Multi-Stakeholder Contribution to Biotechnology Environmental Assessment

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Abstract

Environmental assessments, such as those for biotechnology applications, are typically conducted by small groups of expert assessors, but scholars and practitioners are increasingly interested in involving diverse stakeholders. In addition to other reasons for broader involvement, researchers have proposed that stakeholders could substantively aid assessment by (1) contributing system knowledge; (2) applying diverse conceptual models; (3) helping available knowledge keep pace with assessment needs; and (4) contributing based on their values, as do narrow expert assessors.

Hypothesizing that these types of contribution, suggested theoretically or observed in single workshops, represent key sources of stakeholder contribution across processes, this study examines contribution in several diverse participant processes: an Environmental Protection Agency (EPA) workshop on testing schemes for some engineered microbes compared with another EPA office's testing requirements for other engineered microbes; an MIT-Wilson Center workshop series on synthetic biology environmental assessment research needs; and the Food and Drug Administration's engineered salmon environmental assessment along with diverse stakeholder comments and critiques. The study also identifies practical considerations for enabling multi-stakeholder contribution and applies lessons to broader societal processes. The study analyzes process documents, conversations with conveners and participants, and participant observation. It also reviews knowledge about biological processes representing important areas for assessment and research, discussing complexities of knowledge production and use for assessment.

Stakeholders contributed in each of the four hypothesized ways across the cases, suggesting that diverse involvement could regularly contribute positively to assessment. Stakeholders also (5) challenged standard assessment approaches, challenges that could aid assessment as well. Practical considerations for enabling diverse participant contribution emerge from the cases: Process continuity over time; credible expectations of authority or influence in decision-making; and balance between predefined structure and flexibility and between technical tasks and enabling non-technical input may be key. Work developing approaches in these areas is needed, including on incorporating non-technical inputs, on processes encompassing later assessment stages, on integrating diverse participant processes with governance, and on diverse involvement in other aspects of technology development and execution. Better and increased stakeholder involvement could, through substantive content and incorporation of values, enable science, technology development, and decision-making best to serve society.

Supervisor: Kenneth A. Oye, Professor of Political Science and Data, Systems, and Society

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Summary

Assessing biotechnology applications, such as genetically engineered organisms that might be released or escape into the environment, for potential environmental effects is typically done by professional risk assessors or regulatory officials. Broader involvement is often limited. This study investigates how multi-stakeholder or diverse involvement may contribute to environmental assessment for biotechnologies. It also explores practical challenges and approaches for involving diverse participants and benefitting from their contributions.

In a participatory process, diverse stakeholders work together to evaluate potential environmental effects and help to decide whether or under what conditions to move forward with a technology or a particular use of a technology. Participants could include people who could be directly or indirectly affected or whose views or knowledge might be relevant to an assessment, such as researchers developing the technology, people who live near where the technology would be used, people who could benefit from solutions to a problem the technology tries to solve, ecologists, members of companies wishing to commercialize the technology, people with distinctive perspectives on implications of using the technology, risk assessors, or others.

Researchers observing workshops or discussing multi-stakeholder involvement theoretically have suggested that stakeholders could contribute to assessment by:

(1) Sharing knowledge of ecological, industrial, agricultural, or human systems relevant to potential effects;
(2) Using diverse mental models to think about the biotechnology application or the ecological or other systems involved;
(3) Helping available information keep pace with assessment needs, such as by identifying what research is needed, bringing in knowledge from their own areas, or conducting needed research; and
(4) Applying their values. Researchers argue that every assessment requires decisions involving values, and that diverse stakeholders should contribute and discuss based on their values rather than the assessment's being based on a few professional assessors' values.

This study investigates whether stakeholders regularly contribute in these ways.

This study examines three cases in which diverse participants were involved in activities related to biotechnology environmental assessment:

- An Environmental Protection Agency (EPA) workshop to provide information and develop ecological testing schemes for engineered microbes;
- Workshops to identify risks and develop a research agenda for synthetic biology ecological effects to aid assessment and technology design; and
- Stakeholder input and critique, including public comments and a legal complaint, to the Food and Drug Administration's (FDA's) environmental assessment for a genetically engineered salmon application.

This study finds that in each of the cases diverse participants contributed in each of the four proposed ways, suggesting ways that diverse involvement could aid assessment. Participants also (5) challenged established assessment approaches, for example by trying to include considerations typically omitted from environmental assessment, by challenging whether the typical testing schemes or risk assessment formulas are appropriate for the circumstances and developing alternatives, and by pointing out when knowledge may be insufficient to answer a question. Stakeholders also adhered to established models enough to produce results useful to conveners. Researchers have identified flaws in typical risk assessment approaches, including in the areas that stakeholders challenged, which suggests that the challenges could aid assessment.

The study also finds that decisions involving judgment calls that may stem from values along with scientific understandings, such as decisions about effects or risk factors to consider, research study designs, when and how to use a study result, or how to handle unknowns, regularly occur throughout assessment, suggesting that stakeholders' contributions may be valuable throughout a process rather than only at particular points or separated from scientific investigations. It also finds that even though one reason that people may involve stakeholders is to encourage acceptance of new technologies, acceptance might come only from assessment and decisions that stakeholders see as acceptable, not from processes that only try to encourage acceptance without learning from stakeholders' views.

The cases reveal practical considerations for enabling and benefitting from stakeholder contribution. These considerations include continuity, authority or influence, and balance between structure and flexibility and between technical and non-technical input.

Professional assessors typically work on assessments over time, and a group of assessors may work together over time on different assessments. Multi-stakeholder involvement, however, tends to occur as one-day or few-day workshops. Continuity would help stakeholders contribute, by allowing them to get to know the subject matter, bring in outside knowledge, and think and talk with others about the assessment, and by helping participants with different perspectives develop relationships and work together.

Continuity may raise particular challenges for diverse participant processes. Participants may live far apart or be able to devote only limited time, as the assessment is unlikely to be their primary job. Also, as typically conducted, participatory processes involve substantial convener preparation effort. Exploration of processes integrating stakeholders in ways that require less special effort, and other ways of enabling diverse involvement to happen over time, may prove beneficial.

Professional assessors may reasonably assume that the assessment or other materials they produce will have some authority or effect on real decisions. Diverse participant workshops, however, may be conducted with no expectation of real authority or influence. In each of the cases participants had some expectation or hope of influence, but some were still frustrated by their lack of real influence on decisions. Multi-stakeholder processes' having authority or influence would likely encourage participation and helpful

contribution, and enable those contributions to be used. Both the participatory and the decision-making processes may need to be carefully designed such that recommendations are clear and use of the input is apparent. Stakeholder groups' and decision-makers' working together over time may help, and creative solutions may be needed as to how decision-makers can reliably lend real authority to multi-stakeholder processes.

Current decision-making structures, such as government regulatory agencies, may operate in ways that make real use of multi-stakeholder participation difficult. Due to concerns about bias they may be restricted in whom they may consult. They may be legally constrained in the types of decisions they may make or the factors they may consider. They may be limited in the information they share, and their review processes may be designed such that initial assessments are complete before diverse participants are involved. Changes in regulatory structures could be beneficial, but alternative avenues for stakeholder input and influence should be explored. For example, companies or local governments could decide that they will pursue projects only with diverse participant input and approval, separately from any regulatory decisions. Labs, companies, funders, or other institutions that make decisions about biotechnologies could involve diverse participant groups as advisors. These and other solutions come with challenges, and creativity, goodwill, and experimentation will be needed. In the Lyme Project, biotechnology researchers have said that they will move forward with a community-focused biotechnology project only with local community support, and they are engaging the communities and local governments in a guidance process. This experimental project may become a model for broader involvement in technology guidance and decision-making.

Participatory processes should carefully balance structure and technical content with flexibility and enabling non-technical contributions. Adhering to established assessment models and encouraging participants to express their considerations in technical terms can help a group produce materials that can be useful in existing assessment and decision structures, giving stakeholders the possibility of influence and helping decision-makers benefit from their knowledge and insights. Focusing on technical questions may also help stakeholders with different perspectives work together. On the other hand, recognizing shortcomings of established approaches appears to be a strength of stakeholder involvement, and extensive structure can inhibit those contributions. Many participants may also not be adept in using technical language or scientific concepts, or they may bring important perspectives that cannot easily be expressed in technical terms. Even for participants comfortable with technical concepts, trying to express every idea in standard assessment terms could lead to distortions and confusion. Many multi-stakeholder processes make large efforts to teach participants enough of the science and technical concepts that they can participate. While these efforts may help, they may not really enable people without technical backgrounds to participate fully and comfortably. Continuity appears to help, and involving diverse technical participants who can help with expressing perspectives in technical terms may help, but assessments should also be able to use non-technical input, as well as challenges to assessment approaches. Work on assessment methods may be needed to achieve this goal.

Environmental assessment is meant to enable beneficial developments while protecting that which people hold dear. Involving diverse participants in assessment and decision-making promises to be an important way to further these goals, by producing assessments of maximal quality that carry stakeholder values at their core. Involvement of stakeholders has begun, and more of these efforts, along with work on how assessment, decision-making, and diverse participant involvement are done can help bring about a reality in which technology development and decisions are tuned to benefitting society. Both those involved in convening diverse participant processes and biotechnology decision-makers should involve stakeholders in ways that enable them to contribute to real assessment and decision-making.

Participatory processes could be useful in areas other than environmental assessment for biotechnology. In addition to assessing already-developed biotechnologies and proposed uses, diverse participants could help with decisions in such areas as what technologies to develop, how to design technologies and uses, or what problems to try to solve using a technology. They could evaluate potential social, ethical, economic, or health in addition to environmental effects. Stakeholders could also be involved in assessment and decision-making for other types of technology and for other large decisions or problems.

Chapter 1

Introduction

Responding to assessment complexities and to interest in involving diverse stakeholders, the present study examines several cases to investigate whether and how multi-stakeholder contribution may benefit biotechnology environmental assessment.

Biotechnology and Environmental Assessment

Biotechnology advances and proposed applications may be accompanied by consideration of environmental and perhaps societal implications. Involvement of diverse stakeholders or broader society in environmental assessment has seen increasing interest and investigation, and researchers have proposed a number of reasons to include diverse participants, including the possibility that diverse participants could contribute in ways that improve assessment quality. Dana *et al.* used paired narrow–diverse ecological risk analysis workshops to investigate multi-stakeholder involvement in biotechnology environmental assessment.

Biotechnologies and Environmental Interaction

Genetic engineering includes a growing set of technologies whereby organisms' characteristics are altered through direct genetic manipulation. A broad array of uses for these technologies has been developed and proposed, and many of these have potential environmental implications as engineered organisms and other products of the technology may come, accidentally or deliberately, to interact with the environment.

Genetic Engineering and Synthetic Biology

Modern genetic engineering, direct manipulation of genetic material in order to modify an organism's characteristics, originated in the 1970s.[1] The technology, which began with microbes, initially consisted largely of adding genes to one organism from another or removing genes. Early commercial uses included production of insulin and other desired molecules by inserting genes coding for them into bacteria.[2, 3, 4] Today, genetic engineering is used for agricultural crops, chemicals production, and other applications.

The emerging field of synthetic biology combines elements of earlier genetic engineering, computer science, and other engineering disciplines.[5] Distinctions from earlier genetic engineering include composing DNA sequences rather than simply moving genes, more sophisticated manipulation of cellular mechanisms regulating gene expression, and a broad and ambitious set of technologies and practical applications. Anticipated applications include chemicals production, toxic waste cleanup, medical and environmental sensors, medical devices containing living engineered organisms, vectors transmitting disease immunity to the public, and others.[6] Some applications are already coming online, and research and development of others is moving forward rapidly.

Terminology

No clear line between genetic engineering and synthetic biology has been established, and many classify synthetic biology as a type of genetic engineering. Each technological development, product, and practical application has its own potential environmental, health, and societal implications, and many assessment considerations and approaches span across biotechnology sub-fields. The present work considers assessment of standard genetic engineering and synthetic biology applications, preferring the term most often applied to each technology or application, while referring to "biotechnology" or

"biotechnologies" in general. "Biotechnology" and "genetic engineering" occasionally refer to other techniques such as assisted reproductive technology or traditional animal or plant breeding,[7] which this work does not address.

"Application" often refers to a biotechnology's use, such as biofuels production. Application may also refer to the modified organism along with conditions of use, such as location, facility size and design, and other details. Thus, an application, like an organism, may be subject to careful assessment and to efforts to design for environmental considerations.

Environmental Release

Many if not all intended biotechnology applications involve the potential for engineered organisms or other technological products, such as engineered DNA, to interact with the broader environment,[8] such as ecosystems, agricultural systems, or human bodies. Ecological and health assessment of accidental or deliberate release could contribute to design of the organism itself; to application design, such as decisions regarding locations or monitoring; or to decisions regarding whether to produce the organism or carry out the application altogether.

Projects in laboratory development and some applications, such as microbes engineered to produce chemicals in a reactor,[9] are meant to be contained, but escape can still occur. Even labs operating at Biosafety Levels 3 and 4, designed to contain dangerous pathogens, have reported escapes and laboratory-acquired infections.[10] For contained projects, careful design and assessment of confinement methods,[11] as well as assessment of potential implications of escape, may be appropriate.

In many applications, engineered organisms are somewhat contained, but escapes are likely. In most aquaculture systems escape of farmed fish is inevitable, and researchers argue that escapes should be expected in similar systems for engineered fish.[12] Non-engineered algae cultivated for industrial applications are primarily grown in open ponds. Engineered algae could be grown in such ponds as well,[13] or in more enclosed reactors that still interface with the environment due to needs for sunlight and carbon dioxide.[14] These conditions are vulnerable to releases due to weather events, breaks in confining materials, human agency such as deliberate transport, or other occurrences. For such applications, predicting release likelihoods and frequencies and carefully designing physical confinement measures can be valuable, and predicting and minimizing negative effects of release may also be a focus. Some risk assessors and ecologists recommend that even when confinement is intended, it is often appropriate simply to assume that release will occur and assess implications from that event forward, though escape frequency or quantity may still be relevant.[15, 16]

Many applications involve deliberate release of engineered organisms. Among the earliest deliberate releases were field tests of microbes with ice nucleating genes deleted, meant to protect crops from frost damage.[17] Other deliberate release applications include microbes engineered to degrade toxins in contaminated sites,[18] microbes meant to be

eaten for medicine or nutrition,[19, 20] organisms bearing engineered gene drive meant to alter wild populations by mating with conspecifics,[21] and other modified versions of invasive species released to control an invasive population.[22] For such applications, predicting extent of organism spread may be important, though understanding how the engineered organism may affect receiving ecosystems, as well as investigating any approaches to mitigating undesired effects, may be paramount for sound organism design and application decision-making. For some deliberate release applications, spread in the environment is a neutral or undesirable probability, while for others, it is the goal. Each application likely requires assessment that considers its own goals and methods.

Assessment Information

Assessment to predict environmental effects and aid in design and decision-making may be important for any biotechnology application in which the modified organism may interact with receiving environments.

Environmental Risk Assessment

Environmental risk assessment typically includes steps and tools whereby assessors trace potential causality chains and estimate the nature and likelihoods of undesired ecosystem effects. Alternative actions' estimates can be compared or estimates can be compared with acceptable risk or ecosystem change limits to aid decision-making.[23, 24]

Environmental risk assessment experts may focus on the importance of scientific evaluations and on the necessity of communicating results useful to decision-makers.[25] They may also emphasize conducting a transparent process and communicating areas of uncertainty, which are inevitable in any effort to predict future effects on complex environmental systems.[26, 27]

Information Needs

Environmental assessment for a biotechnology application typically requires substantial information. In addition to information about the engineered organism, the proposed application, and receiving ecosystems, information about similar existing or past applications, biological or ecological processes that may bear on environmental effects, options to confine the organism or otherwise prevent effects, and other topics may be desired.

Environmental assessments often focus solely on data traditionally viewed as "scientific."[28] However, researchers have argued that other types of data, such as information relevant to a decision's ethical, legal, and social implications, should be incorporated into the assessment process as well.[29]

Information may come from existing data or from studies performed for the particular assessment. Inevitably, not all information that may bear on an assessment can be obtained, so assessment processes must prioritize information needs and address uncertainty.

Regulatory and Other Decision-Making

In reviewing biotechnology submissions, regulatory officials review data about an organism or proposed application and may perform formal or informal environmental assessments to decide whether or under what conditions to permit use of an engineered organism.[30] Regulatory agencies request information from submitters, and they may require the conduct of studies or pursue other information. Regulatory agencies may be bound by statute regarding the types of information they may seek, the criteria whereby they may make decisions, or the decisions they may reach, such as whether they must issue a blanket approval or rejection or may approve a submission with restrictions.

Information relevant to environmental assessment serves other decision-making as well. For example, biotechnology companies may use such information to decide what applications to pursue; community groups or environmental organizations may use it to decide whether to seek, accept, or oppose an application; investors, grant-makers, and insurers may use it to make decisions about involvement in a biotechnology project.

Designing Safer Organisms and Applications

Information relevant to engineered organism assessment and decision-making can also inform design of the organisms themselves or application plans. For example, recognition of engineered microbe survival in receiving environments and gene transfer to wild type microbes as environmental hazards has resulted in efforts to engineer microbes to prevent survival or gene transfer upon release.[31, 32, 33]

In discussing environmental risk assessment for transgenic fish, researchers identify a number of genetic modification characteristics that could cause environmental concerns.[34] While they note that these hazards could be analyzed in a risk assessment, in many instances they recommend engineering to avoid the problems altogether. For example, antibiotic resistance genes used in developing and testing alterations can be removed before production of the organism; transgene integration mechanisms that could increase likelihood of later gene movement or transfer can be avoided; transgenic organism lines can be tested and those with characteristics least likely to arouse problems can be chosen for cultivation. The researchers emphasize that risk-reduction measures can be taken even without evidence that harms are likely. Risk assessment tools have limitations, so engineering to address even risks that have not been verified or quantified is a powerful tool in reducing adverse environmental effects. Some other, perhaps further developed, engineering disciplines implement standard safety design measures without evaluating their necessity in each instance.

Assessment Beyond Environment

A biotechnology project may raise considerations other than environmental effects, such as human health, lab safety, security, economic, or socio-cultural effects. Information, assessment, and regulation or other governance may be needed for these areas as well. Engineered organisms intended for human consumption may be assessed for human

health as well as environmental effects.[35] The International Genetically Engineered Machine (iGEM) competition has found student teams at risk of working with organisms that could present health dangers, and iGEM's safety program has found regulations and guidance to be limited and often outdated.[36] Recent work developing yeasts that could produce opiate molecules from sugars indicates the appearance of new security and law enforcement concerns, as well as the need for information and new efforts in assessment and regulation.[37] Perspectives vary regarding whether and when implications beyond environmental effects should be incorporated into environmental assessment processes.

Exchanging Insights Beyond Biotechnology

Assessment is indicated for many new technologies and for other decisions bearing environmental or societal implications. The present study's approaches and findings may be relevant wherever assessment of complex or far-reaching effects is needed.

Important lessons and even specific ecological information from other fields can also inform approaches to or assessment of biotechnologies. Fish strains developed through traditional breeding raise many of the same ecological considerations as those presented by genetically engineered fish.[38] Environmental considerations and assessment approaches needed for genetically modified organisms developed to control invasive species are in many ways similar to those for unmodified organisms intended as biocontrol agents,[39, 40] though differences exist as well.[41] Insights into public response or regulatory processes may be exchanged, such as when individuals engaged in multiple efforts to counter Lyme disease shared insights on public interest and concerns with researchers looking to reduce Lyme disease using genetic engineering.[42] Recognizing where biotechnology assessments can learn from as well as inform assessments for other technologies and decisions can streamline and improve information-gathering and assessment.

Multi-Stakeholder Involvement

Assessment and decision-making for actions bearing environmental implications, such as engineered organism release, are typically conducted by small numbers of narrowly-focused scientific or risk assessment experts,[43, 44] though some practitioners do perceive a role for stakeholders.[45] Scholars and practitioners are increasingly interested in involving diverse stakeholders in assessment processes for biotechnology applications and for other actions bearing the potential for broad or complex effects. Researchers have proposed advantages of diverse stakeholder involvement, including benefits to assessment content or quality.

Terminology – Stakeholder and Expert

This work adopts the common term stakeholder for convenience. The term is imperfect, in part because it suggests that the value of diverse participation comes from having a stake, a particular interest, in the outcomes. Stakeholder has been defined to specify affected parties,[46] which could imply that only those who may themselves be affected have an interest in the outcome, or that participation should be limited to parties who may

be affected. Many multi-stakeholder processes include participants who do not represent directly affected groups, and an individual's or group's participation could be desirable for other reasons, such as a perspective or knowledge-base that could contribute to the outcomes.[47] It may also be difficult to determine, particularly prior to the assessment, who may be affected by a decision. For technologies with the potential for far-reaching effects it may be difficult to include every type of stakeholder. Here, stakeholder loosely refers to groups or their members that may have knowledge relevant to an assessment or a particular perspective on or interest in the outcome, and who, circularly, may be desirable participants in multi-stakeholder assessment processes.

Stakeholder is often contrasted with expert, which problematically implies that scientists or members of institutions typically conducting assessments have no vested interest in the outcomes, that individuals, scientists or otherwise, with interest in the outcomes cannot serve as experts, and that nonstandard knowledge-bases are not valuable forms of expertise. This paper generally uses "narrow expert" to refer to the types of parties typically conducting environmental assessments without multi-stakeholder involvement.

Identifying Stakeholders

For biotechnology environmental considerations, often-cited stakeholders include companies that could commercialize the technology, environmental groups concerned about biotechnology, farmers who may use the organism or be affected by its use, and ecologists. Other stakeholders could include government officials who regulate the organism or application; scientists developing the technology; investors or insurers; community associations in communities affected by a problem that the biotechnology seeks to address or in which an application is proposed; more diverse ecologists, ecological modelers, or other natural scientists; individuals with perspectives on the morality of the technology, application, or goal or who may perceive their cultural or religious heritage affected by the decision; individuals who could be affected by precedents that a decision could set; and others. The list of stakeholders varies by application, and inclusion in a given multi-stakeholder process may be broader or narrower.

The reasons for stakeholder involvement, as well as the political context, may affect selection. For example, for a highly publicized or controversial discussion, it may be important to include representatives of all of the vocal interest groups, or to balance carefully numbers of participants representing different stakeholder groups.[48] For discussions focused on technical details, diverse scientific or other technical knowledge may be emphasized. Detailed guidelines for identifying and selecting stakeholders have been published.[49, 50]

Responsible Research and Innovation

The field of Responsible Research and Innovation (RRI) explores the relationship between scientific and technological developments and the society in which they are embedded. The field examines who is responsible for monitoring or attempting to direct technological development toward benefit and away from harm,[51] as well as the role of

governance in effecting desirable outcomes.[52] Recent initiatives are heir to earlier efforts to grapple with and direct the relationship between science and society, such as environmental ethics,[53] technology assessment, research and engineering ethics, and the ethical, legal, and social implications (ELSI) of research.[54] RRI scholarship has worked substantially on nanotechnology, but it has extended to other fields, including synthetic biology.[55]

RRI has embraced stakeholder and societal engagement throughout the research and innovation process as being politically or morally necessary and as being important for desirable outcomes.[56, 57, 58] The European Union's Horizon 2020 program[59] emphasizes RRI, including stakeholder engagement, and initiatives exist in the United States as well.[60, 61, 62]

Reasons for Involving Stakeholders

Reasons often cited[63] for involving diverse stakeholders or broader societal participants include the arguments that: a) people who will be affected by a decision have a right to participate in the decision-making process; b) involving diverse parties may increase acceptance of controversial decisions or technologies; and c) inclusion of diverse groups' knowledge or perspectives may improve decisions, assessments, or technologies developed (Figure 1).

Expanding on the latter reason, conveners of multi-stakeholder assessments as well as researchers discussing multi-stakeholder involvement in theory have identified and suggested sources of stakeholder contribution that could aid an assessment's quality, integrity, or scientific validity. These researchers suggest that diverse stakeholders could contribute knowledge of ecological, agricultural, industrial, technological, or other relevant systems; that they could apply diverse conceptual models of the systems or assessment; that they could help knowledge available to the assessment keep pace with assessment needs and technology development; and that they could contribute based on their values (Figure 1).

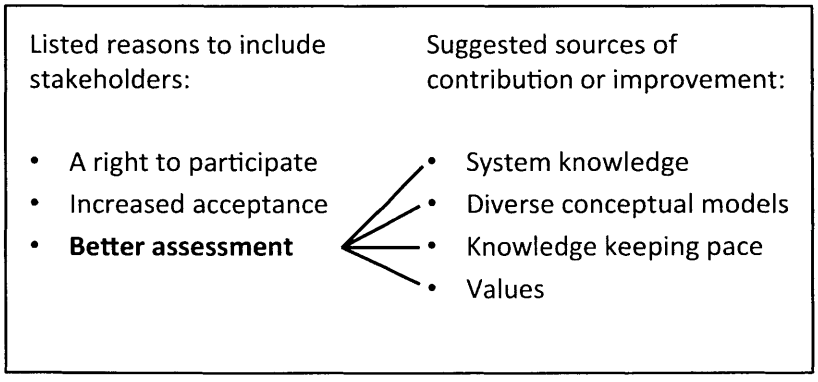

Figure 1. Listed reasons to include stakeholders and suggested sources of contribution or improvement.

