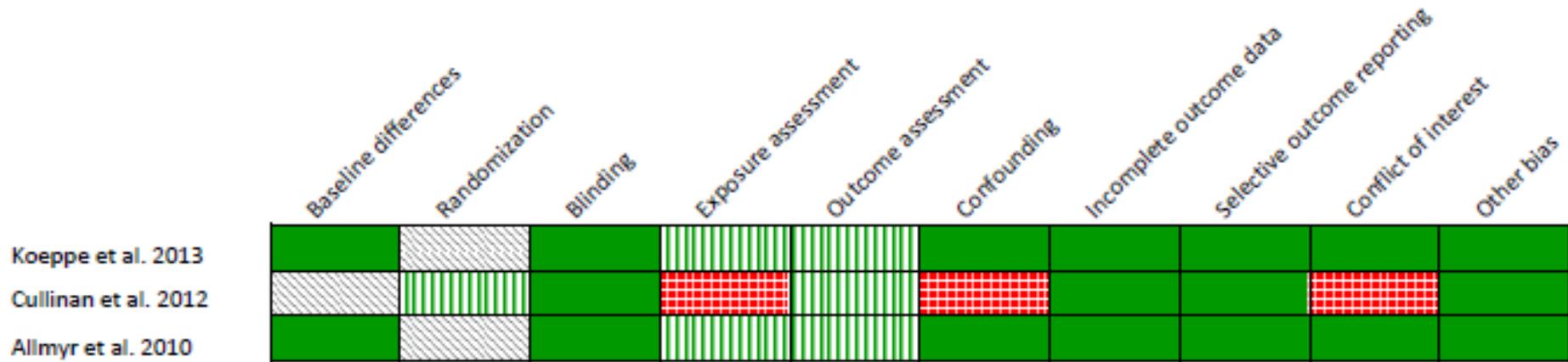


8. Was the study free of support from a company, study author, or other entity having a financial interest in any of the exposures studied?



Rating Quality

Risk of Bias for human studies

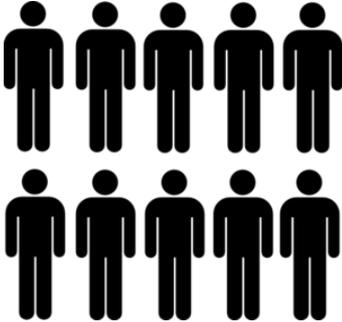


Rating Quality across all studies

Non-human evidence started as “high” quality rating
(comparable to RCTs)



Human evidence started as
“moderate” quality rating



Factors that **DECREASE** quality level

Possible ratings: 0=no change; -1 or -2 downgrade 1 or 2 levels.

1. Risk of bias (study limitations)

- Rated down if most relevant evidence were from studies that suffered from high risk of bias
- Conservative approach: confident that substantial risk of bias across most of body of evidence to downgrade

2. Indirectness

- Rated down if evidence was not directly comparable to the question of interest
- Based evaluation on PECO statement: population, exposure, comparator, outcome

3. Inconsistency

- Rated down for widely different estimates of effect (heterogeneity or variability in results)
- Considered variance in point estimates, confidence intervals overlap, I^2 , tests for heterogeneity



Factors that **DECREASE** quality level

Possible ratings: 0=no change; -1 or -2 downgrade 1 or 2 levels.

4. **Imprecision**

- Rated down if studies had few participants and few events (wide confidence intervals)

5. **Publication bias**

- Rated down if studies were thought to be missing from body of evidence, resulting in an underestimate of true effects from exposure
- Considered if there were early negative studies that were small in size, studies were small and sponsored by industry, unpublished studies showed different results from published studies, search not comprehensive



Factors that **INCREASE** quality level

Only applicable for human evidence

Possible ratings: 0=no change; +1 or +2 upgrade 1 or 2 levels.

