Combining Apples and Oranges: Lessons Learned and Advances Made Through International Collaboration

National Academies Workshop 2

Evidence integration in chemical assessment

Challenges faced in developing and communicating human health effects conclusions

A CENTURY OF SAVING LIVES
MILLIONS AT A TIME

JOHNS HOPKINS
BLOOMBERG SCHOOL
OF PUBLIC HEALTH

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ebtc
Evidence-based Toxicology Collaboration

Acknowledgements

EBTC Colleagues:

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- Sebastian Hoffmann
- Rob de Vries

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Outline

- Introduction on evidence-based methods and systematic review
- Key historical milestones in development of the frameworks
- Unique challenges of applying SR to chemicals risk assessment
- Qualitative and quantitative approaches to evidence integration (EFSA WoE, GRADE, OHAT, WHO IARC)
- Summary of key conclusions of the recent international workshops

Challenges in integrating new science in risk assessment

- **Cognitive bias:**

  "*I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail*." Abraham H. Maslow (1966). *The Psychology of Science*. p. 15.

- **Lack of confidence:**

  How does a regulator know if the new information is reliable?

- **Resistance to change:**

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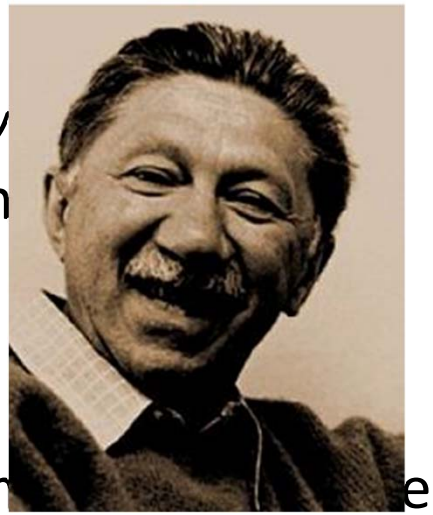


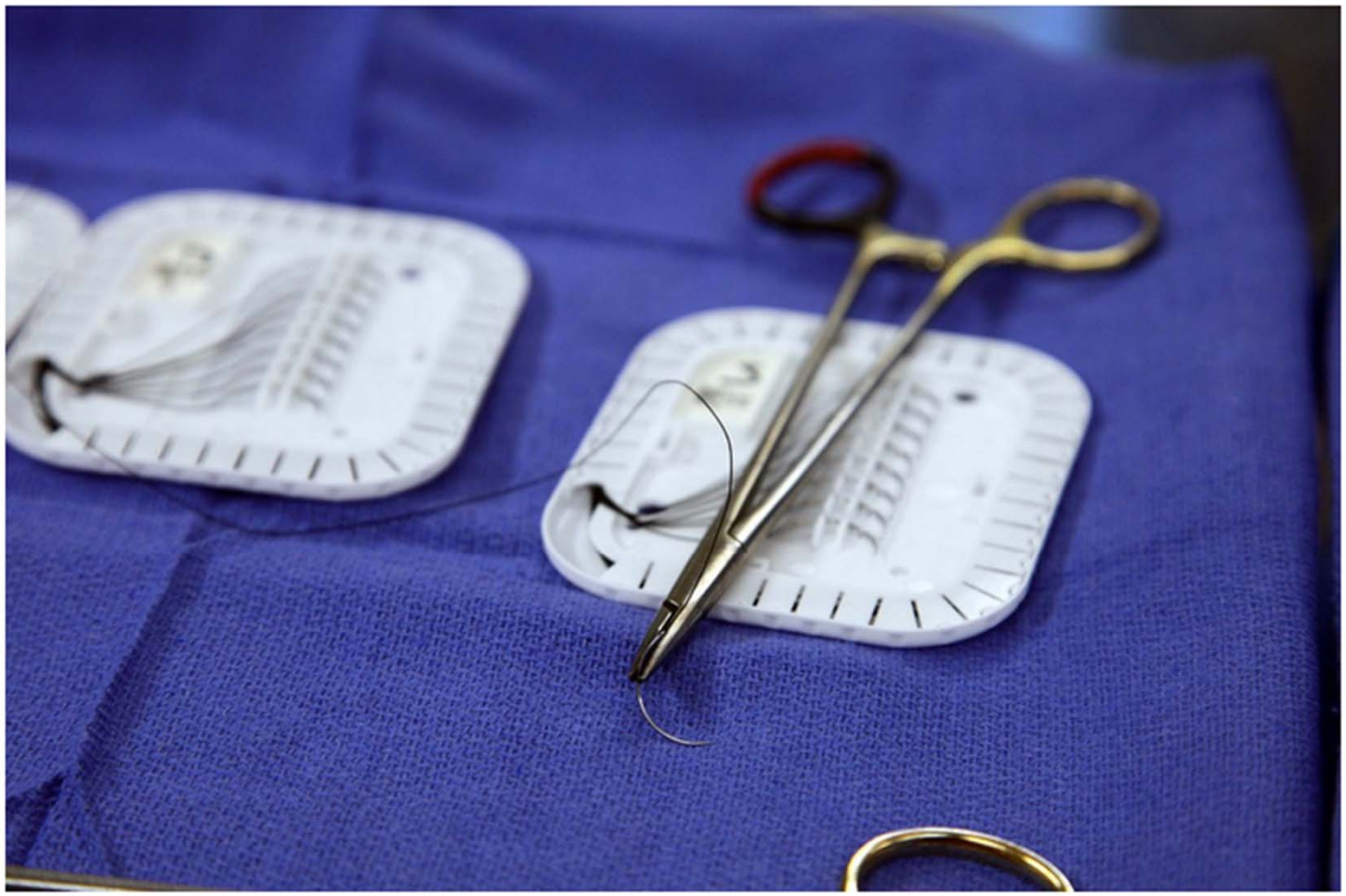
- **Lack of confidence:**

  How does a regulator know if the new inform e?

- **Resistance to change:**

It's Hard for Doctors to Unlearn Things. That's Costly for All of Us.

Procedures live on even after they've been proved ineffective. It can lead to harms and wasted resources.



Part of a doctor's tool kit is learning new things, but also unlearning some things. The second part may be harder than the first. Jim Wilson/The New York Times

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Need for a rigorous reproducible framework to validate the new approaches and integrate them appropriately in risk assessment

Systematic review – some definitions

A systematic review summarises the results of available studies (controlled trials) and provides a high level of evidence on the effectiveness of healthcare interventions. *Adapted from Cochrane*

A systematic review is a research methodology, which allows testing a hypothesis using pre-existing evidence

Why SR in regulatory assessments?

Regulatory assessments need reproducibility and rigor
SR framework provides transparent traceable records

Adapted from Paul Whaley

What are the differences between *A Review* and the Systematic Reviews?

Feature	Narrative Review	Systematic Review
Research Question	Often unclear or broad	Specified and specific
Literature Search	Not usually specified	Explicit search strategy
Study Selection	Not usually specified	Explicit selection criteria
Quality Assessment	Not usually present	Appraisal with explicit criteria
Synthesis	Often qualitative	Often also quantitative

Table adapted from de Vries et al., The ILAR Journal, 2016

History of Evidence-based Methodology in Healthcare

Origin:

- Clinical trials in medicine
- Organized and developed by Cochrane: www.cochrane.org

Field of Application:

- Compare medical treatments

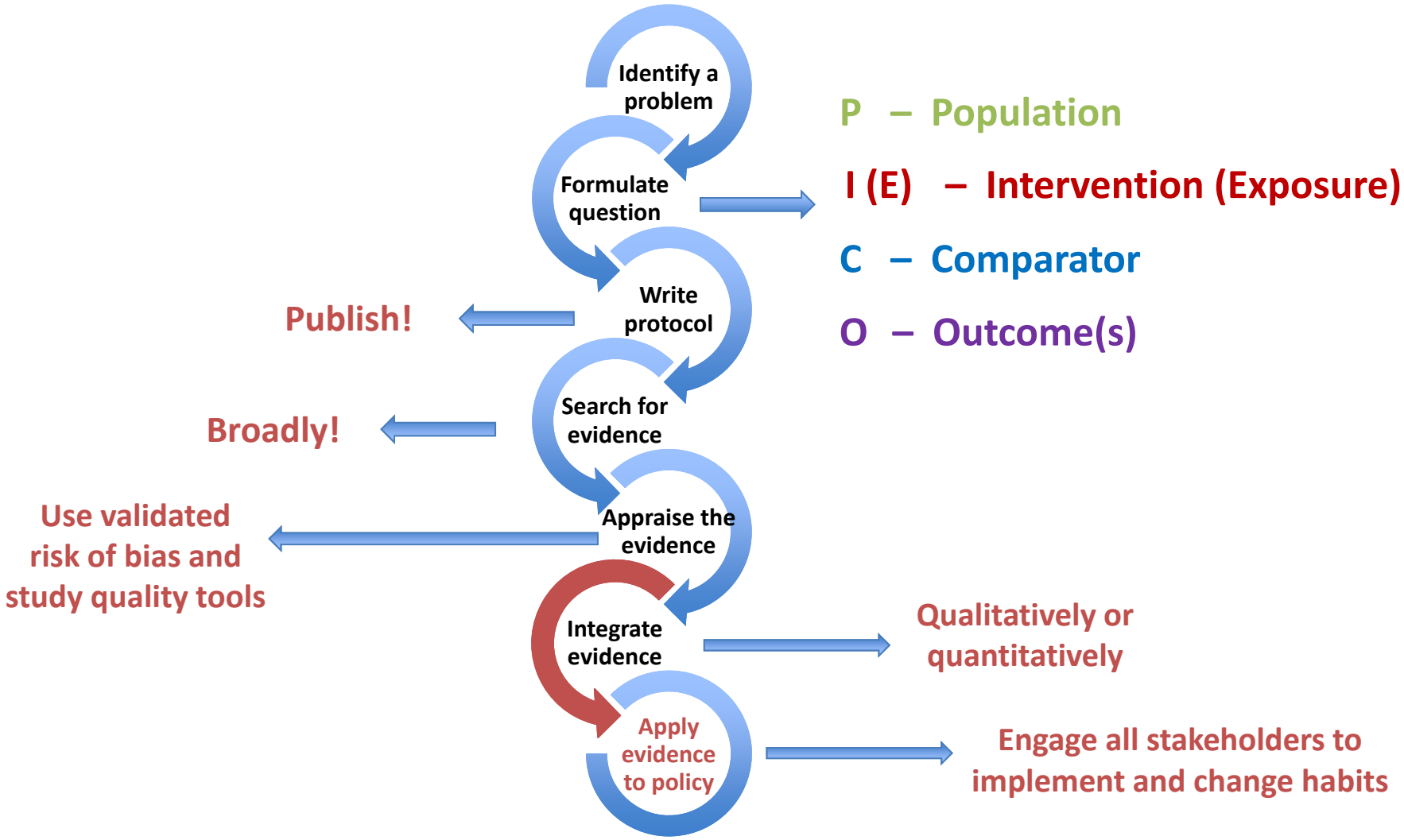
Major Principles:

- Transparency
- Consistency
- Statistical rigor
- Minimization of bias (systematic error) that impacts study quality
- Systematic step-wise approach

Main Instrument:

- Systematic review

Evidence-based Methods Steps



Cochrane Principles of Evidence-based Medicine

1. Collaboration
2. Involving, supporting and training people
3. Avoiding duplication of effort
4. Minimizing bias
5. Keeping up-to-date
6. Striving for relevance
7. Promoting access by wide dissemination
8. Ensuring quality
9. Continuity
10. Enabling wide participation in our work

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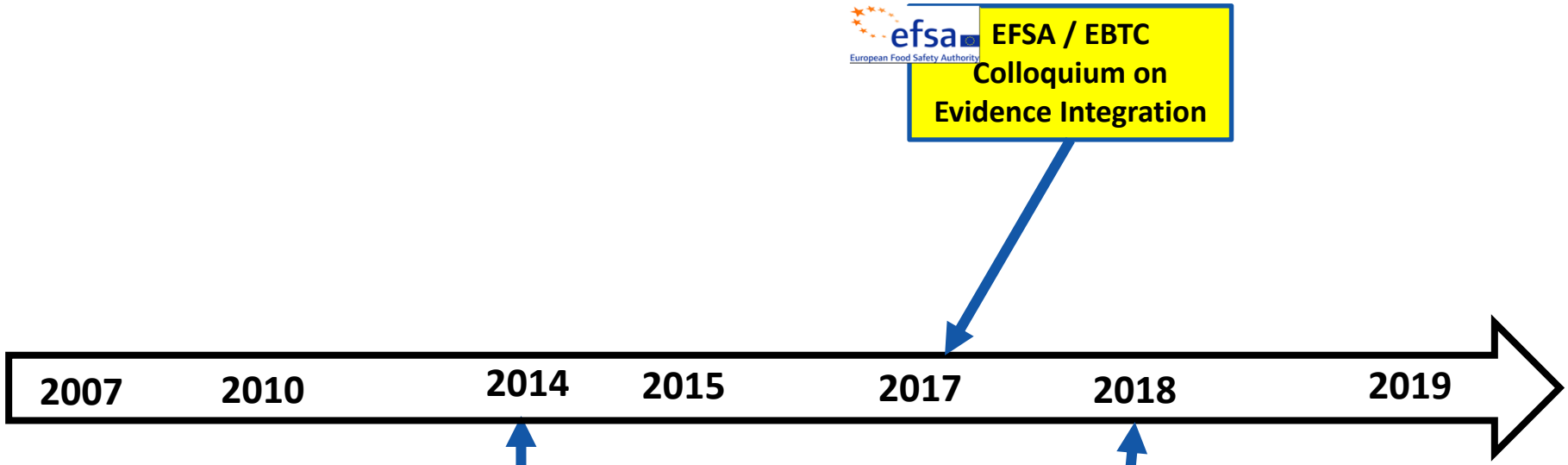
Impact of Cochrane work on clinical medicine

- The standard of clinical medicine was elevated over the four decades of implementing Cochrane principles
- SR is the main benchmark that physicians and healthcare organizations use to compare treatments
- RCTs are a standard in medicine
- RCTs reporting in the literature was standardized

Result: Cochrane's work is internationally recognized as the benchmark of the highest-quality information about the effectiveness of health care

Can this be achieved outside of the field of medicine?

International efforts in bringing SR to risk assessment



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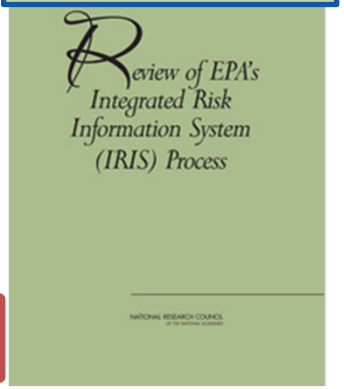
EFSA / EBTC Colloquium on Evidence Integration

2007 2010 2014 2015 2017 2018 2019

The 1st international forum towards an EBT

NAS IRIS Review 2014



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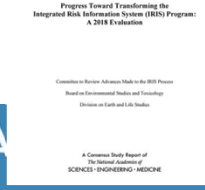

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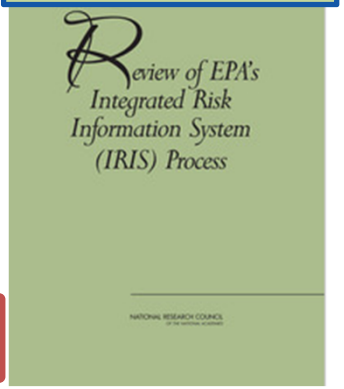

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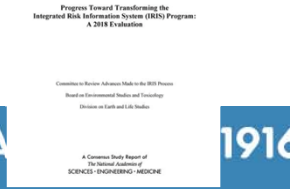

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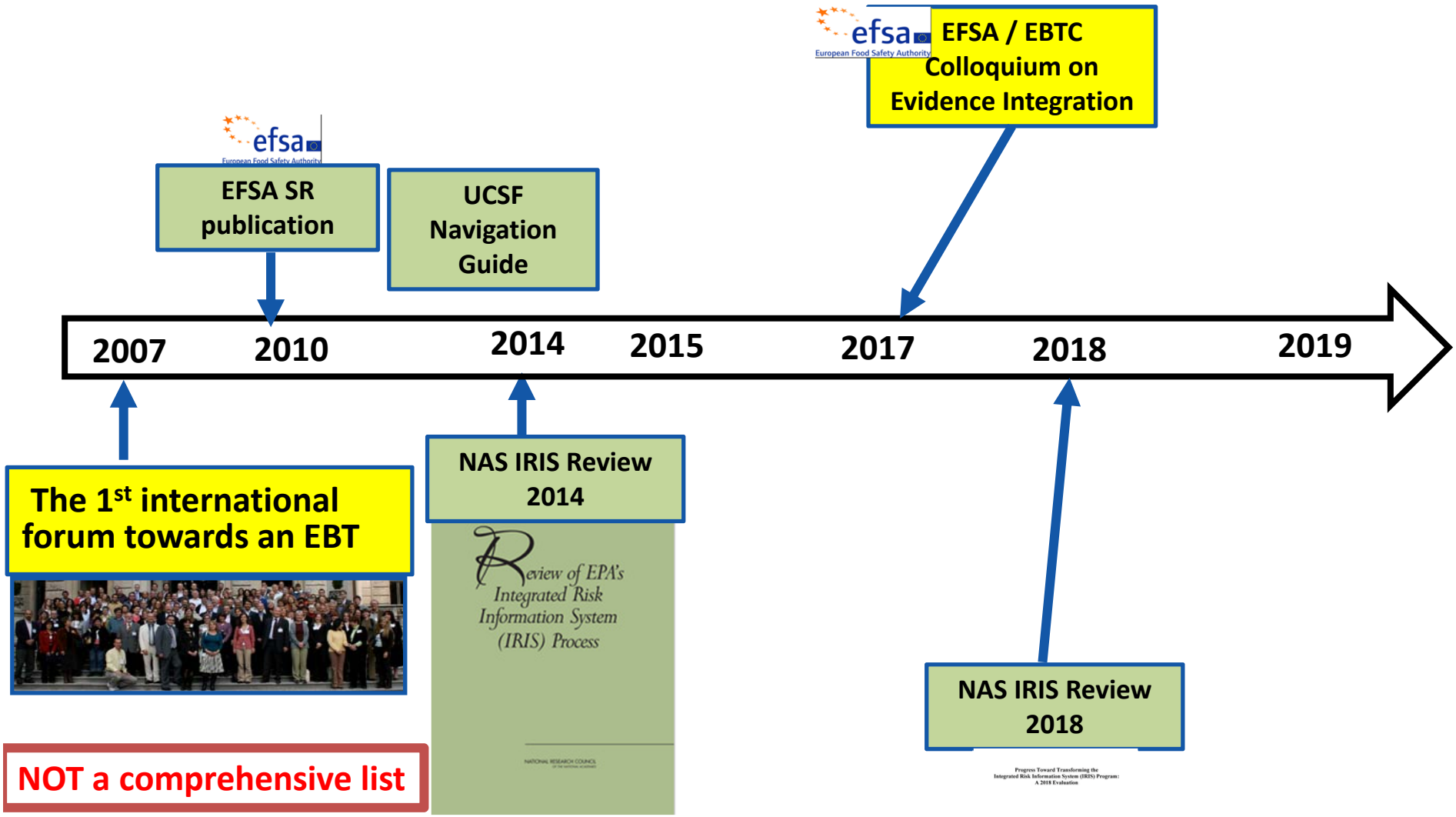

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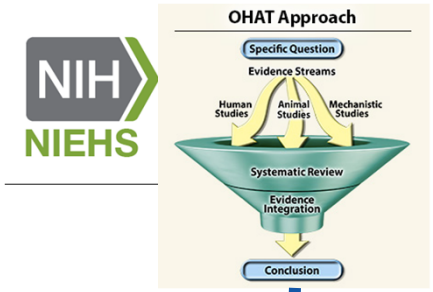

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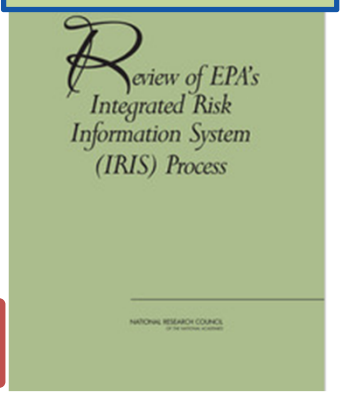

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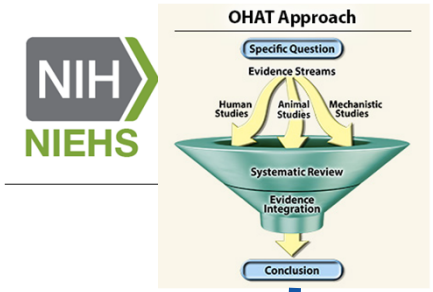

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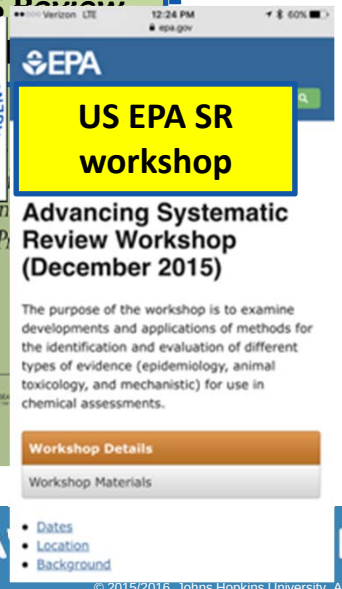
US EPA SR workshop



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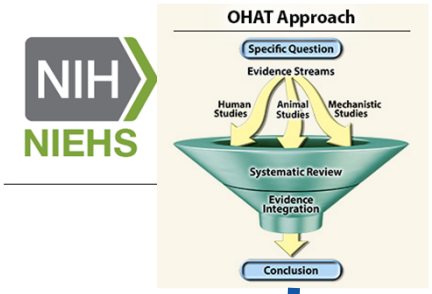

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

EPA

US EPA SR workshop

Advancing Systematic Review Workshop (December 2015)

The purpose of the workshop is to examine developments and applications of methods for the identification and evaluation of different types of evidence (epidemiology, animal toxicology, and mechanistic) for use in chemical assessments.

