Embracing Rigor and Reproducibility in Scientific Research

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Part 1: The Importance of Rigor and Reproducibility in Research

Robert E Chapin, PhD
NIEHS, then Pfizer, now retired
In 2010, Florian Prinz and some others performed an internal review of projects in Discovery at the pharma company Bayer Healthcare in Germany. They asked: How often can we effectively replicate the major findings of a key scientific paper?

The answer: only about 1/3\textsuperscript{rd} of the time. For fully 2/3rds of all projects, there were inconsistencies which either prolonged or delayed the project, or killed it entirely. Put another way: they can trust published results less than half the time.

Many authors and papers have since confirmed similar experiences as Prinz. I had several similar experiences at NIEHS, and then many at Pfizer, where the results from academic papers, especially from high-impact journals, could not be replicated. (and sometimes our own work could not be replicated in our own lab 😞😢)

This is an existential threat to the scientific enterprise. If we cannot believe published results, then 1) why bother? and 2) why fund it?
Oh, wait...the literature doesn’t even agree on what these mean. I like the definitions provided by Hans Plesser, although others will switch the definitions for Replicability and Reproducibility.

**Repeatability** (Same team, same experimental setup): The measurement can be obtained with stated precision by the same team using the same measurement procedure, the same measuring system, under the same operating conditions, in the same location on multiple trials. For computational experiments, this means that a researcher can reliably repeat her own computation.

**Replicability** (Different team, same experimental setup): The measurement can be obtained with stated precision by a different team using the same measurement procedure, the same measuring system, under the same operating conditions, in the same or a different location on multiple trials. For computational experiments, this means that an independent group can obtain the same result using the author’s own artifacts.
Reproducibility (Different team, different experimental setup): The measurement can be obtained with stated precision by a different team, a different measuring system, in a different location on multiple trials. For computational experiments, this means that an independent group can obtain the same result using artifacts which they develop completely independently.

But also see: S.N. Goodman, D., Fanelli, and John P.A. Ioannidis (2016) What does research reproducibility mean? Science Translational Medicine 8(341) ps12
First described in the 1930’s and most recently re-emphasized by Jonathan Schooler at UCSB, this effect says that many published scientific effects seem to diminish with time and number of replicates. (Nature 470:437, 2011). The differences between treated and control groups diminish with time.

Schooler believes that this would be reduced if all data were published, including negative findings.

John Ioannidis has claimed that “Most research findings are false” (PLoS Medicine 2(8): e124, 2005), and then “proved” that very assertion in that article.
1. **Most importantly:** A refusal to acknowledge the scope of the problem by most established scientists. (~climate change denial)
2. → Small n
3. → Insufficient experimental replication
4. The desperate drive to get papers in the “right” journals for institutional and reputational retention.
5. Poor experimental design for the question(s) being asked
6. Poor or inappropriate statistics
7. Lack of blinding during analysis
8. Small effect sizes
9. More tested relationships (hypothesis fishing) and
10. Selective outcome reporting
11. No pre-specification of a relationship to test
12. Reduced replicability is more likely when there is greater flexibility in designs or outcomes

**Probably many causes/contributors:**
We would be remiss if we did not mention the skewed incentive system in science, which, despite many Op-Eds and much public hand-wringing, remains heavily tied to publication of surprising findings in prestigious journals. Funding review panels expect applicants to correctly predict what will happen in their experiments, but even more than that, they love high-impact good surprises. Surprises are more likely to happen when one employs several characteristics from the preceding slide.

This is also closely tied to the idea of a “beefy” CV proving your value as a scientist.

And need we mention the drive of the institutional “publish or perish” mindset?
The need for a strong CV is greatest early in your career, so trainees are most susceptible to all these pressures, and are least in a position to resist them. Trainees have little ability to impact the behavior or strategy of the more established scientists in the lab. Still, the most durable change often comes from the bottom, and if trainees demand methods to combat this problem, their mentors and deans will (eventually....we hope...maybe....) follow.

