

Engaging Expert Peers in the Development of Risk Assessments

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Abstract

The participation of external technical experts in the development of risk assessment documents and methodologies has expanded and evolved in recent years. Many government agencies and authoritative organizations have experts peer review important works to evaluate the scientific and technical defensibility and judge the strength of the assumptions and conclusions (OMB, 2004; IPCS, 2005; IARC, 2006; Health Canada, 2006; US EPA, 2006). Expert advice has been solicited in other forms of peer involvement, including peer consultation in, for example, the US EPA's Voluntary Children's Chemical Evaluation Program (VCCEP). This paper discusses how the principles and practices of peer review can be extended to other types of peer involvement activities (i.e. peer input and peer consultation) to develop high quality risk assessment work products. A comprehensive process for incorporating peer input, peer consultation, and peer review into risk assessment science is outlined. Four key principles for peer involvement— independence, inclusion of appropriate experts, transparency, and a robust scientific process – are discussed. Recent examples of peer involvement in the development of Health Canada's Priority Substances and Domestic Substance List (DSL) programs under the Canadian Environmental Protection Act (CEPA) serve to highlight the concepts.

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1. Introduction

In recent years those both inside and outside of government have called for expert peer review of the scientific basis for government environmental regulations. The call has been for more involvement by external scientists to judge the scientific and technical merit, as well as the quality of documentation, which underlies the basis for regulations and government policies, including policies on risk assessment. In the United States, the federal government now requires external peer review of influential scientific information (OMB, 2004; US EPA, 2006). In Canada, peer review has been an integral component of health assessments for Existing Substances conducted under the Canadian Environmental Protection Act (CEPA) (see: <http://www.hc-sc.gc.ca/exsd>). International bodies, such as the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) have also designed their risk assessment programs to include expert review (IPCS, 2005; IARC, 2006). Engagement of peers is an important component of the US Environmental Protection Agency (EPA) Voluntary Children's Chemical Evaluation Program (VCCEP) in which chemical manufacturers prepare risk assessments on chemicals to which children are exposed (see <http://www.epa.gov/chemrtk/vccep/index.htm>).

This paper discusses how the principles and practices of peer review can be extended to other types of peer involvement activities to develop high quality risk assessment products. Based on the authors' experience conducting expert peer review and consultation for risk assessment documentation in Canada and the US, a comprehensive process for incorporating peer involvement into risk assessment science is proposed. Key principles for peer involvement are identified and discussed. Recent examples of peer involvement in the development of Health Canada's Priority Substances and Domestic Substance List (DSL) programs under the Canadian Environmental Protection Act (CEPA) serve to highlight the concepts. Perceived benefits of peer engagement in the development of specific products are highlighted in the interest of contributing to additional development of more objective criteria for judging the nature and extent of improvement of the quality of risk assessment products resulting from peer involvement.

2. Background and Definition of Terms

Peer review has traditionally been understood by scientists in the context of deciding if a submitted manuscript is worthy of publication or a grant proposal should be funded. However, in the public arena, governments have engaged outside scientific experts to review formally the technical basis of policies since the 1800s (Guston, 2000). Recently, there have been increasing calls for peer review of documents and analyses that support regulation. The calls for peer review are based on a belief that external peer review will promote good science, which will lead to good policy, and that better science increases legitimacy of decisions (Guston, 2002). Expert panels have been commonly convened for review of complex health assessments of Existing Substances under CEPA, and in the US, the EPA has several standing scientific advisory committees (e.g., Science Advisory Board) to provide expert review.

Soliciting advice from scientific peers need not be limited to formal peer review. Scientists have long sought colleagues' opinions on ideas, hypotheses, and works-in-progress. Gathering advice and review from peers can be broadly termed "peer involvement" and can be useful to the development of sound risk assessment work products and decisions. Peer involvement can be formal or informal and engage those both within and outside the authoring organization. US EPA defines peer involvement broadly as the "active outreach to and participation by the broad scientific, engineering, public health, economics and other social science communities beyond the Agency (external), as well as with in the Agency (internal)" (US EPA, 2006, page 12).

In this paper, the term "peer" is defined as experts who collectively are of equal standing, that is, those who have at least the same level of training and experience as the authors of the report. Therefore, they are qualified to evaluate and judge the adequacy of the authors' science and conclusions. Non-technical interested persons are not included in the definition of "peer". While it may also be desirable and appropriate to involve non-technical participants to gain insights into public opinion and priorities, this type of "public" involvement is not the subject of this paper.

Three types of peer involvement are addressed in this paper: peer input, peer consultation, and peer review. In this context, these key terms are defined as follows:

- **Peer input** –soliciting information, data, or opinion from scientific peers, generally at an early stage of a work product's development. For peer input, the emphasis is on appropriate focus, data acquisition and identification of issues. The process may be formal or informal. The experts may be internal or external and may or may not be independent of the authors or of the subject. For example, while not "peers" *per se*, scientists from stakeholder groups may provide input at this early stage in specific areas .
- **Peer consultation** – a formal or informal process to gather independent expert peer opinion and advice on a work product during its development. Peer consultation is most helpful when the document is complete enough to benefit from a review, but the analysis may still be in flux, allowing the experts' comments to be readily considered and influence future direction. Peer consultations may be conducted on an entire work product or on specific issues or analyses. The emphasis is on scientific expert opinion and advice, rather than data acquisition.
- **Peer review** – a formal, external, and independent review of an intended final work product. The intent of a peer review is to gain agreement from a group of external expert peers regarding a document's conclusions and the scientific basis for those conclusions. The emphasis is on agreement by the experts or agreement on the approach and conclusions, with consensus amongst the experts providing additional support and defensibility of the results.