(1) *System knowledge*. Diverse participants, including those with practical knowledge of relevant ecological or human systems, may have insights into environmental effects that technical experts may lack. Conservation biologists have found that hunters possess extensive, useful knowledge of many game species' whereabouts, habits, and changes in population size.[64] Participants in a multi-stakeholder workshop assessing a genetically modified crop found farmers knowledgeable about disposal practices and other aspects of use with implications for escape mechanisms and ecological effects,[65] and participants in a multi-stakeholder workshop on an engineered microbe hypothesized that those close to intended users of the organism could perhaps contribute similarly.[66]

(2) *Diverse conceptual models*. Conceptions of system boundaries and components can greatly affect risk assessment. In one striking example, a study found that while urban traffic congestion is typically assessed for economic costs, largely fuel and time wasted, health effects, which are rarely considered, are substantial compared to the effects normally studied.[67] Thus, decisions about factors to include or other assessment aspects can depend on the assessor's conceptual model of the system and can affect policy decisions. Researchers have hypothesized that diverse stakeholders' conceptual models of receiving ecosystems or the ecological-human environment can help identify components and add insights into potential effects or mechanisms of action.[68, 69] Stakeholders' conceptual models are not inherently superior to those of narrow experts, but diverse participants' contribution could enable discussion based on multiple conceptual models, which could improve assessment over use of a single conceptual model assumed by a small, like-minded group. Researchers have advised analyzing stakeholders' diverse conceptual models as "model uncertainty."[70]

(3) *Knowledge keeping pace*. Workshop conveners have suggested that individuals with diverse knowledge-bases engaging together around new technologies or applications can help assessment-relevant knowledge keep pace with rapid technological advance.[71] Diverse involvement can bring existing knowledge, perhaps not yet disseminated beyond particular circles, to bear in an assessment. It may also provide technology developers, ecologists, and other researchers with insights as to what data would be helpful, further enabling knowledge to keep pace with assessment needs.

(4) *Values*. While some practitioners argue that values and other "non-scientific" elements have no role in environmental assessments,[72] values inevitably play a role in even scientific assessments.[73] For example, determinations regarding potential effects to investigate, evidence to seek or accept, and other details of assessment conduct require judgments in part rooted in values. Researchers have argued that values-based determinations should be made by a broad set of stakeholders,[74, 75, 76] rather than solely by narrow experts engaged for their scientific knowledge or assessment expertise but whose values are not inherently superior to others'. Multi-stakeholder exchange could also result in discussion reflecting diverse participants' divergent values, possibly producing better or more nuanced outcomes than might result from a process involving only like-minded individuals.

The present work hypothesizes that these suggested sources of contribution, proposed theoretically or with reference to a single multi-stakeholder workshop, constitute key sources of stakeholder contribution across processes. They may therefore represent overall mechanisms whereby stakeholders can aid assessment.

Dana *et al.*: Investigating Multi-Stakeholder Involvement

Dana *et al.* investigated multi-stakeholder involvement in an ecological risk analysis for a genetically engineered crop. Their research forms a key basis for the present study.

Paired Ecological Risk Analysis Workshops

Developing methodologies for and exploring effects of stakeholder involvement in genetically modified organism (GMO) environmental assessment, researchers Genya Dana, Anne Kapuscinski, and John Donaldson conducted two ecological risk analysis workshops, one with only narrow experts and one with multi-stakeholder participation.[77] The researchers conducted the two 3.5-day-long workshops in South Africa, where the government had recently called for monitoring for impacts of GMOs on biodiversity. The ecological risk analyses focused on potential biodiversity effects of GM maize engineered to resist pests. Four biological scientists experienced with biotechnology development or assessment participated in the first workshop, and these were joined by eighteen participants representing diverse scientific expertise and practitioner, primarily farming, knowledge for the second workshop.

As described by the researchers, the process encompassed the first two steps of a traditional risk analysis: problem formulation, including identifying the analysis scope and system components, formulating hypotheses of "hazards," occurrences that could lead to harm, and prioritizing hazards; and risk assessment, involving quantifying hazard likelihoods and consequences to determine the level of risk that each hazard poses. The workshops included developing visualized conceptual models of the agro-ecosystems, producing a matrix of maize farmer practices, creating a hazard matrix, prioritizing hazards, and estimating likelihoods and consequences of hazardous events.

The researchers analyzed interviews with participants, compared the two workshops' products, including numbers of agro-ecological system elements and hazards identified, and noted occurrences during the workshops to derive insights into effects of diverse involvement as well as practical considerations for multi-stakeholder processes.

Experiment Findings

The researchers found that involvement of more diverse participants resulted in increased breadth of ecologically-relevant information for identifying biodiversity risks. The diverse group identified more system elements, with a few participants with specialized scientific or practitioner knowledge adding substantially to the specificity of elements identified. The diverse group identified more than twice as many hazards as the narrow group, and experts in particular areas of science or in farming broadened the assessment's ecological comprehensiveness by adding categories of hazards that the narrow group's

assessment had omitted. The researchers note that the diversity of conceptual maps produced in the second workshop contributed to integrating technical and experiential knowledge.

Practitioner knowledge was also valuable in creating the farmer practice matrix. First-workshop participants identified the need to understand human practices around maize production, and second-workshop participants with practical farming knowledge enabled the group to develop a matrix of farmer practices, also illuminating how farming practices could affect levels of risk presented by genetically engineered maize.

Hazard prioritization and risk assessment were more difficult for the diverse than for the narrow group. Second-workshop participants were unable to complete the hazard prioritization; many felt that the process should be designed to incorporate uncertainty. These participants also generated risk assessment values that were scattered and thus not conducive to aggregation or drawing of conclusions. The researchers attributed the difficulties to participants' lack of knowledge and to lack of scientific research in some areas.

First-workshop participants were asked to define "assessment endpoints," system components that are valuable to protect, and "risk acceptance criteria," degrees of change acceptable in assessment endpoints. They found these tasks controversial and could not complete them, and the researchers did not attempt these steps in the second workshop.

Social Learning

Researchers Genya Dana and Kristen Nelson investigated whether the multi-stakeholder process contributed to participant social learning.[78] They define social learning as a process whereby people share, re-frame, and integrate different types of knowledge with their own experiences and then work to create a foundation for collective action. The researchers mention that social learning is critical in integrating knowledge and societal concerns, and that it facilitates effective deliberation, negotiation, and decision-making among diverse actors. They argue that risk analyses require the types of learning and adaptation through interaction and deliberation that social learning fosters, and therefore that social learning may be important to the success of multi-stakeholder environmental risk assessment processes.

The researchers designed the multi-stakeholder process to include elements identified as important for social learning, and they examined participant experiences to evaluate the degree to which social learning occurred. While survey responses suggested that the process had contained components necessary to engender social learning, interviews suggested that social learning had been achieved at varying levels, with some components experienced broadly and others among fewer participants. The researchers' discussion of interviews and survey results provides valuable insights into participant experiences in a multi-stakeholder process.

Present Study

The present study uses a case-based approach to examine multi-stakeholder contribution to biotechnology environmental assessment and to identify practical considerations in involving diverse stakeholders in assessment processes. It also discusses biological processes identified as key across biotechnologies and assessments and as representing important areas for research. Further research using controlled methods, investigation of multi-stakeholder processes taking place over longer time-frames and encompassing more complete assessment processes, and further dialogue with related fields will be valuable.

Questions and Novelty

The present study pursues questions about contributions of and practical considerations for stakeholder involvement. It seeks to make several novel contributions to the research literature.

Research Questions and Hypotheses

This study investigates whether and how multi-stakeholder involvement contributes to biotechnology environmental assessment in ways that might aid assessment quality and validity. It tests the hypothesis that diverse stakeholders regularly contribute in the four ways that researchers and conveners have suggested theoretically or observed in single workshops: through contributing system knowledge; applying diverse conceptual models; helping available knowledge keep pace with assessment needs; and contributing based on their values.

The study seeks to discern practical considerations in convening multi-stakeholder processes, particularly focusing on how process design may affect both offering and utilization of participant contributions. It also extends its results to consider broader societal stakeholder in addition to "professional stakeholder" processes to suggest whether societal participants may similarly contribute positively to assessment and to identify practical considerations in involving societal participants.

Novel Research Contributions

This study expands on Dana *et al.*'s work by increasing the base of cases and by investigating multi-stakeholder involvement in other assessment-related activities, such as development of testing schemes and identification of research needs to inform assessment, as well as by investigating the four hypothesized sources of contribution.

This research advances a framework for investigating how diverse participant involvement contributes to assessment, developing and supporting literature-based proxies to identify contributions that may have the potential to aid assessment quality and validity. It extends empirical findings about stakeholder contribution systematically across cases and it empirically tests theorized sources of contribution. The research develops the practical literature by investigating process attributes as they relate to

participant contribution to shed light on factors affecting contribution and to suggest process design considerations. This work also seeks to contribute to the literature and to practice by examining how multi-stakeholder processes relate to existing governance and by considering possible avenues for real influence in decision-making.

Methods

The study analyzes three cases in which diverse stakeholders participated in processes informing environmental assessment for biotechnology applications. Two of the cases are accompanied by related narrow expert processes, which the study analyzes to identify differences that might illuminate strengths and challenges of diverse participant processes. The study also draws extensively on Dana *et al.*'s paired workshops as a comparator.

The study primarily analyzes documents constituting the processes' written outputs, as well as other relevant documents such as preparatory materials and published papers utilizing process results. It also employs personal communication with conveners and participants, as well as participant observation in one of the processes.

The study examines various process aspects as applicable, such as participant composition, convener goals, process structure and facilitation, assessment methods employed, and approaches to uncertainty. It identifies and analyzes participant contributions, such as hazard identification, system boundary delineation, research study needs or protocol specification, and data analysis considerations. In addition to identifying individual participant contributions, the study seeks to identify contributions arising from interaction among diverse participants, as well as areas of disagreement and other occurrences illuminating diverse interaction and contribution.

The study also investigates the cases for practical considerations distinctive to multi-stakeholder processes and examines how conveners addressed practical considerations and challenges and the results they experienced, drawing observations regarding best practices. In doing so, the study seeks to contribute to the practical literature on stakeholder involvement in environmental assessment.

Cases

The study examines three diverse stakeholder processes, two of which are accompanied by related narrow expert processes.

EPA Regulatory Guidance for Engineered Microbes

The U.S. Environmental Protection Agency's (EPA's) Office of Pollution Prevention and Toxics (OPPT) regulates some engineered microbes for various uses under the Toxic Substances Control Act (TSCA). In 1994, the OPPT, along with Environment Canada, convened a three-day workshop to identify environmental risk factors and develop ecological tier testing schemes to aid in assessing risks for microbes that would be

regulated under TSCA.[79] The EPA officials responsible for regulating engineered microbes under TSCA continue to refer to the results.[80]

This workshop was not meant as a multi-stakeholder process, but it included a diverse group of over eighty participants including academic and government researchers from various fields of ecology and medical microbiology, experts in risk assessment and regulation, and members of industries in which upcoming commercial applications of microbial biotechnology were predicted.

The EPA's Office of Pesticide Programs (OPP) regulates genetically engineered and non-engineered microbes intended as pesticides. In 1989, the OPP published submission and tier testing requirements for microbial pest control agents.[81] These "Subdivision M Guidelines" were developed by seven OPP officials.

The present study analyzes the OPPT tier testing workshop as a diverse participant process, gaining further insight by examining the Subdivision M Guidelines as the product of a narrow expert process bearing a related, though not identical, charge.

NSF PoET-Wilson Workshops

Between 2011 and 2016, MIT's Program on Emerging Technologies (PoET) and the Woodrow Wilson International Center for Scholars, supported by the National Science Foundation Synthetic Biology Engineering Research Center (NSF SynBERC) held a series of workshops to identify research needs and develop research agendas to aid in assessing environmental implications of synthetic biology applications. The workshops focused on specific technologies under development or nearing commercialization, while also broadening the discussions toward research needs for synthetic biology applications more generally. In addition to research needs, the workshops addressed ecological hazards, testing considerations, genetically engineered safeguards to prevent environmental effects, and other topics. Designed as an application of Dana *et al.*'s findings, the workshops included diverse participants, including synthetic biologists, members of environmental organizations, industry members, diverse ecologists, and others.

FDA Salmon Assessment and Public Input and Critique

The first genetically engineered fish to receive United States regulatory review is the AquAdvantage Salmon, engineered to grow more rapidly than wild type Atlantic salmon. The Food and Drug Administration's (FDA's) Center for Veterinary Medicine (CVM) reviewed the application under animal drug regulations, so approval rested on a determination that the genetic alterations are safe for the animal and effective in their objective, and that the engineered salmon is safe for human consumption.[82] The National Environmental Policy Act (NEPA) and the FDA's own policies also required the Agency to assess an approval's impact on the United States environment.[83] In 2015, the FDA determined that the criteria for approval were met[84, 85] and it also found no significant environmental impact.[86]

The CVM solicited public input at various points, though its review, including the environmental assessment, did not include a participatory multi-stakeholder process in which stakeholders work together to develop an assessment or assessment-related materials.

The approval was controversial, and a group of organizations representing diverse stakeholders has filed a lawsuit objecting to the FDA's conclusions, including the environmental assessment findings.[87] The legal complaint initiating the lawsuit[88] includes a detailed critique of the FDA's environmental assessment and incorporates multi-stakeholder input.

This study analyzes public comments, a citizen petition, and the lawsuit complaint as stakeholder inputs, albeit produced outside of a participatory setting such as a collaborative workshop, alongside the FDA's environmental assessment and responses to comments. It seeks to discern how diverse stakeholders could contribute to assessment, as well as differences from participatory processes and insights into diverse contribution within existing governance.

Case Selection

These cases were identified based on a number of factors aiming primarily to provide relevance and common bases for comparison.

All of the cases involve biotechnologies with substantial environmental release considerations. Focusing on biotechnology and environmental implications provides a common basis to enable deeper investigation. Examples of multi-stakeholder involvement in environmental assessment for biotechnology are limited. For the most part, processes meeting these criteria were identified, and accompanying or related narrow expert processes were identified where feasible.

The cases primarily involve the United States, aiding analysis by providing common context, though each of the multi-stakeholder processes includes an international component. The cases are largely current. The currency contributes to the study's interest, as well as enriching the research by facilitating communication with individuals involved in the processes. In addition, multi-stakeholder involvement in environmental assessment and decision-making is a newly developing field, so using current cases increases the common context and may aid in deriving best practices.

Key Biological Processes and Assessment Complexity

Organisms' propensity to survive and thrive in the environment, to engage in gene flow with organisms they encounter, and to evolve over time appear across organisms, ecosystems, and genetic technologies and contribute to many mechanisms whereby an organism could affect a receiving environment. Researchers have identified these characteristics as constituting fundamental challenges in predicting and controlling genetically engineered organisms' behavior.[89] The workshops and assessments examined in this study each identify and discuss these characteristics as being important to analyze

in environmental assessment and as representing key gaps in assessment-relevant knowledge.

These biological processes and their broad relevance suggest several complexities in how knowledge is generated and used in environmental assessments. Assessments require decisions regarding applying knowledge generated for one organism or ecological context to another, identification and roles of hazards versus harms, and data standards, including how studies are conducted and applied. These decisions require judgments for which scientific information cannot fully substitute, and they may represent important areas for diverse stakeholder contribution.

The present study reviews current scientific information about these key biological characteristics. It also describes research studies in these areas to contextualize how assessment-relevant knowledge is generated and to illuminate complexities in conducting and using scientific research to inform assessments.

In part due to these processes' broad relevance, biotechnology researchers are developing genetic approaches to controlling or preventing organism survival, gene flow, and evolution. The PoET-Wilson workshops included discussion of how these engineered safeguards may affect assessment and regulation, and how the safeguards may themselves be evaluated. The present study describes some engineered safeguard development efforts as background and to illustrate how an understanding of environmental hazards could inform technology development.

Findings

This study identifies stakeholder contribution and process considerations distinctive to each of the cases. Consistent observations emerge as well. Across the cases, stakeholders contributed in each of the four hypothesized ways: They contributed substantial valuable system knowledge; applied diverse conceptual models that could enrich and improve an assessment; contributed in ways that did or could enable available knowledge to keep pace with assessment needs; and contributed based on their values, as do narrow expert assessors. These findings suggest that diverse stakeholder involvement could contribute positively to assessment scientific quality and validity. In addition to these hypothesized sources of contribution, diverse stakeholders displayed interest in challenging standard assessment approaches and convener assumptions, largely without compromising process conduct. Evidence from the literature and the cases suggests that such challenges could improve assessment, particularly for emerging technologies.

The cases suggest a role for broader societal, in addition to "professional stakeholder," involvement in assessment, and it appears that broader societal participants could contribute in the same five ways, thus likely aiding assessment as well.

A few practical considerations emerge as possibly key in enabling diverse stakeholder or societal contribution. Continuity over time and credible expectations of authority or influence in real decision-making are both typically inherent in narrow expert

assessments and would likely benefit diverse participant assessments. Navigating and balancing tensions between predefined structure and openness as well as between technical tasks and enabling non-technical input are important as well. Work developing approaches in each of these areas is needed, including work on processes encompassing later assessment and decision-making stages, work on incorporating non-technical inputs into assessments, work on integrating diverse participant processes with governance, and exploration of diverse involvement in other aspects of technology development and execution, such as through advising companies or labs.

Support for substantive stakeholder contribution would ideally come from two angles: Scholars and practitioners interested in convening diverse stakeholder processes should involve stakeholders in ways that enable contributions to aid real decision-making; and individuals bearing decision-making authority should involve stakeholders as partners whose contributions can substantively aid assessment. Environmental assessment fundamentally seeks to guide technology development and decision-making toward best serving society. Through substantive content and incorporation of values, stakeholder involvement may enable assessment more fully to accomplish its aims.

Areas for Further Research

This work is intended to contribute to the analysis of multi-stakeholder involvement in environmental assessment. Further research analyzing diverse participant contribution to assessment would be valuable, particularly as multi-stakeholder and societal involvement develops.

Case Design and Analysis

The cases were not designed as controlled experiments, limiting comparability and introducing confounding factors. Further work with prospective case-control experiments as that conducted by Dana *et al.* would be valuable in analyzing multi-stakeholder contribution as well as in isolating causes and effects in order to establish best practices.

Further use of quantitative analytical approaches, such as numerical comparisons of deliberation components as employed by Dana *et al.*, word or concept frequency analysis of deliberation transcripts, analysis of resulting publications, or other methods of quantifying process results would be facilitated by larger numbers of cases as well as by controlled experimental designs. These analytical approaches could enable further development of conclusions as well as encourage broader utilization of results.

Future Work as the Field Develops

The cases primarily encompass early stages of environmental assessment processes, such as identifying hazards and research needs and developing testing schemes. It is unclear whether any multi-stakeholder group addressing biotechnologies has yet participated in later assessment stages, such as determining risk acceptance criteria, evaluating scientific studies, or deciding whether or under what conditions to implement an application. Exploration of multi-stakeholder involvement in later assessment stages will be valuable.

The cases are largely limited in interaction duration. Longer-term multi-stakeholder processes may be established to see assessments through to completion or for ongoing assessment or guidance for particular biotechnology projects, ecological studies, companies, or governance systems. Investigation of longer-term diverse participant processes will be valuable.

The cases are largely recent, and the field is developing. Over time, it will be possible to investigate how multi-stakeholder processes play out over longer time frames in policy, research, or public perceptions, and these investigations may further aid in identifying best practices for effective deliberation.

The cases focus on technologies currently under active development, nearing, or recently reached commercialization. While researchers discuss the importance of presenting stakeholders with specific scenarios and real details, they also discuss the importance of stakeholder discussions and technology developer or other decision-maker awareness of environmental considerations beginning in the earliest research phases in order to inform technology development.[90, 91] The possibilities and distinct characteristics of early-stage multi-stakeholder processes should be explored.

Dialogue with Related Fields

The reasons for and good approaches to involving diverse stakeholders in assessment and decision-making likely apply beyond environmental assessment for biotechnologies. Work on stakeholder involvement in some emerging fields, such as nanotechnology, is active,[92] and it could develop in more areas. As common methods and challenges are likely, practitioners and researchers should maintain dialogues among the areas in which multi-stakeholder approaches are used.

Researchers have pointed out that some fields navigating complex problems with environmental, public health, or medical components, such as the AIDS crisis, environmental toxins, nuclear waste disposal, and water management, regularly involve stakeholders.[93] The researchers argue that in these fields, stakeholders may be included for perhaps better reasons and perhaps more valued input compared with the motivations and expectations apparent in much recent work on diverse participant processes for emerging technologies. Developers of multi-stakeholder involvement for emerging technologies should learn from practices and experiences in these fields.

Ongoing work seeks to involve broader society or "ordinary citizens" in deliberation on new technologies or on other actions that could have broad effects. A lively literature develops and critiques this field.[94, 95, 96] RRI includes both citizen and multi-stakeholder engagement, and has experienced successes and challenges in integrating "the public" into deliberation processes.[97] The present work explores how lessons from multi-stakeholder processes could be applied to societal involvement. Further dialogue between these fields could benefit both.

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Chapter 2

Biological Challenges and Engineered Safeguards

A few fundamental organism characteristics or biological processes represent key enabling mechanisms whereby engineered organisms may come to affect a receiving environment. These characteristics also challenge efforts to predict effects. These characteristics are the subjects of ongoing research, and they have been identified as demanding further investigation to predict and prevent adverse effects. Bioengineering researchers are also working to develop genetically engineered approaches to addressing these challenges.

Fundamental Processes and Assessment Complexity

Scientific understanding of relevant biological characteristics and processes is crucial for environmental assessment, and research on processes common across systems can enable efficiency and common approaches. On the other hand, judgments on generalizability must be made with care, and scientific knowledge does not substitute for decisions about harm definition and risk acceptance.

Generating Knowledge

While each genetic engineering technology and application raises unique considerations, a few characteristics of living organisms have been identified as playing key roles in environmental effects across organisms, genetic technologies, and ecosystems. These characteristics, including an organism's ability to survive and thrive in an environment, its propensity to exchange genetic material with organisms it encounters, and its tendency to evolve over time, have received attention from various quarters[1, 2, 3] as representing underlying mechanisms whereby organisms may affect their surroundings; as frequently appearing early within chains of events that could lead to environmental harm; and as constituting fundamental challenges in predicting and controlling genetically engineered organisms' behavior in receiving environments. The workshops and assessments analyzed in this study identify and discuss these processes as being important to analyze in environmental assessment and as representing key gaps in assessment-relevant knowledge.

In part because of these processes' broad relevance, biotechnology researchers are working to develop genetic approaches to controlling or preventing them, efforts that may contribute to engineered organisms' industrial value as well as to reducing environmental risk. These safeguard technologies may themselves affect environmental assessment and regulatory consideration.

Familiarity with how knowledge is generated in these fields can be valuable in assessing risks, identifying research needs, and calling for studies. Biological research is complicated. Field and lab studies are often time-intensive, and must often rely on relatively small datasets and statistical analysis. They require choices in microcosm or field test design, and researchers' abilities to detect or measure occurrences is often imperfect. Test organisms or added genetic sequences may often be chosen more for their conduciveness to culture or measurement than for their similarity to likely engineered

strains or to a receiving environment. Development of research tools and approaches is ongoing.

Using Knowledge

Collection and generation of scientific knowledge are only part of the process of using knowledge to inform assessment. Determinations of effects that constitute harm, levels of risk acceptance, how to apply scientific information to the assessment question, and how to treat ongoing uncertainties are necessary as well, and these may present important roles for multi-stakeholder involvement.

Hazards and Harms

The focus here on survival, gene flow, and evolution should not be mistaken for labeling of these processes as necessarily harmful. The processes are identified as key hazards not because their occurrence always causes damage, but because many chains of events that could result in harm contain these events. For example, often an early question in an environmental risk assessment is the chance that the engineered organism will escape its physical confinement. Then in examining the scenario in which the organism does escape, the next question may be the chance that it will survive for an extended period in the receiving environment, as its survival may likely affect its ability to influence the ecosystem. An assessment could find that escape and survival are both likely, but determine that harm is unlikely to result from the organisms' survival in the environment. Conversely, an organism that does not survive long in a receiving environment may still affect the ecosystem.[4]

Events comprising components of event chains that could lead to harm may at times be regarded as undesirable in themselves. However difficult they are, predicting, detecting, or controlling an organism's escape or survival may be more practical than predicting, detecting, or controlling its behavior once it is proliferating in a receiving environment. Risk assessment tools are limited and many potential hazards are subject to high levels of uncertainty, so efforts to predict or prevent events that could potentially result in harm can be powerful tools in assessment or damage prevention, even if links to harm have not been quantitatively established or the likelihoods of harm resulting may be small.[5]

In addition to identifying the occurrences expected to result in undesired consequences, determining what types of ecosystem effects are considered undesirable may be important.[6] Incorporation of an engineered organism as a new component of a receiving environment may itself be considered a harm, or this occurrence could be deemed acceptable. Similarly, the extinction of a variety of small animal could be regarded as harm to be avoided, or an extinction could be deemed acceptable if it does not result in ecological cascades that endanger top predators. Identification of effects regarded as harm or of benefits that must be conferred for a given harm to be acceptable, as well as acceptable levels of risk, may be important components of an assessment and decision-making process. Determining the desirabilities and likelihoods of the risk-bearing activity's intended benefits may be important as well.[7] Researchers have argued that these

determinations, relying on values as well as on understanding of the social, economic, and cultural context, should be made by diverse stakeholders.[8, 9]

Existing Knowledge and Applicability

Awareness of existing knowledge is crucial for those assessing risks, calling for studies, and designing organisms and applications. As the biological processes identified are relevant to many environmental assessments, knowledge about them may be broadly useful,[10] potentially enabling efficiencies in assessment. It is necessary to determine when and how knowledge generated in one context may be applied in other contexts, where the particulars of the organisms or environmental parameters differ. For example, developing widely-recognized or broadly applicable methods or guidance for incorporating common considerations into environmental assessments can help streamline assessment processes and introduce predictability and transparency, while enabling assessments and assessment methodologies to build on each other. On the other hand, generalization must proceed with caution. Availability of data does not necessarily equate to either applicability or sufficiency, and identification of and respect for limits to applicability of information from one circumstance to another is important. Furthermore, standardization among risk assessments or many assessments' relying on the same data or established "facts" can magnify small flaws and can inhibit experts' or stakeholders' challenging established perspectives and methodologies.