Additionally, trainees could demand more “air time” at meetings about this, and help pressure SOT to detail how the Society will address the issue, or could volunteer to lead sessions on this problem and how other Societies are addressing it.
One way to guard against this is to solicit a lab working in the same or similar field to replicate your experiment, with the proviso that they become co-authors on the resulting paper. Note that this assumes effective replication, which is a win-lose experiment, and if it doesn’t replicate, you know there will likely be some ticked-off PI’s. This is an imperfect solution, and I’m hoping you can collectively come up with something better.
Part 2: Experimental Design to Ensure Rigor and Reproducibility

G. Jean Harry, PhD
National Institute of Environmental Health Sciences
Why perform experiments?

- To evaluate hypothesis
- To indulge investigator’s curiosity
- To try out a new method or technique
- To establish the existence of a new phenomenon
- To explore the conditions under which a phenomenon occurs

All are valid reasons to perform experiments but all should be designed in such a way to provided information to the field of study and be interpreted within the specific framework.
Before you begin your research

- Establish a clear understanding of the research questions and objectives
- Ensure that you have a very good understanding of relevant literature
- Establish a conviction of what kinds of data are most needed
- What is the scientific rationale for initiating the study?
- What is the hypothesis that you are testing?
- Do the experiments conducted address this hypothesis?
- Will your findings be relevant and advance the field?
- If you have null findings would they also be meaningful?
- Get early feedback on concepts, approach, experimental design, statistical analysis, data interpretation
- Ensure you are using valid methods
The overall study needs to be set within a framework that identifies
- the importance of the question being asked
- the appropriateness of the experiments
- how the data advances our understanding
- how to move forward

The science (data) does not stand alone
Consult with a biostatistician
Statistics cannot save a bad experimental design!

• Clearly establish what comparisons you want to be able to make
• Outline what you consider to be “experiment controls”
• Identify assay controls that would not be included in the statistical analysis of the experimental effect
• Have pilot data or information in hand to show control variability and robustness of the endpoint
Hypothesis development

• Do your homework and know the status of the research in the area

• As you identify the critical publications that set the basis for your research ideas – do not totally rely on those data
  • Outline pilot studies to determine if you can replicate those findings critical to your study. Remember pilot studies should be designed with the same care as any study.
  • In designing pilot studies, you will need to critically review the methods of the published study and likely find it lacking in important details. Do not hesitate to contact the authors if this is important to your study.
Hypothesis development

• Clearly identify the overall hypothesis
  This can be rather general but realistic as to what can be accomplished

• Develop the specific aims to address the hypothesis
  These should represent the goals that you hope to achieve with the
  experiments thus, they are more focused and specific than the overall
  hypothesis and set the framework for the experiments

• Outline the experiments – ensure that they address the specific aims

As your experiments progress, this will become a reiterative process
  with modifications and adjustments along the way
Once you have your hypothesis and specific aims you now need to work out the model system you will employ. This requires careful consideration:

1. What is the scientific basis for selection of model system?
2. Is this an established model system in the literature?
3. How difficult is the model system?
4. What is the reproducibility of the model system? (e.g., what is the variability of the endpoint of interest)
5. How robust is the endpoint under study?
6. Is it relevant to your overall hypothesis?
For any experiment, the goal of the experimenter is to obtain data that can be interpreted in a manner to address the specific aims of the research. To achieve, this as many variables as possible that could undermine the interpretation of an experimental effect should be placed under experiment control.
The chief antagonist of statistical reliability is “Chance”

“Chance” may refer to the combined effects of uncontrolled variables. If such variables are controllable then chance is a simple excuse for sloppy experimentation.