Workshop Details

Workshop Materials

- Dates
- Location
- Background

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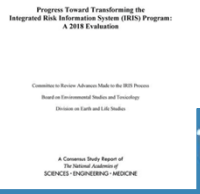

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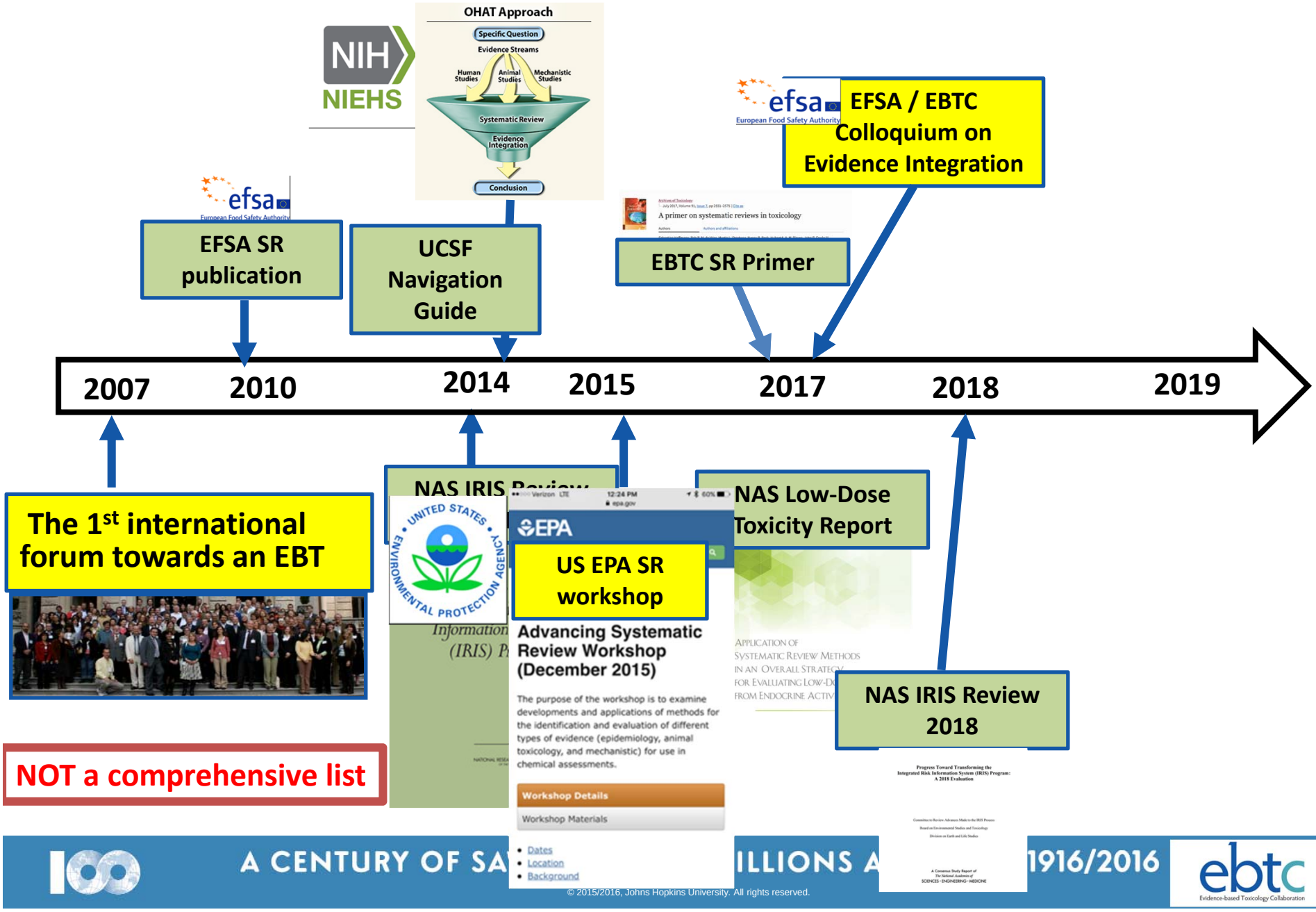

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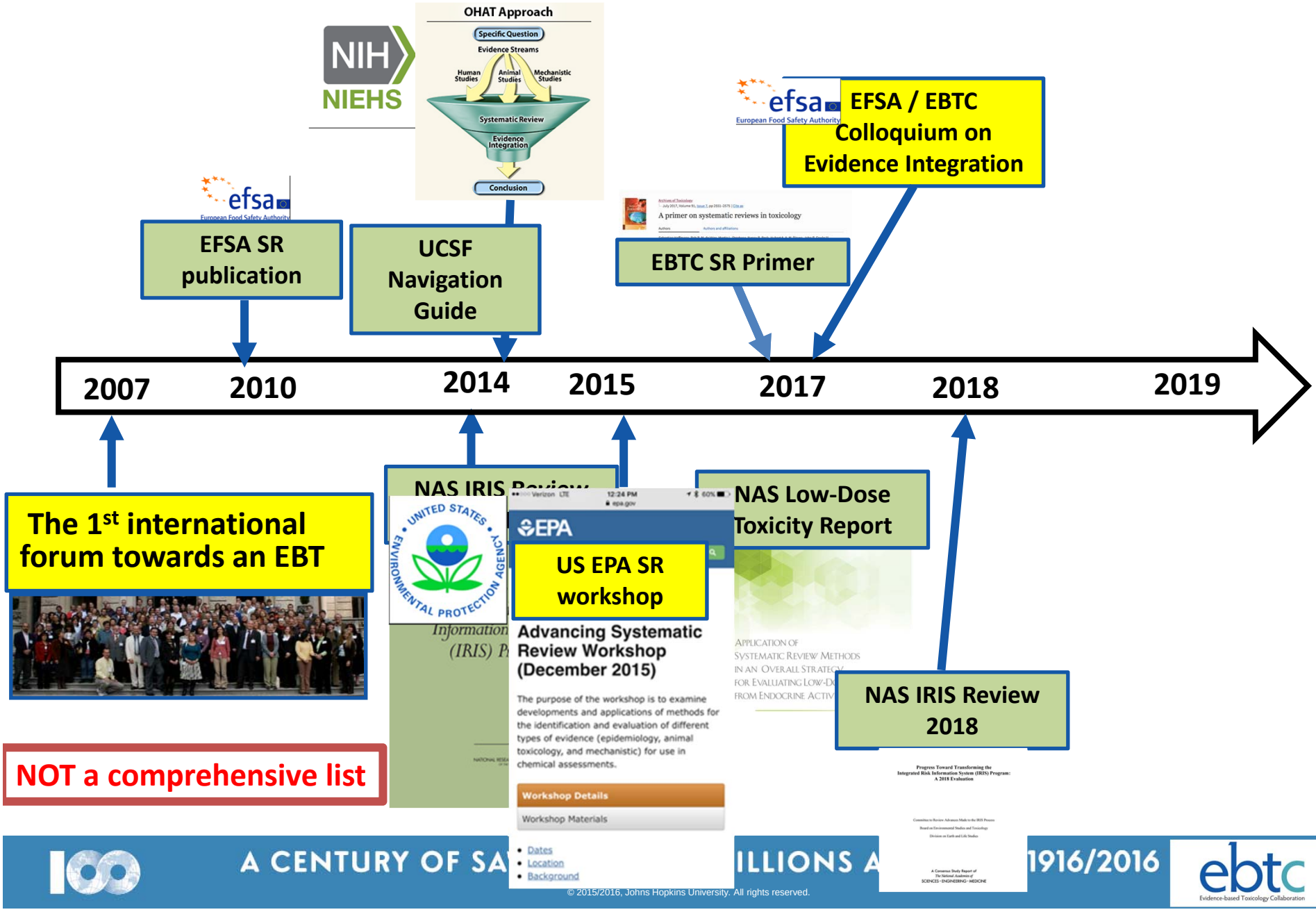

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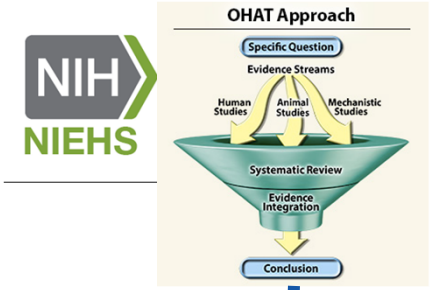

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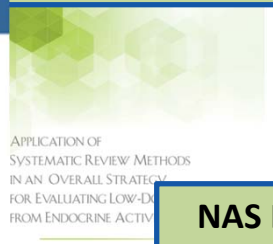
NAS Low-Dose Toxicity Report



