IMPROVING THE USE OF SCIENCE IN REGULATORY DECISION-MAKING:

Dealing with Conflict of Interest and Bias in Scientific Advisory Panels, and Improving Systematic Scientific Reviews

A Report from the Research Integrity Roundtable
The Keystone Center

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EXECUTIVE SUMMARY

Critics of the manner in which science is used in regulatory decision-making processes tend to raise two kinds of concerns. They question the composition of committees that are empaneled to recommend or review the science behind a regulatory decision and they question the way an agency or committee has reviewed the relevant scientific literature, charging that the reviewers used or omitted the wrong studies, and/or that the studies were not appraised appropriately.

The proliferation of such criticisms, warranted or not, is a growing problem for scientists, policymakers, and the public. Over time such charges can erode trust in scientific and regulatory systems and undermine the interests of government, industry, non-governmental organizations (NGOs), academia, and the public. This report seeks to address both types of concerns by suggesting some fundamental guidelines and practices to help reduce the battling over allegations of conflicts of interest, biases, and poor systematic reviews and to clarify what is at issue when disputes do arise.

The report was prepared by a cross-sector working group called the Research Integrity Roundtable (Roundtable) convened and facilitated by The Keystone Center (Keystone). The primary audience for the report is federal agencies and their scientific advisory committees, but the ideas in the report are relevant to many other entities that work at the intersection of science and regulatory policy, including the U.S. Congress, the judiciary, governors, state legislatures, and advisory and deliberative bodies convened by private entities. The Roundtable's report takes as its starting point the work of the Bipartisan Policy Center's (BPC) 2009 report, *Science for Policy Project: Improving the Use of Science in Regulatory Policy,* and seeks to advance some of the BPC report's findings by focusing on, among others, the following questions:

- How should panels be composed and the qualifications of prospective advisory panelists be vetted?
- How should concerns about biases and conflicts of interest of advisory panelists be handled?
- Which studies should agencies review when examining the scientific literature related to a regulatory policy issue?
- How should contending views regarding the relevance of particular scientific results to a regulatory issue and the credibility of those results be addressed?

The Roundtable's responses to these questions seek to further the shared principle of achieving maximum transparency while being alert to concerns about individual privacy and confidential business information. The introductory section of the report provides a general statement on the formation, history, and funding of the Roundtable, along with thoughts on the nature of the problems the report addresses. Section II, titled "Improving the Credibility and Integrity of Scientific Advisory Panels," offers recommendations on some of the issues and tensions involved in assembling an advisory panel with the goal of achieving greater transparency. The final section, titled "Best Practices for a Systematic Review," offers recommendations on how scientific studies and data can be systematically reviewed, also with an eye toward greater transparency. The views expressed in this report are the collective work of the individual members who participated in the Roundtable's work. They are not necessarily the official positions of any of the groups or associations with which individual Roundtable participants are affiliated.

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SECTION I. INTRODUCTION

Science is often just one component of regulatory decision-making, yet it tends to be the central subject of debate when controversies erupt over regulation.[1] It is common to hear a claim that a particular regulatory decision was been driven by, or even required by science, while at the same time others attack the quality or the interpretation of that very same science. This is the case all across the political spectrum (even, or perhaps especially, when scientific interpretations are not what is actually at issue). [2]

Critics of the manner in which science is used in regulatory decision-making tend to raise two kinds of concerns: they question the composition of committees that are empaneled to review the science behind a regulatory decision, and they question the way an agency or committee has reviewed the relevant scientific literature, charging that the reviewers used or omitted the wrong studies, and/or that the studies were not appraised appropriately.

The proliferation of such charges – whether warranted or not – is a growing problem for both scientists and policymakers, and for the public at large. Over time, such charges can undermine support for scientific research and government decisions, as well as leave the public confused and dispirited. They can result in a deficient regulatory system that either tries to solve problems that do not exist, or fails to prevent harms that could be readily avoided, or worse, both. The deterioration of, and/or loss of, public confidence in the integrity of the regulatory system can harm the interests of industry, non-governmental organizations, the government, academia, and the wider public.

With that in mind, this report attempts to lay out some broad principles, guidelines, and practices designed to limit the battling over conflict of interest and bias, and systematic reviews.[3] Some agencies, institutions, and panels already follow some or all of what is recommended in this report. But we believe it is necessary to lay out in one place approaches to the use of science in regulatory policy that are likely to limit criticism and to clarify what is at issue in the disputes that remain.

The overarching notion behind all the recommendations in this report is that the regulatory process is better when there is more consistent and greater transparency in selecting panels, and when there is consistent, transparent, and systematic review and evaluation of the scientific literature. Transparency does need to be weighed against other values – for example, not unduly burdening advisory committee members or dissuading experts from participating – but, in general, transparency not only can eliminate suspicion and innuendo, but also forces participants in the regulatory process to be more explicit and clear in their own thinking.

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[1] Some statutes mandate that science be the only factor in particular regulatory decisions.

[2] As the Bipartisan Policy Center's (BPC) 2009 report notes, "[S]ome disputes over the 'politicization' of science actually arise over differences about policy choices that science can inform, but not determine." Boehlert, S., et al. *Science for Policy Project: Improving the Use of Science in Regulatory Policy*. The Bipartisan Policy Center. (2009) http://www.bipartisanpolicy.org/library/report/science-policy-project-final-report. p. 15. Disputes may, for example, reflect differences in political philosophy or differing economic concerns or the differing statutory mandates that determine agency perspectives. In this report, as in the BPC report, the term "science" refers only to the natural and physical sciences.

[3] For a definition and more in-depth discussion of systematic reviews see Section III.

The Bipartisan Policy Center's (BPC) 2009 report, *Science for Policy Project: Improving the Use of Science in Regulatory Policy,*[4] is the starting point for this report. We share BPC's general analysis and its concern about separating, to the extent possible, science questions from other regulatory issues that are policy matters. This report represents another effort to reach consensus among disparate parties on the issues raised in the BPC report about conflict of interest and bias, and about systematic reviews, and attempts in some cases to provide additional detail on these matters.

This report was prepared by a cross-sector working group called the Research Integrity Roundtable that was convened and facilitated by The Keystone Center (Keystone) (www.keystone.org). The primary audience for this report is federal agencies and their advisory committees, but the ideas in the report are relevant to any entity interested in, or responsible for, matters at the intersection of science and regulatory policy, including Congress, the judiciary, governors, state legislatures, and bodies convened by private entities to review science or regulation, and stakeholders as well.

In 2008, trustees and senior staff at Keystone identified research integrity as an important public policy challenge pertinent to issues in the chemical, agricultural, natural resources, and pharmaceutical domains. Consistent with Keystone's history of exploring an issue prior to any attempt at convening discussions, Keystone secured a grant from the American Chemistry Council[5] (ACC) to undertake an assessment of the issues and to convene a follow-on meeting with thought leaders from industry, government, and non-governmental organizations (NGOs) in December 2009 at Georgetown University.

Building on the valuable work done by BPC, the working group examined matters related to the convening of advisory panels and literature reviews. Among the specific questions asked were:

- How should panels be composed and the qualifications of prospective advisory panelists vetted?
- How should concerns about biases and conflicts of interest of advisory panelists be handled?
- Which studies should agencies review when examining the scientific literature related to a regulatory policy issue?
- How should contending views regarding the relevance of particular scientific results to a regulatory issue and the credibility of those results be addressed?

Based on that initial discussion, Keystone convened the Research Integrity Roundtable on October 6, 2010 in Washington, D.C. Over an eighteen month period, Keystone facilitated four plenary meetings and numerous small group sessions. Roundtable members were drawn from industry, science and environmental NGOs, and professional associations, and were joined by active liaisons from several key Federal agencies. Participants were identified on the basis of their or their organization's interest in and/or expertise in relevant issues, their participation in or use of advisory panels and/or systematic review processes, and/or past experience with multi-stakeholder deliberations on germane topics. ***All participants represented their own views, and not necessarily those of their organizations of affiliation.*** The work of the Roundtable was supported by grants and contributions of time and resources from the organizations and participants involved. A majority of funding was supplied by the American Chemistry Council, with additional funding supplied by the Regulatory and Safety Evaluation Specialty Section of the Society of Toxicology. The Union of Concerned Scientists and the American Chemical So-

[4] Boehlert, S., et al. *Science for Policy Project: Improving the Use of Science in Regulatory Policy*. The Bipartisan Policy Center. (2009) http://www.bipartisanpolicy.org/library/report/science-policy-project-final-report.

[5] Keystone made ACC and all other participating stakeholders aware, in writing, of its long-standing and continuing policy of independence on any issue with which it becomes involved. The Keystone Center Statement of Independence: www.keystone.org/images/keystone-center/mtkg-documents/Statement_of_Independence.pdf.

ciety made in-kind contributions to the initiative. For a full list of Roundtable members and liaisons see Appendix A.

Two Central and Paradoxical Pressures

The work of the Roundtable has important implications for persons interested in issues associated with chemicals, energy, land use, natural resources, agriculture, pharmaceuticals, and other areas in which science informs public policy. All Roundtable participants share a common value in preparing this report: they are committed to ensuring the health, safety, and welfare of the public. The related issues of populating science panels with diverse and highly qualified experts and vetting an array of scientific studies must balance tensions between transparency and protecting legitimate personal or corporate interests.

First, for panel formation, a reasonable balance must be established between transparency and privacy. In the realm of qualifications, for example, how much personal information should be revealed to the public by a prospective panelist who may be willing to serve in an advisory capacity, but may not want every aspect of his or her personal life or financial status released to the public?

In dealing with scientific studies, a balance must be established in developing and applying objective and transparent criteria for establishing data relevance and reliability between the desire for complete datasets and the reality that the relevant scientific literature is populated with studies from a wide variety of sources with varying degrees of data availability. In some cases, when proprietary information is involved, an appropriate balance must be struck between the public's right to know and the legally-based need to protect proprietary formulas, production processes, and related intellectual property.

Use of the Report

The Roundtable has endeavored to develop suggestions that are not focused on any particular current or past controversy, but rather that would improve the formulation of, and debate over, regulatory policy for the foreseeable future. The identification of more uniform procedures, policies, and protocols needs continuing attention to help prevent, manage, and resolve disputes over the use of science in regulatory policy. The views expressed in this report are not the official positions of any of the groups or associations with which individual Roundtable participants are affiliated. Collectively and individually, the Roundtable welcomes and encourages additional conversation, deliberation, and dialogue on the important issues raised in this report.