If the uncontrolled variables are actually unknown then “chance” relates to “ignorance” and science attempts to unmask ignorance. Statistics are used to evaluate the degree of that ignorance.
Controls to consider

1. Model Controls
2. Assay Controls
3. Experimental Controls

Examples:
- Background controls for genetically modified animals or cells
- Identical sham controls that recapitulate exactly the experimental conditions
- Identical vehicle controls for any dosing conditions
- Age and sex matched controls
- Assay positive and negative controls

Always concurrent controls and any experimental conditions being compared
How to “control” for things you cannot control

1. Randomization where appropriate (random assign, random select)
2. Maintain “experimental design” across all assays
3. Replicate findings
4. Value of experimental biological replicates not technical replicates
The overall goal of any data analysis is not only to determine an effect but also to determine the generality of the data.

How representative are the data?
To how many samples/subjects do they apply?

In this regard, examining only the mean +/- SD (SEM), regardless of the sample size, will not provide this information. Rather, identifying the distribution and the % of the sample that falls around the mean will provide information on the generality of the data.
The **Experimental Design** defines:

- How you can analyze the data
- What questions you can ask with your data
- Helps to determine the n size needed and the approach to obtaining that n size and replicates

If you do not establish a good experimental design you will waste your efforts as you will not be able to address your questions and in the worst case – no questions. Experimental design does not mean elaborate or costly study – but a study for which you can analyze your data.
What to analyze

Discuss your project with a biostatistician prior to experiments

Multiple endpoints may be collected but not all may be relevant to the hypothesis

While assay controls are essential for QA they are not appropriate to include in the experimental analysis

Report null as well as positive effects as they apply to the hypothesis
Reproduce your findings

Your scientific reputation is on the line

Remember that all authors are responsible for the accuracy of the data reported.

How to reproduce –
Direct reproduction of critical data
Systematic replication – rather than simply repeating the experiment, use the collected data as a basis for performing new experiments for additional related data e.g. if this then that; if this then not that
Report your findings

Report methods in sufficient details to allow someone else to repeat your experiments.

Report all data – direct experimental data with supplementary material for any supporting data.

Report statistical details for each analysis showing statistical significance (e.g. ANOVA – F value, degree of freedom, p value)
Be Proud of Your Work!
Part 3:
Challenges Toxicologists Face in the Quest for Scientific Rigor

Alternatively, “How Systematic Review is a Platform for Rigor and Reproducibility”

Daniele Wikoff, PhD
ToxStrategies
Evidence Based Toxicology Collaboration
Toxicological Sciences, Regulatory Toxicology and Pharmacology
Challenge: how do we accommodate for rigor and reliability when assessing all available scientific evidence to inform decisions?

(One) Solution = Systematic Review
By definition, a **Systematic Review** is:

- A systematic review attempts to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a specific research question. Researchers conducting systematic reviews use explicit, systematic methods that are selected with a view aimed at minimizing bias, to produce more reliable findings to inform decision making. – Cochrane Colloquium, 2014

- A scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. – IOM, 2011
Benefits of Systematic Review

- Transparency (and reproducibility)
- Rigor
- Reliable and credible (reduce bias)
- *Inherently assess reproducibility*

*Does not fully eliminate subjectivity and scientific judgements*
The Rigor...
Example: IOM - Finding What Works in Health Care – Standards for Systematic Reviews

= 21 Standards and 82 elements of performance
Common Misperception

Systematic Search $\neq$ Systematic Review
# Common Components of SR

<table>
<thead>
<tr>
<th>Phase</th>
<th>Tasks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Problem Formulation</strong></td>
<td>• Scoping, scientific needs/objectives, feasibility</td>
</tr>
<tr>
<td></td>
<td>• Develop PECO question/statement and context</td>
</tr>
<tr>
<td><strong>Protocol Development</strong></td>
<td>• Determine methods for selecting, appraising, and evaluating evidence</td>
</tr>
<tr>
<td></td>
<td>• Document methods (<em>a priori</em>)</td>
</tr>
<tr>
<td><strong>Identify Evidence Base</strong></td>
<td>• Implement search strategy (syntax, databases, etc.)</td>
</tr>
<tr>
<td></td>
<td>• Screen and select studies via inclusion/exclusion criteria</td>
</tr>
<tr>
<td><strong>Individual Study Assessment</strong></td>
<td>• Extract data</td>
</tr>
<tr>
<td></td>
<td>• Conduct critical appraisal for risk of bias (internal validity) and possibly other elements of study quality/relevance</td>
</tr>
<tr>
<td><strong>Body of Evidence Assessment</strong></td>
<td>• Structured synthesis and integration –quantitative or qualitative</td>
</tr>
<tr>
<td></td>
<td>• Considers reproducibility</td>
</tr>
<tr>
<td><strong>Reporting</strong></td>
<td>• Comprehensive documentation of approach, findings, and conclusions in a public forum</td>
</tr>
</tbody>
</table>