Assessors' judgments may legitimately differ regarding applicability of study results to different contexts or sufficiency of data to determine that a risk is either acceptably low or unacceptably high. Researchers have argued that this inevitability of judgment calls on the part of whoever conducts an assessment suggests a need for multi-stakeholder involvement. They argue in part that people with diverse perspectives should discuss the judgment calls together, rather than leaving assessment to a few like-minded individuals whose biases and judgments are not challenged.

Further Assessment Challenges

Other challenges may also affect how scientific information is used in assessment, and require careful consideration and decision-making. Two of these challenges are the assessment timeframe and the prediction of rare events. In these areas and others, stakeholders may play a role in determining how to address assessment challenges and decisions for which scientific information does not fully compensate.

While aspects of many biotechnology applications may be time-bounded, environmental release is by nature potentially ongoing. Scientific studies are typically time-limited. Many determinations of risk for ongoing events may depend on the timeframe with which the assessment is concerned, and determination of the considered timeframe may be necessary for meaningful assessment. Identifying and supporting a timeframe decision is not trivial. An assessment procedure's most practical timeframe may in many instances differ from the timeframe that would ideally be considered. When present, these tensions may be best acknowledged and decisions about how to proceed in their presence articulated.

Rare but high-impact events could include a rare confluence of circumstances that enables an engineered organism to escape, gain a foothold, and begin to thrive in a receiving environment; gene flow or mutation events that enable increased environmental effects; or other events that may be regarded as of very low probability but that would result in substantial ecological damage. These events are often not detectable in research studies, and even if they are detected their rates of occurrence are difficult to quantify. It is unclear that standard approaches to predicting risk are suitable for these types of rare events.[11] In considering the uncertainty surrounding some potential sources of environmental effects, it may be important to consider how the potential for rare but high-impact events should be addressed in environmental assessments and decision-making processes.

In addition to assessment of ready applications, considering possible effects and involving stakeholders may be appropriate beginning in early stages of technology or application research and development, particularly when assessment faces substantial complexities and technology or application design could help address potential problems.

Assessment Complexities and a Role for Stakeholders

Realities of knowledge generation and use, including the need for judgments in such areas as designing studies, applying results to conditions under consideration, determining assessment timeframes, and deciding what effects or risk levels are acceptable, suggest a role for stakeholders in scientific assessment processes. Scientific information cannot fully address these questions, and it is possible that rather than leaving these judgments entirely to a few narrow experts, who may be less likely than diverse groups to question their positions and whose judgment determinations may not be inherently superior to others', diverse stakeholders should be involved. This argument further suggests a role for stakeholders throughout the assessment process, rather than presentation of stakeholders with results and options after a risk assessment has been completed.

Fitness or Competitiveness[12]

An organism's ability to survive and proliferate in a receiving ecosystem is often key in its potential to affect the environment: A released organism that thrives and proliferates may affect the environment in ways not expected for an organism that dies out rapidly or survives only in low numbers.

Many researchers assume that most engineered organisms are likely to be competitively disfavored in receiving environments due to having heavy metabolic loads from extra functions they are engineered to perform, or more generally because they have been modified to differ from naturally evolved forms in ways useful to people but not necessarily beneficial to the organism,[13, 14] and some evidence supports this argument.[15] However, researchers have also challenged the notion that engineered traits can be assumed to reduce ecological competitiveness. For example, researchers have observed that genetic engineering may confer traits, such as drought or cold resistance, salinity

tolerance, pathogen or pest resistance,[16, 17] or more efficient photosynthesis,[18] that did not arise similarly in the parent strain through natural selection, and that could well confer a competitive advantage over non-engineered, or wild type, organisms, favoring proliferation in some receiving ecosystems. Researchers have identified incidences of engineered organisms' surviving and proliferating in receiving environments.[19]

Predicting an engineered organism's fitness, its ability to compete and thrive in a receiving environment, may be important in assessing its potential to affect the environment. Prediction also presents substantial challenges.

Potential Mechanisms of Successful Strains' Effect

Many factors may affect an organism's ability to survive and proliferate, including its resource uptake rate and efficiency, its breadth of survivable environments and ability to withstand changes in environmental conditions, its resistance to hazards such as predation, parasites, antibiotics, and environmental toxins, and its growth and reproduction rates.[20, 21] Particulars of the receiving environment, including other organisms present, are likely to affect these and other factors. The relationships among factors affecting fitness may be unclear, complicating prediction and assessment.

An engineered strain surviving and proliferating in a receiving environment may affect the environment through a number of mechanisms. It could affect local organisms directly through predation or infection. It could also compete with other organisms, obtaining such resources as nutrients, sunlight, or spaces suitable for growth or reproduction. An introduced organism may also alter the environmental conditions; it could release a toxin,[22] alter the cycling of a key nutrient that affects which organisms are favored,[23] or alter other aspects of the biotic or abiotic environment. Researchers have pointed out that despite the common focus on competition, other interactions, such as the potential for engineered strains to engage in mutualistic interactions with local organisms, could also be key to effects on ecosystem function.[24] Many of the mechanisms whereby an engineered strain could affect a receiving environment are similar to those for any introduced organism that thrives or becomes invasive.[25, 26] Ecosystem effects may be magnified through ecological connections whereby alterations in a single species' population may affect other ecosystem components.

Approaches to Assessing Fitness

Researchers have employed a number of approaches to assessing an organism's fitness, including theoretical approaches, lab and field experiments, often involving microcosm systems, and use of mathematical models. Studies assessing survival or competitiveness may also investigate genetic stability, including transferability of added genes or their evolutionary stability in the engineered organism.[27, 28]

Theoretical Assessment of Fitness

Some researchers advocate assessing fitness using information, pre-existing or obtained for the purpose, about characteristics of the organism and the receiving environment.[29, 30]

For example, characteristics of the added genetic material, donor organism, and parent or recipient organism, the method of insertion, and characteristics of the predicted receiving environment could be used to predict an engineered organism's fitness, as well as the likelihood of gene flow with local organisms. Researchers have proposed assessing fitness theoretically using available information in order to determine what if any further information to gather through experiments.[31]

Theoretical assessments of fitness may examine characteristics of the engineered genetic changes to predict how the alterations may affect the organism's chances of survival or competitiveness.[32] Researchers consider capabilities enabled by the added genetic material, including production of a toxin that could inhibit local competitors, increased resource uptake or metabolic efficiency, or survival in a broader range of temperatures or other conditions. Assessors may also evaluate the alterations' stabilities, their propensity toward transfer or toward mutation that may be favored by selection.[33, 34] Considerations may include whether added genetic material is chromosomally integrated or located separately, for example on plasmids, and its size, which affect transfer likelihood, as well as the metabolic loads of genes added or removed, which can affect the tendency for selection against the genes through evolutionarily favored disabling mutations. Assessors also examine the vectors used to introduce new genetic material. For example, if a virus is used as the vector, viral genetic material could remain in the engineered organism and risk producing a pathogen or otherwise affect the organism's characteristics.[35, 36]

Assessors examine characteristics of the donor and recipient organisms. For example, they may consider whether the parent organism is a pest or a pathogen,[37] its geographic range, its ability to survive adverse conditions, or its ability to propagate readily in likely receiving environments. Researchers have proposed assessment approaches determining a parent strain's invasiveness potential and then the transgenes' likely effects on invasiveness.[38]

Researchers have stressed the importance of considering characteristics of the engineered strain itself, particularly due to difficulties in predicting phenotypes of an engineered strain based on information about the parent organism and genetic changes.[39] Considerations may include nutrient or food requirements, hosts, environmental limits to growth and propagation, reproduction rates, special metabolic products or catabolic capabilities, or resistance to disease. In assessing how a genetic change manifests in an engineered strain, assessors may be interested in how added or altered genes' expression is genetically regulated.[40, 41] Researchers have identified characteristics associated with plant invasiveness, and have proposed applying these to considering transgenic crops.[42] Assessors often examine characteristics of the engineered strain in comparison with those of the parent strain.

As an organism's fitness depends heavily on its environment, likely receiving environments are also considered. They may be examined for such factors as temperature, salinity, or other abiotic characteristics that could affect how a strain fares, the availability of biotic or abiotic dissemination agents, the presence of potential mutualistic organisms or food sources, or for anthropogenic factors such as the presence

of antimicrobial substances that could provide an engineered strain with a particular advantage. Closely related organisms' geographic distributions, such as those of a parental strain, may provide clues as to whether an introduced strain is likely to be successful.[43] Researchers have pointed out that some genetic characteristics may be expressed differently in different environments, underscoring the importance of considering the receiving environment and highlighting the potential complexity of analysis.[44, 45] Some researchers also emphasize the release pattern, including the number of organisms and the release frequency, as important for predicting invasion.[46, 47]

Other information specific to the strains and the environment may aid assessment. For example, the engineered characteristic's existence as a variant within the local conspecific population can suggest how the engineered strain may fare,[48] often reducing but not necessarily eliminating concern.[49, 50] For example, considering an engineered organism produced by deleting a single gene, researchers noted that the parent organism exists in the receiving environment and that occasional deletion mutants arise but remain rare, bolstering the theory that the engineered strain is unlikely to be substantially competitive.[51]

Assessing fitness theoretically has several strengths. It may not require devoted field or lab experiments, potentially reducing costs and time required.[52] Assessments can be readily adjusted as new factors are identified, data are obtained, or aspects of the organism design are changed.

On the other hand, predicting how an organism's and a receiving environment's many characteristics will affect how the organism fares may be difficult, particularly in organisms possessing multiple, interacting genomic alterations. In addition, the approach relies on existing, incomplete knowledge of how organismal characteristics affect fitness; subtle interaction effects among organisms and between organisms and their abiotic environment may substantially affect fitness in ways still being identified.[53, 54]

Theoretical assessment approaches were also developed for traditional genetic engineering, which typically involves a single recipient organism and genes from one or a few donors. These approaches may be unsuitable or require substantial adaptation for application to more advanced genomic engineering or synthetic biology, where an engineered organism's genome may be composed of genes from many different organisms or developed artificially, and the "recipient" may be highly modified or even, eventually, entirely artificially composed.

Careful identification of potential receiving ecosystems may also be crucial. A strain's propensity toward success or invasiveness may depend heavily on receiving environment characteristics, and an engineered organism could spread over a wider geographic range or enter different receiving ecosystems from those that might have been expected, particularly if it is able to survive, even without thriving, long enough to spread even gradually over several generations.

Laboratory and Field Experiments

Researchers conduct experiments to predict how organisms might fare in a receiving ecosystem. A number of experimental setups have been used, representing different environments, such as soil systems, aquatic systems, or plant surfaces,[55, 56] and differing in other properties such as whether nutrients and wastes are replenished and removed[57] and how isolated the experimental strains are from environmental interaction and potential escape.[58, 59] Experiments on microbes typically measure competition between strains by growing strains together and determining their relative abundances,[60, 61, 62] or growing strains separately under similar conditions and measuring their population sizes.[63] Researchers have explored using other traits, such as resource uptake, as proxies for competitiveness.[64]

Experiments provide empirical data on an organism's behaviors and tendencies toward success in experimental setups meant to mimic ecosystems, including, for some experiments, the presence of other organisms. However, it is difficult to conduct experiments for a full range of possible receiving environments and to mimic field conditions, particularly the variable conditions often present in receiving environments, in a lab or microcosm.[65, 66] It may be unclear how to use experimental data to predict behavior under other conditions. Particulars of conditions, such as temperature, medium sterility, or nutrient concentrations, may greatly affect results.[67,68, 69] Other components of the experimental design may also require decisions. For example, experiments on engineered strains are often conducted with the parent strain as the comparator,[70, 71] but which strains should be used to predict behavior in a receiving ecosystem is not always clear. Determining how long an experiment should run may also present challenges. Studies have found that strains' relative growth rates and apparent competitive success can be different in the long and short terms,[72, 73] and a study using plants found that substantial variability in outcomes could easily arise from limiting the sample sizes or the number of years over which a study is conducted.[74]

Models

Researchers may integrate experimental data into mathematical models to predict engineered organisms' behavior. Researchers also model competition of non-engineered organisms, developing tools that could be applied to assessing engineered strains. The models typically incorporate a small number of factors, assuming that one or a few factors are the primary determinants of an organism's population size or competitiveness, and researchers may test these assumptions through experiments.[75, 76, 77] Researchers may construct models[78] or use established models. Well-known established models include the Lotka-Volterra model for changes in an organism's population size given information about the population size of a species with which it interacts strongly, such as through competition or predation,[79] and the Monod model, which assumes that each species depends on one limiting nutrient and relates its growth rate to that nutrient's availability.[80]

Models attempt to predict behavior over the long term while typically being more rapid and inexpensive than field or lab studies. However, extrapolation to long timeframes or

different conditions may be difficult.[81] In addition, models' typical focus on just one or a few factors may compromise their value for assessment, as many factors together may affect an organism's success. For example, a study replacing a simpler with a more complex model found that a strain utilizing resources less effectively than another may survive stably with the second, if the first is also more resistant to a common predator.[82] The study further found that some vulnerability to predation could actually aid the first strain's survival through its acting as a "carrier" to a predator to which its competitor is more vulnerable.

Researchers have argued that models' ignoring particular components of real systems, such as spatial heterogeneity, particular elements of populations, or organisms' biology, may limit their ability to predict occurrences in real scenarios.[83] Researchers have also found that models incorporating slightly different parameters can produce very different outcomes regarding organism competition.[84, 85] Particularly in the event of environmental release over time and into different receiving environments, factors not considered or factors determined through modeling to be less important could come to drive survival, competitiveness, or other traits. For example, a researcher discussing a model predicting population growth based on the assumption "that the growth rate of a species will be completely determined by that one nutrient that is most limiting, of all those that are potentially limiting" comments that "The switching that occurs as a species changes from being growth-rate limited by one resource to being limited by another resource is not easily dealt with analytically."[86] Incidentally, the same researcher conducted the empirical portion of his study on algae using sterile technique in order to prevent complication from bacterial competition, and utilized the same clones throughout the experiments in order to avoid variability from genetic changes in the population over time. These sensible and common precautions meant to obtain reasonably consistent data to which models may be meaningfully applied also eliminate factors that could crucially affect an engineered organism's propensity to thrive in real receiving environments.

Complications of Using Fitness

While fitness, or survival and proliferation, is an important consideration in assessing an organism's potential for environmental effects, caution is needed in reliance even on accurate estimates of these factors. Organisms found to survive or compete poorly in a receiving environment may still affect the environment substantially.

Organisms displaying lower fitness may still dwindle slowly, and they may affect the environment substantially before dying out.[87, 88] For the period over which the organisms remain in the environment, within a single generation or over a number of generations, they may compete with local strains, harming their populations, or even alter characteristics of the receiving ecosystem and thereby the competitive landscape for other organisms. The potential for damage over time even from less competitive organisms may be particularly acute when releases are ongoing or repeated over time, or include large numbers of organisms,[89] as is expected for many agricultural, aquacultural, and bacterial biotechnology applications. The expectation of eventual disappearance may do little to reduce environmental effect when the population is frequently replenished.

A strain with reduced fitness relative to other organisms may not die out completely from normal competition.[90, 91] Researchers have stated the perspective that the presence of an engineered species or introduced genetic material in an ecosystem should not itself be regarded as harm,[92] and survival at low numbers enables less opportunity for environmental effect over the short term than do competition and proliferation. Still, long term survival provides the opportunity for a population to increase at a later time when environmental conditions are more favorable.[93, 94] Furthermore, the organism's continued existence presents opportunities for gene flow with local strains and for evolutionary adaptation, both of which may result in the advent of descendent strains with more potential for environmental harm than the original engineered organism.[95, 96, 97, 98]

Organisms with reduced fitness may affect a receiving environment through gene flow.[99] While the engineered organism as a whole may be less fit than local competitors, portions of engineered or foreign genetic material, when incorporated into a local strain's genome, may confer traits enabling ecosystem effects. One researcher argues that assessing the likelihood that an introduced gene will enable invasiveness in local strains upon transfer is key in predicting an engineered organism's environmental effects.[100] For sexually reproducing organisms, engineered strains with reduced fitness hybridizing with local strains in a receiving environment may produce offspring with reduced fitness. If the released population is large, or the local population is small or otherwise fragile, damage to or destruction of the local population could result, with the potential for further ecological effects.[101, 102]

While reduced fitness, even accurately estimated, cannot be assumed to indicate an absence of ecological effects, fitness and persistence in a receiving environment, even to the point of displacement of local species, may not always imply larger effects on the ecosystem. For example, researchers have pointed to redundancy of function among members of ecological communities, particularly microbial communities, to suggest that displacement may be unlikely to result in whole-ecosystem effects[103] (but see [104]), though they also mention that a potentially displaced species could have other value than its ecological role, such as economic or aesthetic value.

Fitness Importance and Considerations

An organism's ability to survive and proliferate in a receiving environment is a key component of many pathways to environmental effects, so predicting fitness may often be an important component of an environmental assessment. No standard method of assessing or predicting fitness exists, and the problem's complexity may make the existence of multiple approaches desirable. Researchers have developed methods involving direct experimentation, theoretical approaches, and modeling, and each approach and methodology possesses strengths and limitations. While assessing fitness is important, organisms may affect a receiving environment through mechanisms independent of indefinite survival or increased competitiveness; fitness tests must not provide false security regarding the potential for environmental effects.

Any procedure to predict an organism's propensity to survive and thrive in a receiving environment involves numerous decisions in test or assessment procedures and conditions considered, as well as in how results are determined and conclusions drawn. These options introduce the possibility of legitimate differences of opinion as to desirable approaches for a given organism and application, as well as legitimate differences of opinion as to what information warrants regarding an organism as of sufficiently low, or excessively high, risk to a receiving environment.

Gene Flow

Gene flow consists of genetic combination between different organisms. Horizontal gene transfer, also called lateral gene transfer or horizontal gene flow, refers to organisms' passing functional DNA through mechanisms other than reproduction. Typically associated with asexually reproducing microbes though occurring in other organisms as well, horizontal gene transfer is increasingly recognized as a common and even dominant evolutionary force.[105, 106]

Sexually reproducing organisms, such as animals and plants, may recombine their DNA through reproduction, and the terms hybridization, cross-breeding, or sometimes gene flow refer to an individual of one genetic type's mating or cross-pollinating with an individual of another, such as another species, to produce viable offspring. In considering environmental implications of biotechnologies, gene flow refers to genetically engineered organisms' combining genetic material with wild type organisms of the same or different species. Here, asexual horizontal gene transfer and sexual hybridization are referred to collectively as gene flow.

Gene flow is an important mechanism whereby engineered organisms may affect a receiving environment, because genetic elements added to an engineered organism may move to or combine with wild type organisms and change their characteristics, and characteristics of an engineered organism may be altered by its gaining genetic elements from its surroundings. These new combinations could enable environmental effects that the engineered organism as designed could not achieve.

For sexually reproducing organisms, the primary mechanism of gene flow is well understood. Sexual reproduction between a modified and an unmodified organism may produce offspring possessing modified genes in combination with genetic material from the unmodified parent. For asexually reproducing microbes, a few mechanisms of gene transfer are fairly well understood, while others are still subjects of early-stage research.

For both sexual gene flow and horizontal gene transfer, flow is more frequent among closer relatives, but it also occurs among more distant relatives, though horizontal gene transfer appears to be possible across much larger phylogenetic distances. Scientists are still exploring how frequently all types of gene flow occur among various taxa. Research also remains to be conducted regarding factors affecting gene flow between engineered and wild type organisms, of the same or different species or strains, and research

illuminating mechanisms and frequencies of gene flow in general can help shed light on these questions.

Assessing an engineered organism's possible environmental effects could include attempting to predict what new combinations could arise and how these could affect the environment. However, predicting and examining fully the possible gene flow events and their potential effects may often be difficult. To avoid these complications, gene flow could be assessed as an undesirable occurrence to be prevented or minimized, even if it is not itself regarded as a harm.

While much remains to be learned, even existing knowledge about gene flow mechanisms, frequencies, and favorable or unfavorable conditions could be used to engineer organisms or to select or design applications so as to reduce gene flow risk.

Microbial Horizontal Gene Transfer

Once thought relatively rare, horizontal gene transfer among microbes is believed to be extremely common. It takes place through a variety of mechanisms, and research has identified both patterns and tremendous diversity in its occurrence. Development and investigation of research methods in this area is ongoing.

Transfer Mechanisms

In contrast with earlier understandings, horizontal gene transfer does not require viruses, special genetic elements such as the "F-factor," transposons or other genetic sequences that readily move within genomes, or small, circular DNA strands called plasmids. Transfer may involve living and dead organisms, with or without external vectors. Scientists have identified a diversity of horizontal gene transfer mechanisms, a few of which are outlined here. Research into transfer mechanisms is ongoing. New mechanisms are being discovered and scientists are still seeking details of even the most well understood mechanisms.[107]

One well-known type of transfer is transformation, which involves active uptake of environmental DNA,[108, 109] such as that from a dead microbe. Organisms may become competent, able to engage in transformation, by expressing genes for the DNA uptake machinery, while other genes are involved in determining when to enter competency. Researchers have identified a number of the proteins that enable transformation, as well as mechanisms regulating competence.

Artificial transformation is commonly induced in the lab, where cells are mixed with DNA fragments after being treated to make them capable of taking up free DNA. Numerous species are "naturally competent," which involves expressing genes for the protein components of the DNA uptake machinery.[110] A number of the proteins that enable transformation have been identified in several species.[111] Competence is often induced by stress, but the particular factors inducing competence differ for different species.[112]

A second well-known type of transfer is conjugation, in which microorganisms form physical structures to attach themselves to other microbes and transfer DNA, often plasmids.[113] The recognized "F-factor" of some conjugative transfer in *Escherichia coli* is responsible for a small portion of gene transfer. The proteins needed to perform conjugative transfer, and the genes coding for them, have been identified in a number of species.[114]

Virus-mediated transfer is also broadly recognized. A virus infecting a cell inserts its genetic material and uses the cell's "machinery" to reproduce the virus's genetic material and make proteins for packaging that material, producing new viruses, which leave the cell and infect other hosts. Horizontal gene transfer may occur when some of the host's genetic material becomes packaged with the viral genetic material and transferred into the next cell infected. For successful transfer to occur, the recipient cell must survive the infection. One study found a 20% survival rate among infected bacteria tested.[115] A commonly discussed type of virus-mediated transfer is transduction, transfer occurring between bacterial cells via bacteriophage viruses.[116]

Transfer occurs through numerous other mechanisms.[117] For example, transfer by phagotrophy involves eukaryotic microbes' that feed by engulfing cells or other particles acquiring genetic material from their food,[118] and gene transfer through feeding is believed to occur among multicellular organisms such as animals as well.[119] Gene transfer agents (GTAs), more common among bacteria than originally thought,[120] are genetically-encoded entities that effect transfer by carrying pieces of the cell's DNA into other cells.[121] Recently discovered, transfer using nanotubes is similar to conjugation in its ability to transfer plasmids and fragments of chromosomal DNA.[122]

Transfer Across Phylogenetic Distances

Horizontal gene transfer can occur across vast phylogenetic distances,[123] suggesting that it could be relevant for every biotechnology application. However, particular factors may enhance or inhibit such transfer, and knowledge of physical and genetic factors that enable or prevent transfer may provide substantial insights relevant to assessing transfer likelihoods as well as to engineering and designing applications to prevent transfer.

Horizontal gene transfer has been found to occur between all the major phylogenetic divisions, including between prokaryotes and eukaryotes.[124] However, closely related organisms transfer DNA more readily,[125, 126] partially because new DNA is most readily incorporated into a chromosome when similar sequences are found in the existing chromosome,[127] which, in nature, is most common between closely related individuals. Virus-mediated transfer and plasmid transfer are not subject to limitations based on sequence similarity.[128] Some bacterial species have been found to favor uptake of DNA from members of the same species by making efficient uptake rely on species-specific DNA sequence "tags,"[129] or by producing enzymes that remove foreign-seeming DNA from the genome.[130]

Successful transfer requires successful expression in addition to incorporation of the genetic material. Research suggests that matching of cellular "machinery" for gene expression is a decisive factor in gene transfer success.[131] Such machinery may be more similar between more closely related organisms.[132] For example, gene transfer from eukaryotes to prokaryotes is thought to be less often successful than the reverse, potentially due to prokaryotes' inability to express properly genes with introns, non-coding segments that are present only in eukaryotic DNA.[133]

Some researchers suggest that genes containing codons in very different proportions from their frequencies in the recipient genome, such as those from species with different codon usage frequencies, are less likely to transfer successfully.[134] However, researchers also found that transferred genes evolve to contain codon frequencies resembling those of the new host,[135] and other studies have found no relationship between codon usage and expression,[136] or, for a fitness-enhancing gene, rapid evolution to full expression of the gene,[137] suggesting that codon usage dissimilarity may not present a large barrier to successful transfer.

Barriers to virus-mediated gene transfer between distantly related species may be due to viral host specificity. While host-specific bacteria-infecting viruses are known, many have broad ranges.[138]

Though it appears to occur,[139, 140] successful horizontal gene transfer to multicellular organisms that produce eggs and sperm is hypothesized to be much rarer than transfer to unicellular organisms, because new genes would need to enter the eggs or sperm in order to be passed to the next generation.[141]

Types of Genes Transferred

Absolute restrictions on types of genes that can be transferred have not been identified, though trends have been identified regarding the commonness of different types of genetic materials' transferring.