SECTION II. IMPROVING THE CREDIBILITY AND INTEGRITY OF SCIENTIFIC ADVISORY PANELS

In 2004, the Government Accountability Office reported that nearly 1,000 advisory committees provide insight, counsel, and advice to the Federal government on a variety of often controversial topics.[6] Federal authorities have described four ways committees can be created[7]:

- Statutory nondiscretionary committees created by Congress and mandated in law,
- Discretionary committees authorized by law,
- Committees established by agencies under the discretionary authority of an agency head, and
- Committees established by Executive Order or other instruments of direction by the President.

Generally, advisory committees operate under guidance and rules issued by the General Services Administration's Committee Management Secretariat which implements the Federal Advisory Committee Act ("FACA")(5 USC App. II).[8] Committees may be of short or long duration—some are empanelled for years— and may focus on (a) matters of science, (b) matters of policy, or (c) matters of science and policy. Although current legal requirements[9] are extensive, improvement in the policies and practices is warranted.

This section of the report is targeted primarily at scientific advisory panels, and the Roundtable is using the BPC report's definition of scientific advisory committees as "advisory committees that are to exclusively address science questions" and supports its recommendation that such panels "should generally consist only of members with relevant scientific expertise."[10] [11]

Additionally, the Roundtable also supports the BPC report's position that all members of scientific advisory committees be appointed as Special Government Employees (SGEs).[12]

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[6] *Federal Advisory Committees: Additional Guidance Could Help Agencies Better Ensure Independence and Balance*. U.S. Government Accountability Office. April 2004. www.gao.gov/assets/250/242039.pdf.

[7] *Types of Federal Advisory Committees. U.S. General Services Administration*. August 31, 2011. ww.gsa.gov/portal/content/248961.

[8] Enacted in 1972, FACA strives to ensure advice provided by the various advisory committees formed is objective and accessible to the public. The Act formalized a process for establishing, operating, overseeing, and terminating these advisory bodies and created the Committee Management Secretariat to monitor compliance with the Act. With limited exceptions, any advisory group that is established or utilized by a federal agency and that has at least one member who is not a federal employee, must comply with the Act. *Federal Advisory Committee Act (FACA) Management Overview*. U.S. General Services Administration. November 20, 2011. www.gsa.gov/faca.

[9] For example, conflicts of interest are defined in 18 U.S.C. 208 and federal ethics regulations (5 C.F.R. Part 2635) dictate the information that is collected and evaluated to determine whether panelists have financial conflicts of interest or an appearance of a lack of impartiality. The provision of waivers for advisory committee members is specified under 18 U.S.C. 208(b) (3). Conditions under which advisory committees may be closed to the public are specified by the Government in the Sunshine Act (5 U.S.C. 552b). Requirements for advisory committee charters, membership balance, and public access to advisory committee records are spelled out in FACA (5 U.S.C. App.) and implementing General Services Administration regulations (41 C.F.R. Parts 101-6 and 102-3).

[10] Boehlert, S., et al. Pg. 5.

[11] The Roundtable uses the terms "committee" and "panel" interchangeably.

[12] Boehlert, S., et al. Pg. 5.

In determining who should be selected for a panel that will review scientific issues related to regulation, it is important to distinguish between concerns about conflicts of interest and bias. We endorse the National Academies' definitions of conflict of interest and bias (see box), and based upon these, we have developed specific recommendations on panel selection and management.

The National Academies' Definitions of Conflict of Interest and Bias

"Conflict of interest refers to: any financial or other interest which conflicts with the service of the individual because it could,1) significantly impair the individual's objectivity or, 2) could create an unfair competitive advantage for a person or organization….

> **"'[C]onflict of interest**' means something more than individual bias. There must be an interest, ordinarily financial, that could be directly affected by the work….The term 'conflict of interest' applies not only to the personal financial interests of the individual but also to the interests of others with whom the individual has substantial common financial interests if these interests are relevant to the functions to be performed….[A]n individual should not serve as a member of a committee with respect to an activity in which a critical review and evaluation of the individual's own work, or that of his or her immediate employer, is the central purpose of the activity, because that would constitute a conflict of interest, although such an individual may provide relevant information to the program activity."
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> **"[B]ias** ordinarily relate[s] to views stated or positions taken that are largely intellectually motivated or that arise from the close identification or association of an individual with a particular point of view or the positions or perspectives of a particular group. Potential sources of bias are not necessarily disqualifying for purposes of committee service. Indeed, it is often necessary, in order to ensure that a committee is fully competent, to appoint members in such a way as to represent a balance of potentially biasing backgrounds or professional or organizational perspectives…. Some potential sources of bias, however, may be so substantial that they preclude committee service (*e.g.*, where one is totally committed to a particular point of view and unwilling, or reasonably perceived to be unwilling, to consider other perspectives or relevant evidence to the contrary). "

[12]*The National Academies Policy on Committee Composition and Balance and Conflicts of Interest for Committees Used in the Development of Reports* (2003). ww.nationalacademies.org/coi/bi-coi_form-o.pdf. Pg. 3-5.

Agencies ranging from the Food and Drug Administration to the Environmental Protection Agency need the best and latest research findings that may be available to help establish policy. That task frequently entails evaluating scientific information that is incomplete, emergent, contested, inconsistent, or uncertain. When federal agencies use panels to help them review science, they need to utilize policies and procedures that eliminate or minimize conflicts of interest, and take into account biases to ensure that advisory panels can be balanced and fair-minded.

In an effort to improve the credibility of federal scientific advisory panels and to enable panels to provide rigorous reviews, the Roundtable identifies the following best practices for establishing, selecting, managing, and evaluating scientific advisory panels for consideration and adoption by agencies. Some

of these best practices are already followed by at least some agencies or even mandated by federal law; in other cases, we propose guidelines that go beyond current regulation.

In keeping with the BPC report, the Roundtable's overall goal is to increase the level of transparency so there is more public information about the members of scientific advisory committees, more opportunity to comment on committee charges and membership, greater clarity about what constitutes conflict of interest and how this is distinct from bias and about when and why a waiver is being granted for a conflict of interest, and how bias should be addressed. This would help the agencies, stakeholders, advisory committee members, and the general public by creating clearer expectations about the standards by which panel membership would be judged.

At the same time, a reasonable balance must be established between transparency and privacy. As the BPC report suggests, any changes in practices should be monitored to see if they "are making it harder to attract advisory committee members." [13]

A. Establishing Scientific Advisory Panels

a. All federal scientific advisory panels and subcommittees, including those put together or managed by contractors, should be subject to the Federal Advisory Committee Act.

b. Any agency convening a scientific advisory panel should post a charter describing the scope of the panel's work and the questions it is supposed to address. Agencies should craft charters consistent with the best practices provided by General Services Administration.[14] A panel's scope can be narrow or broad, but the charter needs to explicitly state the topic(s) to be addressed in a way that will enable other experts and members of the public to understand the panel's mission. The Roundtable is aware that many Federal agencies have adopted this practice; however, we recommend that a charter be required for all federal scientific advisory committees.

c. The charter should specify the duration of the panel, what kinds of expertise are needed to serve on the panel, and how it will be managed. [15] The questions it enumerates for the panel should be clearly articulated, and "explicitly differentiate, to the extent possible, between questions that involve scientific judgments and questions that involve judgments about economics, ethics, and other matters of policy." [16] [17] The charter should be posted early enough to allow public comment when a committee is first announced and whenever it is renewed. Posting the charter should also be used to give the public an opportunity to recommend members for the committee. The charter should be available on the panel's website for the life of the panel, re-distributed to panel members at each panel meeting, and routinely referenced during the panel's work. The charter should include, but not be limited to, the following:

[13] Boehlert, S., et al. Pg. 5.
[14] *Preparing Federal Advisory Committee Charters. GSA Office of Government-wide Policy*, Office of Policy Initiatives. www.gsa.gov/graphics/ogp/preparing_FACA_Charters.doc.
[15] For further discussion on panel management, see Section H.
[16] Boehlert, S., et al. Pg. 15.
[17] As BPC recommends, generally, scientific advisory committees should not be asked to answer questions that go beyond matters of scientific judgment. Boehlert, S., et al. Pg. 17.

1) The most complete and specific information possible about which topics and questions will be addressed. This applies to standing panels convened for an extended duration, not just to those convened to handle a specific issue. For standing or long duration panels, the charter should be reviewed at least bi-annually, and amended as needed.

2) A description of the kinds of perspectives and expertise that will be needed for the panel to be balanced and reflect a diverse spectrum of relevant views, fields, interests, and outlooks.

3) Roles and operational responsibilities of panel staff (designated federal officers, or DFOs), panel chair or co-chairs, panel members, and any others who may have a role in the convening of advisory panels.

4) Roles and responsibilities for the ongoing management of conflicts of interest and biases. The agency's policy for how it will address conflict of interest and bias issues on an ongoing basis should be included or referenced in the charter.

5) Rules for how meetings will be conducted including specific guidelines for panel decision-making: whether decisions will be achieved by, for example, pure consensus, majority votes, or super majority votes; and whether reports may include dissenting opinions. Dissenting opinions should be allowed in panel reports and thereby be made publicly available.

B. Identifying and Screening Panelists

a. Agencies should be engaged in ongoing outreach efforts to encourage scientists to participate in advisory panels. This should be done through means such as presentations at professional meetings, advertising through social media, professional newsletters, and other means that can reach an audience of potential qualified panelists.

b. In selecting panelists, all agencies should require that potential panelists provide their detailed, up-to-date curriculum vitae (CV) with information including, but not limited to, employment, education, training, board membership, testimony delivered, published work, consultancies, appointments, and grants received that go as far back in time as is reasonably possible but in all cases, at least 5 years. (For more detail on disclosure, see c. below.)

c. Before the final appointment of panelists, the agency should post on the appropriate agency website the agency's policies on conflict of interest and bias (and the distinction between them), the panel charter, the CVs of proposed panelists, and any waivers for conflicts of interest,[18] and allow for public comment on the appropriateness of the panelists. The agency need not make the comments or its response to the comments public, but should review and give due consideration to all comments.

[18] For further discussion of conflict of interest waivers, see Section E.

d. Agencies should select scientific advisory panel members based on their expertise and experience, and on their ability to contribute to the panel's deliberations without conflict of interest or undue bias. This applies to any and all potential members, whether from government, industry, academia, or NGOs.

C. Disclosing Interests

a. All prospective panelists must disclose to the convening agency information that is pertinent to determining conflicts of interest and bias. It is incumbent on the agency to provide orientation, guidance, and/or training to prospective panelists on the proper completion of disclosure forms. The Roundtable also endorses the BPC recommendation to make more information publicly available (see inset box).