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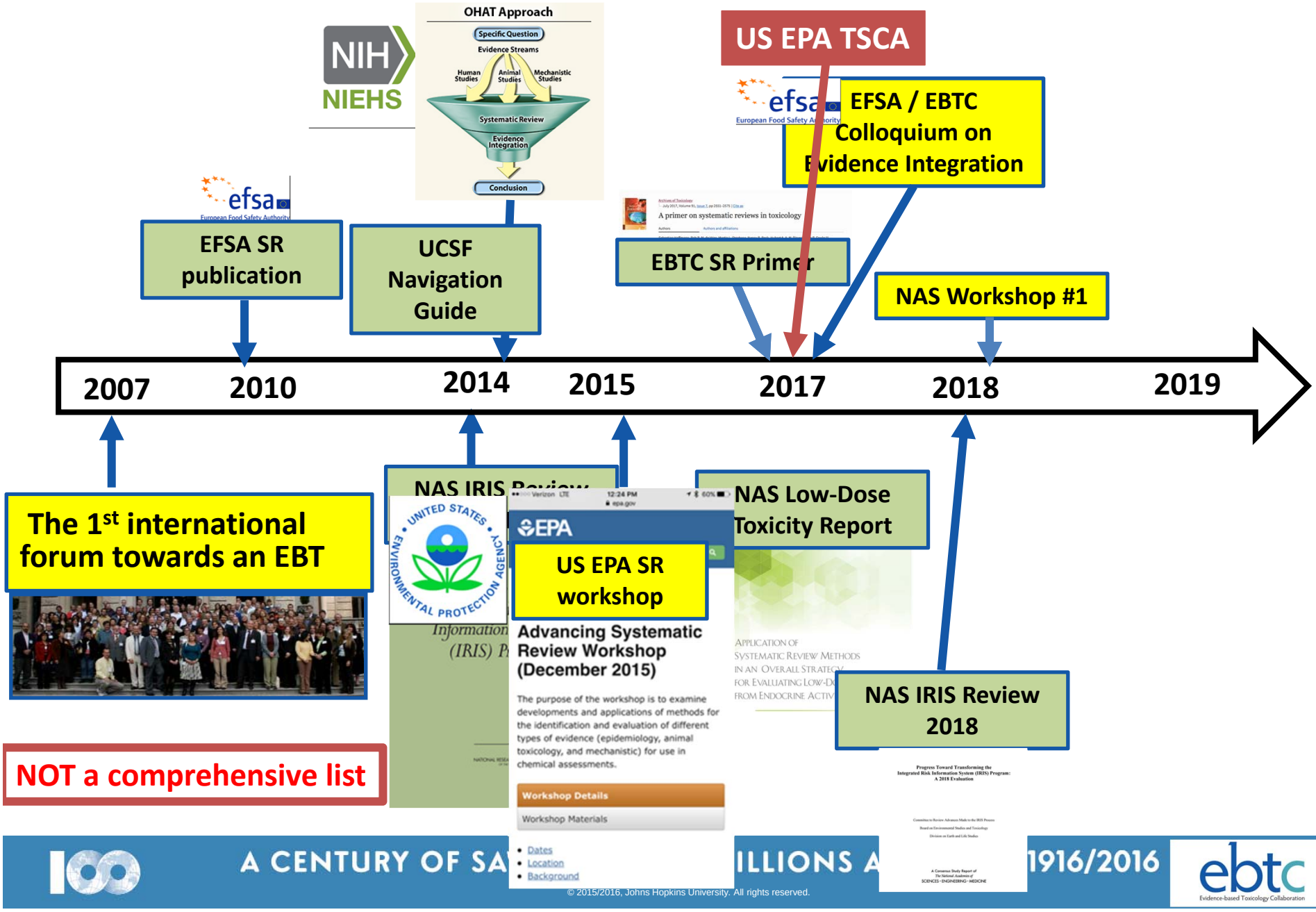

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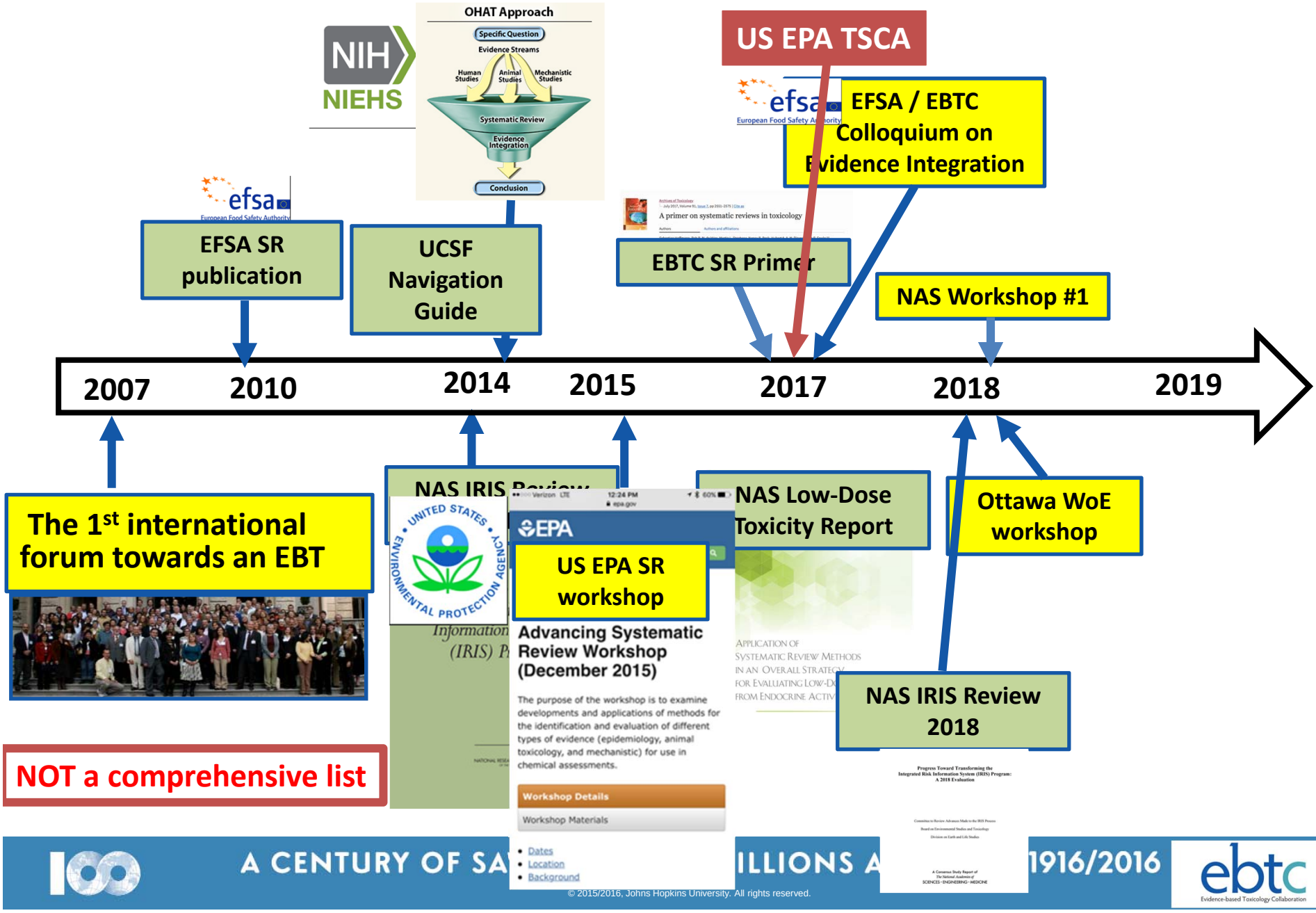

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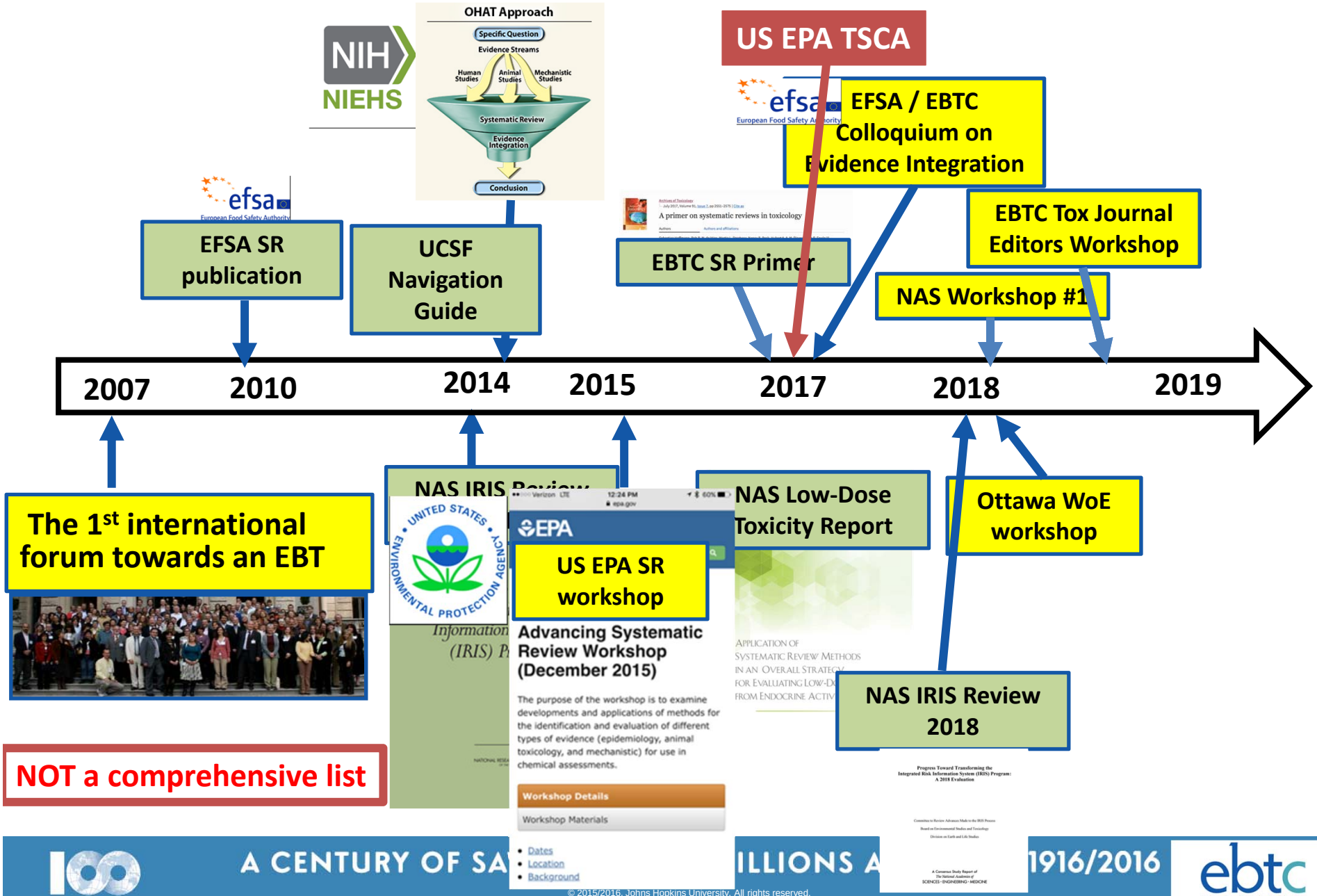