The next section demonstrates how these three types of peer involvement can be incorporated into a comprehensive process that maximizes benefit from peer involvement in risk assessment science.

3. Comprehensive Process for Peer Involvement in Risk Assessment Science

While formal peer review of draft final work products by external scientists is now common practice for risk assessment projects in many parts of the world (OMB, 2004; IPCS, 2005; IARC, 2006; Patton and Olin, 2006; US EPA, 2006), additional peer involvement at earlier stages of product development may improve quality and efficiency. Most risk assessment documents involve three primary stages of development: Problem Formulation (including issue identification and data gathering); Draft Work Product; and Final Work Product. Different types of peer involvement can enhance quality and efficiency at each of these stages and improve the technical robustness of risk methodologies, assessments, and results. A comprehensive process for incorporating this additional peer involvement into all stages of risk assessment development includes three steps: identifying missing data and scientific issues early in product development (Problem Formulation or Issue Identification Stage); seeking advice from peers (consultation) on interim drafts (Draft Work Product Stage); and, formal peer review of the final draft product (Final Draft Work Product Stage). Table I identifies the key type of peer involvement activity at each stage of development, with key peer involvement features for each stage.

Insert Table I here

The scope of the work product and other factors dictate the desirability and usefulness of peer involvement at each stage. Complex work products or those that have significant impact (e.g., methodological approaches that impact entire programs or large numbers of assessments) might benefit from incorporating peer involvement into all stages, while less complex products may be sufficiently addressed with a simple written peer review of the final draft. To determine what level and type of peer involvement would be beneficial at the earlier stages of product development, a number of factors should be considered including scientific complexity and uncertainty, the level of risk involved and magnitude of potential risk, and standard practice within the organization. The greater the significance of these factors, the more peer involvement may serve to enhance the quality and credibility of the final work product.

The Canadian government's efforts to assess human health risks for large numbers of Existing Chemicals under the Canadian Environmental Protection Act (CEPA) serve to illustrate the nature of a comprehensive model including different stages of peer involvement in risk assessment. Canada is the first country to introduce a legislative requirement for systematic priority setting of all chemicals in commerce (Existing Substances). CEPA required that the Ministers of Health and Environment complete categorization" (priority setting) of all of the approximately 23,000 substances on the Domestic Substances List (DSL) by September 2006, with subsequent screening and full risk assessment, where warranted.

CEPA has required, therefore, the development of novel predictive methodology to set priorities based on potential exposure and hazard from amongst thousands of existing

chemicals. As a result, the program provides opportunity for incorporation of increasingly complex and robust models of peer involvement not only for assessments of individual substances or groups thereof (i.e., screening to Priority Substances) but also for development of complex predictive novel methodology (for categorization).

Specifically, then, the program increasingly includes more formal peer input at earlier stages of development for both methodology and assessments. In addition, the complexity of peer input, consultation, and peer review is greater for more robust assessments for substances of highest priority (see Figure I). This approach maximizes efficiency while maintaining the defensibility of output of the three different levels of priority setting and assessments of increasing complexity within the program (categorization, screening assessment, and full assessment).

[Insert Figure I around here]

Full assessments for Priority Substances generally include early peer input to identify relevant data, followed by external panel peer reviews at the end of the process. On the other hand, for screening assessments, an early issue identification stage is envisaged to solicit peer input on identification of relevant data and issues and confirmation of the focus of the assessment. Since screening assessments are less complex, at a later stage in their development, peer review for these assessments is generally restricted to written comments by several external experts (i.e., a letter review). Panel meetings will be convened only where there are subsequent outstanding issues.

Development of methodology for priority setting and assessment of risk often entails all three stages of peer involvement (i.e., input, consultation, and review). Examples from the Existing Chemicals health assessment program under CEPA are included in each section below to illustrate use and potential benefits of peer involvement.

3.1 Peer Input in Problem Formulation Stage (Including Data Gathering and Issue Identification)

In the initial planning or problem formulation stage of development of a risk assessment, the project lead, authors, and decision makers must clearly define the problem or issue to be addressed by the work product. From these efforts, a work plan is developed. This may be fairly straightforward if there are previous similar efforts or if the usual approach is commonly accepted (e.g., a simple site assessment within a program with explicit guidance, or a chemical assessment document). However, in other situations involving novel ideas, development of methodologies, analytical approaches, or complex assessments, the problem formulation stage is a substantial and important effort. In these situations, incorporating peer involvement to help develop the approach can improve efficiency of production and content of the overall work product. In addition, peer input can identify the need for additional data, bring to light unpublished data and studies, and identify key scientific issues that will need to be addressed.

To increase the efficiency of assessment of larger numbers of substances, it is envisaged that screening health assessments for Existing Substances under CEPA will incorporate an early, formal stage of Issue Identification. The objective is to ensure maximum utilization of previously well-documented, peer-reviewed assessments, and adequately and accurately focus on more recent information and critical issues. While the process for input is still in development, it is envisaged to incorporate robust senior internal technical review and external peer input.