1. Large magnitude of effect

- Upgraded if modeling suggested confounding alone unlikely to explain associations with relative risk greater than 2 or very unlikely to explain relative risk greater than 5
- Circumstances for upgrading occur infrequently

2. Dose response

- Upgraded if consistent dose response gradient in one or multiple studies, and/or dose response across studies

3. Confounding minimizes effect

- Upgraded if all possible residual confounders or biases reduced demonstrated effect, or suggested a spurious effect when results show no effect
- Example is autism and vaccination - observational studies showed no association even though empirically confirmed bias that parents more likely to remember vaccination after because of publicity about possible association



Summary of rating quality of the human hormonal evidence

Category	Downgrades	Rationale
Risk of bias	Seven (0); Four (-1)	Two of the three studies, one large and one small, have “low” or “probably low” risk of bias for all domains.
Indirectness	Five (0); Six (-1)	One study (Cullinan et al.) is of an older age group not representative of reproductive age where thyroid is a developmental or reproductive concern; Cullinan et al. exposure assessment by toothpaste use only is indirect.
Inconsistency	Eleven (0)	Although there are few studies on which to base this rating, the results are not inconsistent.
Imprecision	Eleven (0)	Considered downgrade to -1 here, based on Koeppe et al. wide confidence intervals, which is the majority of the data for this outcome.
Publication bias	Eleven (0)	These studies are not uniformly small and there is a larger study (Koeppe et al.) showing no effect for some outcomes. A comprehensive literature search did not identify studies with conflicting results.
	Upgrades	
Large magnitude of effect	Eleven (0)	The studies found null or minimal effects only.
Dose-response	Ten (0); One (+1)	There is no or minimal evidence of a dose-response gradient.
Confounding minimizes effect	Eleven (0)	There is no evidence that residual confounding may be influencing results.
Overall Quality of Evidence (Initial rating is “Moderate”)	Six (Moderate); Five (Low)	



Summary of rating quality of the non-human mammalian hormonal evidence

Category	Downgrades	Rationale
Risk of bias	Nine (-1); Two (0); One (0/-1)	(-1): There is “probably high” risk of bias across several domains; (0): Concern about overall risk of bias does not rise to the level of a downgrade; (0/-1): Most of these studies have “probably high” risk, rather than “high risk,” and this is mostly due to unknown information about the studies.
Indirectness	Twelve (0)	Animal changes (in rodents) are reflective of what is seen in humans and the outcomes are directly relevant to humans.
Inconsistency	Twelve (0)	There is not substantial heterogeneity in studies across postnatal dosing for thyroxine; lack of consistency between post and prenatal dosing has a biological explanation.
Imprecision	Twelve (0)	We judged that the confidence intervals are not wide for the T4 studies or the meta-analysis.
Publication bias	Twelve (0)	Studies include null findings as well as positive findings from studies with high risk for conflict of interest.
Overall Quality of Evidence (Initial rating is “High”)	Moderate	We downgraded one level based on concerns about risk of bias.



Rating Strength of Evidence

CONSIDERATIONS

1. What is the quality of the data?
2. What is the direction of the effect?
3. What is our confidence in the effect?
4. Are there other compelling attributes of the data that may influence certainty?

Sufficient

Limited

Inadequate

Evidence of lack of toxicity



Sufficient evidence of toxicity

The available evidence includes results from one or more well-designed, well-conducted studies, and the conclusion is unlikely to be strongly affected by the results of future studies.

Human: A positive relationship is observed between exposure and outcome where chance, bias, and confounding can be ruled out with reasonable confidence.

Non-human: A positive relationship is observed between exposure and adverse outcome in multiple studies or a single appropriate study in a single species.

Limited evidence of toxicity

Confidence in the relationship is constrained by such factors as: the number, size, or quality of individual studies, or inconsistency of findings across individual studies. As more information becomes available, the observed effect could change, and this change may be large enough to alter the conclusion.

Human: A positive relationship is observed between exposure and outcome where chance, bias, and confounding cannot be ruled out with reasonable confidence.