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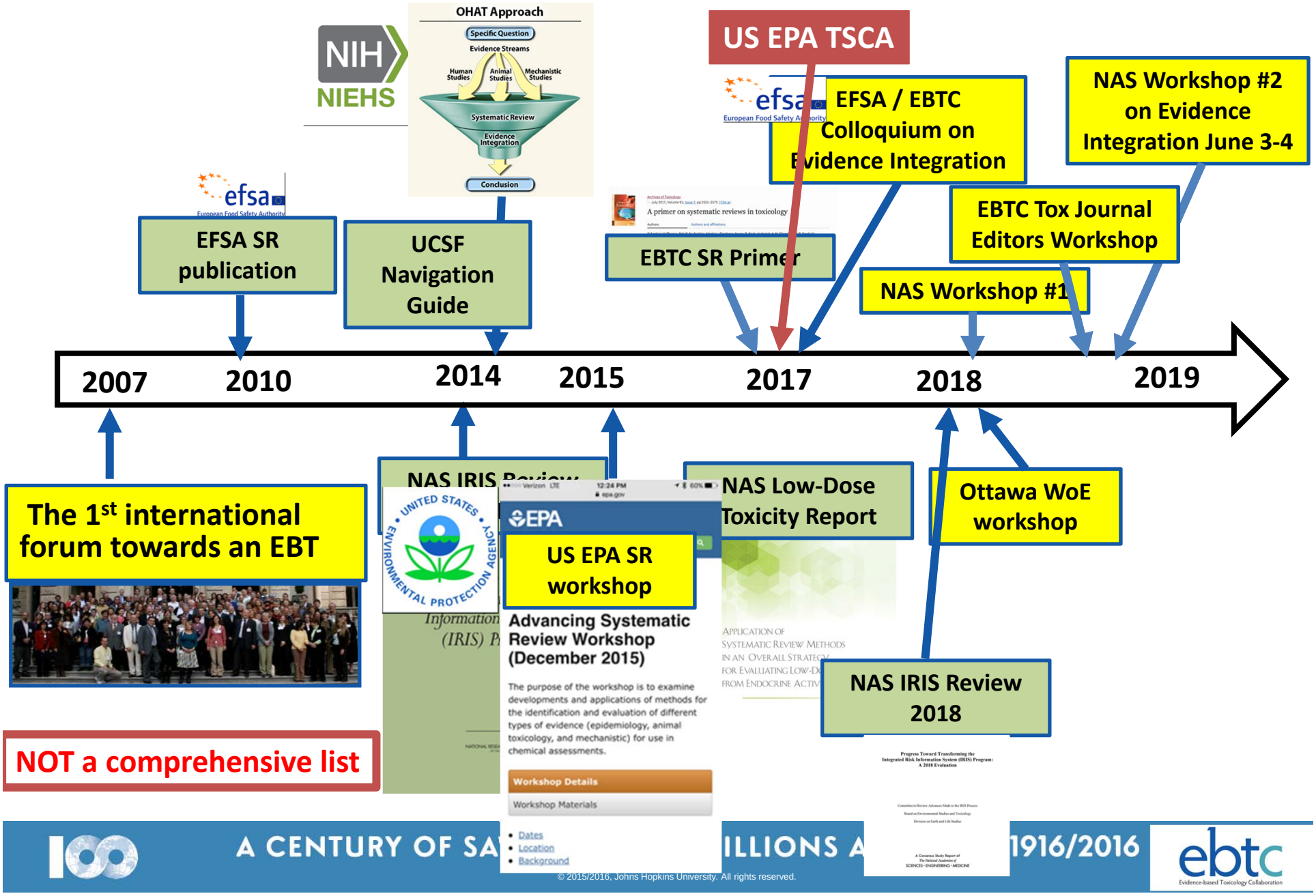

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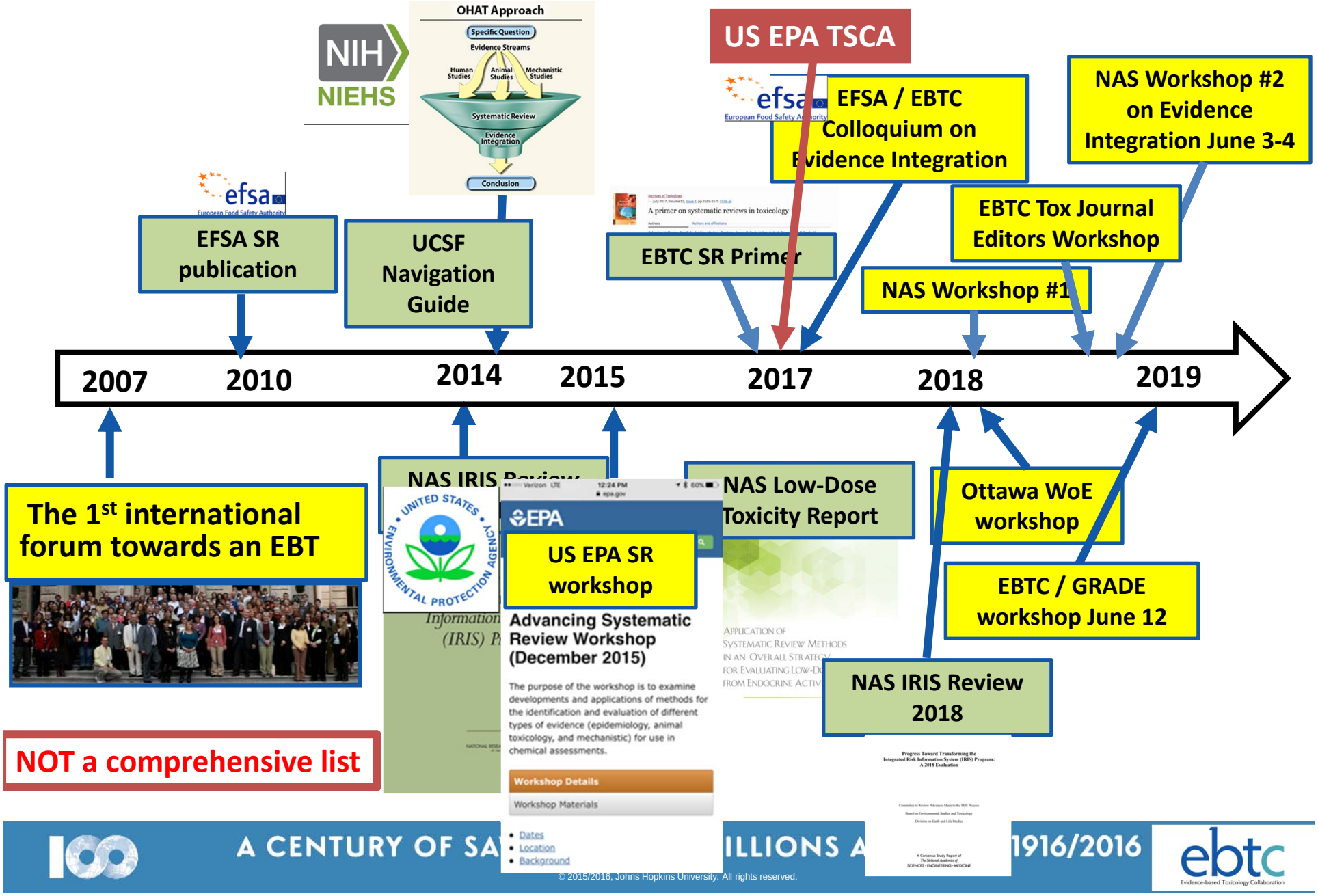

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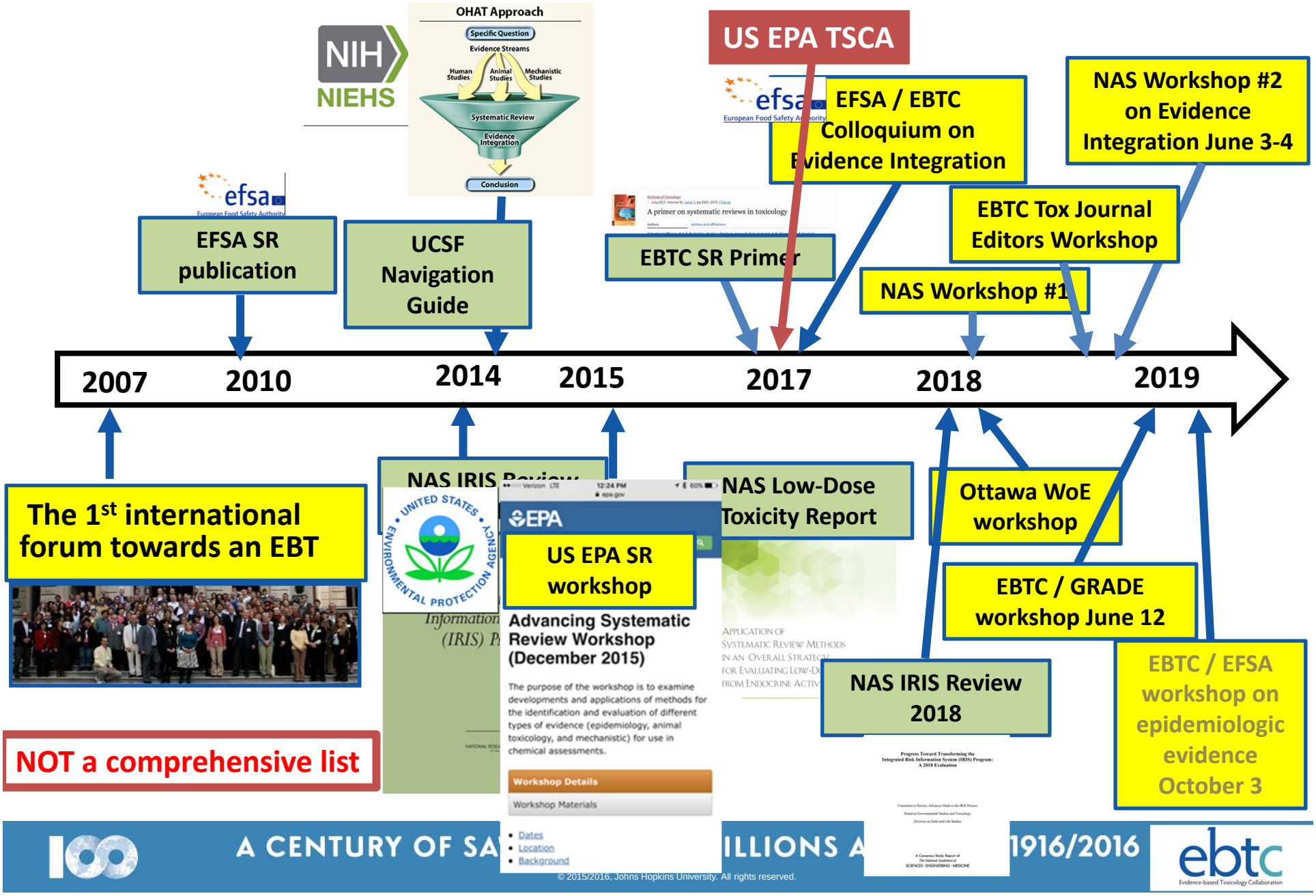
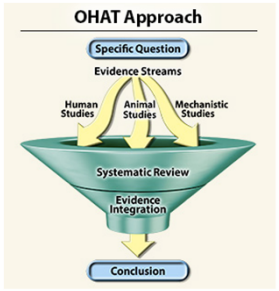