Peer input is the most common type of peer involvement at the problem formulation and issue identification stage. Peer input focuses on gathering data, information and input on issues and proposed focus. It is most useful in early stages of the development of a risk assessment to define the project scope, identify and explore issues, identify needed data, and potential alternative approaches. One of the most common types of peer input is a request for written comments in order to identify relevant data that may have been missed. Other techniques may also include formal and informal meetings, workshops, data calls, teleconferences, and web-based information solicitation and collection. The primary purpose of peer input is to gain information from experts about data, issues, or methodologies that will assist the authors in developing the approach for conducting the work. Peer input may be formal and structured or more informal. It may involve one-way solicitation of input, or a dialog between parties. While not “peers,” non-technical participants (i.e., stakeholders) from political, business, public interest and the general public may also be queried to gain insights into their opinions and priorities.

There can be significant benefit from obtaining input from experts in the problem formulation and issue identification stage. Early identification of issues allows the organization to best target resources and increase efficiency. Peers from both within and outside of the authoring organization can help to identify issues or provide missing and/or essential data. Authors can seek opinions and suggestions from peers in areas that may affect the scoping of the project, including possible options and feasibility, availability of data, and outstanding scientific or science policy issues. Peer input at this early stage leads to a better understanding of the scope, identifies issues to be resolved where resources should be focused, and facilitates collection of data. As a result, the draft document is strengthened by considering complete data sets and targeting resources to focus on, address, and resolve key issues early in the process.

The Existing Substances Division of Health Canada recently invited peer input to assist in guiding the development of the Complex Exposure Tool (ComET), one of several of the simple and complex tools designed to identify, in increasingly discriminating and iterative fashion, priorities for additional consideration from amongst all 23,000 substances on the DSL. This development was necessitated to meet the “categorization” requirement by the mandated deadline under CEPA of September 2006 (Health Canada, 2005).

A one-day workshop was held in the fall of 2004 as part of a larger effort to solicit input and data from scientific peers and others on the proposed construct and information base for ComET. For this workshop, Health Canada was also interested in communicating with and soliciting specific input from stakeholder groups (in addition to input from scientific

peers). Therefore, the benefit of the input received from stakeholders during the workshop is mentioned here, while recognizing that non-scientific stakeholders would not be considered “peers”. ComET is a leads to quantitative plausible maximum estimates of exposure of individuals in the general population by age group based on use scenario (sentinel products and emissions), physical/chemical properties and bioavailability. The tool encompasses estimation of both environmental (far-field) and consumer (near-field) exposure, the latter being based on “sentinel products” — that is, those products yielding the highest estimates of exposure for individuals in different age groups. The tool draws maximally on generic (i.e., non-substance-specific), publicly available information and transparently delineates assumptions and uncertainties. It is designed to be health protective, with conservative choices being made in the absence of data.

ComET is relevant to priority setting for both categorization and screening and constitutes the basis for identification of substances for which exposures of the general population are expected to be minimal and that as a result, deserve little additional risk-based regulatory attention in assessment. There were three goals for the peer input meeting:

- To increase understanding amongst peers and stakeholders of how the “tool” will contribute not only to the CEPA program but also potentially to other government and industry efforts.
- To solicit input, information, and comment on both the architecture of the data base and the supporting available data.
- To encourage collaboration with others to avoid duplication of effort and maximize the impact of resources invested to contribute to development of iterative approaches to efficient priority setting and assessment.

Significant effort was made to engage stakeholders, including the CEPA Industry Coordinating Group and Canadian Environmental Network in the peer involvement efforts. The meeting was announced widely to exposure experts, scientific societies, consumer and public interest organizations, government agencies, academics, companies and industry groups. Specific invitations were targeted to reach exposure assessment experts who could comment on the architecture, as well as industry stakeholders and others who may have useful data to populate ComET. The meeting was open to the public and participants attended in person, by webcast, or by conference call. Health Canada and their contractors described the goals and architecture of ComET and explained what data were currently available. This was followed by a number of breakout sessions on specific areas to solicit input on the proposed construct of the tool and to identify additional sources of data. Over 100 people participated, either in-person or via the conference telephone call or Internet webcast.

By offering interested persons multiple ways to attend the session, participation was maximized in order to gain essential information from a broader group. Use of the live webcast and conference lines allowed additional participation by those who could not attend in person, including Europeans who were considering similar types of information needs for the REACH (Registration, Evaluation and Authorisation of Chemicals) initiative. Those off-site submitted questions via email, and their questions were answered during the

meeting itself in real time. In addition, a recorded version of the webcast was made available after the meeting.

As a result of the peer input workshop, Health Canada obtained data that had not previously been available to them. The data were provided, principally as a result of increased understanding by potentially impacted stakeholders and/or partners of the value in this context of making publicly available, relevant but previously unreleased information, or additionally mining available data to increase its utility for ComET in the interest of leveraging resources to collaborate. In addition, by including key exposure experts, the peer input efforts ensured that the ComET architecture incorporated more inclusively, considerations based on the most recent developments in methodology for exposure assessment.