A Bipartisan Policy Center Recommendation on Disclosure of Qualifications, Finances, and Activities: The Roundtable endorses the following BPC recommendation on disclosure of interests.

"One possibility would be for federal agencies to make publicly available all the information on a panelist's disclosure form except the precise dollar amounts of their stock holdings or compensation and any information on the finances of their spouse or dependent children. At the same time, the agency would disclose the member's educational background and scientific credentials. Ideally, all of this information would be released when committee members' names were put up on the Web for public comment." *Boehlert, S., et al. Pg. 20.*

b. All prospective members of a panel should be held to the same disclosure rules.

c. Financial disclosure forms should require reporting at least the following information from each prospective panelist *for the last three full years* (except where specified otherwise below):

   1) All sources of income, defined as "salaries, fees, commissions, wages and any other compensation for personal services,"[19] including compensated expert testimony.

   2) All investments greater than $1,000 held over the previous year subject to the exemptions of reporting income per 5 CFR 2634.907.[20]

[19] 5 CFR 2634.907 (b) 1. Current law excludes federal income. This report recommends that federal income be disclosed.

[20] For purposes of reporting, investments do not include: bank accounts including certificates of deposit money market mutual funds and accounts; United States government securities and obligations such as treasury bonds and notes; Social Security payments, diversified mutual funds; and income from federal government retirement plans. See 5 CFR 2634.907.

3) All gifts or free services received in the previous year in the amount of $100 or more from a single donor, or gifts from a single entity in aggregate of $250; with the exception of immediate family members.

4) All institutional relationships where there is a direct or predictable financial benefit.

5) All support from grants, cooperative agreements, cooperative research and development agreements (CRADAs), contracts, and all currently pending applications or proposals for such support. Support should include collaborative projects even if the prospective committee member was not the direct applicant or recipient. The list provided should include at least titles and dollar amounts.

6) Current efforts to seek new employment.

7) Where a prospective panelist is self-employed, works in, or is affiliated with a client -based business, the names of the prospective panelist's direct clients.

c. A prospective panelist should disclose the items required in (c) above not only for themselves, but for his or her spouse, dependent children, fiancé(e), and domestic partner. [21] [22]

d. In addition to financial disclosures, to assist in determining bias, the Roundtable recommends the following:

1) "Members of federal scientific advisory committees should be required to disclose to the government information on relevant…professional activities (such as giving talks at conferences and testifying in court) going back five years. Members should also be asked to disclose, to the best of their ability, any relevant professional activities that occurred more than five years prior to their committee service. Any reporting period is inherently arbitrary, but the current disclosure periods need to be extended to get a fuller picture of a member's experience and possible conflicts and biases."[23] [24] Relevant activities include articles, testimony, talks and speeches, service on boards and any other close association with an organization, regardless of whether the activity was compensated.

[21] For a full definition of domestic partner as outlined by the Office of Personnel Management see, http://www.chcoc.gov/transmittals/TransmittalDetails.aspx?TransmittalID=2982.

[22] Federal agencies should consider whether to include any other "immediate household members" in the list of those whose finances should be disclosed. Possible relevant household members would include elderly parents or other relatives.

[23] Boehlert, S., et al. Pg. 19.

[24] The BPC report recommended that financial disclosure forms go back five years, but the Roundtable has recommended a three-year period for that purpose.

2) "An eventual goal would be to make it standard practice for scientists to have a public curriculum vitae (CV) that included all their relevant employment, research support, publications, speaking, testimony, etc. Such a CV would provide much of the information sought on government disclosure forms. Many scientists already post their CV on their websites, and standardizing and expanding this practice would be part of creating a culture of disclosure that would be responsive to, and relevant for more than requirements for service on government committees. Regardless of whether they have such a CV, scientists should be far more attentive to the need to disclose financial relationships and professional activities, including the need to disclose any that develop during service on an advisory committee. But federal agencies must also do their own research on potential committee members; they should not rely exclusively on self-disclosure."[25]

3) Prospective panelists should also be asked a catch-all question to capture information on any other item that may be relevant to the panelist's objectivity or independence.[26]

f. The General Services Administration should create a means by which agencies can obtain disclosure forms of current and potential panelists from each other, when needed, under the same confidentiality protections under which the information was submitted.

D. Determining Conflict of Interest

Like the BPC, the Roundtable believes federal conflict of interest policies should be much more clear and consistent, creating to the greatest extent possible "bright lines that leave as little doubt as possible as to who would be considered to have a conflict."[27] In the current system, too much discretion must be exercised in determining who has a real or, even more problematically, an apparent conflict of interest. This creates uncertainty and confusion for agencies, stakeholders, prospective committee members, and the public, and increases the likelihood that any appointment to a committee will get mired in debate over conflicts of interest with no clear criteria for resolution. Failure to clearly define conflicts also increases the likelihood that conflict and bias will be conflated even though they should be handled differently.

a. Agencies should establish clear, publicly available policies for determining conflicts of interest.[28] While the Roundtable has recommended what information should be disclosed by a prospective panelist, the Roundtable has not delved into the difficult matter of deciding what types of financial connections should be considered a conflict of interest.[29]

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[25] Boehlert, S., et al. Pg. 19.
[26] The World Health Organization. *Declaration of Interests for WHO Experts* (2010) www.who.int/occupational_health/declaration_of_interest.pdf.
[27] Boehlert, S., et al. Pg. 21.
[28] *Environmental Health Sciences Decision Making: Risk Management, Evidence, and Ethics - Workshop Summary*, Institute of Medicine Roundtable on Environmental Health Sciences, Research, and Medicine, Washington, DC: National Academies Press; 2009 www.ncbi.nlm.nih.gov/books/NBK50714/pdf/TOC.pdf
[29] For a further discussion see Appendix 1 in the BPC report. Boehlert, S., et al. Pg. 27.

b. The Roundtable supports the BPC recommendation that "when considering whether a conflict of interest exists, federal agencies should look back two years." [30]

c. Generally, conflicts of interest involve a potential for financial gain or loss to the panelist, the panelist's spouse, or the panelist's employer or client. Caution must be exercised to ensure that panel members are not engaged in evaluating their own work as a central part of a scientific review. However, certain other situations could constitute conflicts such as reviewing the work of a relative or close colleague.

d. Agencies will still have to exercise judgment in determining who best to appoint to a panel. Where there are ample qualified candidates with the desired set of perspectives, agencies may want to carefully consider, for example, whether to appoint someone who has financial holdings or relationships that may put him or her just outside the definition of conflict, or instead to appoint an equally qualified candidate who has a financial profile that is less likely to raise questions.

e. The goal of agencies should be to appoint only panelists who do not have conflicts of interest.

E. Issuing Waivers

a. Waivers should be cautiously and carefully issued, and be the rare exception, not the norm. As in the BPC report,[31] the Roundtable suggests that the federal standard be changed to reflect the National Academy of Sciences' standard which states that a conflicted expert can serve only if it is "unavoidable" to have a conflicted panel member.

b. If a waiver is needed to fill out a panel, then when considering to whom to grant a waiver, an agency may consider whether a potential panelist has ended ownership of the asset or discontinued the affiliation that triggered the conflict determination.

c. Under current practice, two different kinds of waivers are given, depending on whether the matter the committee is reviewing would affect an industry as a whole or would differentially affect a company with which a panelist has a relationship that creates a conflict of interest. Ideally, per the Roundtable's recommendations above, a clearer definition of conflict would eliminate these waiver categories. A matter that affects a stakeholder sector as a whole either would not be considered to create a conflict or would require the same kind of waiver as any other conflict of interest. But while the current system exists, waivers should be fashioned to the specific circumstances involved and granted for limited purposes. The current types of waivers are:

[30] Boehlert, S., et al. Pg. 22. Two members of the BPC panel dissented from this recommendation – the only dissent in the report.
[31] Boehlert, S., et al. Pg. 23.

1) A waiver that permits *participation in a particular matter of general applicability*[32] in which the panelist has a conflict because of a relationship with an entity that is part of a class of entities which could equally be affected by the panel's decision. Notwithstanding the above, SGEs have a statutory (automatic) waiver to work on matters of general applicability involving their employer.

2) A waiver that permits *participation in a specific party matter*[33] in which the panelist has a conflict because of a relationship with a particular entity that is being addressed by the panel that creates the conflict of interest.

d. Panelists with waivers should not be allowed to serve as panel chairs or in other leadership capacities (such as subcommittee chairs).

e. When the convening agency is posting names of prospective panelists for public comment, and then again no later than when the committee's meeting agenda is posted prior to the panel's first meeting, the agency should post on its website a list of all waivers issued and the grounds for granting such waivers. Agencies should provide enough public information about why a waiver was granted for the public to understand what the conflict is and to evaluate whether the waiver is justified.

F. Managing Conflicts of Interest

a. To assist the public and stakeholders in understanding how conflicts of interest are evaluated, agencies should make their conflict of interest policies and procedures publicly available and affirm at each panel meeting that the agency has appropriately evaluated the conflicts of each panel member and found that, to the best of the agency's knowledge, each panelist is free from disqualifying conflicts or has a waiver.

b. The chair of the panel, or the convening authority's designated staff member, should actively manage waivers and recusals and ensure they are exercised in the course of the panel's work.

c. At the first meeting of a panel, or when a new member joins, the panel chairs should remind the panel members of their ongoing duty to disclose any new or previously undisclosed information relevant to conflict and bias determinations. New disclosures should be made and handled in accordance with the same rules and procedures that govern disclosures prior to the panel's first meeting.

G. Managing and Balancing Bias

a. First and foremost, all panelists under consideration for appointment must have the knowledge, training, and experience needed to address the charge to the panel. Agencies need to recognize that all potential panelists will have conscious and unconscious biases, and the panel selection process requires review of the disclosed information and a

[32] Particular matter of general applicability is defined as a particular matter that is focused on the interests of a discreet and identifiable class of persons, but does not involve specific parties. 5 CFR 2640.102(m).
[33] The term typically involves a specific proceeding affecting the legal rights of the parties, or an isolatable transaction or related set of transactions between identified parties. 5 CFR 2640.102(l).

judgment as to the ability of each prospective panelist to participate in open discussion and to consider other perspectives. Panelists selected should be able to have an open exchange of opinions. At a minimum, panelists need to be able to engage in give and take and to consider different views that are supported by alternative data or interpretations of data.

b. The convening agency must make judgments on the biases or prospective biases of panelists. Similarly, panelists should disqualify themselves from serving on a panel if they believe their biases will render them ineffective at fairly weighing the facts and opinions of others who hold alternative views of the matters under discussion.