Because transfer often involves fragmentation of the genetic material, shorter genes are more likely to arrive to a new cell intact, though whole chromosomes have been found to undergo transfer.[142] To be expressed, a gene must have a promoter, a sequence that signals transcription of the gene. Thus, to be expressed, transferred genes must contain their promoters, be acquired along with another promoter, or be inserted into the genome near an existing promoter.[143] Researchers have found that regulatory sequences, such as promoters, may undergo transfer without protein-coding regions and affect recipients' characteristics.[144]

Genes on or near "mobile genetic elements" have been found to transfer more readily than regular chromosomal DNA.[145] These mobile genetic elements can be DNA segments more readily capable of translocation or coding for enzymes that rearrange DNA, such as plasmids, transposons, and integrons.[146] This trend also suggests that engineered organisms could be subject to frequent transfer events, because mobile genetic elements

are often used in the lab to move genetic material into a cell. Some researchers have recommended using other transgenesis methods that produce less vulnerability to transfer. Knowledge of the transgenesis method may be useful for risk assessors seeking to estimate transfer likelihoods.[147]

Researchers have found that genes coding for parts of systems with many tightly integrated elements are less likely to have evolved through horizontal gene transfer.[148] In nature, genes coding for related functions are often located together and may transfer together.[149, 150] In contrast with genes involved in metabolic functions, relatively few "information-processing" genes, coding for such functions as replication, DNA transcription, and translation of RNA into proteins appear to have evolved through transfer.[151] Researchers have found that this apparent function-based preference is likely actually attributable to information-processing genes' tending to exist as tightly integrated systems.[152] A study on *E. coli* metabolic function genes found horizontal gene transfer to be more common for enzymes involved in peripheral reactions such as nutrient uptake than in central reactions such as building the cell's structure.[153] These trends suggest that relatively isolated genes, or those performing peripheral functions, may be those most subject to transfer. These are also the types of genes most commonly altered in engineered organisms.

While genes conferring selective advantage are more likely to proliferate because individuals possessing them are better able to survive and replicate, non-beneficial genes may also be transferred and then passed on through replication.[154] These genes may become beneficial and proliferate later,[155] for example under new ecological conditions or by acting with genes in the new organism.

Transfer Frequency: Evolutionary Studies

Though researchers generally agree that transfer occurs frequently, rather than exceptionally,[156, 157] precise rates of gene transfer are unknown.[158]

Much of the research on frequency and other patterns of transfer takes an evolutionary approach, comparing organisms' genomes to detect genes that may originally have entered a strain through horizontal transfer.[159, 160] Methods include comparing genes' base pair ratios or codon usage,[161] or finding the same genes in distantly related organisms.[162] Evolutionary studies can provide insights important for assessing biotechnology applications. These studies examine gene transfer under natural conditions, and they often seek to detect transfer throughout the genome, rather than measuring transfer of a particular gene.[163] They may provide information on the overall likelihood of gene transfer for a given type of gene, organism, or other conditions, and they shed light on low-probability events that are important in considering risks but that may not appear in more time-limited studies.

However, evolutionary approaches are imperfect, and they may require care in application to engineered organism assessment. Evolutionary methods of detecting past horizontal gene transfer events in existing genomes are flawed and debated.[164, 165]

Furthermore, these studies only detect genes that became stable in the recipient genome over evolutionary timescales; they do not determine how frequently transfer occurs overall or detect transfers as they occur. Research has suggested that many transfer events may be lost from the lineage relatively shortly after they occur.[166]

Evolutionary studies using existing strains likely miss aspects of gene transfer likely to present risks. A strain or genotype may cause health or environmental damage long before it is common in the population, and on relatively short timescales. For example, virulence and pathogenicity characteristics often spread through only a small portion of a bacterial population and cause great damage within a short period.[167] Similarly, an invasive genotype may disrupt an ecological system and then become extinct. As many especially damaging bacterial types eventually become extinct,[168] many transfer events that present risks may not appear in evolutionary studies. Thus, the present primary methods for detecting or estimating rates of gene transfer may be inadequate to address risk assessors' or bioengineers' need to understand gene transfer. Identification of how evolutionary studies may be used for environmental assessment and what gaps must be filled by other types of studies may be valuable.

Transfer Frequency: Lab and Field Studies

Some studies directly attempt to estimate frequencies of horizontal gene transfer events in the environment. These studies may use lab or *in situ* incubated setups meant to mimic environmental conditions, though mimicking a range of conditions remains a challenge.[169]

Studies have attempted to test transfer directly by determining rates of transfer to isolated strains or diverse bacteria in water samples[170] or under various conditions in soil.[171] One study used results of a few lab-based studies to estimate rates of up to one hundred marine virus-mediated bacterial transfers per liter of water per day within the Tampa Bay Estuary,[172] and another lab-based study estimated rates several orders of magnitude higher for GTA-mediated transfer.[173] Studies have also investigated what conditions may affect transfer rates.[174] Many studies focus on particular transfer mechanisms,[175] while others seek to estimate numerical frequencies of gene transfer,[176] or to determine survival rates of cells involved in transfer.[177, 178] Some studies on virus- or GTA- mediated transfer have introduced the viruses or GTAs themselves to potential recipients, while others have detected transfer between cells.[179] Direct studies have typically used antibiotic or toxin resistance genes as indicators of transfer.[180] Testing for transfer of other genes is becoming easier with availability of low-cost DNA sequencing. More studies and methods development to estimate transfer rates under a variety of conditions may be beneficial.

Most attempts to estimate frequencies of current or evolutionary transfer use microorganisms easily cultured in labs.[181] While an engineered strain itself is likely to be of a type easily cultured, most microbial species, and therefore most of the organisms the engineered strain will likely encounter in receiving ecosystems, are presently unculturable in the lab,[182, 183] challenging prediction of transfer likelihoods in receiving

environments. New technologies enabling genetic sequencing without culturing are being utilized to study gene transfer.[184] Investigations of potential gene transfer to assess biotechnology applications may benefit from taking into account knowledge limitations due to researchers' inability to culture most microbial species as well as other challenges in studying horizontal gene transfer. Data imperfection should not be mistaken for phenomenon rarity; those data that do exist point strongly to horizontal gene transfer as a common occurrence that should likely be considered in assessing biotechnology applications' potential effects.

Gene Flow in Sexually Reproducing Organisms

In sexually reproducing organisms, a species is formally a group of organisms whose members are capable of exchanging genes or interbreeding. Practically, however, gene flow between groups considered to be different species is not uncommon. Researchers have found that large numbers of plant and animal species are naturally involved in hybridization with other species.[185] It is reasonable to view species more as "poorly differentiated way-stations in a continuous hierarchy of biodiversity" rather than as "discrete and fundamental units."[186]

In assessing the possibility of gene flow between genetically engineered and wild type organisms, gene flow between the engineered strain and wild type conspecifics, as well as with members of other species, may be due consideration, and knowledge about interspecific and various types of inter-taxon crossing may valuably inform research and assessment. Gene flow frequencies and phylogenetic distances appear to vary substantially and may be a topic of investigation both in general and for a given biotechnology application.

Frequencies and Contributing Factors

Among plants, hybridization between related species is common. Hybridization between crop plants and related weed species is well established,[187] and researchers have investigated hybridization likelihoods and affecting factors.[188] The degree of relatedness affects the likelihood of hybridization,[189] though long-term evolutionary isolation should not be assumed to prevent it.[190] Pollination mechanisms and other aspects of plant biology and ecology[191] affect hybridization, though results are not always as expected: Wind-pollinated plants are typically expected to experience more gene flow than those pollinated by insects or other animals,[192] though insects may also carry pollen over long distances.[193, 194] Plants that are primarily self-pollinating, such as rice and many legumes, are expected to experience lower rates of gene flow, though hybridization may be likely even in primarily self-pollinating species.[195, 196] Varying compatibilities between individual plants rather than between species or varieties may have an effect, and rare events affecting hybridization frequencies but falling outside of recognized and predicted patterns may have a role.[197] Plant hybridization may produce a plant with characteristics intermediate between those of its parents, or with characteristics substantially outside of the range between the parents, such as being larger and more robust or having lower fecundity.[198, 199] While animals with differing numbers of chromosomes rarely produce viable offspring, and viable offspring are typically sterile, plant species with different

numbers of chromosomes can often hybridize, sometimes producing new species that are genetically isolated from both parental types.[200]

Investigations of gene flow rates among cultivated or weedy plants often involve creating experimental plots of varying distances or other factors under investigation and then detecting genetic indicators of gene flow between them and employing statistical methods to draw conclusions.[201] Many potential confounding factors and sources of variability must be considered.[202, 203]

Hybridization is an important force within animal species as well.[204] Research on patterns, causes, and frequencies of hybridization is ongoing.[205, 206] Animal ecology, habits, and physiology must be suitable for hybridization to occur. Hybridization between species that do not normally mate may be promoted by either rarity of conspecifics or abundance of the heterospecific.[207, 208] Introgression, in which the product of the cross mates with members of one of the parental lines to continue the genetic mixing, is more common than once thought,[209] though some species experience hybridization but not introgression,[210] and hybrid sterility is not uncommon.[211] Research has found that even when crosses between two species typically result in inviable or sterile offspring, stable lineages can result from these crosses.[212] In some species, members of only one sex are able to hybridize with a given other species, and sometimes viable hybrid offspring are only members of one sex.[213] While it does not result in cross-bred lines, mating that produces sterile or non-viable offspring may, if it takes place in sufficient numbers, still have population or ecological effects by reducing the wild type population's reproduction.[214] In animals, hybrids are often identified through the observation of intermediate physical characteristics,[215, 216] though hybrids may also have characteristics more extreme than those of either parental strain.[217] Genetic methods have recently been employed to identify hybrids as well.[218]

Engineered Strains Out-Crossing

Genetically modified plants and animals are likely to be able to hybridize or cross-breed with any species with which their wild type parental strain is capable of breeding, so knowledge about the parental strain may be useful for identifying potential mates within an engineered organism's receiving environment.[219, 220] Gene flow from engineered grass to wild relatives has been documented.[221] One researcher discussing crops argues that "... transgenes will eventually escape into the natural environment if there is a compatible relative near the transgenic crop ... , unless [mechanisms preventing reproduction of the transgenic crop altogether are in place]."[222]

Gene flow with unmodified conspecifics is even more likely. Unless the modifications substantially alter its reproductive physiology or mating habits, an engineered organism is nearly guaranteed to be able to breed with wild type members of its own species present in the receiving environment. Gene flow from engineered to non-engineered crops has been well documented.[223] European countries have established buffer zone, or isolation distance, requirements between genetically engineered and traditional cultivated crops in

order to prevent cross-pollination,[224] though some researchers have suggested that distance alone is insufficient to prevent hybridization.[225, 226]

Breeding with wild types to produce organisms with hybrid characteristics, and, if the release is large enough, to reduce substantially the numbers of pure wild type organisms, is an important mechanism whereby engineered organisms may come to affect receiving environments, including wild populations. For many bioengineering applications, gene flow with wild types is unequivocally undesirable, and an environmental assessment would likely include estimation of its likelihood or frequency and prediction of adverse effects that could result. For some applications, however, breeding with wild types is the bioengineering application's mechanism of action. For example, engineered organisms released to control invasive conspecifics by introducing a detrimental transgene[227] and gene drive applications meant to engineer wild populations through bearers' of the engineered genetic material breeding with wild types[228] rely on engineered-wild gene flow to produce the desired effect. For microbes as well, horizontal gene transfer could be a goal. Researchers have experimented with introducing to contaminated material, such as soil or wastewater sludge, microbial strains containing genes, located on mobile genetic elements such as plasmids, for the ability to break down the toxic contaminants, so that the degradation abilities will be transferred to local microbial populations.[229, 230] Environmental assessments should consider and evaluate each application's goals and means.

Genetic Stability and Evolution[231]

Organisms' mutating and evolving away from earlier forms constitutes a substantial mechanism whereby they may come to affect receiving environments in ways that may be difficult to predict or control. The DNA replication process itself as well as external agents and forces produce mutations that may alter an organism's characteristics. Gene flow can also introduce genetic changes on which natural selection can act.

Through genetic changes and natural selection, engineered organisms that have entered a receiving environment may come to display characteristics different from those deliberately engineered, undermining predictability and control.[232] Though more research may benefit assessment efforts, existing information about mutations and selection can be useful for assessing potential environmental implications enabled by evolution, and it can aid efforts to design applications and engineer stable strains.

The present discussion focuses on mutation and evolution in microbes, but many of the principles and considerations are similar for larger organisms. Many microbes have larger populations and shorter replication times than most larger or more complex multicellular species, resulting in greater potential for substantial evolution of characteristics within short timeframes. These differences exist for other organisms as well. For example, mosquitoes that may have over ten generations per year[233] may evolve more rapidly in absolute terms than larger animals that take years to reach maturity.

In reactors or other confined systems, engineered organisms' evolution may be curtailed by periodically cleaning out the reactor and reinoculating it from newly produced or tested lab strains. Once released into receiving environments, however, organisms may be free to evolve indefinitely.

Mutation Rates, Types, Causes, and Repair Mechanisms

Little quantitative information has been published on mutations' effects on engineered systems.[234]

The lower end of mutation rates reported in bacteria is one error per 10^8 to 10^9 base pairs replicated.[235] Similar mutation rates have been reported for prokaryotes and eukaryotes.[236] Based on *E. coli*'s replication rate, 3×10^{-3} changes per genome are expected per hour.[237] Assuming logarithmic growth to a stationary state in cell culture medium, the typical *E. coli* batch culture has approximately 10^{12} cells per liter, so that as the cells reach saturation in one liter of culture they would accumulate on the order of one billion mutations during the last twenty-minute division cycle alone, and the estimated cumulative number of mutations starting from the initial inoculation would be much larger. These numbers include only fixed mutations, those that persist through subsequent replication, rather than mutations that are repaired or that otherwise do not remain. In microbes some engineered genetic constructs fail due to mutation within hours. Approaches exist for extending engineered construct life by preventing mutational damage,[238] and long-lasting constructs are presently maintained for a matter of weeks under adverse selective pressure,[239] an achievement that, while technologically substantial, may or may not significantly reduce estimates of risk upon environmental release.

Single base-pair changes, in which one base (A, T, C, or G) is replaced by another, are the simplest form of mutation. In protein-coding DNA segments these mutations may change nothing in the resulting protein; they may result in a different amino acid's being used, which could affect protein structure and function to large or small degrees; or they may result in larger changes such as truncation of the protein. Genetic material rearrangements, including insertions, duplications, deletions, and inversions, are larger alterations that more often have more disruptive effects.

Single base-pair changes often arise from mistakes in DNA synthesis. Rearrangements may be caused by external factors such as DNA-damaging physical and chemical agents, or by the cell's own genes or gene products. Physical mutagens include ultraviolet light, X-rays, gamma-rays, cosmic rays, ultrasound, and other forces. Chemical mutagens include natural compounds such as aflatoxin, bleomycin, and mitomycin, as well as synthetic compounds such as polycyclic aromatic compounds, deamination reagents, and base analogs.[240] In addition to causing changes within an individual organism's lifetime, mutations in single-celled microbes or in germ cells of multicellular organisms with differentiated germ lines are passed on to future generations.

While mutation can benefit an organism, it is often detrimental, and organisms have numerous DNA repair mechanisms.[241] Many of these mechanisms are specific to particular types or sources of error, while others play more general roles.[242]

DNA repair is generally loyal,[243] but some repair systems do not always precisely restore the original sequence. Scientists have sought to produce microbial strains sustaining fewer mutations by suppressing error-prone repair systems such as the "SOS response" in *E. coli*.[244] These researchers reduced their strain's mutation rate by a substantial percentage. Other researchers have reduced mutation rates by adjusting added genetic material to avoid mutation-prone sequences.[245] While the degree of increased stability achieved could prove useful for producing a strain that would maintain chemical production capabilities for longer, it does not necessarily produce evolutionarily stable strains for purposes of environmental release. Even relatively low mutation rates do not necessarily lend control over an organism's characteristics in a receiving environment.

Evolutionary Pressures on Engineered Organisms

Engineered genetic constructs introduced into a cell often impose a metabolic cost in that the cell must produce additional proteins or perform some additional function, or at least use resources to replicate the construct. Therefore, if the construct does not benefit the organism, mutations preventing expression of the genes or removing them altogether is likely to benefit the organism. Researchers have observed that natural selection often destroys engineered constructs.[246] Favored mutations can occur in an engineered construct itself, or they may occur elsewhere in the genome and indirectly affect the added genes' expression. Researchers have also pointed out that many genetically engineered alterations may benefit the organism in receiving environments,[247, 248] and engineered genetic changes will not necessarily be removed from a population. Even detrimental alterations may be removed only over many generations, and environmental effects could occur while the introduced genetic material remains in the population.

Organisms may undergo other mutational changes that alter their characteristics and may affect interactions with receiving environments. For example, an organism predicted to maintain low numbers due to its inability to consume a food source common in the receiving environment or due to its requiring certain conditions for survival could acquire mutations that broaden its range. Mutation may act together with gene flow to increase organisms' adaptation to receiving environments.

Investigating Construct Stability

Investigating genetic construct stability typically involves culturing the engineered strain for many generations and analyzing its phenotype and genotype. For example, in one study researchers cultured *E. coli* over hundreds of generations and observed a decrease over time in expression of the green fluorescent protein gene they had added.[249] They identified mutations by sequencing the plasmid on which they had added the gene.

Recent sequencing technology advances have permitted greater interrogation of genomic changes under evolutionary pressures. Sequencing technologies now enable sequencing a

bacterial cell line's entire genome at regular intervals to identify mutations occurring during its evolution. One group of researchers investigated changes over time in *E. coli* populations' genomes under selective pressure with resolution of about one day.[250] In addition to applying the selective pressure, an antibiotic, and measuring the resultant antibiotic resistance, the researchers sequenced the entire genome of select cells each day. They determined exactly what mutations had occurred and how they were accumulated. In addition to finding multiple mutation pathways to achieve increasing resistance, the researchers also observed patterns in the types and locations of mutations responding to different selective pressures. More may be learned through the use of new technologies such as genome-wide sequencing.

Detailed studies of genetic changes are often limited to lab environments or simple microcosms and to organisms readily amenable to lab culture. Application of existing knowledge to assessing engineered organisms' behaviors in receiving environments may benefit from considering these limitations.

Work on Engineered Safeguards

Understanding factors influencing ecosystem risk can enable engineering of organisms so as to reduce risk.[251] These design efforts can include developing engineered "safeguards" meant to limit such functions as survival or ability to exchange genetic material. Designing reliable safeguards that withstand evolutionary pressures is challenging, and efforts are ongoing. After discussing a paper reviewing efforts to engineer safeguards against survival and gene flow, this section describes particular recent research initiatives, including advanced recoding to limit survival and gene flow in microbes and designs to reverse or localize engineered gene drive.

Engineered Safeguards Review

Since the 1980s, biological engineers have been developing approaches to controlling genetically engineered organisms' survival in uncontained environments and their ability to transfer added or engineered genetic material to other organisms.

Moe-Behrens and colleagues reviewed[252] genetically-based "intrinsic containment" technologies for microbes. They discuss approaches to preventing survival and horizontal gene transfer, failures of existing approaches, and directions for further improvement.

Approaches to Preventing Survival

One basic approach to preventing survival outside of containment is through weakness of the organism; biological engineers may choose microbial strains that survive poorly outside of laboratory or reactor conditions.

Biological engineers may also use auxotrophy, engineering microbes to require molecules absent from the broader environment, such that the organism dies if it escapes the controlled environment where the molecule is provided. Auxotrophy may be produced by deleting a gene coding for an essential nutrient, so that the organism only

survives when the nutrient is supplied artificially. Engineers may also place a gene coding for an essential nutrient under the control of an artificially supplied molecule, so that the organism only produces the nutrient when the molecule is supplied. Alternatively, engineers may add a gene coding for a toxin, placed under the inhibitive control of an artificially supplied molecule, such that when the molecule is absent the toxin is produced and kills the organism.

Biological engineers may also seek to prevent survival through induced lethality, sometimes termed "kill switches." These mechanisms enable the organism to survive until an inducer signal, such as a particular molecule, is added. In these systems, the inducer signal can "turn on" a gene coding for a substance toxic to the organism. In order to enable cleanup of engineered microbes in a receiving environment without harming other microbes, the inducer signal is not itself toxic. Inducer signals could also be heat or other non-molecular signals, or substances absent from the controlled environment but ubiquitous in the receiving environment.

Approaches to Preventing Horizontal Gene Transfer

To reduce horizontal gene transfer, biological engineers may place the added genetic material in a genomic location less likely to transfer. For example, they may integrate it into the chromosomes rather than adding it to a plasmid, a small circular DNA strand that is more mobile than chromosomes. In part because of their mobility, plasmids are both common choices for artificially adding DNA and more vulnerable to transfer.

Biological engineers have also designed toxin–anti-toxin systems to prevent transfer. In these systems, a lethal gene, such as one coding for a toxin, is added to the engineered DNA segment, such as an added plasmid, and an immunizing gene is added elsewhere, such as a chromosome or another plasmid. The engineered microbe is thus safe from the lethal gene but another microbe taking up the engineered DNA without also acquiring the immunizing gene is killed. In some systems, the lethal gene codes for proteins that destroy DNA, so that the engineered DNA is destroyed if another cell takes it up.

Engineered Safeguard Failures

Genetic safeguards can fail for a few reasons. Mutations, such as those disabling a controlling genetic switch, preventing a toxin's production, or providing immunity to a toxin, are a key cause of safeguards' being disabled. Most survival-prevention safeguards tested under lab conditions or environmental microcosms experience some failure due to mutations. The National Institutes of Health recommends engineered microbe survival or engineered DNA transmission of less than one cell per 10^8 cells, equivalent to survival or transfer in one thousand cells in a culture occupying a two-liter volume. Only a few of the safeguards surveyed meet this limit.

Outside the lab, horizontal transfer can provide microbes with genes that cancel an auxotrophy or otherwise disable the safeguard. Auxotrophy can also be compromised through the missing nutrient's being available in the receiving environment.

Approaches to Improving Safeguards

A number of approaches could help improve safeguard reliability, including approaches using standard existing microbial strains and others involving larger genomic changes. Slowing organism growth, such as by incubating cells at lower temperatures, can reduce the accumulation of potentially safeguard-damaging mutations by producing fewer generations over a given timespan. Many genes produce protein at low levels even when they are "off." Low-level toxin production in organisms with intact safeguards gives individuals with safeguard-damaging mutations an advantage, increasing their numbers even before safeguard activation. Engineering for tight control of safeguard genes could prevent microbes with safeguard-damaging mutations from having an advantage.

Approaches involving more modified organisms include use of strains with "minimal genomes," containing only necessary genes. In these organisms, more mutations are lethal so unexpected evolution or behaviors are predicted to be less likely.

Researchers have also proposed using "orthogonal life forms" relying on artificial genetic languages. These could prevent horizontal gene transfer and also cause auxotrophy for artificial molecules. Researchers have proposed changes to DNA including artificial bases that preferentially bond with each other rather than with natural bases, and alternative DNA geometries instead of the usual double-helix. An alternative geometry's size, shape, and molecular backbone could fail to fit with natural DNA components, or with natural DNA-to-protein translation or DNA replication machinery. Researchers have also proposed synthetic amino acids, four-base instead of the usual three-base codons, and synthetic DNA-to-protein translation machinery. While these options have potential, they are not necessarily fail-proof. Synthetic genetic systems may still interact with natural systems, with potential results including toxicity, and escaped organisms with orthogonal systems could still affect receiving environments.

Recoding to Limit Horizontal Gene Transfer

In nature, every possible DNA base triplet has a coding function, while many triplets share functions, such as multiple codons coding for the same amino acid. Which codon codes for which amino acid or function is nearly universal across organisms.

Researchers have worked to produce "genomically recoded organisms" (GROs), in which one or more codons is reassigned to a different amino acid. To accomplish reassignment, all instances of the target codon must first be replaced with another codon that has the same meaning, in order to preserve the organism's function. For example, to reassign one of the two codons that codes for cysteine, all occurrences of this codon would first be replaced by the other, in order to preserve the occurrences of cysteine. Then, the cellular DNA-to-protein translation apparatus must be redesigned to cause the cell to respond in the new, desired fashion to the reassigned codon, such as adding a different amino acid, rather than cysteine, when the reassigned codon appears.

Organisms with sufficiently altered genetic codes are expected not to exchange DNA successfully with standard-code organisms, due to each organism's being unable to

produce functional proteins using the other's DNA. In addition, GROs could be designed to make proteins using non-standard or synthetic amino acids, expanding possibilities for chemical production using engineered microbes. Furthermore, recoding could produce resistance to viruses, which utilize the host's genetic apparatus to replicate their genetic material and produce their proteins.

Lajoie and colleagues[253] recoded an *E. coli* strain by removing all instances of the "stop" codon UAG[i] and replacing it with another stop codon; removing the DNA coding for the cellular apparatus that reads UAG as "stop"; and then introducing a cellular apparatus that reads UAG as coding for non-standard amino acids.

The *E. coli* strain without the UAG codon or the apparatus to express UAG as "stop" displayed normal physiology and metabolism, though slower growth than the parental strain.

The researchers tested how well their recoded strain incorporated each of a few non-standard amino acids (NSAAs) when a gene containing UAG was added to the genome. They found that when the correct NSAA was provided, the GRO strain incorporated it in the UAG locations.

The GRO exhibited enhanced resistance to one of the two virus strains tested, likely because it lacked the machinery to read the virus's UAG codons as "stop." The researchers hypothesize that recoding of more codons could produce complete resistance to natural viruses and move further toward prevention of horizontal gene transfer. Viral infection is one mechanism whereby horizontal gene transfer occurs and inability to translate natural organisms' proteins could impair horizontal gene transfer through other mechanisms as well. The researchers did not test their GRO for rates of horizontal gene transfer directly.

Recoding to Limit Survival

Researchers sought to create a "synthetic auxotroph," an organism requiring a synthetic molecule for survival and growth.[254] They began with the *E. coli* strain they had engineered[255] to contain no TAG stop codons,[ii] to lack the cellular machinery that reads TAG as "stop," and to contain machinery causing the cell to add a synthetic amino acid (sAA) when TAG occurs in the DNA sequence, thus "reading" TAG as specifying a synthetic amino acid.