Non-human: The data suggest a positive relationship between exposure and adverse outcome, but there are important limitations in the quality of the body of evidence.

Inadequate evidence of toxicity

The available evidence is insufficient to assess effects of the exposure. Evidence is insufficient because of: the limited number or size of studies, low quality of individual studies, or inconsistency of findings across individual studies. More information may allow an assessment of effects.

Evidence of lack of toxicity

Human: No relationship is observed between exposure and outcome, and chance, bias and confounding can be ruled out with reasonable confidence. The available evidence includes consistent results from more than one well-designed, well-conducted study at the full range of exposure levels that humans are known to encounter, and the conclusion is unlikely to be strongly affected by the results of future studies. The conclusion is limited to the age at exposure and/or other conditions and levels of exposure studied.

Non-human: Data on an adequate array of endpoints from more than one study with at least two species showed no adverse effects at doses that were minimally toxic in terms of inducing an adverse effect. Information on pharmacokinetics, mechanisms, or known properties of the chemical class may also strengthen the evidence. The conclusion is limited to the species, age at exposure, and/or other conditions and levels of exposure studied, and is unlikely to be strongly affected by the results of future studies.



Definitions of “Strength of Evidence”

Derived from:

- International Agency for Research on Cancer. Preamble to the IARC Monographs (amended January 2006). Lyon: World Health Organization, 2006.
- U.S. Environmental Protection Agency. *Guidelines for Reproductive Toxicity Risk Assessment*. Washington, D.C.: Risk Assessment Forum; 1996.
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<http://www.uspreventiveservicestaskforce.org/uspstf07/methods/benefit.htm>



Strength of Evidence Results

	Rating	Rationale
Human Hormone	Inadequate	The available evidence is insufficient to assess effects of the exposure. Evidence is insufficient because of: the limited number or size of studies, low quality of individual studies, or inconsistency of findings across individual studies. More information may allow an assessment of effects.
Rodent Hormone	Sufficient	We found sufficient evidence that exposure to triclosan alters hormone levels in rats, based on reduced thyroxine levels.



Integration of each evidence stream for thyroxine



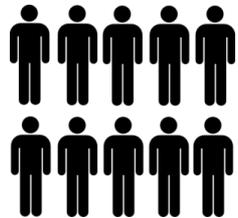
Sufficient

Limited

Inadequate

Sufficient

Known to be toxic



Limited

Probably toxic

Possibly toxic

Inadequate

Possibly toxic

Not classifiable



Conclusion for Triclosan case study

Based on our evaluation using the Navigation Guide criteria, we concluded that there was “sufficient” non-human evidence and “inadequate” human evidence of an association between triclosan exposure and thyroxine concentrations, and consequently, triclosan is “possibly toxic” to reproductive and developmental health.



Integrating the streams of evidence for PFOA (1st case study)