Wikoff and Miller, 2018; [https://doi.org/10.1093/toxsci/kfy109](https://doi.org/10.1093/toxsci/kfy109)
Global Use of Systematic Review (By Authoritative Bodies)
Challenge - Transitioning to Evidence-Based Toxicology (from evidence-based medicine)

- Different questions (e.g., comparative effectiveness of an intervention vs. characterization of hazard and risk)
  - PECO vs. PICO
    - Population, Exposure/Intervention, Comparator, Outcome
    - Need flexibility; in toxicology risk assessment, often need more than yes/no

- Different evidence base (i.e., RCTs vs. laboratory animal/observational epi studies)
  - Need tools tailored to these types of evidence
  - Need methods that accommodate highly heterogeneous data
  - Need approaches to answer different questions
Example: Study Quality

Not just relevance - multiple aspects of study validity are important

**OHAT Risk of Bias Rating Tool for Human and Animal Studies**

**Introduction**

This document is written to outline the assessment of whether the design between exposure and outcome (Higgin) of bias rating tool presents a parallel animal studies to facilitate consideration with common forms and categories.

This tool was developed based on the Quality (Dowman et al. 2012) of Interventions (Sherer et al. 2014), McMaster University (2013), and Guidance Guide (Johnson et al. 2013, Woolfolk and Sutton 2010), common risk of bias instructions (Moher et al. 2001, S. Krath et al. 2013, Wells et al. 2014).

For each study, risk of bias is assessed and a study may increase risk of bias for not

**Table G-8: Metric Weighting Factors and Range of Weighted Metric Scores for In Vitro Toxicity Studies**

<table>
<thead>
<tr>
<th>Domain Number/Description</th>
<th>Metric Number/Description</th>
<th>Metric Score</th>
<th>Metric Weighting Factor</th>
<th>Weighted Score</th>
<th>Rationale (Table G-14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Test Substance</td>
<td>1. Test Substance Identity</td>
<td>2</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Test Substance Source</td>
<td>1</td>
<td>0.5</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>3. Test Substance Quality</td>
<td>1</td>
<td>0.0</td>
<td></td>
<td></td>
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<tr>
<td>2. Test Design</td>
<td>4. Negative and Positive Controls</td>
<td>2</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Positive Controls</td>
<td>2</td>
<td>0.0</td>
<td></td>
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<tr>
<td></td>
<td>6. Animal Procedures</td>
<td>1</td>
<td>0.0</td>
<td></td>
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<tr>
<td></td>
<td>7. Standards for Test</td>
<td>1</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Exposure Characterization</td>
<td>8. Proportion and Duration of Test Substance</td>
<td>1</td>
<td>0.0</td>
<td></td>
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<tr>
<td></td>
<td>9. Consistency of Exposure Administration</td>
<td>1</td>
<td>0.0</td>
<td></td>
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<td></td>
<td>10. Recording of Concentrations</td>
<td>2</td>
<td>0.0</td>
<td></td>
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<tr>
<td></td>
<td>11. Endpoint Duration</td>
<td>2</td>
<td>0.0</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>12. Number of Exposure Groups and Dose Grouping</td>
<td>1</td>
<td>0.0</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>13. Metabolism Analysis</td>
<td>1</td>
<td>0.0</td>
<td></td>
<td></td>
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<tr>
<td>4. Test model</td>
<td>14. Test Model</td>
<td>2</td>
<td>0.0</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>15. Number per Group</td>
<td>1</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Outcome Assessment</td>
<td>16. Outcome Assessment Methodology</td>
<td>2</td>
<td>0.0</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>17. Consistency of Outcome Assessment</td>
<td>1</td>
<td>0.0</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>18. Sampling Methodology</td>
<td>1</td>
<td>0.0</td>
<td></td>
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<td></td>
<td>19. Blinding of Observations</td>
<td>1</td>
<td>0.0</td>
<td></td>
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<tr>
<td>6. Concluding/Handleable Control</td>
<td>20. Concluding Variables in Test Design and Procedures</td>
<td>1</td>
<td>0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21. Documented Data Exposure</td>
<td>1</td>
<td>0.0</td>
<td></td>
<td></td>
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<tr>
<td>7. Data Presentation and Analysis</td>
<td>22. Data Interpretation</td>
<td>1</td>
<td>0.0</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>23. Estimation of Error</td>
<td>1</td>
<td>0.0</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>24. Statistical Analysis</td>
<td>1</td>
<td>0.0</td>
<td></td>
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<tr>
<td></td>
<td>25. Reporting of Data</td>
<td>1</td>
<td>0.0</td>
<td></td>
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<tr>
<td></td>
<td>Sum of all metrics scored</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Range of Overall Scores, where**

Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factor

<table>
<thead>
<tr>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 and 2.7</td>
<td>1.7 and 2.3</td>
<td>1.3 and 1.0</td>
</tr>
</tbody>
</table>

Is my study a high-quality study?
Systematic Review in Risk Assessment

Figure S-1, NAS, 2014; https://www.nap.edu/catalog/18764/review-of-epas-integrated-risk-information-system-iris-process
How might systematic review impact you?

- Important to understand the global movement towards use of systematic review (and other evidence-based methods)
  - Consider these approaches when designing research questions
  - Peer-review journal standards, etc., are evolving
- Important to understand that studies will be critically appraised for reliability (and reproducibility)
  - Highlights the importance of complete reporting and consideration of internal validity aspects (bias) during study design and conduct
- Peer-review of systematic reviews requires understanding of the method (as well as the topic of the underlying evidence base)
Actions You Can Take
From the perspective of a journal editor....

◆ Don’t underestimate the value of planning an experiment
◆ Consider structured abstracts
◆ Ensure complete reporting (allow for reproducibility)
  ❖ Heavy emphasis on completeness of methods
  ❖ Report all findings (including null findings)
  ❖ Utilize repositories (e.g., Open Science Framework, Zenodo, Dryad) and supplemental material for raw data
◆ Cover all aspects of validity
  ❖ (see, for example, tools from SciRAP http://www.scirap.org/)
◆ Stick to the science
Selected Reading: SR in Toxicology

**A primer on systematic reviews in toxicology**

Sebastian Hoffmann,1,2 Rob M. de Vries,1 Martin L. Stephens,1 Nancy B. Beck,3 Robert A. A. M. Veldink,4 John R. Revie5 Julie E. Goodney5 Thomas Hartung5 Ian Kimber5 Monja M. Lohr5 Kristina Thayer5 Paul Whitley5 Daniëlle Wiikoff5 Akiya Takeda5

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Abstract: Systematic reviews, properly carried out, provide a transparent, methodologically rigorous means of summarizing evidence on a previously studied research question to a well-established approach in toxicology. Systematic reviews are expected to provide a potential tool for assessing toxicological framework of evidence-based approach to risk assessment, thereby promoting appropriate risk management and adopting systematic reviews being explored. To provide a common stage for conducting and analyzing reviews, we highlight summarized and assess various methods of application on the systematic review process (i.e., the “why,” “when,” and “how” of conducting systematic reviews). We have identified the specific needs of toxicological questions and have given an overview of the different methods and tools that can be used to address these questions.