3.2 Peer Consultation in Draft Work Product Stage

At different times during development, a draft work product may benefit from the advice of peers to determine completeness of data coverage, to identify gaps in data or understanding, to gain comment on selection and application of approaches and analyses, or to evaluate the scientific strength of conclusions. Peer consultation is of most value at this draft stage of development because it allows for interaction between the authors, sponsors, and the expert peers and solicitation of advice from the individual experts, which can be considered in the analyses and documentation.

Peer consultation is an evolving concept in the field of risk assessment that contributes in the development of draft work products. It involves the formal solicitation of review and advice from experts, usually at an early stage of development when approaches and analyses may still be evolving prior to establishing a position or deciding on a preferred approach. Peer consultations do not usually seek to provide consensus approval (as would be the case for peer review). Rather, the output of a peer consultation is opinions, advice, and recommendations of the individual experts or group that may be used to improve the document or guide further efforts. A peer consultation may be held to review an entire document, or be focused on data and approaches to a specific issue or analysis.

Commonly, peer consultations are conducted either through a written (letter) review process involving one or more individuals, or by a group in a face-to-face meeting or teleconference. The format of the peer consultation will depend upon the complexity of the issues and the goals of the authors and sponsors. When soliciting written comment from experts, the request may be targeted to specific individuals and groups, or a broader net might be cast to invite comment from any interested expert. Convening an expert panel to meet in person with the authors allows for maximum interaction amongst participants, which can ensure better communication and understanding of the issues and recommendations. For a complex project, several rounds of written reviews or meetings may be held, in an iterative fashion for a single issue, or on different issues. The choice of peer consultation technique and timing depends on the complexity and controversy of the scientific issues and the need for expert advice.

Conducting a peer consultation for a draft risk assessment product can potentially, provide many benefits. In a peer consultation, experts can evaluate the strength, appropriateness, and defensibility of the work product's analyses and conclusions, and provide recommendations for improvements. A peer consultation meeting provides the opportunity for interaction among the experts, authors, and sponsors. The interaction of a meeting allows for complex concepts to be more fully expressed by all participants and a common understanding or new ideas may emerge from the discussions. The advice and recommendations of expert peers can assist the authors in identifying scientific weaknesses and addressing them, as well as selecting the best data or decisions or modifying focus of next steps in methodology development. Incorporating peer consultation prior to a peer review can help avoid the "rough draft syndrome" at a late stage wherein the authors may submit a less than complete work, expecting the peer reviewers to provide guidance on how to proceed, which is not the intended objective of peer review. Peer consultation also increases awareness of the program content and expands familiarity with sources of expertise for increased opportunities for future collaboration.

Peer consultation has been incorporated into various aspects of the Health Canada Existing Substances program to garner expert advice about a variety of chemical specific risk issues. For example, in relation to aluminum salts which were included on the second Priority Substances List under CEPA, it was determined that the available data were inadequate as a basis for completion of the mandated risk assessment (Health Canada, 2000) and peer consultation has contributed considerably to the design of relevant studies.

This peer consultation involved a committee of scientists from universities, government, laboratories, industry, and consultants who assisted Health Canada by providing expert advice on the design of research to address data gaps for aluminum. This maximized access to a broader range of specialized expertise than would have been available within governments, or to a single group of stakeholders, and facilitated collaborative interface with potential partners internationally in the conduct of the research. Preparation and posting of the report of the meeting maximized transparency as a basis for additional input from interested parties.

In another example, iterative peer consultations were helpful in the development of complex methodology related to the systematic identification of priorities for assessment (i.e., categorization) from amongst the thousands of chemicals on the Domestic Substances List (Health Canada, 2005). The complex hazard tool (ComHaz) is another of several of the simple and complex tools designed to iteratively identify in increasingly discriminating fashion, priorities for additional consideration from amongst all 23,000 substances on the DSL. It involves hierarchical consideration of various sources of information (including reviews, empirical data, [quantitative] structure-activity analysis, and comparison with analogues) for a range of endpoints of toxicity, which are also considered in stepwise fashion.

Genotoxicity is a critically important component of the tool, due to the availability of data for comparatively large numbers of substances, for this endpoint. The objective of an initial peer consultation held in March 2002, was to review a scoring system for this

component developed by genetic toxicologists within Health Canada (ILSI, 2002). This system differentiated between mutagenicity, clastogenicity and indicator assays in *in vivo* tests in mammals and *in vitro* tests, and incorporated, as well, consideration of predictions generated by (quantitative) structure activity relationship [(Q) SAR] models. Specifically, the panel at the peer consultation responded to a request to assess the degree of confidence/uncertainty in a number of variants of the scoring system in the context of priority setting for existing chemicals to be taken into consideration in further development of the tool.

The construct of the ComHaz tool is hierarchical, not only in consideration of sources of data but also complexity of consideration. The first stage is based on a conservative “first hit” approach for data and endpoints based on specified criteria; the next stage involves consideration of weight of evidence for qualitative endpoints of capture (e.g., cancer, genotoxicity). This latter aspect was the subject of an additional consultation (TERA, 2005a), which built on the output of the prior genotoxicity consultation. In the second peer consultation, a group of experts in both genotoxicity and quantitative structure activity was convened to evaluate Health Canada’s draft *Complex Hazard Tool (ComHaz) Preliminary Weight of Evidence Framework for Genotoxic Carcinogenicity*. The framework was a work in progress and the purpose of the peer consultation was to access advice from leading experts on how it might be further developed as one element of an approach to efficiently set priorities based on hazard for large numbers of chemicals. Through written review and conference calls, experts considered the relative weighting of empirical data versus (Q)SAR predictions, the relative weighting of predictive power of the underlying assays for (Q)SAR output within a line of evidence, the appropriate integration of a (Q)SAR battery, simple indicators of model robustness, and application of analogue/surrogate approaches. The panel made several recommendations concerning weighting of analogue/surrogate approaches as a separate line of evidence, and resulted in the framework giving equivalent weighting to SAR and QSAR.