SR in risk assessment is driven by the agencies' needs and international collaborations



US EPA TSCA

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NAS Workshop #2 on Evidence Integration

EFSA SR publication

NAS Workshop #1

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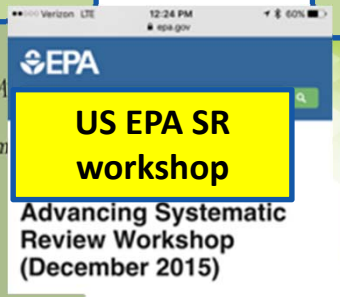

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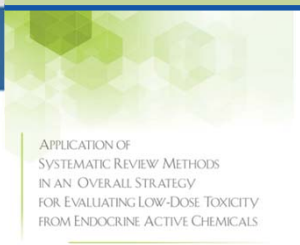

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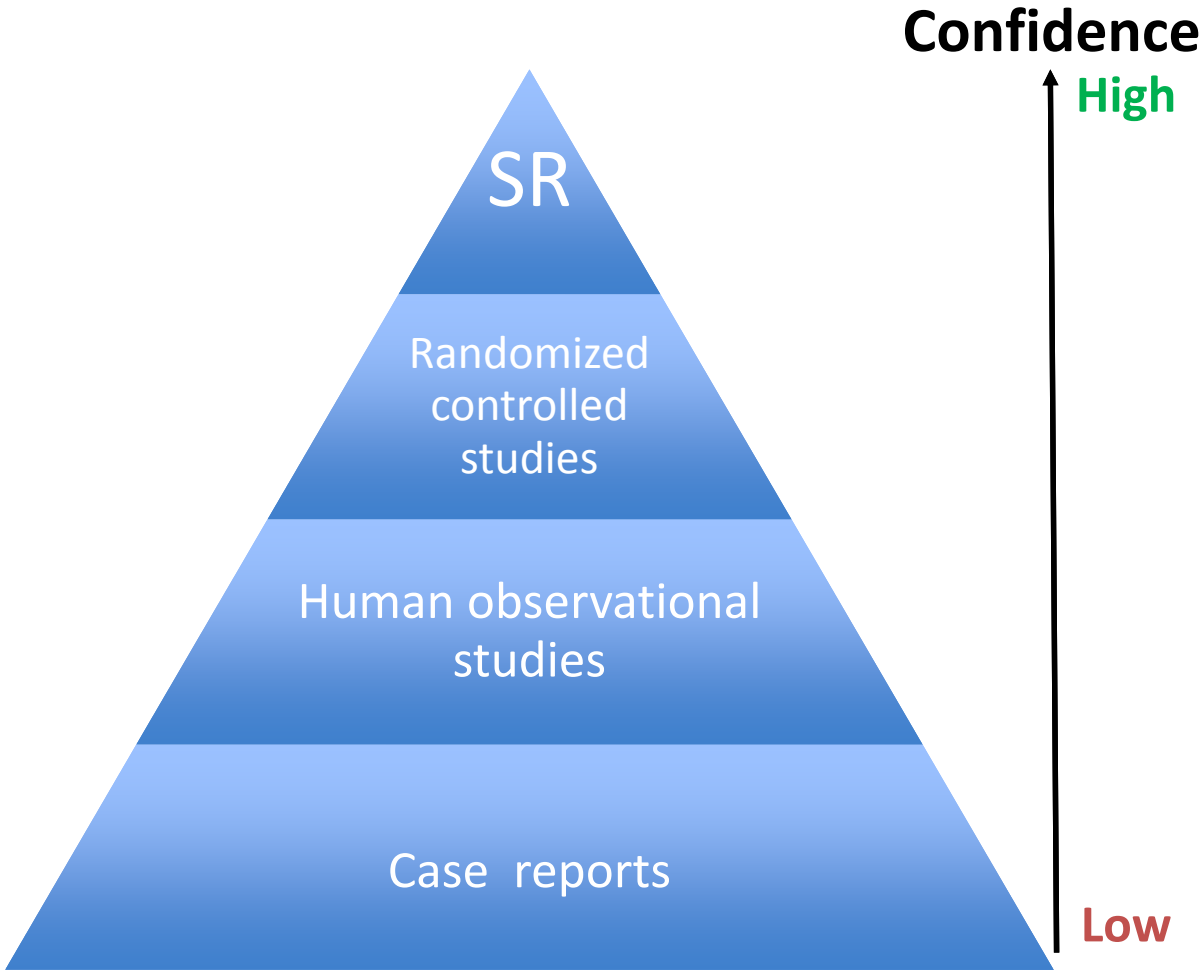
Systematic reviews are the highest level of evidence in healthcare



Various but well-defined study designs (mainly RCTs, with some cohort, case-control studies)

Single species: human

Toxicology – a unique challenge or just a new field of SR application?

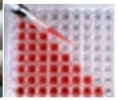
SR → **New**

Randomized controlled studies

→ **Rarely possible**

Epidemiological / observational studies → **Various designs**

Legacy animal, and new (*In vitro, In silico*)



→ **Heterogeneous populations, designs, new science**

Toxicology – a unique challenge or just a new field of SR application?

SR → **New**

Randomized controlled studies

→ **Rarely possible**

Epidemiological / observational studies → **Various designs**

Need tools tailored to these types of evidence and their integration in risk assessments

Evidence integration framework in SR

Evidence integration is evidence into streams of:

- Different populations of patients
  - In clinical medicine: different patient populations
  - in toxicology context: different species
- Different types of studies
  - In clinical medicine: RCTs, observational studies
  - In toxicology: Epidemiological, animal, *in vitro, in silico*

The goal:

Summarize the effect in each stream

The process:

- Certainty of the evidence for the effect is assessed for each stream
- Integration is a function of combined certainty across each stream, generating a judgement of the overall level of confidence in the evidence

Adapted from Paul Whaley

Challenges in evidence integration

- **Within an evidence stream:**
  - study design
  - Risk of bias (internal validity)
  - consistency of the outcome measure

- **Across evidence streams:**
  - Study design
  - External validity (aka directness, applicability, generalizability, consistency)
  - Exposure (in vitro to in vivo extrapolation, in silico predictions)
  - Human relevance, species concordance

Photo credit: Telegraph.co.uk

Adapted from Laura Martino, EFSA

Integrating mechanistic information in SRs

Mode-of-action (MoA) or adverse outcome pathways (AOP) knowledge is now available.

Examples:

- OHAT framework: mechanistic data can inform changes to the level of evidence
- 2019 update to the IARC preamble: mechanistic evidence is a distinct stream in its own right

What can be done to systematically incorporate mechanistic evidence into systematic reviews of chemicals' exposures?

Adapted from Paul Whaley

Qualitative Approach:

NTP Office of Health Assessment and Translation (OHAT)

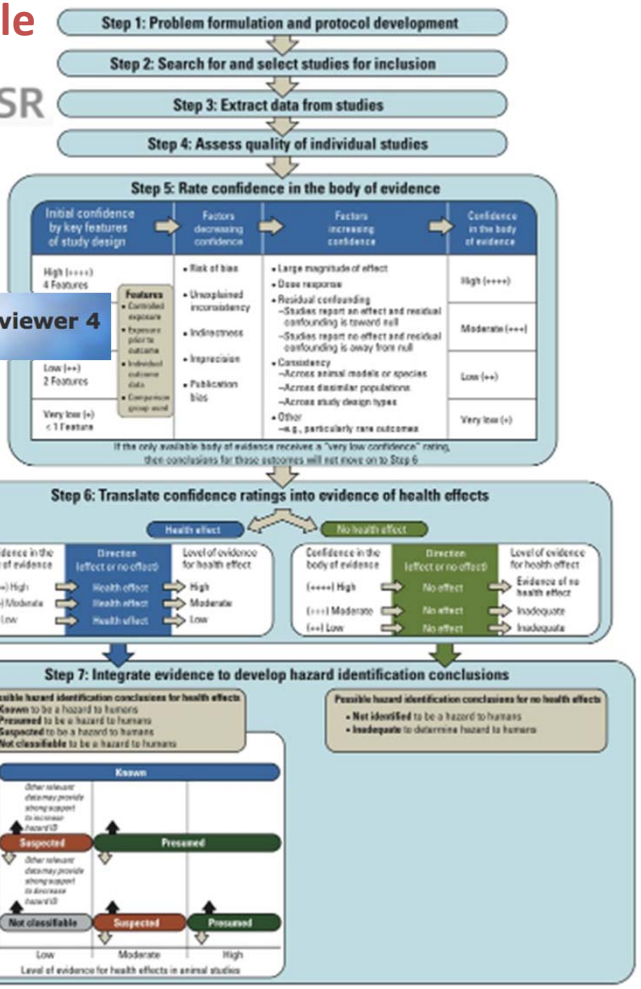
Software tools available

DistillerSR

SciOme

sysrev

EPPI-Reviewer 4



7-step framework for SR and evidence integration

Applications:

- PFOA/PFOS immunotoxicity
- Air pollution and children's health
- Mountaintop removal mining

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

Lisbon - October 2017

EFSA-EBTC Colloquium on

Evidence integration in risk assessment: the science of combining apples and oranges

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2018.EN-1396

EVENT REPORT

APPROVED: 8 March 2018

doi:10.2903/sp.efsa.2018.EN-1396

EFSA Scientific Colloquium 23 –
Joint European Food Safety Authority and
Evidence-Based Toxicology Collaboration Colloquium

Evidence integration in risk assessment: the science of combining apples and oranges

25–26 October 2017
Lisbon, Portugal

European Food Safety Authority

EFSA / EBTC Colloquium Goals

- Build on EFSA's pioneering experience in SR
- Bring together international stakeholders to discuss the state-of-the-art and challenges in evidence integration in risk assessment in:
    - Healthcare
    - Food safety
    - Environmental health
    - Occupational health
- Learn from each other