Using this recoded strain, the researchers sought to develop a strain that would grow only if provided with synthetic amino acids (sAAs), by inserting TAG codons into genes necessary for cell function, particularly those whose products cannot be functionally obtained from nearby non-restricted microbes, such as genes enabling cell replication or DNA translation into proteins. They chose genes dispersed across the genome so that a

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[i] Codons are often written using their RNA counterparts, in which U replaces T. In Rovner *et al.* (2015), discussed below, this codon is referred to as TAG.

[ii] In Lajoie *et al.* (2013), discussed above, this codon is referred to as UAG.

single horizontal gene transfer event would not compromise the containment. The researchers inserted TAG codons at the beginnings of the genes or in place of codons for natural amino acids.

The researchers also experimented with inducing mutations in the coding for the cellular machinery reading TAG as one sAA to cause it instead to read TAG as each of two other sAAs. The resulting strains relied on these other sAAs instead, demonstrating the ability to engineer reliance on different sAAs.

The researchers used several approaches to reduce progressively the rates of "escape," or cells with mutations enabling them to grow without the sAA:

First, the researchers introduced TAG codons into one or two essential genes. They quantified the degree of escape for each resulting strain by taking the ratio of the number of cells that grew on media lacking the sAA to the number that grew on media containing the sAA and obtained "escape frequencies" ranging from 10^{-3} to 10^{-7}.

Next, the researchers tried two approaches: First, they combined sequences from different strains to produce strains with more TAG occurrences. Those with two TAGs had escape frequencies of 10^{-7} and 10^{-8}, and those with three had frequencies of 10^{-9}.

Again using their original recoded strain, the researchers then tried substituting TAG in a set of more important genomic locations. They obtained escape frequencies of 10^{-5} to 10^{-7} for strains with one TAG codon, 10^{-9} for strains with two TAG codons, and less than 10^{-11}, below the test's detection limit, for a strain with three TAG codons. This strain revealed escape mutants after two days.

The researchers then determined what mutations had enabled escape in the lowest-escape strains and made other genetic changes to make these mutations cause non-viability. The resultant strains had escape frequencies below 10^{-12}, below the test's detection limit.

The researchers conducted tests on these lowest-escape strains. To mimic a potential horizontal gene transfer event, they added two genes that could assist in escape and observed little or no growth. To investigate stability over time, the researchers monitored samples for seven days, finding no survival without the sAA. After twenty days they tested the entire growth culture, rather than samples, and found no escape mutants. To investigate whether proximity of non-auxotrophic microbes could provide missing molecules and enable growth, they grew one of the new strains with other *E. coli* strains and found that the new strain still did not grow without the sAA, including on blood agar, chosen to suggest a medical setting, and soil extracts, chosen to suggest an outdoor setting.

Safeguards to Control Gene Drive Spread

Proposed safeguards for RNA-guided gene drive systems are meant to enable genetic reversal of changes, prevention of changes in a particular population, or temporal or spatial localization.

Gene Drive

RNA-guided gene drive promises to enable rapid genetic engineering of wild populations of sexually reproducing organisms.[256] In nature, genes exhibiting "drive" bias the rules of genetic inheritance to be inherited by nearly all offspring rather than only half, which enables them to spread quickly through a population over generations, even without conferring a fitness benefit.

RNA-guided gene drive systems typically consist of (1) a recoded DNA sequence, meant to replace a particular wild type sequence to produce a desired trait, and (2) the drive apparatus: genetic material identifying and causing cutting of a target genetic sequence during cell replication. When an individual bearing a gene drive mates with a wild type individual, when the paired chromosomes align for cell replication the drive apparatus causes the wild type target sequence to be cut, and the cell's repair mechanisms re-create the gene based on the only available template, which is the gene drive, including the recoded sequence and the drive apparatus. Thus rather than the offspring's inheriting one engineered and one wild type copy of the gene, and passing the engineered version to half of its offspring, it bears the gene drive on both matching chromosomes and passes it to all of its offspring. This biasing of inheritance, repeatedly conferring the engineered gene to nearly all of an individual's offspring, as the drive is successful nearly all of the time, spreads the drive through the population much more rapidly than would occur with an ordinary gene. Over a number of generations, many or all of a population's organisms may come to possess the engineered genes.

Gene drive systems may be used to spread new characteristics or to spread genes to cause a population to diminish rapidly, termed "suppression drives." They have been proposed for such diverse applications as combatting vector-borne diseases such as malaria and Lyme disease, suppressing invasive species, and reducing pesticide and herbicide resistance in agricultural pests.

Gene drive developers have proposed ways of using gene drive to protect against a drive's undesirable effects: "Reversal drives" are meant to reverse a gene drive's genetic effects by overwriting the change with a new drive bearing the original wild type genetic sequence. "Immunizing drives" are meant to protect a portion of a population from a gene drive by making some individuals' genetic material different from the target sequence. "Daisy-chain drives" are meant to keep a gene drive temporary or spatially localized by designing it to rely on components that do not exhibit inheritance-biasing drive.

Reversal Drives

A reversal drive[257] carries the original wild type target genetic sequence that the initial, or primary, drive is designed to change, and is programmed to cut the primary drive's recoded sequence. When an individual bearing the primary drive mates with one bearing the reversal drive, all of the offspring theoretically bear the wild type sequence, along with the gene drive apparatus.

A reversal drive could be used when a gene drive is released accidentally or is determined after release to be undesirable. If it has not yet affected the entire population, a primary drive is expected to continue to spread with each generation, but the reversal drive also spreads through the affected population and overwrites the change. It may "catch up" and prevent the primary drive from affecting the entire population, particularly if it is released in large enough numbers. If an individual bearing a reversal drive mates with a wild type individual, the reversal drive is expected to be inherited according to normal principles of genetic inheritance because it does not recognize the wild type genetic sequence as a cutting target.

A reversal drive is meant to spread through a population over generations and overwrite an introduced genetic sequence with the original wild type sequence. It is not designed to reverse population or ecological changes brought about by the primary drive. For example, if the primary drive reduced the population size and this reduction caused other ecological changes, the population and ecosystems may or may not recover as the reversal drive restores the original genetic sequence.

Immunizing Drives

Gene drive systems are designed to affect only a specific target genetic sequence. Immunizing drives[258] are meant to prevent a gene drive's action by driving through the population a change to the target sequence, one that does not itself confer a trait change, so that it does not match the primary drive's target sequence.

An immunizing drive could be used to protect a semi-isolated sub-population from a gene drive. This use would apply, for example, to a population spanning two locations, such as an island and a mainland, whose respective sub-populations occasionally interbreed. A gene drive released in the population is expected eventually to affect both sub-populations. With a primary drive to be released, for example on the mainland, an immunizing drive could first be released on the island to cause the island-dwellers' genetic sequence to differ from the target sequence, so that the primary drive would not affect it. If the immunizing drive is present in all or most island individuals before a drive-bearing mainland-dweller mates on the island, the primary drive is expected to spread on the island only according to normal principles of genetic inheritance. The island population has been "immunized" against the primary drive by bearing its own drive with a genetic sequence slightly different from the wild type.

In this scenario, if the primary drive spreads to the island before the immunizing drive has spread, then the island population will likely be affected, and if an island-dweller

bearing the immunizing drive mates on the mainland before the primary drive has spread, the mainland population could also become immunized against the primary drive. Thus, immunizing drives for sub-population protection may be most effective where the amount of time over which the drive will remain in the population can be predicted and monitored, and natural or human-mediated migration events temporarily controlled.

In addition to protecting a semi-isolated sub-population, immunizing drives could be used to stop the spread of a gene drive released accidentally or determined to be undesirable. "Immunizing reversal" drives, targeting both the altered and the wild type sequences and replacing them with a new sequence functionally similar to the wild type, could prevent drive spread through unaffected portions of a population and also reverse it in affected portions. The researchers have proposed immunizing reversal drives as possibly the most rapid approach to addressing released undesired drive systems.[259]

Daisy-Chain and Other Daisy Drives

Researchers have proposed daisy-chain drives, whose exhibition of drive-type spread is expected to diminish over time, for geographically localizing alterations or causing population changes without permanently maintaining altered organisms.[260]

In normal RNA-guided gene drive systems, the recoded sequence containing the trait-affecting alteration is flanked by the drive apparatus that directs target sequence cutting, and the target sequence is the recoded sequence's wild type chromosomal pair, or homologue, so that the recoded sequence becomes present on both paired chromosomes and exhibits inheritance drive. However, the cutting and recoded components could be located in different places in the genome, such as on different chromosomes, such that they are not necessarily inherited together. In daisy-chain drive, sometimes called daisy drive, systems, components placed in separate genomic locations cause one another to exhibit drive, and not all components exhibit drive.

In a three-element daisy drive, one added genetic element, C, contains only the apparatus to cut a particular genetic sequence, with no trait-changing recoded sequence. It is not programmed to cut its own homologue, but rather to cut a sequence elsewhere in the genome. As Element C's homologue is not cut for C's replication, C does not exhibit drive. It is inherited by half of offspring, and if it is disfavored by natural selection its frequency in the population is expected to diminish over time.

Rather than cutting its own homologue, element C cuts a different location, the site homologous to element B, a second added sequence. Element B does not drive itself by cutting its own homologue; instead, it exhibits drive only when C is also present, because C cuts B's wild type homologue site. Because with C present B exhibits drive but C does not, B may be inherited by nearly all offspring while C is inherited by only half. In the offspring that do not inherit C, B does not exhibit drive and is inherited by only half of the next generation. Thus B trails C in diminishing across generations.

In this three-element chain, B also does not itself contain a trait-changing recoded sequence. Instead, B cuts a third genomic cite, which is the homologue of the final added element, A. Element A only exhibits drive when B is present to cut its homologue. Element A does not contain cutting apparatus; it is the "cargo" element, containing a recoded gene for the desired trait change.

In this system, the elements' spreads are limited by their reliance on one another for drive. Payload element A can spread rapidly through drive, but only when B is present in the same organism; otherwise its spread is limited by normal principles of inheritance and natural selection. Modeling has found that daisy drive systems cause initial rapid increases in cargo element frequency, followed by gradual decreases. Under some circumstances, the increase could be enough to cause an entire population or group of organisms to carry a trait, or to accomplish another desired aim. Developers hypothesize that elements' frequencies' diminishment over time will correspond to diminishment as a gene drive system spreads across a geographic area, potentially enabling localized gene drives.

Daisy drives consisting of more linked elements are expected to be stronger and longer-lasting than shorter chains: As organisms bearing a drive system mate and spread the genetic elements, all elements except the bottom one, C in the present example, exhibit drive. As C diminishes, B exhibits drive in fewer and fewer organisms. As B then diminishes, A ceases to exhibit drive. Shorter chains thus result in earlier diminishment of the cargo element, while longer chains delay this diminishment.

Some daisy drive applications could involve repeated releases of drive-bearing organisms to maintain sufficient frequencies of the bottom element (C) for as long as desired before allowing it to diminish. Daisy drives have been proposed to carry immunizing or reversal drives, in order to produce the immunizing or reversal effect without permanently altering every organism in the population. While as long as it is disfavored by natural selection a daisy drive is expected eventually to be removed from the population, resultant population and ecological changes are not necessarily reversed.

Designing daisy drives encounters the practical problem that a genetic recombination event, in which similar pieces of DNA exchange locations during cell replication, sometimes bringing nearby genetic material with them, could cause a lower element in the chain, such as C, to become co-located with a higher element, such as A. This occurrence would result in A's adopting C's function as well, such that A would cause B to drive. As B already causes A to drive, the result, a "daisy necklace," would be a self-perpetuating system that would behave as a normal gene drive rather than diminish due to reliance on non-drive elements. Such recombination is not unlikely because scientists use a limited set of sequences to operate the gene drive apparatus or control added genes, so the operational sequences in different daisy drive elements could be similar or identical.[261] Researchers have found high rates of recombination in some types of RNA-guided gene drive systems.[262] To prevent the recombination, developers are identifying and characterizing operational sequences expected to differ enough to avoid the problem.[263]

Researchers have proposed other types of daisy drive systems, including "daisyfield," "daisy quorum," and "daisy restoration" drives, to address localization and reversal further. In daisyfield systems,[264] multiple "daisy elements" located throughout the genome each cause the cargo element to exhibit drive. The daisy elements do not themselves exhibit drive, so when a daisyfield organism mates with a wild type, the offspring should inherit half of the daisy elements on average. With the number of daisy elements expected to diminish with each generation, the cargo element is expected to exhibit drive for a limited number of generations and then behave according to normal inheritance and natural selection. Daisyfield systems may avoid the daisy necklace problem by not relying on multiple cutting-and-copying genetic sequences that could become a self-sustaining drive through recombination.

Daisy quorum drives[265] are designed to spread through a population like daisy-chain drives until the driving elements have been lost; then the altered version's fitness depends on its frequency, such that the trait increases when most of the population is altered and decreases when most of the population is wild type, due to a property in which altered–wild type mating produces offspring compromised compared with those of same-type mating. Such a system is expected to produce a region of altered organisms within a wild type population. If the altered region is mostly isolated, the alteration is expected likely to remain. If it is embedded in a larger wild type region, it is expected to shrink slowly and disappear unless more drives are released. Release of many wild type organisms into the altered region or of a few suppression drive organisms targeting the alterations is expected to reduce the altered organisms' numbers enough to trigger elimination of the engineered sequence. Daisy restoration drive[266] is meant to act as an immunizing reversal drive to prevent spread of and reverse an unwanted drive locally. It is tied to a quorum effect to enable the drive's own elimination from the population.

Biological Processes, Knowledge, and Stakeholders

Many complex factors may be examined in assessing biotechnology applications' environmental implications. Each application includes unique aspects, and applications may also share important components. Survival, gene flow, and evolution may play important roles in many engineered organisms' potential to affect receiving environments. Research regarding these and other elements common among applications may provide information helpful to many assessments, and engineering efforts to safeguard against these processes or otherwise to control organisms' behaviors in receiving environments could prove broadly valuable. Despite the potential applicability of understanding or control of these processes to many environmental assessments or applications' engineering, respect for biological systems' diversity and unpredictability and for the limitations of scientific knowledge and research methodologies is needed. The inevitable judgment decisions regarding how to use, and perhaps even how to generate, scientific knowledge to evaluate implications and make decisions may be places for diverse stakeholder involvement.

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Chapter 3

Microbe Tier Testing Workshop and Regulatory Guidelines

A workshop in which diverse participants conveyed information and developed testing schemes to aid regulatory officials reviewing microbial biotechnology products provides insights into contributions. It also suggests challenges and approaches in convening diverse participant processes. Examination alongside testing requirements developed by agency officials provides further insights.

Case Background

Two offices within a single government agency are responsible for regulating genetically engineered microbes for different uses. Within a few years, officials in one office published testing requirements for product submitters, and the other office engaged diverse participants in a workshop to develop testing schemes as internal guidance for regulatory officials. The testing requirements and the workshop bear some similarities in charge and product, though they differ in important ways. Examining the products may shed light on how diverse participants might contribute to a testing framework for environmental assessment, as well as on other strengths and challenges of diverse participant processes.

Regulation of Genetically Engineered Microbes

In the United States, the Environmental Protection Agency (EPA) is one of the Federal agencies that regulates genetically engineered microbes. Engineered and naturally existing microbes meant to be used as pesticides[i] are regulated by the Office of Pesticide Programs (OPP) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), under which the OPP also regulates chemical pesticides. Certain genetically engineered microbes meant for other purposes are regulated by the Office of Pollution Prevention and Toxics (OPPT) under the Toxic Substances Control Act (TSCA), an act originally designed to regulate some industrial chemicals.

[i] In FIFRA, "pest" includes any insect, rodent, nematode, fungus, weed, or other organism formally declared to be a pest. (FIFRA, sec. 2(t))

The OPP, FIFRA, and Subdivision M

Under FIFRA, the OPP is responsible for obtaining data sufficient to ensure that registered pesticides "will not cause ... unreasonable adverse effects to humans or the environment."[1] The Office has promulgated requirements for companies submitting applications for registration of a pesticide, including information to be submitted and tests to be conducted in support of an application.

Though since replaced by other documents, Subdivision M of the Pesticide Assessment Guidelines[2] originally described the data requirements and testing protocols for biochemical and microbial pest control agents, including microbial pesticides that are the products of genetic engineering. Subdivision M, which was originally finalized in 1982 and was then revised in 1989,[3] includes data requirements relevant to potential harm to humans, livestock, agricultural crops, and the environment.

Tier Testing

Subdivision M employs tier testing schemes for data requirements. The EPA has used tier testing in a number of areas for decades. As used by the EPA, tier testing is meant to minimize the testing needed and thus the burden on submitting companies. The tests are typically arranged such that negative results, results not indicating an adverse effect, in a lower tier are supposed to provide a high level of confidence in the product's safety, and only positive results trigger higher levels of testing, which may be more expensive or time-consuming.[4]

Subdivision M Preparation

Regulatory officials within the OPP prepared the Subdivision M Guidelines.[5] Though the officials drew from existing tier testing schemes and data requirements, such as those for chemical pesticides, the testing requirements were composed to fit microbial pesticides' special properties. The Office employed no diverse participant or multi-stakeholder process for the Guidelines' preparation.

The OPPT, TSCA, and the Microbial Biotechnology Workshop

In 1994, the Health and Environmental Review Division, OPPT, along with the EPA's Office of Research and Development and Environment Canada's Commercial Chemicals Evaluation Branch, held a workshop to develop ecological tier testing schemes for naturally occurring and genetically engineered microbes that would be regulated under TSCA or under the Canadian Environmental Protection Act.[6]

The OPPT has no formal regulatory test data requirements for companies submitting data for approval of engineered microbes. The workshop was intended to produce internal guidance for the regulatory agencies regarding considerations or information to request from submitters. OPPT biotechnology staff responsible for regulating engineered microbes under TSCA continue to refer to the ecological tier testing schemes developed in this workshop.[7]

Workshop Participation and Structure

The workshop included over eighty individuals, including members of academia, regulatory agencies, and industry, and covering diverse areas of expertise such as microbial ecology, plant pathology, medicine, environmental assessment, and industries in which applications of microbial biotechnology existed or were expected. The diverse participants were included for their specialized knowledge.

The workshop, which took place over two and a half days, was carefully structured to result in participants' creating tier testing schemes. Before the workshop, conveners circulated an issue paper discussing released microbes' ecological effects, tier testing schemes, and the EPA's and Environment Canada's regulation of microbes. The paper includes overviews of a few existing tier testing schemes such as the OPP's Subdivision M Guidelines, as well as a draft tier testing scheme for the workshop.[8, 9]

Participants were first divided into groups based on expertise and were asked, guided by printed questions, to discuss hazard and exposure for particular applications, important potential ecological effects, or microbial pathogenicity and toxicity, or to develop a strawman tier testing scheme. Later, participants were divided into other groups based on expertise and were asked to use the strawman scheme and the information generated earlier to develop tier testing schemes for contained, semi-contained, and intentional release technologies.[10]

Consultants working with the Agencies played key roles in arranging the workshop, including producing the issue paper, identifying participants, and later compiling the report summarizing the discussions and presenting the tier testing schemes.

Similar and Different Charges

The two EPA offices' charges and scopes in regulating engineered microbes, and particularly the charges for the tier testing workshop and the Subdivision M Guidelines, appear to overlap, though important differences occur as well (Table 1).

OPPT Tier Testing Workshop	OPP Subdivision M Guidelines
Scope	*Scope*
° Microbes for various applications	° Microbial pesticides – toxicity expected
• Engineered and non-engineered microbes	• Engineered and non-engineered microbes
• Includes environmental effects	• Includes environmental effects
° Does not include health effects	° Includes health effects
Product	*Product*
• Tier testing schemes	• Tier testing scheme
° Unofficial internal guidance	° Official requirements for submitters
Process	*Process*
° Produced by diverse participants	° Produced by Agency officials
° Few-day workshop	° Work over years

Table 1. Initial comparison and contrast between the OPPT tier testing workshop's and the OPP Subdivision M Guidelines' scopes, product types, and processes. (• apparent similarity; ° apparent difference)

Organisms Addressed

Both the OPPT workshop and the Subdivision M Guidelines address both naturally occurring and genetically engineered microbes, and both were produced by offices with substantial experience regulating chemicals.

Under FIFRA, the OPP is responsible for regulating conventional chemical as well as biological substances used as pesticides. Subdivision M addresses microbial and biochemical pesticides. The present analysis examines Section A of Subdivision M, which addresses specifically microbial pesticides, both those that are naturally occurring and those that have been genetically engineered.

Under TSCA, the OPPT is responsible for regulating some chemicals as well as certain genetically engineered microbes. The workshop addressed both genetically engineered and naturally occurring microbes, due to the reasoning that they may have similar exposure and effects scenarios or that naturally occurring microbes could serve as a baseline,[11] and that some applications that may come to use genetically engineered microbes currently use naturally existing strains. In addition, co-convener Environment Canada regulates engineered and naturally occurring microbes under the same regulations.[12]

Pathogenicity and Toxicity

Being pesticides, products submitted to the OPP are likely to exhibit pathogenicity or toxicity, so the Subdivision M Guidelines may be expected to focus on this area more than might the OPPT's guidance. However, both offices may encounter microbes exhibiting and those not exhibiting these traits, and both are also required to review submissions for environmental effects, which could arise from other sources, suggesting some overlap of charges.

According to FIFRA, pesticides include in part "any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest."[13] As such, they may be likely to display toxicity or pathogenicity. The statutory language also appears to suggest an expectation that many pesticides are toxic or poisonous.[14] It is thus likely that testing for adverse effects under Subdivision M would include substantial pathogenicity and toxicity testing, such as to detect these effects in non-target organisms. Some may argue that addressing pesticides implies that the OPP should focus heavily on pathogenicity and toxicity in considering environmental effects. However, the statute also regards as potential pesticides such substances as defoliants, desiccants, plant regulators, and nitrogen stabilizers,[15] suggesting the possibility of a variety of mechanisms of action and potential environmental effect avenues.

FIFRA requires the Agency to ensure that pesticides it registers will, under normal use conditions, "not generally cause unreasonable adverse effects on the environment,"[16] defining unreasonable adverse effects on the environment in part as including "any unreasonable risk to"[17] "water, air, land, and all plants and man and other animals living therein, and the interrelationships which exist among these,"[18] as well as some human dietary risks from pesticide residues on food.[19] Subdivision M is framed as enabling the Agency to have "sufficient data to determine that the pesticide ... will not cause (or significantly increase the risk of) unreasonable adverse effects to humans or the environment,"[20] and the Guidelines emphasize the importance of ensuring that there will not be unreasonable adverse environmental effects.[21]

Regulating microbes intended for other purposes, the OPPT includes pathogenicity and toxicity as important considerations and potential effect mechanisms, though the OPPT's tier testing schemes might focus less on these areas and proportionally more on other ecological effect mechanisms. Thus, while a difference in focus is likely between Subdivision M and the OPPT's tier testing schemes, their considerations appear to overlap as well.

Intentional Release Applications

The OPPT workshop addressed contained, semi-contained, and intentional release applications. In addressing pesticides, the Subdivision M Guidelines are focused toward intentional environmental release contexts. When examining the OPPT workshop alongside Subdivision M, the present analysis focuses primarily on workshop results for intentional release applications and on aspects in other ways conducive to comparison. OPPT workshop participants determined that escape from contained and semi-contained applications is possible, and various components of the workshop results may be relevant.

Regulation and Internal Guidance

Despite resemblances in scope and overall charge, the Subdivision M Guidelines' and the tier testing workshop report's purposes differ in ways likely to affect content substantially. The Subdivision M Guidelines represent official regulatory requirements for product submitters, such as companies, whereas the tier testing workshop report is

meant as internal guidance for regulatory officials' reference. As such, Subdivision M includes detailed testing protocols and reflects an agency office's polished decisions, while the tier testing workshop report includes a record of discussions and its considerations and tier testing schemes are likely much less polished.

Approach to Case Analysis

The present analysis examines results of the OPPT tier testing workshop, seeking to discern what inclusion of diverse participants might have contributed and to identify other lessons regarding diverse participant processes. It seeks to develop further insights by examining the workshop results alongside the Subdivision M Guidelines to identify differences between the two, including strengths and weaknesses of each, that may provide insights into diverse participant contribution.

The analysis refers to the written guidance with which OPPT workshop participants were provided, including the issue paper and discussion questions, to differentiate participant contributions from points and approaches suggested by conveners. The case also provides an opportunity to examine the role of convener guidance in enabling and shaping diverse participant contribution.

The OPPT workshop was conceived as a gathering of scientists, not as a multi-stakeholder workshop, and it did not include diverse stakeholders as might have participated in a deliberately multi-stakeholder process. The analysis aims to discern what the diversity present at the workshop contributed, and the presentation leaves room for considering what other stakeholders might add to processes meant to include them.

Participant Contribution in the OPPT Workshop

The OPPT workshop's diverse participants contributed their expertise and perspectives to the tier testing schemes and the guidance to regulators.

Information Based on Expertise

Participants were included for their expertise, and the working groups into which they were divided were organized so as to maximize participants' ability to contribute based on their areas of expertise. Participants drew on their particular practical and academic backgrounds to contribute information, as well as to develop predictions, estimates, and rules of thumb. Participants contributed system knowledge that agency officials or other narrow experts might not possess, and their participation enabled knowledge available to agency regulators to keep pace with rapidly developing industries.

Industry – Technical Information

The industry members appear to have conveyed detailed information about industrial applications in which microbes were used and engineered microbes could come to be used.[22] For example, the groups tasked with identifying hazard and exposure for each of a number of industries described the sizes of the reactors or other locations in which the

microbes are or would be located and concentrations or numbers of microbes that might be used, while noting variation among facilities and applications. They also described the types of environments in which the applications may be expected. They identified species and genera of microbes that were being or were likely to be used and approaches used in industry to identify desirable microbes, as well as desirable microbial characteristics for each industrial use and characteristics for which microbes were being or were likely to be artificially enhanced. They further identified routes of environmental exposure, release, and spread, potential hazards that the microbes or their by-products could present, and existing measures to prevent release or spread. They also compared hazards from microbe use with hazards in the corresponding conventional, often chemical-based, technologies.