In the first consultation, experts were principally endpoint specialists; in the second, modelling expertise was critical to ensure familiarity with the available (Q)SAR software and approaches. Interactions amongst the experts and Health Canada developers during these consultations allowed for greater understanding of the tool and framework’s purpose and how the models and result could be used. Experts were screened for independence, to insure they had not done prior work for Health Canada on developing the QSAR weight of evidence framework; and also for conflict of interest, in particular to exclude those who may be directly paid by or actively affiliated with (Q)SAR modeling software companies (both those whose models served as the basis for Health Canada’s proposed framework and competing commercial models).

Another significant benefit of these peer consultations is increasing the familiarity of the broader scientific community with current challenges in risk assessment in a regulatory context to stimulate relevant additional work. Consideration of complex and novel questions in peer consultation to address progressive regulatory mandates often presents considerable challenges in communication of the requirement for input. This is often related to the variation in context of the objectives from traditional applications with which

the experts are most familiar. That investment in this area is warranted, however, is underscored by the considerable potential benefit in improvement of the final product, based on robust consideration of a wide range of expertise and creative input.

3.3 Peer Review of the Final Draft Work Product

In many organizations, near final risk assessment documents are routinely peer reviewed by one or more independent experts, that is, those outside of the authoring organization who were not involved in the development of the document and have no conflicts of interest with the work product or sponsors. The Presidential/Congressional Commission on Risk Assessment and Risk Management in its 1997 report notes the critical importance of peer review in regulatory decision-making to “enhance the credibility of agency decision and position and to improve their technical quality” (Presidential Commission, 1997, p. 103). For risk assessment products, peer review involves an in-depth assessment of the inclusiveness (i.e., comprehensive coverage), assumptions, calculations, alternate interpretations, methodology, and conclusions. Peer review panels often seek to reach consensus or common agreement regarding the adequacy of the product reviewed.

The authors should be fairly certain that their work product is nearly final, is well documented and transparent, that the data are complete, that the analyses and techniques used are scientifically defensible, and that the conclusions are well supported. The peer review can take place through the individual letter reviews by one or more experts, or may involve one or more meetings of experts to discuss the document and reach group conclusions.

Expert peer review assists in explicitly delineating the uncertainties inherent in any scientific process, and perhaps the risk assessment process in particular. For example, experimental methods and analytical techniques adopted in environmental and human health risk assessment often are controversial and may not have wide scientific consensus. Improvements in methodology are continually introduced. Because risk assessments rely upon significant scientific judgment and assumptions, these assumptions must be critically evaluated. Testing the assumptions and communicating and understanding the uncertainties is important to be able to provide decision makers with a fuller understanding of the strength of the assessment and conclusions. In risk assessments, strength-of-evidence or weight-of-evidence approaches are commonly adopted in which the body of knowledge is assessed to reach conclusions regarding a chemical or agent’s potential to cause human health risk.

The Health Canada Priority Substances program involves both peer input and two stages of peer review for more complex health assessments. Early in the process, draft supporting text is sent to technical experts within stakeholder groups for input on the adequacy of coverage – i.e., whether any key data or studies are missing or issues unidentified. Later, in the first stage of peer review, the supporting documentation, draft hazard characterization, and dose-response analysis are sent to selected experts for written review. Finally, for the more complex and controversial assessments, a panel of experts is convened to review the draft final supporting documentation, hazard characterization, and dose-response analysis.

For more recently introduced screening assessments, a stage of peer input (“Issue Identification”) and written peer review is envisaged. Consideration is being given, currently, to development of a continuing series of meetings for peer review of multiple screening assessments.

This routine incorporation of extensive peer input and review in the assessment of Existing and Priority Substances contributes considerably to the defensibility and integrity of output. It has also contributed considerably in the communication of program objectives and resulting engagement and access to a wide range of expertise.

Beneficial impact for individual substances has included, for example, maximal utilization of available data in drawing conclusions (e.g., quantitation based on epidemiological data for acrylonitrile and ethylene oxide to bound estimates of dose-response from animal studies). On occasion, it has verified the need for additional analyses of the output of key studies forming the basis of conclusions in previous assessments based on consideration of their adequacy by Health Canada authors. This has led to the conduct of more appropriate studies to inform risk assessment.