    1) Biases must not prevent panelists from engaging in the panel's discussion with an open mind and from evaluating as objectively as possible all presented data, models, methods, and conclusions.

    2) Because biases exist, an agency should strive to engage a wide range of perspectives of qualified scientific experts. We endorse the BPC report's statement that, "Agencies should not shy away from including scientists on a panel who are considered 'outliers' on the question(s) under consideration, provided that the scientist is a respected practitioner in a relevant field and the committee as a whole fairly represents the mainstream." [34]

H. Managing Panels

a. Pre-Meeting Preparations

    1) The federal government should create a manual and training program for SGEs and panel staff that covers conflicts of interest, bias, ethics, and meeting protocols. The manual and training program materials should be publicly available.

    2) Well trained chairs and staff are needed to help lead panels. Panel chairs and agency staff assigned to the panel should receive training prior to the panel's first meeting. Training for panel chairs should include guidance on the management of divergent perspectives between and among members of the panel.

b. Ongoing Panel Management

    1) The information reported on disclosure forms should be updated annually by panelists, or more frequently if required by the convening agency. As noted above, the information on disclosure forms also need to be updated whenever a panelist acquires a new asset or enters into a new affiliation relevant to conflict and bias determinations (*e.g.*, changing employment, joining a board, etc.).

[34] Boehlert, S., et al. Pg. 24.

2) If an allegation of an undisclosed conflict of interest or bias is raised after a panel has been convened, the agency should take reasonable steps to expeditiously resolve the allegation in the same manner it handles such allegations made when it is setting up committees.[35]

3) Agencies should undertake succession planning for chairs of continuing panels and ensure the training and orientation of new chairs.

4) Panelists should be periodically reminded of the statutory requirements that govern the questions the panel is addressing.

5) DFOs and panel staff must ensure that panelists alert the agency to any conflicts of interest that may arise during the life of the panel, and must watch for problematic biases and ensure they are not adversely affecting the panel.

6) Panel meeting agendas and presentations should be made publicly available as rapidly as possible. The public should be given an opportunity to participate in at least some meetings of every panel and such sessions should be conducted in a fair, balanced manner that gives adequate time to all views. In general, this means affording all individuals participating in a public comment period equal time to address the panel, but there may be exceptions. For example, a panel might want to allow relatively equal time to different points of view or to different sectors (*e.g.*, industry vs. NGOs) rather than giving equal time to each individual.

c. Work Product of Panel

1) Electronic disclosure of records, meetings, webcasts, transcripts, etc., should occur within 30 days of the panel meeting on the appropriate agency website.

2) The Roundtable endorses the policy that "except when explicitly stated in a prior agreement between an agency and a Federal Advisory Committee (FAC), all reports, recommendations, and products produced by FACs should be treated solely as the findings of such committees rather than of the U.S. Government, and thus are not subject to intra- or inter-agency revisions." [36]

I. Evaluating Panels

Agencies should implement continuous improvement management programs to ensure that panels are providing high-quality and credible advice from relevant experts. Public engagement in the review process of panels is encouraged. Evaluations should include reviewing meeting charters, panel selection procedures, and panel effectiveness. More specifically, evaluations should examine:

[35] See Section A for further discussion on allegations of conflict of interest and bias.

[36] Holdren, J., *Assistant to the President for Science and Technology and Director of the Office of Science and Technology Policy, December 17, 2010 Memorandum.* www.whitehouse.gov/sites/default/files/microsites/ostp/scientific-integrity-memo-12172010.pdf.

a. The clarity of charters, including how well charters explicitly differentiate between questions that involve scientific judgments and questions that involve matters of policy.

b. The effectiveness and quality of ethics training developed for panelists, chairs, and panel staff.

c. Whether the agency has taken reasonable steps to verify information provided by panelists on conflict of interest forms, including the utilization of existing databases and sources of public information.

d. How well conflicts of interest and member biases have been addressed, including, but not limited to, the panel members' and the public's satisfaction with an agency's process to evaluate conflicts of interest and bias.

e. The number of waivers granted by the agency.

f. The panel's ability to consider in a timely manner public comments made at meetings and the panel's treatment of public and stakeholder engagement generally.

g. The panel's ability to obtain a variety of perspectives for presentations to the panel.

h. The number of meetings closed to the public, and the extent to which the closed door meetings were in compliance with FACA.

i. The number of panelists who resign or are removed from the panel due to conflicts of interest.

j. The ability of the agency and panel to retain panel members.

k. The frequency of panel chair rotation on continuing panels.

SECTION III. BEST PRACTICES FOR CONDUCTING A SYSTEMATIC REVIEW

Systematic reviews are a critical part of developing or evaluating a science-based regulation since they are the means by which an agency or panel reaches conclusions about the science relevant to a particular policy matter. Since debates about regulation often focus on whether a given regulation is consistent with the best, most reliable and most recent available science, systematic reviews often come under scrutiny. Even when no questions arise about the make-up of a panel, and certainly when they do, critics of a regulatory decision may dispute whether an agency or a panel has properly evaluated and interpreted the available scientific literature relevant to a regulatory decision – what sources were considered and how they were utilized.[37] Unlike charges of conflict of interest or bias, this is not fundamentally a charge about the motives of an agency or panel, but rather about the design, conduct, and quality of the scientific assessment.

Systematic Review

A systematic review[38] is a structured evaluation of the strength of the overall evidence to determine what the available scientific literature indicates about a question with policy relevance. It is a tool to assist relevant experts in evaluating the strength of the scientific evidence informing a decision-making process.

Such reviews conducted by agencies, industry, NGOs, professional societies, academic institutions, and others involve many decisions that may be more complex and vexing than is commonly understood, such as which studies to include in a review, how to weigh the studies, and how to compare studies that reach different conclusions. Concerns often arise regarding the appropriate interpretation and application of data and studies; controversy is possible at each step of this process.[39]

A set of broadly accepted "best practices" is needed to guide such assessments. This chapter attempts to lay out what those best practices should be. This is done in broad strokes because each field of science[40] and each area of regulation raises slightly different questions and problems, has different conventions, and functions under different statutes. Despite this, broad principles can still be laid out.

For policymakers, adoption of best practices for systematic reviews can help ensure a consistent, transparent, and defensible review of science that can bolster regulatory decision-making. Decision-makers need to recognize that there is a wide range of scientific literature and that not all studies are equal in relevance or credibility. A responsible policymaker should require that a systematic review follow an analytical approach that has clearly articulated standards, transparent processes, and robust analysis of the scientific literature.

[37] Scientific literature for this purpose encompasses peer-reviewed articles, "gray literature," and analytical and predictive tools.

[38] "A systematic review is a high-level overview of primary research on a particular research question that tries to identify, select, synthesize, and appraise all high quality research evidence relevant to that question in order to answer it." *Evidence-based health care and systematic reviews.* The Cochrane Collaboration. www.cochrane.org/about-us/evidence-based-health-care. The Roundtable suggests that synthesized work such as meta-analysis can also be included in a systematic review.

[39] One area that continues to generate considerable controversy is the review and assessment of the effects of chemical substances, both natural and synthetic, particularly when these assessments seek to define the impacts at environmentally-relevant levels of exposure.

[40] Science for decision-making includes an array of scientific issues ranging from the evaluation of the level of risk posed by chemicals to assessments of ecosystems services.

Many systematic reviews conducted by and for federal regulatory agencies are done well, but greater consistency of practice will lead to better regulatory decision-making and will improve the acuity of the debate over proposed regulatory actions. Improving systematic reviews will not inherently move regulatory actions in any particular direction – the final regulatory decisions could produce more or less stringent regulations. However, making the process more transparent will enhance credibility. The entity carrying out the review should make it clear, as early in the process as possible, how studies will be selected, analyzed, and weighed, and they should describe in the conclusions the impacts of their scientific assumptions.

The guidance provided in this report is relevant not only to scientists, but also to policymakers and regulatory decision-makers. Scientists interested in making their studies and data sets useful to decision-makers should familiarize themselves with the best practices for a systematic review described below, since these practices encompass criteria that are increasingly important to decision-makers. Researchers who expect or hope their findings will contribute to sound public policy must become sensitive to the needs of the "practitioners" in question – the users of scientific data and studies.

No systematic review can eliminate uncertainty. Regulatory decision-making must be conducted with the best information available at the time. This is even truer in crisis or emergency situations. Systematic reviews should clearly state the levels of uncertainty (whether those are expressed in a qualitative or quantitative way or both). How to deal with that uncertainty is a policy judgment. Science is only one of many factors when making regulatory decisions.

This framework for conducting a scientific review builds on Chapter 3 of the BPC report.[41] Additional resources for conducting a systematic review can be found in Appendix C.

Systematic Reviews[42]

Systematic reviews employ several layers of evaluation. In this report, we break these layers down into discrete, consecutive steps to emphasize the need for transparency and evaluation in each, but in reality, these aspects of a review are likely to occur iteratively. The steps this report discusses are:

A. Problem Formulation
- Formulate the problem to be addressed by the systematic review

B. Relevance Assessment
- Delineate and document specific criteria for relevance
- Identify the studies that may be relevant to the specific problem being evaluated

C. Credibility Assessment
- Delineate and document specific criteria for credibility
- Evaluate the relevant studies for credibility
- Eliminate those that do not pass a meaningful threshold for credibility
- Evaluate the relative credibility of the remaining studies

D. Weighing Evidence and Drawing Conclusions
- Delineate and document how the studies will be weighed to reach conclusions
- Describe the conclusions reached and the rationale for them

[41] Boehlert, S., et al. Pg. 41-44.

[42] This treatment assumes a non-emergency situation, recognizing that it may sometimes be necessary for policy-makers to make decisions without a complete review of the literature.

Systematic reviews begin with formulating the scientific question for the target application (i.e., regulatory issue) – the problem that needs to be addressed. The key task then is to identify the studies that are relevant to that problem, and evaluate each relevant study for credibility.

Criteria established for relevance and credibility should be developed and made public before the selection of studies to be included. All decisions, the reasoning used to reach conclusions, and the process through which they are made should be documented with citations and be made available to the public. For example, if it is concluded that a data analysis did not use the correct statistical test, or that a given assay has not proven to yield reliable results to describe a given endpoint, then this should be documented and reference(s) that support the conclusion should be cited.