The participants provided other details that regulators could find helpful, such as describing "staged applications," in which different stages of a metabolic process are achieved by different microbes,[23] and explaining when a company might add chemicals to encourage the growth of native microbes and when microbes themselves may be added.[24] For some applications participants also described the current state of the industry, such as indicating when use of microbes was in experimental stages.[25] Rather than being limited to reporting on their own industries and practical experience, industry members were able to apply their knowledge to making predications and estimates about related industries as well.

Industry – Motives and Operations

In addition to technical information, industry members shared insights regarding industry motives and operations that could be relevant to ecological assessment. The participants mentioned that companies have financial interests in preventing specialized or engineered organism release. They explained that a company wishing to patent an engineered organism has an interest in preventing release to prevent claims that it is naturally occurring,[26] and that companies may wish to prevent release in order to maintain their proprietary knowledge of specialized or engineered organisms.[27]

Industry members contributed other information regarding companies' operations. For example, discussing closed-system chemical production, participants noted that occupational safety regulations requiring controls on worker exposure would contribute to reducing likelihood of organism release. Participants also described the Good Industrial Large Scale Practice (GILSP) guidance criteria on which some Canadian producers rely, which includes information requirements and safety screening regarding characterization of genetic elements, pathogenicity, environmental interaction and competitiveness, and other characteristics that could be relevant to ecological assessment.[28] Participants suggested that microbes meeting GILSP criteria may present minimal hazard, and the group used these criteria as guidance for what information to request in parts of one of the tier testing schemes.[29]

Schemes Reflecting Current Industrial Diversity

In addition to contributing information based on their knowledge and informed predictions about the industries, the participants used their industry experience to construct testing schemes reflective of the state of risk knowledge. Introducing the scheme for contained technologies, the report noted that

> Because the group participants ranged from individuals with considerable knowledge of and experience with their products to people working with novel products that are not well characterized, the tier testing scheme was modified to allow approval based on how much information is available regarding the ecological risks associated with the microorganism.[30]

The ability to craft a testing scheme attuned to the current state of knowledge in different industries may be seen as a strength of diverse participation. On the other hand, creating a flexible testing scheme based on each industry's existing knowledge could amount to lowering testing and thus health and environmental standards in order to minimize testing burden. Diverse stakeholder input has the potential to benefit an assessment process, but the potential for undesirable influence due to interested parties' perspectives must be considered.

Other Knowledge of Systems and Testing

Participants outside of industry contributed information based on their distinctive knowledge as well. Diverse experts in areas related to microbial pathogenicity and toxicity created a list of pathogenic species within genera frequently used in the technologies considered at the workshop. These participants also described the state of knowledge, indicating that several incomplete lists of frank pathogens exist but that searches within the literature would likely be necessary to secure the requested information, and that identification of opportunistic pathogens is even more difficult. The participants offered to help expand the list using information sources available at their offices and institutions.[31] The pathogenicity and toxicity group further applied its knowledge to developing a list of characteristics associated with or predictive of plant pathogenicity and of information that should be gathered about an organism or the intended application to aid in prediction. The group also identified tests that would be valuable in assessing pathogenicity and toxicity in some types of organisms.[32]

Participants knowledgeable in other areas also contributed insights from their existing expertise regarding testing and assessment approaches, in addition to factual information about the ecological and industrial systems. For example, an academic microbial ecologist contributed a list of desirable characteristics of assessment methods for ecological effects of engineered microbes, referencing a paper he had recently published on the subject.[33]

Inviting diverse participant knowledge for designing testing schemes or regulator guidance may have been more helpful to the OPPT officials regulating miscellaneous engineered microbes than it would have been to the OPP officials regulating microbial pesticides, because the former Office would have been beginning to regulate industries with which it lacked experience, whereas the latter would have been familiar with the

pesticide industry and with considerations common to pesticides, although regulation of microbial pesticides, including engineered microbes, may have been relatively new. Still, broader expertise could be helpful in many contexts. Diverse participant inclusion incurs its own efforts and costs, and whether or not to use this model may weigh differently for each endeavor.

Divergences Among Participants

References to differences of opinion among participants appear throughout the workshop report, suggesting that participants contributed based on their diverse backgrounds and perspectives, potentially enriching the discussion and improving the resultant testing schemes. In some instances, participant contributions diverging from conveners' or from the majority of participants' initial assumptions directly influenced the testing schemes, while in other instances divergent opinions did not directly affect the testing schemes but may still be valuable for having been voiced and recorded.

Examples of Divergences

The workshop included substantial discussion about microcosms. The discussion questions asked whether there are suitable microcosms for evaluating various microbial characteristics in the environment, such as survival and dispersal. They also asked about the design of suitable microcosms, about alternatives, such as mesocosms, if microcosms are not suitable tools for evaluation, and about how microcosms' validity as simulations should be assessed.[34] Participants' opinions differed regarding whether ecological endpoints could be determined using microcosms, though the group "generally agreed" that microcosms are legitimate simulations of the natural environment.[35] Cost may have contributed to participants' perspectives, as the report noted that the group "generally agreed" that a large majority of needed fate information could be obtained with "less costly" microcosms rather than "extremely expensive" mesocosms.[36]

Participants also diverged regarding the conditions and microbial characteristics that should be tested. It appears that some members of the Ecological Effects and Exposure/Fate Endpoints group (group C/D) suggested that microbes be tested in both "stressed" and "non-stressed" environments, with "non-stressed" environments representing healthy natural ecosystems and "stressed" environments representing those with particular anthropogenic characteristics that may lend the microbe an advantage, such as the presence of antimicrobial substances to which the added genetic material confers resistance.[37] This group as a whole adopted the suggestion, stating that "the studies *should be* performed on 'stressed' and non-stressed environments."[38] In designing tier testing schemes, other groups incorporated this stance, though they did not adopt its importance as the original group did, articulating, for example, that "Testing *may be* performed in stressed as well as in unstressed environments, *as suggested by group C/D.*"[39] The report's Executive Summary summarized that "It was *generally agreed* that *ideally*, studies should be performed on 'stressed' and 'non-stressed' environments."[40] Divergences regarding the importance of testing in each of these two types of environment appear to have remained, and two of the testing schemes cautiously reflected the idea.

The report suggests differences in perspective among participants regarding the likelihood of release of organisms from an industrial system. Discussions about the industries strongly emphasize low likelihoods of release. For example, the report mentions about one group performing technology-based hazard and exposure identification that

> ...the group emphasized that a properly operated system has multiple barriers to prevent organism release, as well as systems for containing microorganisms in the event of accidental releases and preventing their dissemination. The strains ... are quite specialized to highly specific environments, and are not expected to compete well with naturally occurring organisms in other environments.[41]

In discussing dissemination methods, it specifies that "Although these are hypothetical scenarios, incorporating all possible modes of dissemination in a worst-case scenario is necessary."[42] Overall, while the possibility of release is mentioned, participants appear to have focused on explaining why it is unlikely. The group designing a testing scheme for contained technologies, however, "assumed that incidental or accidental releases of microorganisms could occur in any closed system"[43] and mentioned that contained systems are "commonly associated with" "low levels of exposure."[44] The positions regarding likelihood of release are not contradictory, but they suggest the contribution of different underlying perspectives regarding whether release should be viewed as a highly unlikely event or as a reasonable or even expected possibility.

Importance of Divergences

In their study of multi-stakeholder participation in an ecological risk analysis in South Africa,[45] Dana *et al.* found that the diverse participant group contributed more system elements and connections among them than did the narrow expert group, and they imply that diverse contribution can be valuable independently of whether or not any given contribution affects the final assessment outcomes. In the OPPT workshop, not every opinion expressed was directly reflected in the tier testing schemes, but discussion of diverse perspectives could enable more good positions and solutions to be selected in the schemes' construction.

The workshop report includes some of the differences of opinion that arose in the discussion. OPPT officials are still using the report over twenty years after the workshop. Even those opinions that were not reflected in the tier testing schemes or that did not achieve consensus may be valuable considerations for some situations, and their invitation in the workshop and inclusion in the report could prove helpful to regulatory officials evaluating each submission.

Furthermore, in some instances practical considerations prevented a perspective's full reflection in the testing schemes but the divergent opinion can be valuable later, when new technologies may open new testing possibilities. For example, some participants believed that microbial exposure can never be assumed to be absent or even low enough to be of low concern, because a microbial population may drop below detection limits and then grow again at a later time,[46] and the group discussed this problem extensively.

Recent development of more powerful DNA sequencing technologies has enabled much lower detection limits of genetic material in the environment. In the recent PoET-Wilson workshops, individuals who had been involved in the OPPT tier testing workshop emphasized the potential importance of the new sequencing technologies for addressing the longstanding problem of microbes surviving in low numbers and then growing back.[47]

Reflection of Values

While many of the differences of opinion may be articulated in factual terms, each of them could also be rooted in differences in values and perspectives that may stem from participants' different backgrounds and interests. For example, whether testing in stressed environments is viewed as necessary or merely ideal and optional could be as much a matter of underlying concern about effects or of interest in reducing testing burden as one of scientific opinion regarding the levels of risk and what information the additional testing will reveal. Whether one regards accidental release and hazard as highly unlikely or as nearly inevitable may be as much a question of perspective and preferred risk acceptance levels as one of differing likelihood calculations. Whether or not one regards microcosms as providing sufficient or sufficiently reliable information may reflect level of concern about risk or degree of aversion to costly or time-consuming testing as much as it reflects estimation of microcosms' capabilities.

One of the reasons cited for including diverse stakeholders in assessment processes is that these values-based judgments are inevitable throughout the assessment process, and that these decisions are best made by stakeholders through discussion and deliberation, so that stakeholders' values can be incorporated, rather than leaving these value judgments to narrow experts whose values-based decisions are not intrinsically better than those of other stakeholders. The present findings support the position that these values-based judgments are present throughout the assessment process, including in the early stages of designing testing regimens, lending further weight to arguments that diverse stakeholders should be included throughout assessment processes rather than offered a set of options after tests and calculations have been completed.

Challenging Convener Frameworks

Participants appear to have been able to challenge assumptions implied in the workshop's provided structure, though they may also have minimized divergence from the tasks specified.

Examples of Challenging Frameworks

In several instances, participants challenged the approaches implied in the discussion questions, offering alternatives based on their knowledge. For example, the group tasked with discussing microbial pathogenicity and toxicity was asked a number of questions about phenotypic or genotypic characteristics predictive of pathogenicity, as well as what research should be conducted to establish additional predictive characteristics.[48] While they suggested some characteristics, the participants determined that bioassay results would be "much more informative" than lists of traits indicative of pathogenicity,[49] and

they mentioned several examples of helpful tests. They also determined that rather than research to establish predictive characteristics, research should expand existing lists from their focus on small numbers of species with public health or agricultural importance to inclusion of more environmentally important species.[50] The guiding questions appear to have been valuable in directing participants regarding what information was sought, while the flexibility to diverge from the questions' particulars also enabled useful contributions.

The pathogenicity and toxicity group also found that the issues raised in the discussion questions were "not amenable to across-the-board solutions" but should instead be addressed for individual technologies and applications.[51] The group recommended consultation with expert panels to develop application-specific analysis, along with creation of a database about specific applications that could serve as a tool for regulatory review. In the PoET-Wilson workshops as well, many participants were uncomfortable with the idea of developing standardized tests, safety measures, or standards for acceptable study results, instead opining that each application's characteristics should dictate testing and safety measures. There too, conveners appeared more interested than participants in exploring the potential for standardized approaches.

Some participants challenged both discussion questions asking about the population density and persistence duration that should be considered survival of an introduced microbe[52] and to a degree the tier testing framework itself by opining that exposure can never be assumed to be low enough to be regarded as being of low concern, both because a microbe's population may drop below detection limits and then grow back at a later time, and because novel genes may transfer to indigenous microbes.[53] These concerns were partly incorporated through the recommendation that due to the possibilities of regrowth and gene transfer, periodic tests be conducted even after introduced organisms or genes cannot be detected[54] and through a note in the contained applications scheme that regrowth would trigger higher tier testing. The concerns' articulation could have contributed to informing regulatory officials' considerations in ways exceeding their incorporation into the testing schemes.

Participants diverged from convener frameworks regarding testing competitiveness. One group's discussion questions inquire about testing a microbe's competitiveness against existing microbial populations, asking

> What constitutes a valid test of microbial competitiveness? Is there a concern with the competitive ability between a GEM [genetically engineered microbe] and its parent, or between a GEM and the indigenous populations, or both?[55]

Members of this group were concerned about competitiveness and interested in identifying competitive advantages.[56] However, the group decided that determining competitiveness is less important than determining survival, and some participants believed that competitiveness could not be accurately tested. As a result, the group decided that it was not necessary to test competitiveness independently of survival.[57] This recommendation appears largely to have been adopted in the tier testing schemes, even though participants in other groups as well were concerned about competitiveness.[58]

The group creating the uncontained applications testing scheme relied on the formula expressing risk as the product of hazard and exposure, and the description of this scheme notes that overall evaluation of low concern requires either the exposure or the hazard to be of low concern. Some participants, however, suggested that the risk formula and probability assessment may not be appropriate for determining ecological risk associated with uncontained microbe applications.[59] These points represent a challenge by some participants of assumptions or approaches often inherent in risk assessment and testing frameworks, and implied in the issue paper.[60] In the workshop, these opinions were recorded, but they were not directly incorporated into the testing schemes and there is no evidence of extensive discussion of these perspectives. It appears that although participants articulated these diverging views that, if pursued, could have more deeply changed the exercise and its outputs, they still chose to pursue the exercise as structured.

Some participants challenged the tier testing model. Even though the workshop and briefing materials were designed to facilitate production of tier testing schemes, the group developing a scheme for uncontained technologies diverged from this model, instead developing a scheme that "resembles a decision tree more than the traditional tier testing scheme."[61] This group envisioned more complex feedbacks among components of the testing system. With some important differences, overall the scheme resembles a tier testing scheme like those in the briefing materials, but with the conditions for proceeding from one tier to the next presented more prominently.[62] Even with many similarities between the scheme developed and tier testing schemes, the articulation of differences in perspective and emphasis may still be valuable. Furthermore, it is unclear whether the scheme fully addressed participants' reasons for diverging from a tier testing scheme or whether the group sought a compromise that would address some of their concerns while generally maintaining the framework that they felt the conveners were seeking.

Considerations for Structure and Flexibility

The workshop's structure and guidance assisted participants in conveying information and developing tier testing schemes useful to the regulatory offices. However, extensive guidance and structure also bear the potential to curtail challenging of conveners' assumptions or other assumptions inherent in the process. One cited way that stakeholders may contribute to assessments is by employing diverse conceptual models. As such, while it may be important for conveners to provide structure to guide the deliberations, the possibility of participants' challenging assumptions and conceptual models inherent in the provided structure may also be positive components of stakeholder contribution. It is not obvious how ideally to balance encouraging participants to contribute fully based on their values and perspectives and encouraging participants to adhere to a provided structure in order to produce materials desired by conveners. Ideal balances may vary among processes.

OPPT workshop participants' challenging existing frameworks, at times in ways that influenced the workshop's outcomes, may be further relevant in comparison with the Subdivision M Guidelines, in which some questioning of existing frameworks' applicability may have less readily resulted in changes to the testing scheme itself.

Insights into Participant Contributions

Examination of the OPPT tier testing workshop indicates ways in which diverse participants contributed. Participants with expertise in industry or in ecological fields contributed both information and predictions based on their knowledge. Participants with knowledge of industry also contributed information about the industries' operations and companies' interests that could influence environmental effects. Differences of opinion among participants suggest that participants contributed based on their diverse backgrounds and perspectives and may indicate a richer discussion than would have occurred with a narrower group. Participants also challenged some assumptions implied in the provided structure, suggesting that the extensive structure still left room for development or expression of divergent perspectives, though participants also largely conformed to the provided framework and may have minimized expression of fundamental differences or incorporation of divergent views into the testing schemes.

In accordance with the four hypothesized sources of contribution whereby diverse participants might aid environmental assessment, participants contributed information regarding ecological effects, industrial, and technological systems; they worked from diverse and sometimes divergent conceptual models; they enabled the knowledge available for the testing schemes to keep pace with current developments in science, industry, and ecological assessment methods; and their contributions reflected their values and underlying perspectives.

Examining the OPPT workshop results alongside the Subdivision M Guidelines developed a few years earlier by OPP regulatory officials may suggest additional insights.

The OPPT Workshop Alongside Subdivision M

A number of differences appear between the OPPT workshop and the Subdivision M Guidelines. Overall, the OPPT workshop may approach testing needs more broadly, focusing on assessing environmental effects generally and on microbes in their own right, while the Subdivision M Guidelines focus on toxicity and pathogenicity and on comparisons between microbes and chemicals. The OPPT workshop report also further discusses considerations regarding particular system components, such as exposure routes and the potential for horizontal gene transfer. In some instances, both the OPPT workshop participants and Subdivision M discuss a challenge to existing frameworks, but the workshop participants adjusted the testing schemes to account for the challenge explicitly while Subdivision M maintains existing frameworks but may address the problem in other ways.

Some of the workshop's breadth likely derives from convener direction rather than from the participants, but some appears to come from the participants themselves. Some of the workshop's breadth compared with Subdivision M could also derive from differences between the types of products that each addresses.

In compiling Subdivision M, the OPP officials could have been limited in their flexibility to diverge from earlier testing schemes or data requirements, and some observed differences may be artifacts of this limitation. However, the Subdivision M Guidelines remark on differences between chemical and biological pesticides,[63] and they note that "the biological pesticides are most appropriately characterized for health and environmental safety by testing schemes which take their unique characteristics into account,"[64] so it is unclear how large a role these limitations may play.

The Subdivision M Guidelines also exhibit strengths over the OPPT workshop report, and these differences suggest possible weaknesses in diverse participation processes, as well as practical considerations for diverse participant process design.

System Components and Hazards

In their paired ecological risk analysis workshops, Dana *et al.* found that the diverse participant group contributed system components and system boundaries, as well as hazards and mechanisms of exposure, that the narrow group did not think of.[65] The OPPT workshop participants discussed system components and mechanisms of exposure that the Subdivision M Guidelines do not mention. As the Subdivision M Guidelines are a polished regulatory document while the OPPT workshop report is meant to reflect discussions, the officials creating the Subdivision M Guidelines could have considered these components and chosen to omit them. However, the OPPT workshop report indicates what elements participants felt were most important, as it indicates perspectives that participants chose to omit from the testing schemes and opinions that were recorded as alternative perspectives. Examination of the workshop report and the Subdivision M Guidelines may thus consider elements deemed suitable for inclusion rather than elements mentioned altogether, although caution is still needed due to the two documents' very different purposes. Some elements included in the OPPT workshop report and absent from the Subdivision M Guidelines represent substantial areas of consideration or areas that other experts have determined to be key in assessing microbes' environmental effects, increasing the likelihood that diverse participants' urging inclusion could represent a positive contribution. Procedural considerations or interest in maintaining existing frameworks could also have prevented incorporation of some considerations directly into the Subdivision M testing schemes.

Even though the inclusion criteria for the workshop report and the Subdivision M Guidelines differ, comparison suggests that the workshop participants included elements that the OPP officials did not. The differences may suggest broader consideration of system elements and hazards or a willingness to include more nonstandard elements among the workshop participants than for Subdivision M.

Exposure Sites and Dispersal Mechanisms

The Subdivision M Guidelines focus nearly exclusively on the site of application of the microbial pesticide as the site for which environmental assessment is needed, while the OPPT workshop report discusses more broadly sites that the organism may contact. The

workshop report also discusses more broadly and may lend more importance to mechanisms of organism dispersal.

The application site appears to be the only point of origin that the Subdivision M Guidelines discuss for released microbes. For example, the Guidelines mention only the application site as relevant to the potential for aquatic exposure, and they mention only the application site and resultant potential for aquatic exposure in establishing the need for aquatic testing.[66] Even though the Guidelines state that manufactured precursors to the final product are within the scope of regulation,[67] they do not mention the manufacturing site as a potential source of exposure.

In addition to direct application to water, the Guidelines indicate that "less obvious or borderline uses," such as application to forests, drainage ditches, riverbanks, partly aquatic crops, and widespread application to major crops if grown near bodies of water also require aquatic testing,[68] suggesting that the Guidelines are interested in identifying the potential for aquatic contact. The Guidelines state that some test data on both terrestrial and aquatic organisms are usually needed "regardless of the pesticide's site of outdoor application and apparent potential for exposure [because] ... [o]ften, there will be spread to adjacent areas, due to drift,"[69] and they require inhalation exposure testing, which may suggest that the Guidelines include air as the relevant dispersal mechanism besides water, and that they endeavor to address dispersal potential broadly within the general testing provisions. They indicate the possibility of insect transport beyond the application site, commenting that testing on plants may require physical separation of treatment plants from controls if the tested substance is readily disseminated by such mechanisms as wind and insects,[70] though they do not discuss this mechanism in indicating possible exposed locations.

Although it attaches importance to the application site, requiring a description of the site's characteristics, the OPPT workshop report mentions the potential for inadvertent release at production sites as well as application sites, noting for agricultural applications, those applications regulated under TSCA likely most similar to many of those addressed by the Subdivision M Guidelines, that "Although microorganisms are intentionally released at the application site, point source releases can also occur at production facilities."[71] The report also mentions various mechanisms of inadvertent release or dispersal, including surface water, ground water, flood runoff, and aerosols, as well as worker activity, equipment activity or failures, waste deposition, biological carriers such as animals, and sampling for monitoring.[72]

The two documents' guidelines regarding microcosms for testing also appear to suggest a difference in focus regarding release sources and dispersal. The workshop report states that "The microcosms should represent the recipient environment as well as environments through which the organism may pass,"[73] while the Subdivision M Guidelines mention only the test substance's "target ecosystem"[74] or the "proposed use site"[75] in discussing microcosm design.

There does not appear to be reason to expect that microbes regulated by the OPPT under TSCA are more likely than microbial pesticides to be accidentally released in locations other than the site of use, or to be spread through means other than simple air and water dispersal. The differences between Subdivision M and the workshop report in discussion of exposure sites and dispersal mechanisms could in part reflect differences in perspective or other differences arising from obtaining input from more and diverse versus fewer and narrower parties. In agreement with Dana *et al.*'s findings, the diverse group may have drawn broader system boundaries and included more hazards.

Some of Subdivision M's testing requirements, such as some testing of aquatic organisms even for terrestrial uses, may be meant to address additional means of transport or sites of origin that are not explicitly listed but that the officials could have determined are addressed sufficiently through broadening the testing requirements. The differences may also stem from increased care in Subdivision M to avoid the testing burden that would be imposed by considering more receiving environments and dispersal mechanisms, or from other political or economic considerations, though the Guidelines appear to seek extensive determinations of exposure potential, such as the potential for aquatic contact, and the tier testing workshop participants also display sensitivity to testing burden.

Potential for Gene Transfer

Both Subdivision M and the workshop report mention the potential for an introduced microbe's genetic material, including engineered DNA, to be transferred to other microbes in a receiving environment. The documents appear to treat this consideration differently.

Subdivision M mentions the possibility of gene transfer briefly and does not require testing. The Guidelines request information about the rate of gene transfer of genetically altered material, "to the extent possible,"[76] in the preliminary information to be submitted about a product.[77] In discussing potential residues of concern on crops, the Guidelines mention that residues of concern include the genetic material itself, and that recipients of the genetic material could also constitute a residue of concern, and therefore that ease of genetic exchange is important in determining potential residues of concern.[78] The Guidelines do not call for testing to determine ease or rate of genetic exchange, even though other characteristics included in the initial identifying information, and the nature of other substances that could be residues of concern, are subject to testing requirements.

The workshop report mentions several times the potential for gene transfer as a key hazard that could result in an engineered microbe's having environmental effects,[79] even though not all participants deemed it likely.[80] The report also mentions gene transfer as a reason to discount survival as a predictor of the potential for ecological effects.[81] The tier testing schemes developed in the workshop require testing for the genetic material's persistence, its propensity to transfer, and how it might be expressed in recipient organisms.[82] One of the testing schemes even emphasizes the point that if data on transfer do not already exist, tests must be performed.[83] The workshop discussion questions mention the potential for gene transfer,[84] but the importance placed on this potential and

on the genetic material's persistence in the environment appear to have come from participants. Furthermore, participants in work groups not receiving questions about transfer also mentioned transfer as a concern.

The potential for gene transfer may represent an instance in which both a narrow expert group and a diverse participant group were aware of a potential hazard, but they treated it differently. A number of experts and advisory bodies in environmental considerations for engineered organisms have emphasized gene transfer as a key mechanism whereby engineered microbes may come to affect a receiving environment, and have called for research about the propensity for transfer.[85, 86, 87, 88] This work suggests some validity in the diverse group's approach to this hazard mechanism, including its decision to require testing.

Political or other practical considerations could have prevented Subdivision M's calling for gene flow testing. This difference between the workshop and Subdivision M could also be attributable in part to the OPP's being most experienced with regulating chemical pesticides; potential for gene transfer is a prime difference between chemicals and microbes. It could also suggest adherence to particular tier testing models, which, in focusing on estimating hazard and exposure, may not have a readily apparent place for gene transfer testing. Some of these possibilities suggest that diverse participants could aid assessment processes in adopting broader perspectives and avoiding blind spots associated with narrow experts' areas of experience or established models. Arguably, a different group of narrow experts could have chosen to emphasize and test for gene flow; including diverse participants in a discussion-based process may serve to reduce the overall number of blind spots, particularly as the blind spots' natures cannot always be anticipated. This observation further suggests potential benefit of processes' encouraging expression of diverse perspectives even in the presence of convener models and assumptions. Some of the possible explanations for the difference also suggest that were diverse participants to be involved in processes developing real regulatory requirements or decisions, political or other practical considerations, including reasons to adhere to established models, could play a larger constraining role than they do in the more flexible, but also less influential, avenues through which diverse parties are typically involved.