For example, in 2000, the supporting documentation, draft hazard characterization and dose-response assessment on ethylene glycol were reviewed by a panel of experts convened by Toxicology Excellence for Risk Assessment (*TERA*) (*TERA*, 2000). At the conclusion of the peer review meeting, Health Canada authors had continuing unanswered questions regarding the pathological findings of a key study. Additional input was solicited from one of the authors of this study and Health Canada’s revised analysis was submitted to the same peer review panel for additional review. A conference call was held with the panel and at this meeting the study author participated to answer questions regarding the study and kidney pathology. An additional expert in pathology was brought in by *TERA* to serve as an advisor to the panel and to provide independent opinion on the histopathological analysis for this and another critical study. The content of the draft documentation prepared by Health Canada and subsequent input from peer review resulted in suspension of the assessment and conduct of an additional chronic study by industrial stakeholders (Environment Canada and Health Canada, 2000). More recently, the Existing Substances program has collaborated with a consortium of industrial stakeholders to sponsor the ethylene glycol category for consideration in the Organization for Economic Co-operation and Development (OECD) High Production Volume Chemicals program. This peer review illustrates the benefits of the need for flexible process to engage the appropriate experts sufficiently (in multiple meetings if necessary) to resolve technical issues.

4. Application of Peer Review Principles to Peer Involvement

A successful peer involvement program requires active support of management. Management responsibilities in scientific peer review were discussed in a recent report by the International Life Sciences Institute (ILSI, 2005; Patton and Olin, 2006). The authors describe nine areas of responsibilities to agency managers on shaping peer review programs, including: creating a peer review culture; determining the need for and form of

the peer review; defining and distinguishing the review processes; planning and allocating resources; assessing the readiness of the work product for review; developing the “charge,” selecting reviewers and matching expertise; and, use of peer review comments in completing the report. When management addresses well these responsibilities, the organization builds a solid foundation for a peer involvement program.

Working from this foundation of management responsibilities, four broad principles are identified that are important for consideration and organization of peer involvement activities for each stage of product development. Adherence to these principles contributes to the quality of work products and integrity of peer involvement in risk assessment. These principles are independence, inclusion of appropriate expertise, transparency, and robust scientific process.

4.1 Principle 1: Independence

Independence is defined as both distance from the development of the work product and freedom from institutional or ideological bias and conflicts of interest. At early stages of project scoping, data and issue identification, independence is not as critical. Input from those who work closely in the same organization as the authors or from individuals with strong biases or even conflicts of interest may be permitted in order to acquire important knowledge and insight. In these situations, however, it is wise to ask participants to disclose any potential basis for perceived lack of independence to ensure that all are informed and aware. At later stages, independence becomes more important.

Independence of the peers and the review process is critical in the last stage of peer review to ensure the scientific adequacy and strength of a risk assessment. At this point, a lack of impartiality on the part of the peers may result in the peers not challenging weak data, analyses, or conclusions, and may damage the credibility of the review. Peer reviewers must also be independent in that they should not work in the same agency or organization as the authors, nor work closely with the authors. They should also not have contributed significantly in the development of the work product. However, in some situations with complex assessments, it may be beneficial to involve the same peers in a series of peer consultations or reviews, covering distinct issues or portions of the assessment. The conclusions and recommendations from earlier consultations and reviews may contribute to the work product at later stages.

At the later stages, the reviewers must also be free of conflict of interest with the authors, sponsors and affected parties to ensure independence and establish credibility. Conflict of interest is defined by the US National Academy of Sciences (NAS) as:

“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...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.” (NAS, 2003)

Potential conflict of interest needs to be evaluated for each reviewer prior to selection; and a clear and unambiguous conflict of interest policy applied.

Those organizing a peer review should also be independent of the work product so as to be objective when selecting the reviewers, developing the charge questions, conducting the review, and reporting the results.

4.2 Principle 2: Inclusion of Appropriate Expertise

The success of a peer involvement hinges on the participation of highly qualified “peers” -- those who are qualified through training and experience to offer scientific opinions on the questions and issues at hand. Those responsible for organizing peer reviews agree that appropriate expertise is the primary factor in selecting reviewers (NAS, 2003; OMB, 2004; ILSI, 2005; SOT, 2003; and *TERA*, 2005b). For risk assessment products, it is essential to identify and involve experts from fields such as toxicology (including sub disciplines such as pathology), epidemiology, biochemistry, statistics, and modeling. The peer review of ethylene glycol discussed above highlighted the importance of having essential expertise available to resolve key issues and questions.

There are a number of considerations in selecting experts for peer involvement. It is helpful to have the peers come from diverse backgrounds and affiliations (e.g., government, academia, industry, environmental or public interest groups, consulting) to provide a range of scientific perspectives. Peers should not “represent” a particular interest or group (e.g., industry, government, or environmental) rather, as the NAS points out a wide range of perspectives is “often vital to achieving an informed, comprehensive, and authoritative understanding and analysis of the specific problems and potential solutions to be considered by the committee.” (NAS, 2003, page 2). In addition to perspective, if there are clear opposing views on key issues, those different views should be included. Organizers should ask questions to evaluate how strongly panel candidates hold to these opposing views, since a panel could be ineffective if members hold views so strongly that they are not able to consider new data and work toward consensus. Organizers should document their panel selection and note situations where clearly opposing views on key issues have been addressed in the panel selection.

For panel meetings on more significant and complex risk assessments, it is important that a sufficient number of peers are included to ensure that all important aspects are addressed with duplication in critical areas so that the multiple qualified experts can meaningfully exchange ideas and opinions. In addition, a balance of three types of expertise is essential: scientists knowledgeable about the subject chemical, those with experience in the disciplines relevant to assessment of animal and human health effects, and experts in risk assessment methodologies and practices.

In addition to selecting the right types of expertise, an experienced chairperson will make sure that all views are heard, keep the discussion on subject, and be able to summarize and synthesize the diverse statements and discussions in a meaningful way.