Strength of Evidence in Non-Human Systems

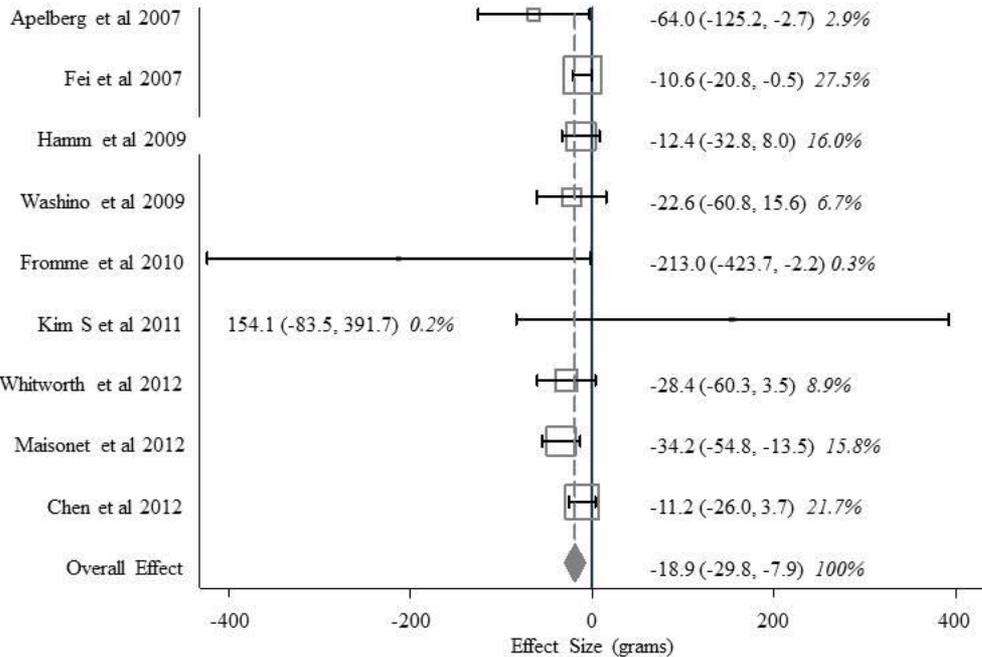
		Sufficient	Limited	Inadequate	Evidence of Lack of Toxicity
Strength of Evidence in Human Systems	Sufficient	Known to be Toxic to Human Reproduction			
	Limited	Probably Toxic	Possibly Toxic		
	Inadequate	Possibly Toxic	Not Classifiable		
	Evidence of Lack of Toxicity	Not Classifiable			Probably Not Toxic



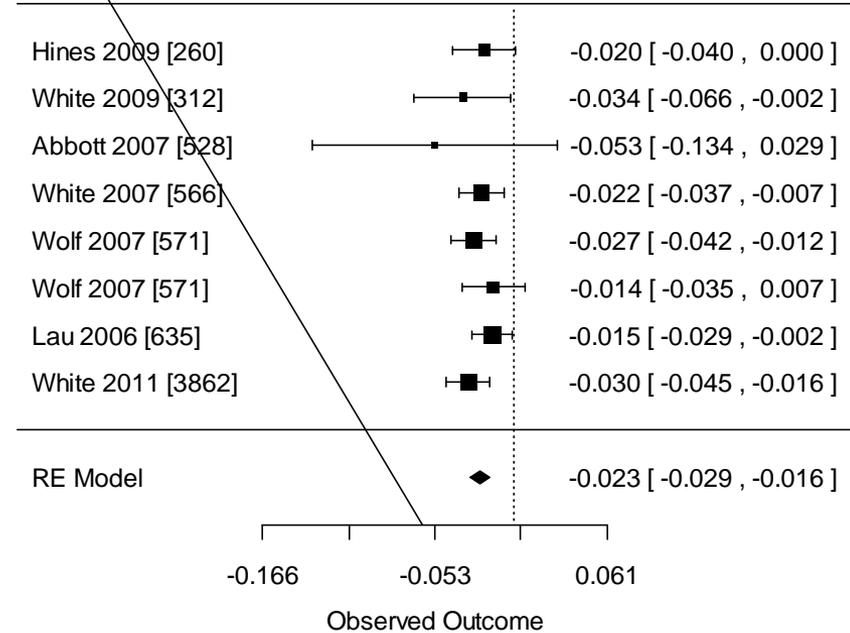
Conclusion: Human exposure to **PFOA is known to be toxic** to human reproduction and development based on sufficient evidence of decreased fetal growth in both human and non-human mammalian species.



Meta-analysis is a very useful tool



Grams change in birth weight per 1 ng/mL PFOA increase



Mean change in body weight (g) per 1 mg/kg BW/day PFOA dose



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- Forsythia Foundation
- Passport Foundation
- Johnson Family Foundation
- Heinz Endowments
- Rose Foundation
- Kaiser Permanente
- Planned Parenthood Federation of America
- UCSF Phillip R Lee Institute for Health Policy Studies



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