In describing the Subdivision M Guidelines' background, the Guidelines mention that "It was also decided [upon the Guidelines' publication] that any additional data that would be required for the registration of genetically modified microorganisms would be determined on a case-by-case basis by EPA."[89] The OPP officials may be relying on this provision to enable them to require testing for gene transfer or for other considerations that do not readily fit into, or were for other reasons excluded from, the testing scheme. Officials familiar with this option and with interaction between regulatory offices and submitters may be more comfortable using this option, while OPPT workshop participants, many of whom were not further connected to regulatory processes, may be more likely to include within their schemes all considerations they view as highly important.

Mechanisms of Environmental Effect

The workshop report and the Subdivision M Guidelines differ sharply in their descriptions of how microorganisms could come to affect the environment. Overall, the Subdivision M Guidelines focus on a microbe's pathogenicity or toxicity as the primary effect mechanisms, whereas the workshop report pursues several others. Some argue that this difference stems entirely from differences between pesticides and the applications considered in the workshop. However, it could also suggest that the groups employed different conceptual models of the system, including a broader perception of the system's components and their interactions on the part of the diverse group.

In introducing testing of hazard to non-target organisms, the Subdivision M Guidelines state that "Pathogenicity and toxicity appear to be the major effects of concern regarding exposure of terrestrial and aquatic organisms to microbial pesticides."[90] The subsequent sentences indicate that the Guidelines essentially equate non-target organism exposure along with pathogenic or toxic effects of the exposure with environmental effects more generally. The Guidelines focus heavily on determining pathogenicity and toxicity, and examination of the microbes' environmental interactions is limited to determining non-target organisms' exposures in order to enable predictions of pathogenic or toxic effect arising from product use.

The OPPT workshop participants identified other mechanisms whereby the organisms could affect their environments. The participants identified "maintenance of the stability of the ecosystem"[91] as the most important ecological "endpoint," an ecosystem effect or indicator useful for judging potential for effects. They also identified effects on primary production, cycling of limiting nutrients, and community structure and diversity as important endpoints for which testing should be conducted. The report's discussion of each endpoint makes clear that these are affected primarily by microbial characteristics other than pathogenicity and toxicity.[92] The report also suggests that these endpoints and others discussed are viewed as indicators of effect, rather than as stand-alone effects or effect mechanisms. Furthermore, the tier testing schemes consider "other ecological effects" as separate hazards alongside toxicity and pathogenicity.[93]

Microbes intended as pesticides are much more likely to be pathogenic or toxic than are those intended for the applications that the OPPT considers under TSCA. This difference in applications likely in part explains, and some argue that it fully supports, the difference in approach. However, a microbe intended as a pesticide could affect the environment through mechanisms that would not be revealed by pathogenicity and toxicity determinations, and the OPP is charged with regulating for environmental effects in general. Furthermore, the workshop participants considered uncontained applications in which pathogenicity or toxicity are important concerns, and they appear to have regarded examination for other mechanisms of environmental effect as being important in these applications as well.[94]

Conveners' frameworks could have contributed to the workshop participants' consideration of effect mechanisms other than pathogenicity and toxicity, but they are

unlikely entirely to explain the differences from Subdivision M. The subgroups into which conveners divided participants included a group working on pathogenicity and toxicity and a group working on other ecological effects and endpoints, and the latter group was asked to identify ecologically significant endpoints other than pathogenicity or toxicity.[95] However, consideration of ecological effects arising from sources other than pathogenicity or toxicity appears not to have come entirely from workshop conveners. The participants were readily able to develop lists of endpoints and to discuss in detail endpoints unlikely to be influenced by pathogenicity or toxicity, such as mineralization and losses of limiting nutrients.[96] Participants also discussed in detail without reference to pathogenic or toxic effect mechanisms endpoints that could have been thus attributed, such as changes in ecological community structure or composition.[97] In addition, the report mentions a participant's paper, published in the year prior to the workshop, about how ecological effects of introduced microbes should be assessed,[98] and the paper considers diverse effect mechanisms and microbial characteristics of concern.[99]

The OPPT workshop participants' ready discussion of a variety of effect mechanisms, particularly in contrast with Subdivision M's emphasis on pathogenicity and toxicity, suggests that conveners may affect workshop outcomes through decisions regarding what participants to include. For example, conveners who did not view other effect mechanisms as important might not have invited participants possessing broader ecological knowledge. Similarly, the OPPT workshop conveners could have left gaps in their own participant list based on their understanding of the system. Determining whom to include in a diverse participant or multi-stakeholder process, and who should make these determinations and by what mechanisms, remains a challenge.

Dana *et al.* found that diverse stakeholders can employ different conceptual models of a receiving ecosystem or ecological-human interaction to add insights regarding potential effects or mechanisms of action.[100] The tier testing workshop's diverse participants appear to have employed different conceptual models from the model that the Subdivision M Guidelines appear to reflect, considering and recommending testing for a broader set of mechanisms whereby introduced organisms could enter and affect receiving environments.

Approaches to Testing

The tier testing schemes developed in OPPT's workshop and that of the Subdivision M Guidelines differ structurally. The differences may suggest that the narrow expert group developing the Subdivision M Guidelines tended to apply existing protocols and approaches while the workshop participants more readily diverged from existing models.

Tier Testing Structure

The tier testing schemes developed in the workshop bear structural differences from that in Subdivision M, including less segregation between hazard and exposure testing, while they maintain attention to efficiency as a goal of tier testing schemes. The Subdivision M testing scheme strictly segregates between different types of testing, primarily hazard and exposure testing. In general, Tier I tests hazard, specifically pathogenic or toxic effects at

high doses, Tier II tests exposure based on the microbes' persistence and proliferation in the environment, and Tier III tests hazard using predicted exposure levels. Any other concerns, such as organism identification and genetic material persistence, are not tested within the scheme, and may be provided with the initial data submission to support the application. The Guidelines require separate testing to support setting of tolerances for residues on food.[101] The Guidelines provide for deviations from the testing scheme, but they maintain the pathogenicity-toxicity hazard-exposure framework; for example, demonstration of absence of exposure, which would normally be Tier II, could negate the need for some Tier I hazard testing.[102]

The testing schemes developed in the workshop test hazard and exposure in the same tier, and are generally centered around sets of concerns or questions. For example, in the scheme for contained applications, Tier 1 includes a list of concerns to be addressed through testing if they remain following initial submission, such as "Lack of persistence (survival) information," "Skimpy identification" such as poor characterization requiring more extensive taxonomy or other identification approaches, and "Uncertainty about host range of organism (pathogenicity)."[103] The subsequent tier includes an additional list of concerns to be addressed in the event that data addressing the Tier 1 questions do not sufficiently resolve concerns. Similarly, in the scheme for semi-contained applications, Tier 1 includes an array of tests to assess each of exposure and hazard, such as fate models and tests examining exposure controls to assess exposure, and tests examining by-product toxicity and various ecological effects to assess hazard.[104] The scheme for uncontained applications is articulated as a more complex "decision tree" rather than as a tier testing scheme. This scheme as well includes series of exposure and hazard concerns together for testing. It segregates tiers primarily based on the tests' lengths, with Tier 1 including short-term testing to address concerns remaining upon review of initial submission information and Tier 2 including longer-term and more complex testing to address questions remaining after Tier 1 testing.[105] Thus, maintaining regard for testing efficiency, the workshop groups developed schemes addressing the consideration, identified as well in the Subdivision M Guidelines, of interplay between hazard and exposure. Their schemes also incorporate testing of concerns other than pathogenicity and toxicity, including determination of information that the Subdivision M Guidelines request but omit from testing requirements.

The differences could suggest greater willingness or tendency on the part of the diverse group to diverge from existing frameworks, as well as employment of different conceptual models of the risk and testing system. The differences do not necessarily represent a superior outcome from the diverse group. Instead, they may suggest that diverse participants can contribute development of diverse approaches. Consideration of alternatives has value in enabling identification of better approaches.

The OPP officials developing the Subdivision M Guidelines could have considered and decided against utilizing alternative testing schemes. Furthermore, the tier testing workshop was meant to provide internal guidance to regulatory officials rather than actionable requirements for submitters, and the scheme described in Subdivision M may best enable use by submitters or may accord with other considerations or constraints.

Different conceptual models or alternative approaches may be valuable contributions that diverse participants can provide, but these benefits may be weighted against the need, if any, to maintain particular structures. These considerations may affect when diverse participants are involved altogether, as well as the direction with which they are provided and their role in shaping final products.

Role of Field Trials

One of the testing schemes developed at the workshop differs from the Subdivision M Guidelines regarding the conditions under which field trials are conducted. In Subdivision M, positive results, suggesting a potential problem, trigger the next level of testing. Results from testing at Tier I indicating that the substance produces toxic or pathogenic effects at high doses may trigger Tier II testing to determine environmental exposure. If exposure is then also predicted, Tier III testing may be used to determine whether the toxic or pathogenic effects occur at predicted exposure levels. If Tier III testing finds that effects occur at levels to which organisms are likely to be exposed, Tier IV, simulated or actual field testing, may be used to discern further whether adverse effects are likely from use.[106] Thus, in Subdivision M's scheme, if the testing suggests that the microbial pesticide will cause adverse effects if applied in the environment, the next step is to conduct field release trials.

In the OPPT workshop, groups developing tier testing schemes for different types of applications took different approaches. Like Subdivision M, the testing scheme for semi-contained applications calls for field testing when concerns are not all resolved in the previous tiers.[107] However, the group developing a scheme for uncontained applications made field trials a component of testing that would take place only if the results of other testing or exposure mitigation suggest that adverse effects will not occur.[108] The discussion of this scheme states that "Either the exposure must be of low concern or the hazard must be of low concern for a product to proceed to Tier 3 field testing"[109] and mentions that if concerns exist, testing is needed to address the concerns before the product may undergo field testing.[110]

The Subdivision M Guidelines discuss the problem inherent in using field trials when harm is predicted:

> The Agency recognizes the possible shortcomings in using simulated or actual field tests (Tier IV) as the final test of the safety of a [microbial pesticide]. If an agent has progressed through the tier system and requires a field test, it must have displayed significant adverse effects in some or all of the previously conducted laboratory tests. This fact might argue against the use of a field test, since such a test could release potentially hazardous microorganisms, with the potential to proliferate in the environment and pose widespread environmental risk, unless adequate quarantine measures could be taken. Therefore, before any Tier IV field test is to be undertaken, the applicant should discuss its plans with the Agency concerning potential hazards. If the Agency determines that a Tier IV field test would pose an unacceptable risk, then the [microbial pesticide] would not likely be acceptable for registration.[111]

The scheme also mentions that field testing may occur only "when the Agency is reasonably confident that quarantine methods can confine the [microbial pesticide] to the test area..."[112] The Guidelines' use of the standard structure despite the problem articulated may be due in part to adherence to a framework developed for chemical pesticides. The Guidelines mention several times that an important difference between chemical and microbial pesticides is that the latter may proliferate and spread in the environment more than the former, challenging fate prediction and containment, and they here employ the usual scheme but with containment stipulations. Some of the workshop participants, by contrast, diverged from the established structures, creatively addressing the problem by designing a scheme in which field trials occur only when the risk is considered low.

Here as well, other considerations may have favored the Subdivision M Guidelines' maintaining established testing schemes. The OPP officials developing the Guidelines may also have been more familiar or more comfortable than were the workshop participants with regulatory officials' option to require submitters to inquire with the Agency in advance of conducting field trials, or possibly with the Agency's risk or containment assessment for microbes presenting concerns.

Discussing engineered organism assessment, ecologists Tiedje *et al.*'s recommendations appear to include elements of each of the schemes' approaches, though they may tend toward the workshop group's approach of determining low risk levels before conducting field trials. They state that

> Initial information on the potential for establishment and possible effects ... should be obtained from laboratory microcosm and mesocosm studies, or from tests in a contained greenhouse. Assuming these preliminary studies reveal no unacceptable risks, further information should be obtained from carefully planned small-scale field trials ...[113]

They also mention that "We encourage the use of small-scale field tests, when justified by previous laboratory and/or greenhouse studies, under conditions that minimize dispersal and under appropriate regulatory oversight."[114]

Subdivision M Strengths

A pair of marked strengths of the Subdivision M Guidelines over the OPPT workshop report suggest benefits of ongoing work on a particular assessment problem or area, which diverse stakeholder deliberations often lack. One of the strengths may also point to political challenges in involving stakeholders in regulatory processes.

A Polished Testing Regimen

The Subdivision M Guidelines constitute a published regulatory document addressed to potential product submitters. They include detailed data and testing requirements, test procedures, instructions to contact the Agency for guidance in areas with less developed testing requirements, instructions on waivers and other special conditions, and references to published works. While the OPPT workshop report mentions some particular tests, it

includes much less detail regarding procedures, and it is not a polished document that could serve as instructions for submitters.

The charge from the OPPT workshop conveners was not to produce a polished document, but rather to develop responses to discussion questions and produce testing schemes for the convening Agencies to use as internal guidance. Producing a polished document may be infeasible for a diverse participant workshop, possibly due in large part to a lack of time and continuity. Political factors may also have contributed to the conveners' not seeking a polished document.

The OPP officials developing the Subdivision M Guidelines worked in the same Office and composed the Guidelines over time. In contrast, the OPPT workshop participants had less than three days to formulate responses to the discussion questions and develop tier testing schemes. The workshop participants had largely not worked together before, so any development of working relationships took place within the workshop, which also included informational presentations and whole-group discussions of the subgroups' work in addition to subgroup work time. In addition to these time and operational constraints, the participants had little if any opportunity to consult with colleagues or investigate published literature during the workshop. While these conditions may enable diverse participants to share and discuss their knowledge and perspectives, they are much less conducive to developing a polished document making detailed use of established testing protocols and suitable for use by product submitters. Furthermore, unlike the OPP officials who produced the Subdivision M Guidelines, many workshop participants were unfamiliar with tier testing schemes and regulatory processes, possibly further making it more practical for the participants to share their existing knowledge than to develop a regulatory document at the level of the Subdivision M Guidelines.

In the FDA salmon case, the diverse stakeholders bringing the lawsuit did not convene and deliberate together in order to produce the legal complaint. Instead, the organizations discussed and shared information, and one of the organizations collected the information and input. A much smaller group of legal and subject matter specialists, who were associated with the spearheading organization and had worked together over time, composed the complaint. This model of diverse stakeholder input that a smaller group compiles into a polished document may work well in many instances. However, unlike typical multi-stakeholder processes, the diverse stakeholders represented by the lawsuit are all ideologically aligned regarding the matter at hand and contributed their respective knowledge to advance a common cause. A model in which a small, narrower group of individuals uses diverse participant discussions to compose a polished product may or may not work as well in situations involving opposed interests.

In addition to practical difficulties with creating a polished document in a workshop setting, political considerations may have prevented the OPPT workshop conveners from seeking any product appearing to be a polished regulatory manual or guide. The report emphasizes the workshop's role as providing internal guidance and the fact that it produced no regulatory requirements.[115] This point was particularly important in consideration of the potential for conflicts of interest arising from including industry

members. In discussing how workshop conveners handled these potential conflicts of interest, an EPA official emphasized the workshop's non-binding nature as merely scientific discussions regarding appropriate considerations for engineered microbes, as well as the fact that it created no regulatory requirements for industry.[116] While under some circumstances, inclusion of diverse participants appearing to produce balance, such as similar numbers of industry and environmental organization members, could alleviate some concern, regulatory agencies may well prefer to avoid creating scenarios in which members of a regulated industry or other interested parties contribute or appear to contribute directly to regulatory requirements.

Ongoing Deliberation – Effectiveness Requirements

The OPP officials' ongoing engagement with the statutes and regulatory work appears to have contributed to the Subdivision M Guidelines' development. For example, in discussing requirements, existing for chemical pesticides as well,[117] that a product's performance be demonstrated in order for it to be registered, the Guidelines state that performance data are generally required only for products that could be used for health-related purposes, such as to control disease-spreading pests and for products identified as posing a risk of unreasonable adverse effects.[118] According to the Guidelines, "The Agency, in testimony before Congress, stated that it is most concerned about ensuring a product's effectiveness when a lack of efficacy could result in adverse human health effects," and that the efficacy data waiver conditions were determined "in keeping with this concern."[119] While drawing from existing experience can limit perspectives, it can also be an asset. The discussion of testimony before Congress also suggests that the officials benefitted from opportunities to consider over time details of the regulatory needs, as well as to draw from discussion in a variety of contexts. As in many diverse participant workshops, OPPT workshop participants did not have these opportunities.

Diverse Participant Workshop and Narrow Expert Guidelines

Examining the OPPT workshop report alongside the Subdivision M Guidelines suggests ways in which diverse participants may contribute to a process of designing assessment testing schemes. The OPPT workshop participants discussed or emphasized system elements and hazards that the Subdivision M Guidelines omitted or did not emphasize, including mechanisms of organism dispersal and environmental effect and emphasizing the need to investigate gene transfer. Workshop participants also appear to have approached the tier testing structure itself more flexibly to address such challenges as field trials' role within a testing scheme. In some of these areas, the Subdivision M Guidelines mention a concern or challenge while largely retaining existing testing schemes and perhaps using alternative mechanisms, such as Agency approval of individual tests or the option of requiring additional testing, while the workshop participants more substantially altered the testing frameworks.

These observations may accord with previous findings that diverse participants may identify system components and hazards that a narrow group omits. It also suggests that a diverse group may be less restrained by existing frameworks and more likely to include different elements or employ diverse models. While this flexibility may be a strength of

diverse stakeholder processes, it could also constrain the contributions' utility if outcomes must adhere to particular frameworks. In each instance of difference, the officials developing the Subdivision M Guidelines may have considered and rejected elements or models more similar to those reflected in the workshop report, and practical circumstances could have inhibited some considerations' incorporation, raising questions about how diverse participant input should be directed and how it can integrate with existing regulatory needs.

Some Subdivision M strengths over the workshop results suggest the importance of ongoing exposure and interaction and opportunities for outside reference and consultation in developing regulatory assessment tools. Diverse stakeholder processes typically lack continuity, and this deficit may diminish their capabilities.

Practical Lessons and Considerations

Examining the OPPT workshop suggests a number of practical considerations for involving diverse participants in activities related to biotechnology environmental assessment. It may also indicate considerations particular to a regulatory context.

Need for Extensive Preparation

Workshop participants varied widely in their areas of knowledge and their levels of understanding of the regulatory context. They included individuals with extensive knowledge of risk assessment and EPA regulation, as well as individuals who lacked this background and were included because of their areas of research or expertise, such as in particular industries.[120] The workshop required substantial preparation as well as ongoing support for participants lacking background in risk assessment, regulation, and tier testing.

Participant Preparation and Support

Before the workshop, conveners developed and distributed an issue paper of approximately 100 pages, to provide relevant background. The paper describes the United States and Canadian regulatory contexts, existing tier testing schemes and testing protocols, and biological, ecological, and risk assessment concepts that could be valuable for developing the testing schemes.[121] The workshop itself began with presentations about the regulatory contexts and existing tier testing schemes,[122] aimed toward participants who had not read the issue paper.[123]

In addition to briefing materials and presentations to provide background information, conveners made efforts to guide participants toward understanding and completion of the tasks as desired. Conveners provided each working group with detailed discussion questions,[124] and they placed one EPA representative in each group to answer questions about risk assessment and to help participants remain targeted toward the workshop charge.[125] Facilitators assisted in each of the group discussions as well.[126]

The workshop activities were structured to guide participants in creating tier testing schemes: Draft tier testing schemes created by the OPPT for the genetically modified microbes regulated under TSCA were presented in the issue paper and at the workshop. The issue paper notes that some components of these schemes "represent a subset of potentially important [components]" and that "It is hoped that the workshop participants will identify the [components] ... of greatest importance."[127] In addition, one of the working groups of the first portion of the workshop was charged with developing a strawman tier testing scheme for the groups then developing schemes for contained, semi-contained, and open release applications to modify.

Discussing Dana *et al.*'s ecological risk analysis workshops in South Africa, researchers Dana and Nelson mention the importance of providing "adequate education and access to information before and during the process."[128] In the PoET-Wilson workshops, briefing materials were needed on the technologies and applications under discussion, as well as on concepts expected to be relevant, and the workshops included technical presentations.

Support Effectiveness and Guidance Considerations

The extensive guidance appears to have been effective in enabling participants to develop suitable responses to the workshop charge. The conveners regarded the workshop as a success, and the participants conveyed information and developed tier testing schemes useful to the regulatory agencies, even though some participants lacked prior experience with such schemes or even with regulatory frameworks. Some participants did possess experience with regulation and tier testing, and inclusion of these participants may have aided the group in developing useful testing schemes.

This success in developing tier testing schemes under guidance may contrast with an occurrence in the PoET-Wilson workshops. A convener of those workshops, familiar with the tier testing schemes produced at the OPPT workshop but less familiar with the workshop's preparatory materials, privately expressed the hope that the PoET-Wilson participants would arrive through discussion at a testing scheme concept along the lines of the OPPT's schemes. However, the exercise conveners did not provide or mandate this model, and participants did not arrive at this idea on their own. It appears that a tier testing scheme was not needed as it was for the OPPT workshop, and the naturally flowing nature of the discussion and addressing particular topics were higher priorities, such that requesting such a scheme would have proven a detriment. The convener may also have decided that if the participants did not propose a tier testing scheme they may not view it as the most suitable tool, and that participants' knowledge and insights, rather than conveners' concepts of tools that might prove useful, should guide the outcomes.

This occurrence suggests that detailed instructions may be needed if particular output types are sought. Dana *et al.*'s workshops similarly included substantial support to enable participants to produce the desired ecological risk analysis. Conveners divided the risk analysis task into discrete steps, and the facilitator described each activity and guided participants through completing the tasks.[129] Desire for particular types of outputs may stand in tension with benefitting from participants' knowledge and perspectives by

enabling them to develop approaches. At the same time, guidance regarding the type of output sought may enable participants to share their knowledge and perspectives in ways most useful to those receiving the results. Based on their goals and other considerations, processes may vary in the extent of guidance they should provide.

Divergence from Convener Framework

The workshop participants diverged at points from the conveners' framework, while the workshop structure also appears to have curtailed some divergence. In multi-stakeholder workshops, interest in encouraging perspectives divergent from convener assumptions may stand in tension with interest in completing particular tasks or discussion topics. Workshop design and conduct hold some power to control divergence, and workshops should be designed carefully with these considerations in mind.

Divergences, Incorporated and Unincorporated

In some instances in which participant perspectives diverged from convener assumptions, the final product reflected the participants' perspectives. For example, the group developing a testing scheme for open applications designed a decision-tree rather than a tier testing scheme more strictly aligned with the models provided.[130] Some groups declined to answer particular discussion questions. For example, the ecological effects group responded to a question about tests of microbial competitiveness by saying that it is unnecessary to test competitiveness because determining competitiveness is less important than determining survival and because accurately measuring competitiveness may be impossible.[131] The pathogenicity and toxicity group responded to questions about characteristics predictive of pathogenicity by stating that bioassay results would be "much more informative" than lists of predictive traits.[132]

In some instances, participants appear to have questioned the workshop's structure or assumptions, but set these challenges aside to complete the task as outlined. For example, while some participants were concerned that the formula expressing risk as the product of hazard and exposure may not be appropriate for determining ecological risk associated with uncontained microbe applications, this hesitation did not affect the testing scheme design; the participants merely "suggested that the assessor may want to consider" the formula's suitability.[133] Some participants stated that exposure may never be low enough to be regarded as being of low concern, because a population may drop below detection limits and then increase at a later time, as well as because genes may transfer to indigenous microbes.[134] If pursued, this concern could substantially challenge risk assessment and tier testing scheme bases, but the participants chose to compete the tasks as outlined. Several discussion questions asked about suitability of microcosms, and the report records that "Some participants suggested that ecological endpoints can be determined with microcosms, which the group generally agreed are legitimate approximations ... ,"[135] suggesting that some participants were not comfortable with extensive use of microcosms for testing. It appears that in these instances, while the participants raising objections harbored ongoing concerns they chose to articulate the concerns and then allow the discussion to proceed as planned, perhaps favoring this approach over drawing attention from the task or engaging in dispute. These findings

accord somewhat with Dana and Nelson's finding that some participants limited their contributions to avoid criticizing others' views or because they felt they lacked knowledge.[136]

Participants may have similarly curtailed pursuing concerns or divergent perspectives at other points. They could have chosen not to express their opinions altogether, or the workshop report could have omitted some divergent perspectives. For example, it is unclear whether the testing scheme that was articulated as a decision tree but generally retained many tier testing scheme characteristics entirely reflected the participants' perspectives on an ideal testing approach, or whether they chose only to alter the provided model slightly, in order to incorporate their perspectives to some degree while creating a scheme that they felt would still be useful or desirable to conveners.

Desirability of Divergence

It is likely that overall, participants wish to contribute in ways that conveners will find most useful. The desired level of room for divergence from a workshop's assumptions or framework may vary depending on convener needs. Pursuing every diverging viewpoint may hinder the discussion from advancing through planned topics or activities, and it may lend undue focus to one or a few participants' misgivings or perspectives, preventing other participants from contributing fully. In addition, in many instances, as in the OPPT workshop, conveners may wish to gain from participants' knowledge or perspectives in particular areas while still producing an output meeting a previously identified need or conforming to a particular structure. On the other hand, participants contributing perspectives differing from those of conveners or of other participants may enrich and improve the discussion and workshop products. Participants with diverging perspectives may also wonder why they were invited if their ideas are not welcomed. In the OPPT workshop, a more flexible structure could have produced better testing schemes or enabled further development of diverse ideas to enrich the agencies' perspectives when reviewing submissions. On the other hand, tighter control could also have resulted in less discussion of broadly diverging perspectives and therefore more focus on the questions to which the agencies were seeking answers, and testing schemes even more useful to the agencies. The ideal level of control likely depends on the needs associated with each workshop.