Selecting the right peers also involves ensuring that they are independent of the authors and sponsors and can provide objective opinions (see Principle 1 above). It also entails that they are prepared to dedicate sufficient time and effort to familiarize themselves with relevant background materials. For this reason, it is often helpful to solicit submission of written comments prior to discussion at any review meetings. As discussed above, independence of peers is essential for peer review, but may not be as important for other peer involvement activities.

4.3 Principle 3: Transparency

Peer involvement activities should be transparent, so that those both within and external to the process can evaluate how the activity was organized and conducted, and judge for themselves the adequacy and credibility of the process and the results. In the context of peer involvement, the word “transparency” encompasses more than just the need to reveal the names of the reviewers. Rather, transparency refers to a philosophy that encourages open communication about the basis for and nature of the important decisions made during the process of conducting a review, to enable judgment of its credibility. Particularly critical in this context is the basis for selection of the reviewers and sufficiently detailed record of the panel members’ deliberations and basis for conclusions and recommendations. Transparency is most significant and important for peer review of a near final product, where expert judgments are being made on the adequacy of the product; but transparency is also a good practice for other peer involvement activities. Efforts to be transparent can range from the simple -- making public the list of peers consulted on an issue and reports on the use of their input – to more involved, open meetings with the public in attendance. When panel meetings are held, interested parties and the public may be invited to observe the proceedings and examine the same materials as the reviewers. Those responsible for peer involvement activities should be careful to insure that all relevant peers have access and the opportunity to input, to avoid an actual or perception of favoritism to one party over another.

Transparency is enhanced with good documentation of the process and results. If real-time observation of a meeting is not planned, then at a minimum the process and results should be fully documented so that the interested parties have a clear picture of how the peer review was organized and the results obtained. For example, a report of a peer review would include identification of the reviewers and their credentials, how the reviewers were selected; the questions the reviewers were asked to address, the materials that they reviewed; and, the reviewers’ major comments and conclusions.

4.4 Principle 4: Robust Scientific Process

To insure high quality peer involvement, it is important for the focus to be on the science – the robustness of the available data, the analyses, and the defensibility of the conclusions. The focus of the peer involvement should be on the scientific evidence and conclusions, and not policy or implementation issues (these need be addressed in equally transparent fashion but in separate efforts).

Robustness is dependent on a number of key factors. Appropriate experts must be involved, the experts must be asked the proper questions to address critical areas, the materials should be complete enough to facilitate a high quality process, and the results of the peer involvement should be well documented. A robust scientific process that addresses the first three principles will contribute to robust scientific results and work products.

An essential element of a robust peer involvement process is involvement of scientists who have the requisite expertise to provide input or evaluate the work product. For peer input, the scientists may be self-selected and volunteer their information and opinions. However, for peer consultations and reviews, the person or organization selecting the peers need to have a sufficient understanding of the key scientific issues and methods in order to identify the necessary expertise to address those issues and to insure that the right types of expertise are brought to the process.

Robustness also implies that the scientific completeness of the questions being asked the peers. Where there is peer involvement in early stages, critical scientific issues will be identified by all participants, contributing to robustness. The broader the expertise of the peers involved, the greater the input and perspectives. However, for a peer review, it is preferable to have a third party, independent of the work product, develop the charge to peer reviewers. The charge asks reviewers focused questions regarding direction and scope of the document to guide their review. It should focus on the critical issues and questions to be efficient, but allow the reviewers to raise issues that might be important, but not initially identified or anticipated. The authors and sponsors may contribute the questions and issues they wish to see addressed, but an independent party should make sure the charge is complete and the questions objectively presented. Experts involved in peer reviews and consultations should be given the opportunity to raise issues for discussion independently to ensure that no key issues or critical questions are missed.

Robustness also involves insuring that the materials are complete and transparent so that the peers can provide meaningful input or opinion. Those organizing peer involvement need to ensure that the materials are sufficiently robust so as to maximize the value of the review by peers.

Finally, those preparing reports on the peer involvement activities (e.g., peer review report) should sufficiently comprehend the review materials, so that the report accurately characterizes the discussions. This requires the engagement of experienced risk assessment scientists who understand the issues under discussion. For peer reviews, the report should document how the panel reached its conclusions and contain unambiguous recommendations that are presented in a way that is useful to the authors.

5. Conclusions

Increased efficiency in completion of defensible assessments, including incorporation of tailored approaches to peer input, consultation, and review is essential to meeting expanding mandates worldwide to consider health impact of exposure to much larger numbers of existing chemicals, which were introduced into commerce with little or no

pre-market assessment. In this paper, developments in the nature of a process for various stages of peer involvement have been described and illustrated through consideration of specific examples highlighting perceived benefits in scientific robustness and quality of the end products.

It is hoped that these examples are helpful in increasing understanding of the potential contribution of expert peers in the identification of additional data, alternate analytical approaches, and weaknesses in logic and reasoning. Experts' participation can strengthen the risk assessment and enhance the credibility and public confidence of the results. Peer involvement contributes to communication within the scientific community and beyond. Further to the evolution of distinct stages of peer involvement described here and their perceived benefits, additional development of measurable criteria that would permit a more objective analysis of the impact of peer involvement on the quality of risk assessment products would be a logical next step in additionally strengthening the basis for peer review and other peer involvement's expanded role within the US government (OMB, 2004; US EPA, 2006), as well as international governments and health agencies (see for example <http://www.hc-sc.gc.ca/exsd>; IPCS, 2005; IARC, 2006).