First and foremost, all studies should be evaluated using a consistent and transparent set of criteria, although not all studies should be given equal weight; studies that are better designed, better conducted, and more transparent should be afforded greater weight. In addition, information on what entities or individuals funded a study should be readily available, and, in general, the data on which conclusions are based should be available, regardless of who funded or conducted the study. While peer review is desirable, all studies, whether peer reviewed or not, should be assessed against the same standards for relevance and credibility in the systematic review process.[43] All studies actively considered in the problem formulation step should be listed in a publicly available bibliography for review.

The conclusions should be based on the integration of relevant and credible studies and reliable data which requires weighing evidence and drawing conclusions on the totality of scientific evidence. This does not mean giving all studies or data equal weight. It means determining, after reviewing the credible literature as a whole, which interpretations are most persuasive. This is done by considering study types, credibility, and quantity of evidence. To the extent possible, this would include reviewing evidence both for and against the statement/hypothesis, relevance to the target/affected population(s), replication of study results supporting the statement/hypothesis, and overall consistency of the evidence. After weighing the evidence, the reviewers draw scientific conclusions to inform the decision-making process.

Challenges presented for conducting scientific assessments of proprietary business information

Systematic reviews of scientific assessments should be as transparent as possible, meaning that the reasoning used in the reviews should be made as explicit as possible and the materials used in the reviews as available as possible. The goal is for experts who were not involved in the review, policy-makers, and the public to be able to make an informed judgment about whether they agree with the methodology and conclusions of the review and to raise informed questions about it.

However, companies need to be able to protect their intellectual property to remain competitive, and companies also need to protect their investments in studies that are part of the research and development process. The legitimate need for protection must be balanced, however, against the public interest in the disclosure of relevant studies and data.

[43] As the BPC put it, "In general, papers in high impact, peer reviewed journals should be given great weight, and papers that have not been peer reviewed should be treated with skepticism….Peer review is a necessary, but not sufficient determinant of quality." Boehlert, S., et al. Pg. 41-42.

Confidential Business Information (CBI) is defined as trade secret information or commercial or financial information that the source claims as confidential (*e.g.*, the identity of certain components in a formulated product or a new chemical substance or a process or similar intellectual property). The criteria for what constitutes CBI are established by law, and regulatory agencies have the authority and responsibility to determine whether particular information meets the criteria for classification as CBI and how CBI is dealt with in regulatory proceedings. For example, the Environmental Protection Agency, under certain statutes and regulations, will disclose the results of health and safety studies while keeping confidential the trade secret or identity (structure) of the tested chemical substance or mixture.

Agencies should review their laws, regulations, policies, and practices to ensure that CBI and other proprietary claims are not being used to protect information that need not be confidential. As the BPC report concluded, CBI is an overused category today.[44] Agencies have a responsibility to inform all stakeholders of the methods and manner they employ to determine what material is granted CBI status, and how it is reviewed and analyzed. Current law allows Federal advisory committees to review CBI or other protected information and data, by having the relevant agency obtain agreements/appropriate security clearances for each member, irrespective of affiliation, prior to their final appointment and by permitting those portions of meetings which need to address such materials to occur in closed sessions.

The members of the RIR recognize that there are differing views [45] [46] on whether means should be devised for sharing such confidential information (in ways that do not compromise confidentiality) with outside parties, such as non-governmental organizations, that believe they have a legitimate interest in evaluating such information. This question could best be pursued in a subsequent cross-sector dialogue in which the key federal agencies are engaged along with stakeholders.

Important questions on CBI for further deliberation include:

- What constitutes CBI, how broadly should it be defined, and how consistent should the definitions be across federal agencies?
- Under what circumstances should agencies challenge CBI designations?
- Is there value in a "look back" provision that would require agencies periodically to reassess the CBI status of a given study that had been used in a regulatory study so CBI classifications do not automatically become permanent?
- What other entities should have access to CBI to allow those entities to make better, more informed decisions?
- What other parties should be allowed access to studies in which there is a proprietary interest (but which are not designated as CBI) – *e.g.*, via contractual relationships with companies or agencies?

[44] Boehlert, S., et al. Pg. 43.

[45] Walls, M., "Without chemical trade secrets, innovation in America could become a spy game." American Chemistry Matters. American Chemistry Council. March 19, 2012. http://blog.americanchemistry.com/2012/03/without-chemical-trade-secrets-innovation-in-america-could-become-a-spy-game/; Franz, C., "TSCA Protects Confidential Chemical Identities in Health and Safety Studies From Disclosure." January 19, 2012. American Chemistry Council. www.whitehouse.gov/sites/default/files/omb/assets/oira_2070/2070_01202012-1.pdf.

[46] Denison, R., "Striking the right balance between right to know and right to intellectual property protection." April 13, 2012. http://blogs.edf.org/nanotechnology/2012/04/13/striking-the-right-balance-between-right-to-know-and-right-to-intellectual-property-protection/#more-1802; Denison, R., "Smoke and Mirrors: ACC lawyers are working hard to rein in your right to know." March 1, 2012. http://blogs.edf.org/nanotechnology/012/03/01/smoke-and-mirrors-acc-lawyers-are-working-hard-to-rein-in-your-right-to-know/#more-1741.

A. Problem Formulation

The problem formulation process articulates the scientific questions that need to be answered to inform the policy process. The more specific the problem articulation, the greater the likely value of the review's eventual conclusions.

B. Relevance Assessment

Next, studies need to be reviewed individually to determine if they are relevant to that problem. Criteria for relevance that are specific to the problem should be delineated and documented in advance. The relevance assessment should begin by considering the widest possible array of studies; the criteria may be appropriately revisited as the assessment proceeds and the quality and quantity of available scientific information becomes more apparent.

For example, if it turns out that relatively little work has been conducted on the most narrowly defined iteration of a problem, then problem formulation should be revisited and new criteria may need to be identified. Alternatively, it may be necessary to conclude that sufficient relevant studies or data do not exist to address the problem.

Each study and other information identified should be evaluated against a series of threshold questions, and the explanation for its consequent inclusion or exclusion should be clearly documented. An external entity reviewing this assessment process should be able to understand easily why a given study was or was not included, whether the criteria for inclusion seem reasonable, and whether those criteria were applied consistently.

It is important to note that a study that is determined not to be directly relevant to addressing the problem under consideration may have utility for other purposes. For example, some studies may provide useful background information or may provide support for the validity of methods used for measurements in other studies or may deal with an analogous problem.

Example of Relevance Assessment in a Risk Assessment of a Potentially Toxic Chemical

This box is included to illustrate one way of conducting a relevance assessment, and perspectives differ on its utility and applicability. Also, when this methodology is used, those applying it may have widely varying perspectives on each of the elements of the assessment. For example, there may be disagreement over whether a particular experimental animal model is an "appropriate model" for evaluating effects on humans.

I. Have the studies specified and measured the exposure or environmental change that is the subject of the statement and/or hypothesis?
  a. Appropriate rationale for, and selection of, the most appropriate model.
  b. Relevance to target context of the species tested (strain, sex, age, timing of exposure).
  c. Rationale for, and selection of, the most appropriate route of exposure and dose range.

II. Have the studies appropriately specified and measured the specific effect(s) that is the subject of the statement and/or hypothesis?
  a. Identification of the validated methods to measure the endpoints.
  b. Reliability and reproducibility of the methods to detect the endpoints.

C. Credibility Assessment

The systematic review should delineate and document specific criteria for assessing the credibility of scientific studies. The criteria are then used to evaluate the relevant studies for credibility, eliminating those that do not pass a meaningful threshold and evaluating the *relative* credibility of the remaining studies.

The credibility assessment should rely on externally relevant criteria[47] to the extent possible, to ensure the integrity and standing of the systematic review process in the eyes of the scientific community, stakeholders and the public. In contrast to the relevance assessment where the criteria may be appropriately revisited as new information becomes available, the criteria for credibility should generally be more stable throughout the assessment. Any changes made should be documented.

Some important elements of *scientific credibility* may include:[48]

- Whether the research objective and design are appropriate;
- Whether the hypothesis or questions (or in more open-ended studies, the approaches) under consideration are clearly stated and testable;
- Whether the study is reproducible, and whether the results have already been replicated;
- Whether the conduct of the study conforms to acceptable standards (*e.g.*, methods used, sample size, time of exposure, Good Laboratory Practices (where applicable), etc.);
- Whether the analysis of data is reasonable, and clearly presented;
- Whether the extrapolations required can be reliably supported by the data; and
- Whether conclusions or applications are supported by the data.

Important examples of *non-scientific credibility* may include:

- Whether funding sources and other competing interests are disclosed;
- Whether the investigators' own financial conflicts are disclosed;
- Whether the principal investigator has the freedom to publish, authority to analyze and interpret results, and control over study design.[49] As the BPC stated, for published studies, "Agencies and scientific advisory committees should be extremely skeptical of a scientific study unless they are sure that the principal investigator(s) (as opposed to the sponsor or funder) had ultimate control over the design and publication of the study."[50] However, as Conrad and Becker point out, control of study design is not applicable in cases where the design of the study is determined in advance by explicit regulatory agency direction. For example, Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and Toxic Substances Control Act (TSCA) require adherence to test guidelines that prescribe experimental study design elements, and the Organization for Economic Co-operation and Development imposes similar requirements.[51]

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[47] Externally relevant criteria includes generally accepted scientific practices and principles as described by authoritative sources.

[48] Conrad, J. and Becker, R., *Enhancing Credibility of Chemical Safety Studies: Emerging Consensus on Key Assessment Criteria*. Environmental Health Perspectives, Jun. 2011; 119(6). http://ehp03.niehs.nih.gov/article/fetchArticle.action?articleURI=info%3Adoi%2F10.1289%2Fehp.1002737.

[49] Conrad, J. and Becker, R. Pg. 760.

[50] Boehlert, S., et al. Pg. 42.

[51] Conrad, J. and Becker, R. Pg. 760.

- Whether the study was reviewed independently (*e.g.*, via peer review, or by an appropriate regulatory agency);
- In areas, such as pharmaceuticals, where a public registry of studies has been created, whether the study is (or key test elements are) posted in a relevant public registry; [52] and
- Whether the data and methods were publicly released.

A study should not be stricken from consideration *a priori* because of its funding source, but the funding source is a relevant factor in assessing credibility. The systematic review should include establishing and documenting the funder's involvement with any given study, and any restrictions placed on the study's release.

D. Weighing Evidence and Drawing Conclusions

The review should delineate in advance how evidence will be weighed, and then document how the evidence is weighed to reach conclusions. Final documentation should articulate the level of uncertainty.