Lisbon Colloquium Structure

HI: hazard identification
HC: hazard characterisation
DG: discussion group

Welcome & objectives

Intro to HI
Lecture 1: Introduction to evidence integration for HI: overview of qualitative and quantitative methods and challenges

Intro to HC
Lecture 5: Introduction to dose-response modelling to derive health-based guidance values: current practice and challenges

Lecture 2: Integrating evidence within and across evidence streams using qualitative methods

Lecture 3: Recent developments for combining evidence within evidence streams: bias-adjusted meta-analysis

Lecture 4: Quantitative approaches to combining evidence across evidence streams

Lecture 2: Combining evidence on multiple endpoints in dose-response assessments: multivariate models

Lecture 7: Lecture Other quantitative methods for combining multiple studies and endpoints




Author: Laura Martino, EFSA

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DG1
Qualitative methods for integrating evidence within- and across evidence streams for HI

DG2
Bias-adjusted meta-analysis

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Lecture 2: Combining evidence on multiple endpoints in dose-response assessments: multivariate models

Lecture 7: Lecture Other quantitative methods for combining multiple studies and endpoints




Author: Laura Martino, EFSA

Lisbon Colloquium Structure

HI: hazard identification
HC: hazard characterisation
DG: discussion group

Welcome & objectives

Intro to HI
Lecture 1: Introduction to evidence integration for HI: overview of qualitative and quantitative methods and challenges

Intro to HC
Lecture 5: Introduction to dose-response modelling to derive health-based guidance values: current practice and challenges

DG1 Qualitative methods for integrating evidence within- and across evidence streams for HI

DG2 Bias-adjusted meta-analysis

DG3 Quantitative approaches to combining evidence across evidence streams for HI

Lecture 2: Combining evidence on multiple endpoints in dose-response assessments: multivariate models

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DG1
Qualitative methods for integrating evidence within- and across evidence streams for HI

DG2
Bias-adjusted meta-analysis

DG3
Quantitative approaches to combining evidence across evidence streams for HI

DG4
Using multiple endpoints and multiple studies for dose-response modelling: quantitative approaches




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Lisbon Colloquium Conclusions – current state-of-the art in evidence integration

<u>Qualitative</u> methods currently used or being actively adapted:

- GRADE (more guidance is needed, e.g., GRADE workshop on *in silico* computational models)
- OHAT NTP framework

<u>Quantitative</u> methods (i.e., bias-adjusted meta-analysis) **promise:**

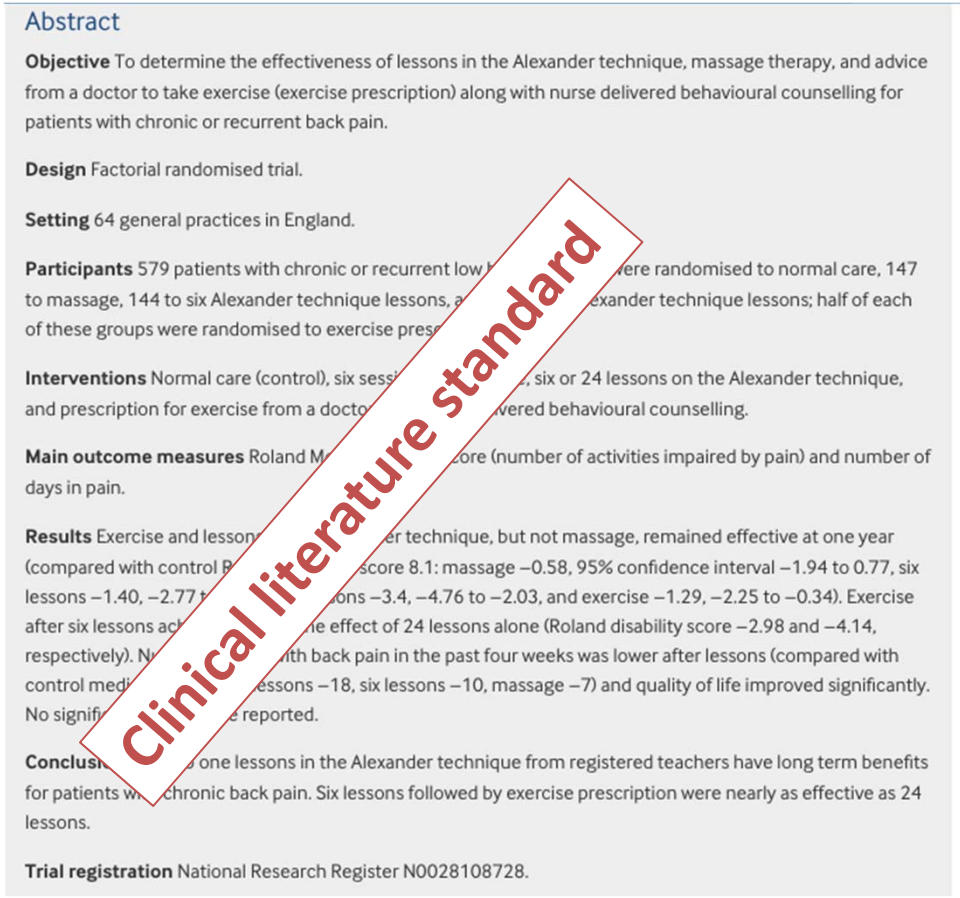
- Reduce subjectivity
- Identify sources of uncertainty and variability
    - **Purported drawbacks:** complexity, lengthy explanation may be necessary

Comment: all new approaches go through this period of adaptation

Lisbon Colloquium Identified Barriers

- **Published literature limitations:**
  - More data (*in vivo*, *in vitro*, computational, regulatory, individual animal / experiment data) is needed
  - Structured abstracts in published literature
- **Experimental design improvements:**
  - Appropriate design (e.g., power calculations) to address research questions
- Need for a distinct separation of assessment of study quality and reporting of study quality
- Need for operationalizing the concept of biological plausibility
- Need for a sustainable common open data depository

Lisbon Colloquium Identified Barriers



Abstract

Objective To determine the effectiveness of lessons in the Alexander technique, massage therapy, and advice from a doctor to take exercise (exercise prescription) along with nurse delivered behavioural counselling for patients with chronic or recurrent back pain.

Design Factorial randomised trial.

Setting 64 general practices in England.

Participants 579 patients with chronic or recurrent low … were randomised to normal care, 147 to massage, 144 to six Alexander technique lessons, a… exander technique lessons; half of each of these groups were randomised to exercise pres…

Interventions Normal care (control), six sess…, six or 24 lessons on the Alexander technique, and prescription for exercise from a docto… vered behavioural counselling.

Main outcome measures Roland M… core (number of activities impaired by pain) and number of days in pain.

Results Exercise and lesson… er technique, but not massage, remained effective at one year (compared with control R… score 8.1: massage −0.58, 95% confidence interval −1.94 to 0.77, six lessons −1.40, −2.77 t… ons −3.4, −4.76 to −2.03, and exercise −1.29, −2.25 to −0.34). Exercise after six lessons ac… e effect of 24 lessons alone (Roland disability score −2.98 and −4.14, respectively). N… ith back pain in the past four weeks was lower after lessons (compared with control medi… essons −18, six lessons −10, massage −7) and quality of life improved significantly. No signifi… reported.

Conclusi… one lessons in the Alexander technique from registered teachers have long term benefits for patients w… chronic back pain. Six lessons followed by exercise prescription were nearly as effective as 24 lessons.

Trial registration National Research Register N0028108728.

Clinical literature standard

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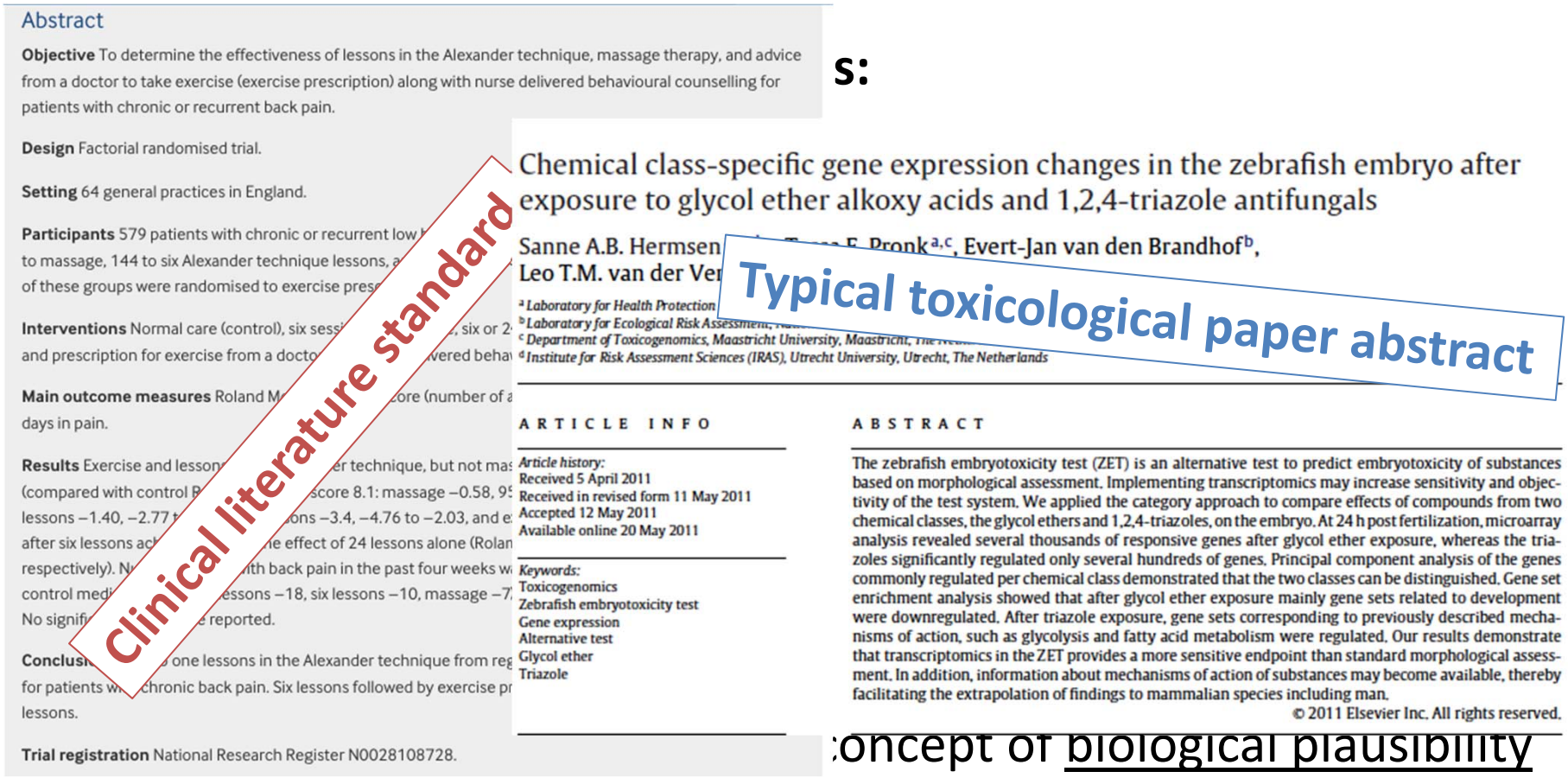