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Table I. Summary of the three stages of risk assessment development, the types of peer involvement techniques that can be used and the issues and questions appropriate for that stage.

Development Stage	Type of Peer Involvement	Questions and Issues to be Addressed
Problem Formulation, Issue Identification, and Data Gathering	Peer Input Data requests Workshops Meetings , informal or formal Informal discussions Expert Elicitation to fill data gaps or address uncertainties	Is there an accepted standard approach available? Are there previous relevant examples to follow? Are there data or analytical tools to suggest? Do outside parties have additional data/information? Are there outstanding science or science policy issues that must be resolved or addressed? Should additional studies be conducted or data collected? What is the available budget and timeline?
Draft Work Product	Peer Consultation Requests for written comments or review Panel meetings or conference calls On single issues or entire work product	Were all the appropriate data identified? Were the data interpreted correctly and presented in sufficient detail? Are there alternative approaches that should be considered? How can the work be strengthened and improved?
Final Draft Work Product	Peer Review Written or letter review Panel meetings or conference calls On near final work product	Focused and formal charge questions covering: The completeness and strength of the data presented The defensibility of the assumptions The use of appropriate analyses and methods The strength and defensibility of the conclusions The strength and scientific defensibility of the rationales provided for choice of: study, effect, level, models, uncertainty factors, etc. More specific questions regarding key chemical or document specific issues

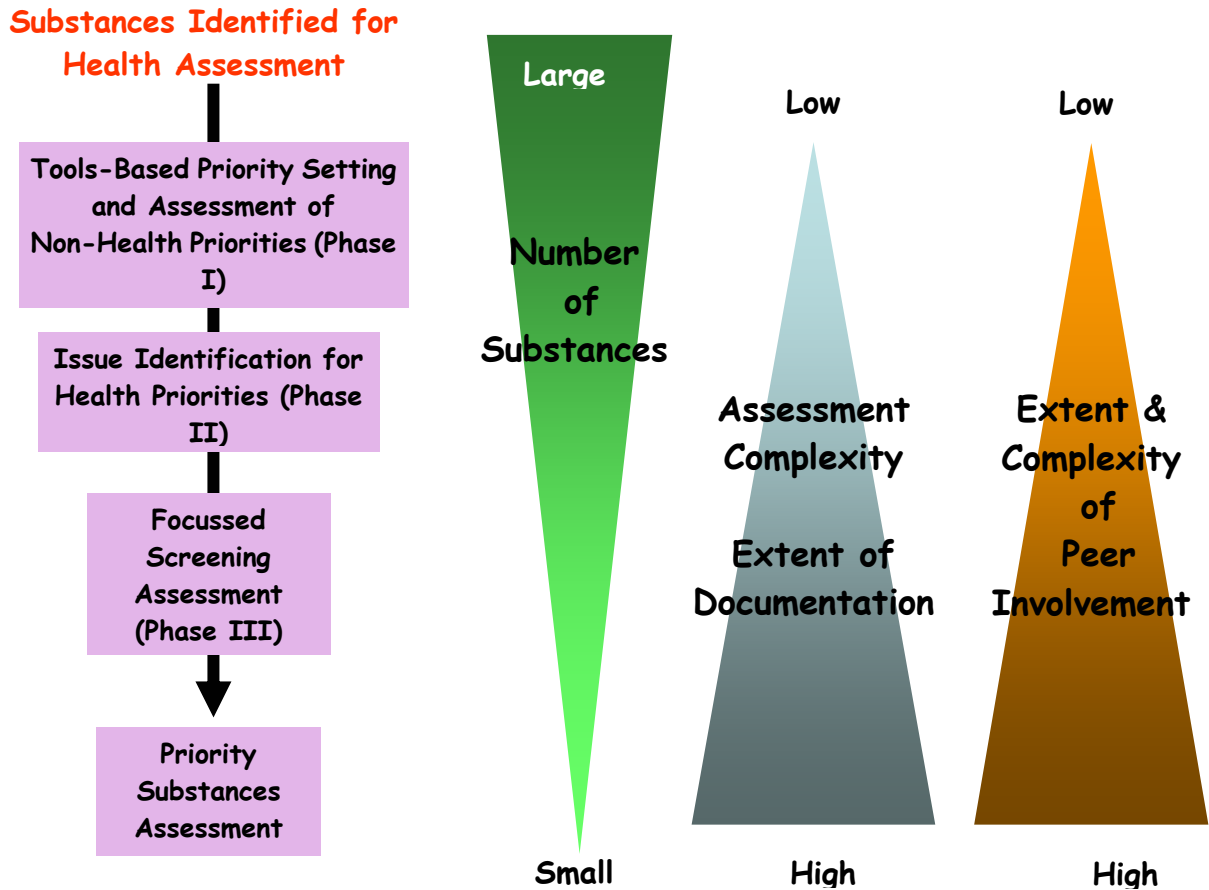


Figure I. Health assessment complexity for peer involvement. As chemicals are screened for more detailed assessments, the complexity of the assessments increase along with the extent and complexity of the peer involvement activities.