A structured, systematic and transparent framework should be used to assess the overall evidence. This involves an evaluation of the results of the studies from which scientific conclusions can be drawn, integrating the information and rating the strength of the total body of available evidence. Contradictory and negative evidence is also evaluated, weighed, and factored into the conclusion. The systematic review process is based upon the premise that the best understanding is derived not from any single study alone, but rather from the totality of evidence of the most credible studies.

Some important considerations in weighing evidence include:

1. An appropriate process for integrating each study type and assessing its credibility, with attention to utility, reliability, reproducibility, and consistency where possible;
2. A transparent process for considering the number of the various types of studies and, where relevant, sample sizes; and
3. The overall consistency of the total body of evidence.

Most well-accepted science is based on a multitude of studies, preferably confirmed by repetition and/or reproduction. Any one result may be suspect, but confidence rises if that result is independently replicated. Nevertheless, reproducibility is not practical or feasible for all types of studies and varies by field. While laboratory experiments should be repeatable, in other situations, such as ecological studies, replication may not be possible. Reproducibility is an important criterion but not the only criterion for weighing the evidence.

Similarly, confidence in the results of a study is increased when there is consistency of results across independent studies. Likewise, confidence is decreased when results are inconsistent across independent studies.

[52] This consideration is aspirational for many fields. For example, such registries are not yet extant for the fields of toxicology and epidemiology.

Example: One Framework for Assessing the Totality of Evidence in a Systematic Review for Evaluating Hypotheses of Causality

A systemic review entails looking at the totality of all credible studies, including studies which had negative results, taking into account the quality, strengths and limitations of each study. The conclusions of a systematic review should be based not on any single study alone, but rather on the totality of the evidence; it should not be based on studies of poor or questionable quality. For some fields of science, particularly epidemiology and health risk assessment, the Bradford Hill criteria can be particularly useful for this, as they provide a structured framework to analyze a body of scientific evidence to evaluate hypotheses about causal relationships. Following analysis of the evidence employing each of the criteria, the results are integrated to develop a more complete understanding of the extent to which the totality of the evidence does, or does not, support a hypothesis of cause and effect. This does not mean that all the Hill criteria need to be met to indicate causality, but rather that confidence in causality will be stronger as more criteria are met. Note, however, that the results of the evaluations using the criteria are not absolute proof for or against causation (see quotes below from Bradford Hill).

Aspects to Evaluate in a Systematic Review to Assist in a Determination of Causality

1. Strength of association (relative risk, odds ratio)
2. Consistency
3. Specificity
4. Temporal relationship (temporality) - not heuristic; factually necessary for cause to precede consequence
5. Biological gradient (dose-response relationship)
6. Plausibility (biological plausibility)
7. Coherence
8. Experiment (reversibility)
9. Analogy (consideration of alternate explanations)

"None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question — is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect."

"All scientific work is incomplete — whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have or postpone the action that it appears to demand at a given time."

Bradford Hill, A., "The Environment and Disease: Association or Causation?," Proceedings of the Royal Society of Medicine, 58 (1965), 295-300. http://www.edwardtufte.com/tufte/hill.

Example of a Classification System for Weighing Evidence and Drawing Conclusions

The following example of a classification system is from the 2004 U.S. Surgeon General on Tobacco and Disease that provided a standardized four-level system for describing strength of evidence.

Hierarchy for Classifying Strength of Causal Inferences on the Basis of Available Evidence

1. Evidence is sufficient to infer a causal relationship.
2. Evidence is suggestive but not sufficient to infer a causal relationship.
3. Evidence is inadequate to infer the presence or absence of a causal relationship (evidence that is sparse, of poor quality, or conflicting).
4. Evidence is suggestive of no causal relationship.

Surgeon General's Report. "Introduction and Approach to Causal Inference." (2004) www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/chapter1.pdf

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Constructive comments on the draft report were provided by several outside reviewers (listed below) who were chosen based on their expertise and diversity of perspectives on the policy, science, and technical matters addressed in the report. Roundtable members considered all of the comments received from these reviewers in finalizing the report and the Roundtable thanks these individuals for their constructive criticisms and suggestions. (Note: although these outside experts reviewed a draft of the report, they did not see the final report before its release.) Outside expert reviewers: Gail Charnley, Ph.D., HealthRisk Strategies; James A. Popp D.V.M., Ph.D., Stratoxon, LLC; Jennifer Sass, Ph.D., Natural Resources Defense Council; J. Michael Scott, Ph.D., University of Idaho; and Vanessa Vu, Ph.D., U.S. Environmental Protection Agency.

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Appendix A

Research Integrity Roundtable Members and Liaisons

Throughout the dialogue, Roundtable participants were understood to represent their personal views and not necessarily those of the organizations with which they are affiliated. Affiliations are noted below for purposes of identification only and do not imply official endorsement of the contents of this report. Employees of government agencies listed below served as liaisons rather than consenting parties; their participation in Roundtable discussion served to raise invaluable questions and perspectives, and focus deliberation on outcomes that are both needed and implementable.

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*Withdrew from participation prior to the dialogue's conclusion due to a change in professional status.

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Appendix B

Comparison of Conflict of Interest Policies – Selected Institutions[1]

	National Academies Panels (2003)	International Agency for Research on Cancer Monographs (2003)	Food and Drug Administration FACA Committees (2008)	Environmental Protection Agency FACA Committees (no single date)	National Institutes of Health Office of Extramural Research (2004 & 2011[2])
Definition of conflict of interest	"Any financial or other interest which conflicts with the service of the individual because it (1) could significantly impair the individual's objectivity or (2) could create an unfair competitive advantage for any person or organization."	"Conflict of interest means that the expert…has a financial or other interest that could unduly influence the expert's position with respect to the subject-matter being considered."	Conflict is not explicitly defined; it is determined through use of an "algorithm," which works through determining whether there is a conflict, whether the conflict is disqualifying, and whether to provide a waiver. "The term `financial interest' means the potential for gain or loss to the employee (or persons/organizations whose interests are imputed to him) as a result of governmental action on	"18 U.S.C. §208 prohibits all employees (including Special Government Employees: SGEs) from participating in any particular Government matter that will have a direct and predictable effect on their financial interests." This section of U.S. Code talks about acts affecting a personal financial interest. The definition reiterates what is in the Code section.	*For principal investigators and institutions: "Financial conflict of interest (FCOI) means a significant financial interest that could directly and significantly affect the design, conduct, or reporting of Public Health Service (PHS)-funded research." (See definition of "Significant Financial Interest" below under types of financial conflicts.)* For peer reviewers: "A Conflict Of Interest exists when a reviewer has an

[1] This chart was created by and used in the Bipartisan Policy Council's report. With help from Roundtable members, the Keystone Center has updated this chart to reflect changes made to institutional policies. Boehlert, S., et al. *Science for Policy Project: Improving the Use of Science in Regulatory Policy*. The Bipartisan Policy Center. http://www.bipartisanpolicy.org/library/report/science-policy-project-final-report.

[2] In 2011, the NIH policies on conflicts of interest for principal investigators and institutions were revised. With assistance from Roundtable members, Keystone has updated the Appendix provided in the BPC report to reflect the changes to the NIH policies in ***blue***. Information used to update the chart was drawn from 76 FR 53283, updated August 25, 2011. http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=f67ea01984581d3934103b5074c05500&rgn=div5&view=text&node=42:1.0.1.4.22&idno=42 - 42:1.0.1.4.22.6 (accessed on July 9, 2012).

	National Academies Panels (2003)	International Agency for Research on Cancer Monographs (2003)	Food and Drug Administration FACA Committees (2008)	Environmental Protection Agency FACA Committees (no single date)	National Institutes of Health Office of Extramural Research (2004 & 2011[2])
			the particular matter." Certain financial interests are generally considered too "remote" to be disqualifying, such as ownership of mutual funds.		interest that is likely to bias his or her evaluation." "Real Conflict Of Interest means a reviewer or a close relative or professional associate of the reviewer has a financial or other interest in an application or proposal that is known to the reviewer and is likely to bias the reviewer's evaluation of that application or proposal."
Apparent conflict of interest	"Conflict of interest requirements are objective and prophylactic. They are not an assessment of one's actual behavior or character, one's ability to act objectively despite the conflicting interest, or one's relative insensitivity to particular dollar amounts of specific assets because of one's personal wealth. Conflict of interest requirements are	"An apparent conflict of interest exists when an interest would not necessarily influence the expert but could result in the expert's objectivity being questioned by others. A potential conflict of interest exists with an interest which any reasonable person could be uncertain whether or not should be reported."	"In some cases, an employee will have a financial interest or relationship that, while not a disqualifying financial interest, may cause a reasonable person with knowledge of the relevant facts to question his impartiality in the matter. See 5 CFR 2635.502. Such matters should be evaluated under this regulatory standard and, if appropriate, an impartiality determination should be requested."	"5 C.F.R. Part 2635, Subpart E contains provisions intended to ensure that an employee takes appropriate steps to avoid an appearance of a loss of impartiality in the performance of his/her official duties. Where an employee knows that a particular matter involving specific parties is likely to have a direct and predictable effect on the financial interest of a member of his/her household, or knows that a person with whom he/she	No additional language.

	National Academies Panels (2003)	International Agency for Research on Cancer Monographs (2003)	Food and Drug Administration FACA Committees (2008)	Environmental Protection Agency FACA Committees (no single date)	National Institutes of Health Office of Extramural Research (2004 & 2011[2])
	objective standards designed to eliminate certain specific, potentially compromising situations from arising, and thereby to protect the individual, the other members of the committee, the institution, and the public interest. The individual, the committee, and the institution should not be placed in a situation where others could reasonably question, and perhaps discount or dismiss, the work of the committee simply because of the existence of such conflicting interests."			has a covered relationship is or represents a party to such a matter, and where the person determines that the circumstances would cause a reasonable person with knowledge of the relevant facts to question his/her impartiality in the matter, the employee should not participate in the matter unless he/she has informed the agency designee of the appearance of a problem and received authorization from the agency designee."	
Distinction between conflict and bias?	"Questions of lack of objectivity and bias ordinarily relate to views stated or positions taken that are largely intellectually motivated or that arise from the close	No specific language, but see wording under Relevant non-financial interests and disqualifying activities later on in this chart.	No specific language, but see wording under Relevant non-financial interests and disqualifying activities later on in this chart.	No specific language, but see wording under Relevant non-financial interests and disqualifying activities later on in this chart.	No specific language, but see wording under Relevant non-financial interests and disqualifying activities later on in this chart.