**FORUM ARTICLE**

The emergence of systematic review in toxicology

Martin L. Stephens,1 Kaylin Bett,3 Nancy B. Beck, Vincent Cogliano,4 Kay Dickerson,5 Sr Thomas Hartung,5 Roberta W. Scher2

John Hopkins Center for Technology Writer, Takeda

Environmental Protection Public Health, Baltimore Administration, College Washington University

CA: Toxicology Assessment and Translation

European Food Safety Authority

implementing systematic review techniques in cancer risk assessment: Challenges, opportunities and recommendations

Paul Whitley1, Grigori Kafkafi,2 Marlene Agrestano3, Elisa Auer,4 Diane Berti,3 Gary Bittner5, David Boggs2, Chen Callier5, Cura Demmers5, Rafael Daneo Davidson5,20 Rex Hintz5,20 Melina Catap-Burgos20, David Gove20, Sebastian Hoffmann,20 Jochen Lam,20 Toby Leser5,20 Lyn Ley5,20 Steven Lipworth,20 Sarah Mackenzie-Rees5, Olivia Martin,20 Catherine Meade,20 Monika Meyn-Baron5, James Miller20, Camilla Peirce5, Andrew Rowley5, Aleksander Sepani5, Calvin Stewart5, David Taylor5

The concept presented here draws upon the collective experience of the authors and suggests that systematic reviews need to be a fundamental part of the research process. A systematic review in cancer risk assessment is a method for synthesizing specific research questions. It can provide a powerful method of evidence-based practice to identify actionable, evidence-based, and effective strategies to reduce cancer risk. The authors present a framework for conducting systematic reviews in cancer risk assessment, including the identification of key review questions, the selection of appropriate studies, and the synthesis of results. The framework can be used to guide the development of evidence-based strategies to reduce cancer risk.

**EDITORIAL**

Systematic reviews in toxicology

Danielle S. Wiikoff5 and Gary W. Miller5,6,7

Trbldoctime, Inc., Asheville, North Carolina 28804, Editor-in-Chief, Toxicologic Sciences, and Department of Environmental Health, Atrium School of Public Health, Emory University, Atlanta, Georgia 30322.

The concept presented here draws upon the collective experience of the authors and suggests that systematic reviews need to be a fundamental part of the research process. A systematic review in cancer risk assessment is a method for synthesizing specific research questions. It can provide a powerful method of evidence-based practice to identify actionable, evidence-based, and effective strategies to reduce cancer risk. The authors present a framework for conducting systematic reviews in cancer risk assessment, including the identification of key review questions, the selection of appropriate studies, and the synthesis of results. The framework can be used to guide the development of evidence-based strategies to reduce cancer risk.

**FORUM ARTICLE**

Implementing systematic review techniques in cancer risk assessment: Challenges, opportunities and recommendations

Paul Whitley1, Grigori Kafkafi2, Marlene Agrestano3, Elisa Auer4, Diane Berti3, Gary Bittner5, David Boggs2, Chen Callier5, Cura Demmers5, Rafael Daneo Davidson5, Rex Hintz5, Melina Catap-Burgos20, David Gove20, Sebastian Hoffmann, Jochen Lam, Toby Leser5, Lyn Ley5, Steven Lipworth, Sarah Mackenzie-Rees5, Olivia Martin, Catherine Meade, Monika Meyn-Baron5, James Miller20, Camilla Peirce5, Andrew Rowley5, Aleksander Sepani5, Calvin Stewart5, David Taylor5

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**FORUM ARTICLE**

As a field, toxicology presents a unique set of challenges and opportunities to the conduct of systematic reviews. Systematic reviews in toxicology are expected to provide a potential tool for assessing the framework of evidence-based approach to risk assessment, thereby promoting appropriate risk management and adopting systematic reviews being explored. To provide a common stage for conducting and analyzing reviews, we highlight summarized and assess various methods of application on the systematic review process (i.e., the “why,” “when,” and “how” of conducting systematic reviews). We have identified the specific needs of toxicological questions and have given an overview of the different methods and tools that can be used to address these questions.
Thank you!

See you in Anaheim...!