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Typical toxicological paper abstract

Chemical class-specific gene expression changes in the zebrafish embryo after exposure to glycol ether alkoxy acids and 1,2,4-triazole antifungals

Sanne A.B. Hermsen , Evert-Jan van den Brandhof[b], Leo T.M. van der Ver

[a] Laboratory for Health Protection
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[c] Department of Toxicogenomics, Maastricht University, Maastricht,
[d] Institute for Risk Assessment Sciences (IRAS), Utrecht University, Utrecht, The Netherlands

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Triazole

ABSTRACT

The zebrafish embryotoxicity test (ZET) is an alternative test to predict embryotoxicity of substances based on morphological assessment. Implementing transcriptomics may increase sensitivity and objectivity of the test system. We applied the category approach to compare effects of compounds from two chemical classes, the glycol ethers and 1,2,4-triazoles, on the embryo. At 24 h post fertilization, microarray analysis revealed several thousands of responsive genes after glycol ether exposure, whereas the triazoles significantly regulated only several hundreds of genes. Principal component analysis of the genes commonly regulated per chemical class demonstrated that the two classes can be distinguished. Gene set enrichment analysis showed that after glycol ether exposure mainly gene sets related to development were downregulated. After triazole exposure, gene sets corresponding to previously described mechanisms of action, such as glycolysis and fatty acid metabolism were regulated. Our results demonstrate that transcriptomics in the ZET provides a more sensitive endpoint than standard morphological assessment. In addition, information about mechanisms of action of substances may become available, thereby facilitating the extrapolation of findings to mammalian species including man.

s:

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- Need for a sustainable common open data depository

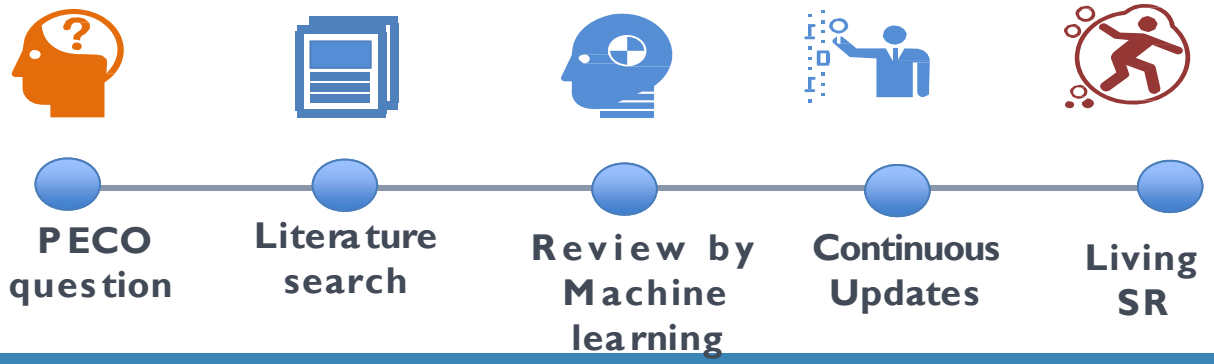
Lisbon Colloquium Conclusions – future directions

- Continue adaptation and validation of GRADE and NTP OHAT methodologies to hazard identification and risk assessment
- Continue developing quantitative methods such as bias-adjusted meta-analysis and build more use cases
- Consider developing a (GRADE-based) framework for ascertaining biological plausibility

Lisbon Colloquium Conclusions – future directions 2

- Work is best progressed led by a community of knowledge of toxicologists, epidemiologists, regulators and statisticians
- This community is collaboratively developing, testing & harmonizing new tools
- This community should also promote training opportunities on the various methods and regular exchange through scientific conferences and workshops.

Future: AI-powered living SR:



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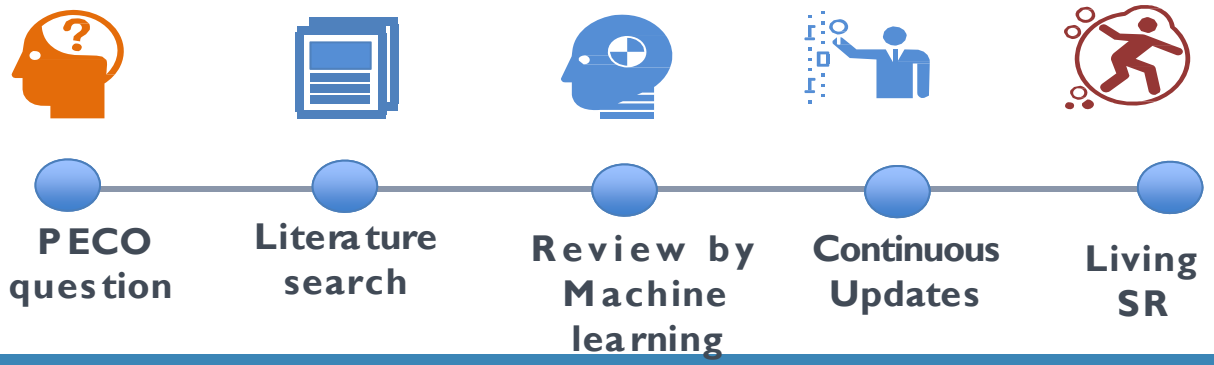


Ottawa Expert Workshop

Agenda:

Session 1: Recent Advances in Risk Science Including New Approach Methodologies in Weight of Evidence Evaluation (Chair: T. Hartung)

Session2: Summarizing the Evidence (Chair: Jeff Lewis, ExxonMobil)

Session 3: Qualitative Data Synthesis (Chair: Kris Thayer, US EPA)

Session 4: Quantitative Data Synthesis (Chair: Greg Paoli, Risk Sciences International)

Steering Committee:

Tara Barton-Maclaren, Health Canada;

Thomas Hartung, Johns Hopkins;

Daniel Krewski, University of Ottawa;

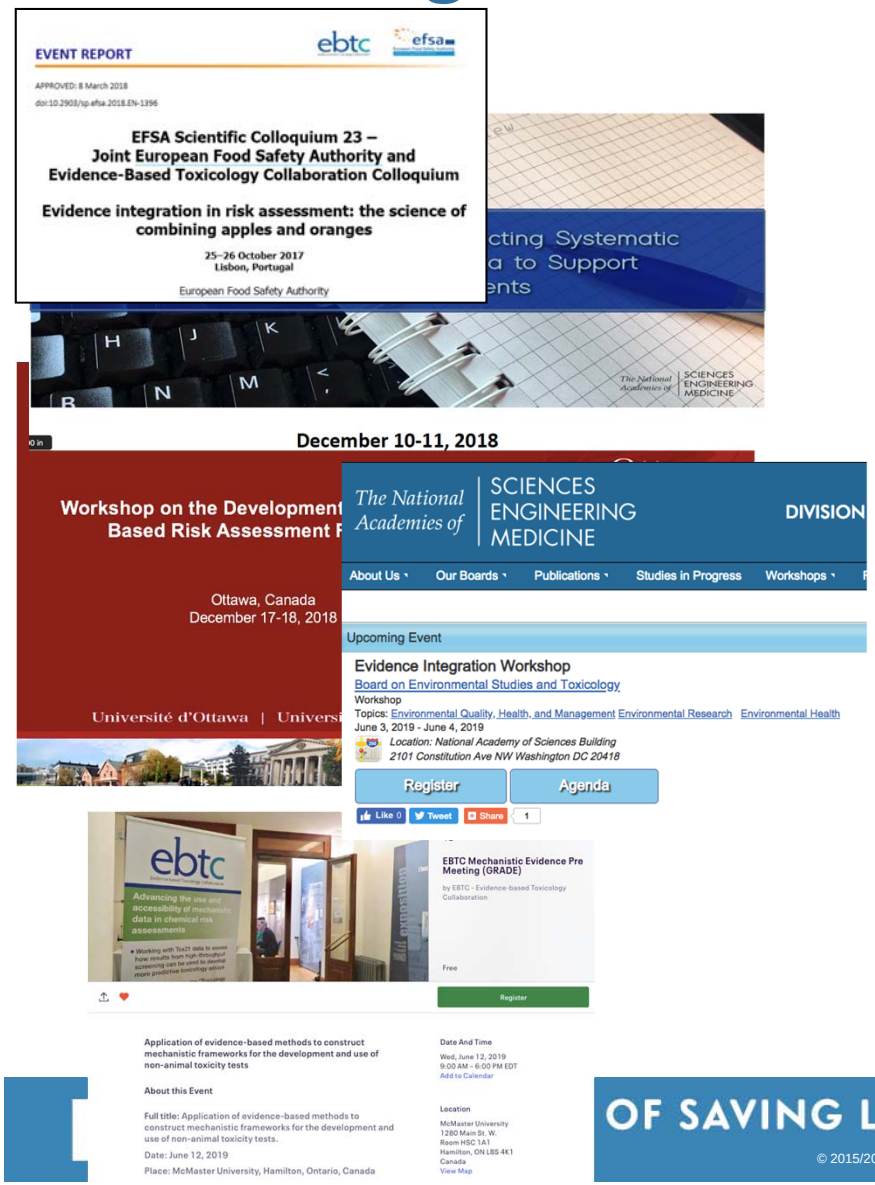
Kristina Thayer, US EPA;

Jeff Lewis, Exxon Mobil Biomedical Research.

Output: Workshop report to be published in ALTEX

Follow-up: Another meeting is planned for Fall 2019 TBD

Building the momentum and the community of knowledge



Closing remarks:

- The foundation of SR in healthcare is laid down by Cochrane
- Fit-for-purpose adaptation of tools is led by international government agencies (EFSA, NTP OHAT, US EPA)
- Interdisciplinary community of knowledge is already active, building momentum following Cochrane example
- Immediate tasks of the community are to harmonize the terminology and validate new tools
- The community could convene a regular yearly (?) science forum with series of webinars / projects during the year
- This community should also develop methodology and practical training opportunities for all stakeholders

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CAAT

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US EPA:

Kris Thayer

Michelle Angrish

Tox Strategies:

Daniele Wikoff

Questions?

Thank You!

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