	National Academies Panels (2003)	International Agency for Research on Cancer Monographs (2003)	Food and Drug Administration FACA Committees (2008)	Environmental Protection Agency FACA Committees (no single date)	National Institutes of Health Office of Extramural Research (2004 & 2011[2])
	identification or association of an individual with a particular point of view or the positions or perspectives of a particular group. Potential sources of bias are not necessarily disqualifying for purposes of committee service. The term `conflict of interest' means something more than individual bias. There must be an interest, ordinarily financial, that could be directly affected by the work of the committee."				
Types of financial conflicts	Employment relationships; consulting relationships; stocks, bonds, and other financial instruments and investments including partnerships; real estate investments; patents, copyrights, and other intellectual property interests;	"Different types of financial or other interests, whether personal or with the administrative unit with which the expert has an employment relationship, can be envisaged and the following list, which is not exhaustive…For example, the following types of situations should be	"Some examples of an employee's personal financial interests would be stocks or investments that he owns, his primary employment relationship, his consulting work, patents/royalties/ trademarks owned by him, his work as an expert witness, and his	Employment or consulting, whether or not for compensation, for the last 2 years preceding the date of filing. Includes: employee, officer, director, trustee, general partner, proprietor, representative/ executor of any business, consulting firm, non-profit, labor organization, or	*"A financial interest consisting of one or more of the following interests of the Investigator (and those of the Investigator's spouse and dependent children) that reasonably appears to be related to the Investigator's institutional responsibilities: (i) With regard to any*

	National Academies Panels (2003)	International Agency for Research on Cancer Monographs (2003)	Food and Drug Administration FACA Committees (2008)	Environmental Protection Agency FACA Committees (no single date)	National Institutes of Health Office of Extramural Research (2004 & 2011[2])
	commercial business ownership and investment interests; services provided in exchange for honorariums and travel expense reimbursements; research funding and other forms of research support.	declared: 1. a current proprietary interest in a substance, technology or process (e.g. ownership of a patent), to be considered in - or otherwise related to the subject-matter of - the meeting or work; 2. a current financial interest, e.g. shares or bonds, in a commercial entity with an interest in the subject-matter of the meeting or work (except share holdings through general mutual funds or similar arrangements where the expert has no control over the selection of shares); 3. an employment, consultancy, directorship, or other position during the past 4 years, whether or not paid, in any commercial entity which has an interest in the subject-matter of the meeting/work, or an ongoing negotiation concerning prospective	teaching/speaking/writing work."	educational institution. Any organization or person with whom you are negotiating or have an arrangement concerning prospective employment. Any positions held with professional societies. Any compensated expert testimony for the last 2 years preceding the date of filing. Any source of research or project funding (e.g., grants, contracts, or other mechanism) in the last 2 years preceding the date of filing from any source. Any assets currently held for investment. Stocks, bonds, annuities, trust holdings, partnership interests, life insurance, investment real estate or a privately-held trade or business. Sector mutual funds, which are funds invested in a particular industry, business, or location. Individual holdings of retirement plans like 401(k)s or IRAs. Holdings of	*publicly traded entity, a significant financial interest exists if the value of any remuneration received from the entity in the twelve months preceding the disclosure and the value of any equity interest in the entity as of the date of disclosure, when aggregated, exceeds $5,000. For purposes of this definition, remuneration includes salary and any payment for services not otherwise identified as salary (e.g., consulting fees, honoraria, paid authorship); equity interest includes any stock, stock option, or other ownership interest, as determined through reference to public prices or other reasonable measures of fair market value;* *(ii) With regard to any non-publicly traded entity, a significant financial interest exists if the value of any remuneration received from the entity in the*

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		employment or other association with such commercial entity; 4. performance of any paid work or research during the past 4 years commissioned by a commercial entity with interests in the subject-matter of the meetings or work; 5. payment or other support covering a period within the past 4 years, or an expectation of support for the future, from a commercial entity with an interest in the subject-matter of the meetings or work, even if it does not convey any benefit to the expert personally but which benefits his/her position or administrative unit, e.g. a grant or fellowship or other payment, e.g. for the purpose of financing a post or consultancy. With respect to the above, an interest in a competing substance, technology or		investment life insurance or variable annuities. Defined benefit pension plans. Language above from Form 3110-48.	*twelve months preceding the disclosure, when aggregated, exceeds $5,000, or when the Investigator (or the Investigator's spouse or dependent children) holds any equity interest (e.g., stock, stock option, or other ownership interest); or (iii) Intellectual property rights and interests (e.g., patents, copyrights), upon receipt of income related to such rights and interests."*

	National Academies Panels (2003)	International Agency for Research on Cancer Monographs (2003)	Food and Drug Administration FACA Committees (2008)	Environmental Protection Agency FACA Committees (no single date)	National Institutes of Health Office of Extramural Research (2004 & 2011[2])
		process, or an interest in or association with, work for or support by a commercial entity having a direct competitive interest must similarly be disclosed."			
Look-back period for conflicts	"The term `conflict of interest' applies only to current interest."	Varies: see above.	"Disqualifying financial interests include only financial interests that are currently held."	Varies: see above.	*For principal investigators and institutions, "Significant financial interest exists if the value of any remuneration received from the entity in the twelve months preceding the disclosure and the value of any equity interest in the entity as of the date of disclosure, when aggregated, exceeds $5,000."* For reviewers, also includes professional associates ("any colleague, scientific mentor, or student with whom the peer reviewer is currently conducting research or other significant professional activities or with whom the member has conducted such activities") over the

	National Academies Panels (2003)	International Agency for Research on Cancer Monographs (2003)	Food and Drug Administration FACA Committees (2008)	Environmental Protection Agency FACA Committees (no single date)	National Institutes of Health Office of Extramural Research (2004 & 2011[2])
					past 3 years.
Monetary limits for disclosure	No threshold stated.	No threshold stated.	No threshold stated.	"Assets that are valued at more than $1,000 or that generate more than $200 per year in income must be reported."	No threshold stated.
Individuals included in policy	"Consideration must be given not only to the interests of the individual but also to the interests of the individual's spouse and minor children, the individual's employer, the individual's business partners, and others with whom the individual has substantial common financial interests. Consideration must also be given to the interests of those for whom one is acting in a fiduciary or similar capacity (e.g., being an officer or director of a corporation, whether profit or nonprofit, or serving as a trustee)."	Partner and employer.	"1) You, your spouse, minor child, general partner, 2) Organization in which you serve as an officer, director, trustee, general partner or employee, and/or 3) Entity with whom you are negotiating or have any arrangement concerning prospective employment."	Spouse; minor child; general partner; organization in which the individual serves as officer, director, trustee, general partner or employee; person or organization with which the employee is negotiating or has an arrangement concerning prospective employment.	*For principal investigators, the "investigators spouse and dependent children."* For reviewers: relatives (a parent, spouse, sibling, son or daughter or domestic partner) and professional associates.

	National Academies Panels (2003)	International Agency for Research on Cancer Monographs (2003)	Food and Drug Administration FACA Committees (2008)	Environmental Protection Agency FACA Committees (no single date)	National Institutes of Health Office of Extramural Research (2004 & 2011[2])
Relevant non-financial activities	Access to confidential material; reviewing one's own work; public statements and positions; employees of sponsoring agencies.	Potential experts asked: "Do you have, or have you had during the past 4 years, an employment or other professional relationship with any entity directly involved in the production, manufacture, distribution or sale of tobacco or any tobacco products, or directly representing the interests of any such entity?" "Is there anything else that could affect your objectivity or independence, or the perception by others of your objectivity and independence?"	Focus appears to be exclusively on financial conflicts.	"Any reason that you might be unable to provide impartial advice on the matter to come before the panel or any reason that your impartiality in the matter might be questioned; any previous involvement with the review document(s) under consideration including authorship, collaboration with the authors, or previous peer review functions; service on previous advisory panels that have addressed the topic under consideration; any public statements on the issue that would indicate to an observer that you have taken a position." Language above from Form 3110-48.	For principal investigators and institutions: Not specified. For reviewers: Longstanding scientific or personal differences with an applicant.
Disclosure to institutions and to the public	Forms required. In addition, committees are asked to discuss the issues of committee composition and balance and conflict of	Declaration form required. Also required is disclosure of any change in circumstances. Information disclosed on the form may be made available to	Forms required. Potential committee members must fill out either OGE Form 450 or FDA Form 3410. This form will not be disclosed to any requesting	SGEs are required to file a confidential financial disclosure report (EPA Form 3110-48) when first appointed to participate in an advisory activity, and	*"The information that the Institution makes available via a publicly accessible Web site or written response to any requestor within five business days of*

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	interest, and the relevant circumstances of their individual members, at the first committee meeting and annually thereafter. Disclosure of relevant information is a continuing obligation for the duration of the committee activity. Information is held confidentially, except that under FACA, names and bios will be released and subject to public comment.	persons outside of World Health Organization only when the objectivity of the meeting or work has been questioned such that the Director-General considers disclosure to be in the best interests of the Organization, and then only after consultation with you.	person unless authorized by law.	then annually thereafter. Regular Government Employees are required to submit either an OGE Form 450 (Confidential Financial Disclosure Report) or an SF-278 form (Public Financial Disclosure Report) as appropriate under regulations promulgated by the Office of Government Ethics (OGE). Names and short lists of prospective panelists may be made available for public comment.	*a request, shall include, at a minimum, the following: the Investigator's name; the Investigator's title and role with respect to the research project; the name of the entity in which the significant financial interest is held; the nature of the significant financial interest; and the approximate dollar value of the significant financial interest (dollar ranges are permissible: $0–$4,999; $5,000–$9,999; $10,000–$19,999; amounts between $20,000–$100,000 by increments of $20,000; amounts above $100,000 by increments of $50,000), or a statement that the interest is one whose value cannot be readily determined through reference to public prices or other reasonable measures of fair market value."* Forms required. The applications and proposals and associated materials

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					made available to reviewers, as well as the discussions that take place during review meetings are strictly confidential and must not be disclosed to or discussed with anyone who has not been officially designated to participate in the review process. Reviewers have to fill out both pre- and post-review certifying forms.
Disqualifying Activities	”Except for those situations in which the institution determines that a conflict of interest is unavoidable and promptly and publicly discloses the conflict of interest, no individual can be appointed to serve (or continue to serve) on a committee of the institution used in the development of reports if the individual has a conflict of interest that is relevant to the functions to be performed.”	“Conflict of interest will, depending on the situation, result in (i) you being asked not to take part in the portion of the discussion or work affecting that interest, (ii) being asked not to take part in the meeting or work altogether, or (iii) if deemed by WHO to be appropriate to the particular circumstances, and with your agreement, you taking part in the meeting or work and your interest being publicly disclosed.”	“If an individual or her spouse or minor child has…financial interests whose combined value exceeds $50,000, she generally would not participate in the meeting, regardless of the need for her expertise.” “The following list includes the…financial interests that are considered so significant that a waiver would not be issued: •The SGE or his/her employing institution receives (or is negotiating) a contract, grant, or	Presence of any conflict of interest directly with a “covered entity” is a disqualifying conflict. “The term `covered entities’ is used to refer to those types of entities whose activities or interests may be affected by EPA decisions…in such a way that individuals having financial or other relationships with such entities may have a financial conflict of interest or an appearance of a lack of impartiality (including a lack of independence or	*For principal investigators appears to be greater than $5,000 for a given year.* For reviewers: “A reviewer who has a real conflict of interest with an application or proposal may not participate in its review.” “A reviewer shall have a real conflict of interest if he/she (1) has received or could receive a direct financial benefit of any amount deriving from an application or proposal under review; (2) has

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		IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. A difficulty arises when an expert with relevant knowledge and experience has a real or apparent conflict of interest. The selection of experts with real or apparent conflicts of interest can erode confidence in the integrity and impartiality of the results. This creates a tension between two competing ideals: evaluations developed by the best-qualified experts versus evaluations whose integrity and impartiality are above question. The new category of invited specialist allows the IARC Monographs to achieve both ideals. [Language quoted from different sections of IARC documents.] "An invited specialist is an	Cooperative Research and Development Agreement (CRADA) from a firm that is the sponsor of the product application that is the subject of the particular matter involving specific parties to be discussed at the advisory committee meeting, and the SGE is or will be the principal investigator or co-principal investigator on the same product/indication that is the subject of the meeting. •The SGE or his/her employing institution receives (or is negotiating) a contract, grant, or CRADA from a firm that is the sponsor of a product labeled for the same indication (or, if an investigational product, that has the same indication for use) as the product that is the subject of the particular matter involving specific parties to be discussed at the advisory committee meeting, and the SGE is or	bias). In particular, covered entities include companies or persons that manufacture or provide wholesale distribution of pesticide products registered by the EPA, are currently seeking a pesticide registration or other relevant regulatory or adjudicatory finding from EPA, or companies whose corporate parent, subsidiary, or affiliate engages in such activities. `Covered entities' also can include consulting firms, non-profit organizations, labor organizations, or educational institutions with financial interests in the entities listed above."	received or could receive a financial benefit from the applicant institution, offeror or principal investigator that in the aggregate exceeds $10,000 per year (for reviewers who are federal employees the amount is $15,000 per year); this amount includes honoraria, fees, stock or other financial benefit, and additionally includes the current value of the reviewer's already existing stock holdings, apart from any direct financial benefit deriving from an application or proposal under review." "If the reviewer feels unable to provide objective advice, he/she must recuse him/ herself from the review of the application or proposal at issue."

	National Academies Panels (2003)	International Agency for Research on Cancer Monographs (2003)	Food and Drug Administration FACA Committees (2008)	Environmental Protection Agency FACA Committees (no single date)	National Institutes of Health Office of Extramural Research (2004 & 2011[2])
		expert with critical knowledge and experience who is recused from certain activities because of a real or apparent conflict of interests. These activities include serving as meeting chair or subgroup chair, drafting text that discusses cancer data or contributes to the evaluations, and participating in evaluations reached by either consensus or vote. Invited specialists are available during subgroup and plenary discussions to contribute the benefit of their knowledge and experience. Invited specialists also agree to serve in their individual capacities as scientists and not as representatives of any organization or interest. Their conflicting interests are fully disclosed to the meeting participants and in the IARC Monograph."	will be the principal investigator or co-principal investigator on the competing product. •The SGE or his/her employing institution receives (or is negotiating) a contract, grant, or CRADA from a firm that is the sponsor of the product that is the subject of the particular matter involving specific parties to be discussed at the advisory committee meeting, and the SGE is the head of the department that is conducting or will conduct the studies on the same product/indication that is the subject of the meeting, and the SGE: -Receives or will receive personnel or salary support; or -Designs/will design or advises/will advise on any aspect of the clinical trial(s); or -Reviews or will review data or reports from the clinical trial(s).		

	National Academies Panels (2003)	International Agency for Research on Cancer Monographs (2003)	Food and Drug Administration FACA Committees (2008)	Environmental Protection Agency FACA Committees (no single date)	National Institutes of Health Office of Extramural Research (2004 & 2011[2])
			•The SGE or his/her employing institution receives (or is negotiating) a contract, grant, or CRADA from a firm that is the sponsor of a product labeled for the same indication (or, if an investigational product, that has the same indication for use) as the product that is the subject of the particular matter involving specific parties to be discussed at the advisory committee meeting, and the SGE is the head of the department that is conducting or will conduct the studies on the competing product, and the SGE: -Receives or will receive personnel or salary support; or -Designs/will design or advises/will advise on any aspect of the clinical trial(s); or -Reviews or will review data or reports from the clinical trial(s)."		

	National Academies Panels (2003)	International Agency for Research on Cancer Monographs (2003)	Food and Drug Administration FACA Committees (2008)	Environmental Protection Agency FACA Committees (no single date)	National Institutes of Health Office of Extramural Research (2004 & 2011[2])
			The relevant part of 5 CFR 2635.502 says: "Where an employee's participation in a particular matter involving specific Parties…would raise a question in the mind of a reasonable person about his impartiality, the agency designee may authorize the employee to participate in the matter based on a determination, made in light of all relevant circumstances, that the interest of the Government in the employee's participation outweighs the concern that a reasonable person may question the integrity of the agency's programs and operations. Factors which may be taken into consideration include: (1) The nature of the relationship involved; (2) The effect that resolution of the matter would have upon the financial interests of the person involved in the		

	National Academies Panels (2003)	International Agency for Research on Cancer Monographs (2003)	Food and Drug Administration FACA Committees (2008)	Environmental Protection Agency FACA Committees (no single date)	National Institutes of Health Office of Extramural Research (2004 & 2011[2])
			relationship; (3) The nature and importance of the employee's role in the matter, including the extent to which the employee is called upon to exercise discretion in the matter; (4) The sensitivity of the matter; (5) The difficulty of reassigning the matter to another employee; and (6) Adjustments that may be made in the employee's duties that would reduce or eliminate the likelihood that a reasonable person would question the employee's impartiality."		

Appendix C

Resources for Conducting a Systematic Review

The references and links below suggest resources for agencies and other entities interested in formulating their own specific approaches to the task of conducting a systematic review. This set of resources is not meant to be comprehensive and the sources are not necessarily consistent with each other, but they illustrate a range of current practices and thinking.

Examples of systematic reviews

The following are systematic review frameworks used by organizations and agencies. While there are differences, common elements are used in all the systems.

1. National Guideline Clearinghouse, Agency for Healthcare Research and Quality, US Department of Health & Human Services
   www.guideline.gov

   The Clearinghouse is a comprehensive database of systematic clinical practice guidelines from government agencies and health care organizations. Describes and compares guideline statements with respect to objectives, methods, outcomes, evidence rating scheme, and major recommendations.

2. Center for Food Safety and Applied Nutrition, US Food and Drug Administration
   www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/ucm073332.htm#system

   Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims – Final IOM (Institute of Medicine). 2008. Improving the Presumptive Disability Decision -Making Process for Veterans. Washington, DC: National Academies Press.

3. Cochrane Reviews, The Cochrane Collaboration
   www.cochrane.org/cochrane-reviews

   Systematic evidence reviews that are updated periodically by the Cochrane Group. Reviewers discuss whether adequate data are available for the development of EBM guidelines for diagnosis or management.

Information on agency-specific systematic reviews

1. A Roadmap for Revision (pp. 151-167) in Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde (2011), Board on Environmental Studies and Toxicology (BEST), National Academy Press, Washington, DC.
   www.nap.edu/openbook.php?record_id=13142&page=151

2. Evidence-based Toxicology (EBT) Collaboration
   http://caat.jhsph.edu/programs/workshops/ebt.html

   A group of toxicologists with backgrounds in industry, government oversight, academia and animal welfare have created the EBT Collaboration to foster the development of a process, based on the Cochrane Collaboration in Evidence-based Medicine (EBM), for quality assurance of new toxicity tests for the assessment of safety in humans and the environment.

3. Special Issue: Evidence-Based Toxicology (EBT), Human and Experimental Toxicology, February/ March 2009; 28 (2-3).
http://het.sagepub.com/content/28/2-3.toc

Proceedings of the 1st International Forum towards Evidence-Based Toxicology

4. Establishing an Evidence-Based Framework (136-149) in Improving the Presumptive Disability Decision-Making Process for Veterans. IOM (Institute of Medicine). 2008. National Academies Press. Washington, DC.
www.nap.edu/openbook.php?record_id=11908&page=136

Examples of problem formulation for a systematic review

1. The Design of Risk Assessments (Problem Formulation pp. 77-79) in Science and Decisions: Advancing Risk Assessment (2009), Board on Environmental Studies and Toxicology (BEST), National Academy Press, Washington, DC.
www.nap.edu/openbook.php?record_id=12209&page=77

2. Problem Formulation, Technical Overview of Ecological Risk Assessment, US Environmental Protection Agency.
www.epa.gov/oppefed1/ecorisk_ders/toera_problem.htm

Examples of relevance assessment in a systematic review

1. Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease, Institute of Medicine. 2010. National Academies Press. Washington, DC.
www.nap.edu/catalog.php?record_id=12869

2. IOM. 2007a. Cancer biomarkers: The promises and challenges of improving detection and treatment. Washington, DC: The National Academies Press.
http://books.nap.edu/catalog.php?record_id=11892

3. IOM. 2007b. The future of drug safety: Promoting the health of the public. Washington, DC: The National Academies Press.
www.nap.edu/catalog.php?record_id=11750#toc

4. Analysis Phase: Ecological Effects Characterization, Technical Overview of Ecological Risk Assessment, US Environmental Protection Agency.
www.epa.gov/oppefed1/ecorisk_ders/toera_analysis_eco.htm

Examples of the delineation and documentation of weighting studies to reach conclusions

1. Hill, A.B. 1965. The environment and disease: Association or causation?, Proc. R. Soc. Med. 58:295-300.

2. DHHS (US Department of Health and Human Services). 2004. The Health Consequences of Smoking: A Report of the Surgeon General. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Atlanta, GA [online]. Available: www.cdc.gov/tobacco

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