Aspects of process structure and facilitation may affect whether and how participants express divergent perspectives. The description of workshop goals, as well as the types of tasks included, instructions' level of detail, and even amounts of time allotted for particular tasks all operate to welcome or hinder discussion of divergent perspectives, and they signal to participants the types of responses welcomed. A facilitator's solicitation of and responses to divergent perspectives act to maintain the desired pace and level of focus directly and they also cue participants regarding whether or not to express their diverging perspectives. In the OPPT workshop, each group included a facilitator, one of whose roles was to aid the group in producing responses, as well as an EPA representative, one of whose roles was to aid the group in adhering to the charge.[137] The tasks' specificity and the desire that they be completed as outlined both appear to have

been high in this workshop, though how heavy-handedly the facilitators or Agency representatives performed their roles is unclear. While it is impossible to anticipate what circumstances or opinions may arise, conveners should consider how closely they wish to adhere to their framework and how much they wish to encourage the expression or pursuit of fundamentally diverging perspectives, in order to structure the workshop accordingly.

Potential for Participant Bias

While diverse stakeholders can bring their distinct knowledge and perspectives to an environmental assessment activity, their inclusion also bears the risk that they will convey information biased in favor of their interests. The potential for bias does not mean that participants are not deliberating in good faith. Even participants deliberating in good faith may bring strong perspectives or assumptions related to the nature of their work or interests. Gaps or biased information may also arise from relying on practitioners for knowledge or predictions for which their experience is not ideally suited. Any assessment process, including those involving only narrow experts, may involve bias, but particular challenges and solutions may exist for diverse stakeholder processes. In addition, while participant bias could exist in any deliberation, deliberations meant to inform regulatory processes may experience some distinct concerns. The OPPT workshop conveners' approaches to addressing bias may be informative in considering diverse participant process design.

Possible Instances of Bias

A prominent potential source of bias in the OPPT workshop was the possibility that industry members discussing their industries with regulators and aiding in crafting regulatory tools could provide information or advice favorable to their interests. In identifying hazards and exposure potential, some workshop participants appear to have emphasized the low likelihood of organism release or the effectiveness of standard industrial containment practices. For one set of applications, the report records that

> ...the group emphasized that a properly operated system has multiple barriers to prevent organism release, as well as systems for containing microorganisms in the event of accidental releases and preventing their dissemination. The strains ... are quite specialized to highly specific environments, and are not expected to compete well with naturally occurring organisms in other environments.[138]

The report also qualifies the discussion of dispersal methods as referring only to "hypothetical scenarios."[139] Groups discussing other applications also appeared to emphasize the low likelihood of release, though their discussion was more nuanced:

> Releases resulting from inadvertent leaks or large-scale accidents could result in microorganisms entering the natural environment on a large scale; however, the likelihood of release can be reduced by the use of certain industrial containment measures.[140]

To what extent individual participants sought to minimize the perceived likelihood of release is unclear. Some participants closely familiar with the industries appear genuinely to have perceived release as being highly unlikely and to have shared this information, while also describing how and where it could occur.

Potential bias in favor of industrial interests also appears in the discussion of microcosms. The report records that participants generally agreed that microcosms would be suitable for obtaining most needed information, particularly because microcosms are substantially less costly than mesocosms. The report emphasizes that while mesocosms could provide additional information, their use must be "well justified" due to the additional cost and time they require.[141] This emphasis on microcosms and on minimizing testing costs could well have arisen from industry participants' misgivings regarding cost. On the other hand, the conveners also expressed interest in microcosms through the discussion questions,[142] and a stated objective of the tier testing structure is to minimize testing burden on industry.

In introducing the tier testing scheme for contained applications, the report states that

> Because the group participants ranged from individuals with considerable knowledge of and experience with their products to people working with novel products that are not well characterized, the tier testing scheme was modified to allow approval based on how much information is available regarding the ecological risks associated with the microorganism.[143]

Testing schemes' responsiveness to the industries' current state may be beneficial. However, when testing for safety or ecological effects, obtaining sufficient information to predict effects may be of prime importance, and in industries for which less is known, requiring that more information be obtained could be the most responsible approach. Here, participants may have emphasized flexibility over rigorous assessment, potentially allowing industries to provide less safety or ecological information simply because they do not yet possess it. While it is unclear how this approach affected the details of the proposed testing scheme, this framing could represent an instance of industry members or other participants sympathetic with concerns about burdening industry, likely through contributing based on their own perspectives and concerns rather than through any deliberate attempt to undermine the regulatory process, offered a scheme in effect favoring industry convenience over assessment rigor.

Possible Gaps or Information Mismatches

Obtaining information through practitioner deliberation can result in information gaps when relying on participant knowledge from adjacent fields. For example, in discussing fuel production and biomass conversion, the report lists six microbial genera whose members possess genomes that could be useful for degradation of cellulose and other molecules, another organism often used as a recipient of these genes, and *Saccharomyces cerevisiae*, which it mentions has been used to produce ethanol from corn starch. The report then states that "This subgroup based its discussion on the extensive experience with the use of *S. cerevisae* [sic] in the corn-ethanol industry."[144] While surely relevant and helpful, it is unclear how well the information drawn from experience with this particular organism and use matches other organisms and uses of interest.

Problems of prediction and of application of knowledge to adjacent fields arise in other types of processes as well, as assessors must inevitably choose proxies and apply

knowledge to related areas in which less is known. Although the problem is not unique to diverse participant processes, conveners should recognize that involving practitioners having substantial practical experience in areas of interest does not remove problems of proxies or prediction. In addition, practitioners with experience in a particular area may be more, or less, reliable than a narrow expert in applying the knowledge to predicting results in related areas. Problems of prediction or proxies may be particularly acute for emerging technologies such as areas of biotechnology, in which new fields and industries are arising rapidly.

Approaches to Addressing Potential for Bias

In the OPPT workshop, conveners addressed concerns of bias through workshop structure and participant balance. The subgroups developed schemes meant to be useful for any application using the given level of containment rather than for particular industries or technologies,[145] an arrangement that could limit the possibility of representatives of a particular industry creating a testing scheme favoring their technology. Conveners also composed the groups of a mixture of participants possessing different types of backgrounds, such as ecologists together with industry members, an arrangement serving in part to minimize bias. An occurrence suggesting that the workshop experienced some success in this regard is that even though the initial discussions of the technologies include statements emphasizing the low likelihood of organism release, the introduction to the contained applications' testing scheme mentions that "The group did not define the level of containment that would qualify as a closed system but, rather, assumed that incidental or accidental releases of microorganism could occur in any closed system."[146] Designing diverse participant processes to include an appropriate mix or balance of individuals is important. At the same time, a key potential strength of diverse participant processes is that participants can challenge and counterbalance each other's biases. Narrow expert processes include fewer inherent opportunities for assessor biases to be challenged.

The potential for bias, or for appearance of bias, may also affect the role a diverse participant group may be given in a regulatory process. In addition to addressing bias through workshop design, the conveners addressed concerns about bias or conflict of interest by making clear that the workshop results were just scientific discussions about possible appropriate considerations, and that they were not binding and did not constitute regulation for industry.[147] While diverse participant workshops may produce information and guidance valuable to regulatory agencies, agencies' use of such deliberations or their products may be limited due to concerns about appearance of bias.

Time and Continuity

The OPPT workshop's time-constrained and self-contained format likely negatively affected participants' abilities to contribute. Diverse participant processes may be inherently time-constrained as typically structured, and creating continuity presents challenges and tradeoffs.

Time Constraints

The workshop appears to have encountered substantial time constraints. The report mentions participants' abridging discussion due to lack of time. One of the groups identifying hazards and exposure routes for particular industries omitted most discussion of hazards due to lack of time.[148] Similarly, the group discussing ecological effects and endpoints was "unable to discuss fully the ecologically significant exposure and fate endpoints" due to time constraints,[149] and included brief responses to several of the discussion questions in lieu of more thorough discussion. It is likely that with more time flexibility additional points or ideas could have been exchanged or further discussion could have resulted in understandings in areas of disagreement. These observations accord with Dana and Nelson's finding, in investigating participants' experiences of Dana *et al.*'s multi-stakeholder workshop, that some participants limited their participation due to time constraints, real or perceived.[150]

Despite the limitations, the timeframe may have been optimal under the circumstances. Conveners regarded the workshop as successful. The PoET-Wilson workshops were constrained to single day or 1.5-day workshops due to participants' time constraints, so extending the tier testing workshop beyond its 2.5 days may have been impractical.

Lack of Continuity

Participants' abilities to contribute may also have been limited by a lack of opportunities to engage over time with the questions or considerations. For example, participants in the pathogenicity and toxicity subgroup composed a preliminary list of pathogens and noted that "This list can be expanded by members of the subgroup (using available information resources in their respective offices and institutions) ... ,"[151] suggesting that the workshop's contained format somewhat limited these participants' ability to contribute. This group also proposed the creation of a database of expert analyses regarding particular biotechnology applications.[152] Although the workshop report does not say that these participants offered to contribute to the database, it is possible that with ongoing engagement they may have enabled its formation. Aside from circulation of draft summary reports for review, little if any follow-up with workshop participants took place.[153]

The officials who developed the Subdivision M Guidelines appear to have benefitted from ongoing engagement with the regulatory and scientific considerations, evidenced, for example, by the discussion of testimony before Congress regarding waiver conditions for efficacy data. This occurrence, as well as references in the Guidelines to Agency experience gained through reviewing submissions over time,[154] suggests that individuals composing testing or assessment guidelines may benefit not only from their own knowledge and expertise but also from engaging over time with a project or an area of regulation. Diverse stakeholder involvement tends to occur as relatively brief, isolated interactions rather than through ongoing participation in extended processes.

While follow-up or extended engagement could increase participants' abilities to contribute, such activities may be very difficult to effect, and they may not always be a

priority for workshop conveners. In the OPPT workshop, the conveners felt that they gained sufficiently from the workshop. They conducted other workshops over time, with different foci and largely involving different participants. Developing extended relationships with participants in order to solicit their input over time may not accord with the agencies' needs or priorities. Furthermore, while participants may be able to contribute more with extended engagement opportunities, not all participants willing to attend a single three-day workshop are necessarily interested in longer-term involvement.

Challenges to Multi-Stakeholder Processes

While any assessment process may face time constraints and continuity gaps, these challenges appear to represent weaknesses particularly inherent in multi-stakeholder processes as typically conducted. Diverse stakeholders are likely to have other commitments that limit the time they may devote to a workshop, and they are largely unlikely to be engaged in the particular assessment problem on a long-term basis. By contrast, narrow experts such as agency officials or consultants are likely to be geographically proximate, work together regularly on the assessment tasks or closely related problems, and have time to devote to the project over both the short and longer terms. Furthermore, as typically conducted, multi-stakeholder processes involve efforts in workshop design, creation of briefing materials, and other arrangements, while experts working together typically require no such special engagement efforts.

Multi-stakeholder workshop conveners may find it valuable to consider in advance what extended engagement, if any, they wish to enable, as well as how to maximize participants' ability to contribute even in a contained workshop. Materials distributed in advance that provide a good understanding of what types of knowledge or information will be requested, opportunities for limited follow-up to fill gaps identified at the meeting, and participation of people engaged with the particular questions or assessment need on a longer-term basis, such as agency regulators, could help extend participants' perspectives and increase their ability to contribute. Although, as appears to have been the case for the OPPT workshop, a self-contained and time-limited format may provide conveners with the input they desire, exploration of how diverse participant processes or contribution could take place over longer timeframes may also be valuable.

Lessons from the OPPT Workshop and Subdivision M

Examination of the OPPT workshop, which gathered participants from industry, academia, and regulatory agencies to provide information and develop ecological testing schemes for microbes in various industries, suggests strengths and challenges of diverse participant processes. Examination of the workshop alongside the Subdivision M Guidelines, microbial pesticide testing requirements developed by a small group of regulatory officials, provides further insights.

The diverse participants contributed substantial information and crafted testing schemes based on their distinctive, deep knowledge of the ecological and industrial systems. The detail in the workshop report and testing schemes, regarding both ecological systems and effects and the technologies and industrial uses, suggests that bringing together ecologists

and industry members may enrich a discussion. The breadth of effects and testing considerations advanced and some differences of opinion among participants suggest employment of diverse conceptual models that can expand discussion, and a diversity of options for deliberation can positively affect outcomes. Sharing industry practices and new ecological assessment research in an area of rapidly developing technology, participants enabled the knowledge available to the regulatory Agencies to keep pace with developments. The diverse participants also appear to have contributed based on their values in ways that may have enriched the discussion and outcomes. Participants also displayed willingness to answer questions and craft testing schemes in ways that diverged from existing structures, while still seeking to produce schemes and information useful to conveners.

A diverse participant workshop presents challenges and requires substantial effort to execute. Effort may be required to provide participants with the background information needed to contribute fully, and exploration of diverse perspectives must be carefully balanced with completion of tasks as designed. Potential for bias and time constraints that may exist in any process may present particular challenges in diverse participant settings. Distinctive challenges may also arise in involving diverse stakeholders in regulatory settings. The OPPT workshop provides insights into convening diverse participant workshops, and it suggests approaches to addressing the challenges.

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[3] Subdivision M, pp. 3-5: III. Background of Subdivision M and IV. Revisions to Subdivision M.

[4] Subdivision M, p. 5.

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[14] FIFRA, e.g. secs. 2(v), 12(b)(5).
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[25] Tier Testing Report, p. 12.
[26] Tier Testing Report, p. 6.
[27] Tier Testing Report, pp. 19, 22-23.
[28] Tier Testing Report, p. 22.
[29] Tier Testing Report, pp. 23, 34-35.
[30] Tier Testing Report, p. 34.
[31] Tier Testing Report, pp. 30-31.
[32] Tier Testing Report, pp. 31-32.
[33] Tier Testing Report, pp. 24-25.
[34] Tier Testing Report, App. B, 7th p.
[35] Tier Testing Report, p. x.
[36] Tier Testing Report, pp. xi, 30.
[37] Tier Testing Report, p. 25.
[38] Tier Testing Report, p. 25, emphasis added.
[39] Tier Testing Report, p. 52, emphasis added; see also p. 45.
[40] Tier Testing Report, p. x, emphasis added.
[41] Tier Testing Report, pp. 5-6.
[42] Tier Testing Report, p. 8.
[43] Tier Testing Report, p. 34.
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[50] Tier Testing Report, p. 32.
[51] Tier Testing Report, p. 30.
[52] Tier Testing Report, App. B, 6th p.
[53] Tier Testing Report, pp. 29, 50.
[54] Tier Testing Report, p. 28.
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[56] Tier Testing Report, p. 25.
[57] Tier Testing Report, p. 28.
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[60] "Issue Paper: Development of Ecological Tier Testing Schemes for Microbial Biotechnology Applications," Unpublished paper prepared by Clement International Corporation, December 14, 1993, p. 68, in "Part III: Concepts for Consideration in the Development of an Ecological Tier Testing Scheme for Microorganisms."
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[67] See, for example, Subdivision M, pp. 33, 44, 51, 160.
[68] Subdivision M, p. 103.
[69] Subdivision M, p. 92; see also p. 103.
[70] Subdivision M, p. 143.
[71] Tier Testing Report, p. viii; see also p. 16.
[72] Tier Testing Report, e.g. pp. 8, 10, 16, 18.
[73] Tier Testing Report, p. 24.
[74] Subdivision M, p. 165.
[75] Subdivision M, p. 175.
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[77] Subdivision M, pp. 23-24.
[78] Subdivision M, p. 84.
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[80] Tier Testing Report, p. 23.
[81] Tier Testing Report, p. 29.
[82] Tier Testing Report, pp. 36, 40, 42, 45, 46, 50.
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[85] Reviewed in: T. Kuiken, G. Dana, K. Oye, D. Rejeski, Shaping ecological risk research for synthetic biology. *J Environ Stud Sci* **4**, 191-199. (2014). doi: 10.1007/s13412-014-0171-2. See "Revisiting ecological risk history for engineered microorganisms," p. 196.
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[105] Tier Testing Report, pp. 48-49.
[106] Subdivision M, e.g. pp. 93, 104.
[107] Tier Testing Report, p. 44.
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[109] Tier Testing Report, p. 50.
[110] Tier Testing Report, p. 51.
[111] Subdivision M, p. 110.
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[113] J.M. Tiedje, R.K. Colwell, Y.L. Grossman, R.E. Hodson, R.E. Lenski, R.N. Mack, P.J. Regal, The planned introduction of genetically engineered organisms: Ecological considerations and recommendations. *Ecology* **70**, 2, 298-315 (1989), p. 305.

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[139] Tier Testing Report, p. 8.
[140] Tier Testing Report, p. 20.
[141] Tier Testing Report, p. 30; see also pp. xi, 24.
[142] Tier Testing Report, App. B, 7th p.
[143] Tier Testing Report, p. 34.
[144] Tier Testing Report, p. 20.
[145] EPA official, pers. comm., December 7, 2016.
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Chapter 4

PoET-Wilson Workshops

A series of multi-stakeholder workshops held with the primary aim of identifying hazards and sources of uncertainty relevant to ecological assessment of synthetic biology applications provides insight into stakeholder contribution as well as practical considerations for engaging diverse parties. The workshops were conceived and structured as an application of Dana *et al.*'s findings in their study on multi-stakeholder environmental risk assessment.[1]

Case Background

The Program on Emerging Technologies (PoET) at MIT and the Synthetic Biology Project at the Woodrow Wilson International Center for Scholars in Washington, DC convened a series of six workshops between 2011 and 2016 (Table 2). The workshops were sponsored by the National Science Foundation's Synthetic Biology Engineering Research Center (NSF SynBERC), and some sessions were also sponsored by other NSF bodies or by the United States Environmental Protection Agency (EPA). These "PoET-Wilson workshops" engaged diverse participants in discussions and exercises to identify research needs and discuss other considerations around synthetic biology applications. The workshops focused on applications involving deliberate or expected environmental release and on genetically engineered safeguards.

No.	Date	Title	Prompting Cases
1	Jan 13, 2011	Beyond Containment: Assessing, Testing and Demonstrating Safety on Release of Synbio Devices and Chassis	Arsenic biosensor; rE.coli (recoding); bioremediation (atrazine, petroleum)
2	July 28, 2011	Comprehensive Environmental Assessment and Synthetic Biology Applications Workshop	Algae (cyanobacteria) for sucrose production
3	June 29, 2012	Managing Uncertainty: How to Assess, Test and Demonstrate Safety for Applications of Synthetic Biology	rE.coli; algae (cyanobacteria) for sucrose production
4	Dec 14, 2012	Data Needs and Testing Methods for Assessing the Safety of Environmental Introduction of Synthetically Designed Algae for Biofuel Production	Algae for biofuels production
5a	Jan 8-9, 2014	Creating a Research Agenda for the Ecological Implications of Synthetic Biology	Nitrogen fixation; gene drives; gene flow for bioremediation
5b	Jan 16-17, 2014	Creating a Research Agenda for the Ecological Implications of Synthetic Biology	Bio-mining; crowd-funded glowing plants; open techs for plant synthetic biology
6	June 20, 2016	A workshop on Testing Technical Safeguards to Limit Risks of Synthetic Biology Applications	Recoding (versions of rE.coli); gene drive safeguards

Table 2. The PoET-Wilson Workshops. All of the workshops took place at the Wilson Center, Washington, DC, except 5a and 5b, which took place at MIT, Cambridge, MA, and at the Joint BioEnergy Institute (JBEI), Emeryville, CA, respectively.

Content and Format

The one to 1.5-day long workshops were conducted largely as guided discussions, in which a facilitator guided participants through conversation centering around sets of discussion questions. A few of the workshops included activities to facilitate thinking or discussion. For example, in one workshop participants were asked to vote and present cases for their highest priority research topic, and in another, participants developed a list of traits of an "ideal organism" engineered for biofuels production, to aid later discussion. The workshops or sessions within them began with technical presentations about the technologies on which the discussion was to focus, and sometimes with presentations providing other background, such as on biological concepts, risk assessment frameworks, or regulatory structures. Preparatory materials circulated before each workshop provided the agenda as well as background on the technologies, biological concepts, and other bases for discussion.

To foster candid discussion, workshops were conducted under a version of the Chatham House Rule:[2] participants were permitted to use and convey statements made at the

workshops, but were asked not to reveal speakers' identities or affiliations without the speaker's permission.

Prompting Cases

The workshops focused on specific technologies or applications as concrete prompts for discussion, and also sought generalizable points. Mentioning reasons for centering discussion around cases, a report presenting some workshop results explained that

> These dialogues were rooted in common reference points through the use of case studies ... . The chosen applications were selected to illuminate near- and long-term research needs, and to provoke consideration of a wide range of possible ecological implications. They also facilitated the development of a shared language for attendees hailing from a wide variety of fields.[3]

Most of the prompting cases (Table 2) were technologies or applications that were sufficiently developed for details to exist that could spur substantive discussion, but early enough in development that many technical details remained open, and that the case was not yet politicized or undergoing regulatory review.

Some prompting cases were specific technologies fairly advanced in development with some application details known and companies engaged in moving the projects forward. These cases included an arsenic sensor under development by the company Lumin and intended for use testing water in developing countries with high drinking water arsenic levels, and a project to develop glowing *Arabidopsis thaliana* plants, funded through a crowd-funding web site and promising contributors such items as glowing plant seed packets or genetic engineering kits to produce their own plants.[4] Other cases consisted of more general areas in which development was active and companies engaged, such as use of engineered microbes for bioremediation or biomining or algae for biofuels. Prompting cases also included technologies under development without specific commercialization plans or connection with companies, and often substantial flexibility as to uses and even technical development. These cases included work on recoding technologies that could serve to limit survival or gene flow, work on nitrogen fixation pathways for non-leguminous plants, a technology for sucrose production in algae, and gene drives and their safeguards.

Prompting cases were largely different for each workshop, although some overlap occurred: Workshops 2 and 3 both discussed a technology using algae for sucrose production, followed by a workshop focusing on algae for biofuels production more generally; workshops 1, 3, and 6 all discussed versions of "rE.coli," a project to recode *E. coli* in ways that could prevent survival and gene flow.

Contributions, Not Consensus

The workshops focused toward revealing and discussing ideas and opinions rather than toward reaching consensus. A report on results of some of the workshops mentioned that "Importantly, the workshops were not intended to result in consensus; instead, they were designed to achieve material saturation, wherein the majority of unique areas of concern are discussed."[5]

The workshops also included minor efforts to encourage participants to prioritize considerations or to determine the level of agreement among participants. In one workshop, participants were asked to vote on their highest priority research area of those identified, and in another, participants were asked to state how they would allocate a limited research budget. At moments the facilitator sought a general sense from participants regarding their level of agreement with a statement, though level and breadth of agreement were generally determined implicitly through conveners' watching participants' reactions.[6]

The workshops' seeking to reveal more ideas, perspectives, and relevant knowledge rather than to reach agreement aligns with Dana *et al.*'s workshops,[7] which encouraged each participant to develop a conceptual model of the system and to work together to generate lists of hazards and other assessment components without narrowing or critically evaluating the lists or reaching consensus. The researchers' analysis used the numbers and diversity of system elements and hazards as key metrics, implying value in contribution of elements for consideration rather than only in their inclusion in a final assessment product or direct influence on a decision.

Evolving Agendas

The workshop agendas included identification of hazards, such as engineered organism characteristics that could cause ecological effects, but they focused on identification and prioritization of knowledge gaps and research needed to inform environmental assessment, as well as on approaches to research and testing. In discussing research and testing approaches, the workshops addressed methods and considerations for obtaining knowledge about receiving ecosystems and biological processes such as gene flow, as well as testing of engineered organisms to predict effects. While not always the focus, engineered safeguards, including how their effectiveness might be tested and how their use might affect assessments, appeared throughout the series.

Conveners used results of each workshop to design subsequent workshops, such that the agendas and objectives evolved over the series. For example, a few workshops generally delineating areas in which research should be undertaken prompted a pair of workshops[8] involving more participants with technical backgrounds in areas of biology, ecology, and technology development to develop a more detailed research agenda. Conveners were sensitive to technological and political developments in the field and designed workshop agendas accordingly. After funding was not forthcoming to act upon the more detailed research agenda, conveners shifted focus toward testing of engineered safeguards and other factors affecting safeguard adoption.[9]

Participants

Modeled after Dana *et al.*'s workshops, the PoET-Wilson workshops deliberately included diverse stakeholders. Researchers developing synthetic biology technologies, members of environmental organizations, ecologists, regulatory officials, and biotechnology industry members participated in each of the workshops. At various

workshops, participants also included insurance industry members, members of venture capital firms, grantmaking agency officials, members of institutes or companies specializing in standards or measurement technologies, members of national security or law enforcement agencies, intellectual property lawyers, policy researchers and analysts, Science, Technology, and Society researchers, ethicists, and others. The ecologists' and technology developers' areas of work and the regulatory agencies and industry segments represented varied somewhat over the workshops.

Participants were invited individually, and separate invitations were issued for each workshop. Some participants were contacted without prior familiarity to conveners, but many were existing contacts through the convening teams' substantial networks in relevant fields, and a few were recommended by other participants. The NSF Engineering Research Center SynBERC, which co-sponsored the workshops, included researchers at several universities as well as industry members and provided a ready network of potential participants, including synthetic biology engineers whose work in the consortium benefitted from their technologies' inclusion as prompting cases.

Numbers of participants ranged from 25 to 48, with workshops typically including about 35 participants. Each session included some overlapping and some different participants from other workshops; regarding 5a and 5b together as a single workshop, several participants other than conveners were present at nearly every or every workshop, while many were present at only one or two workshops.

Outputs

Written materials arising from the workshops included summaries and reports, and researchers also published papers using the results. The convener teams produced anonymized notes of the workshop discussions. Draft notes were circulated to participants for review and correction, and then final versions were distributed. For some sessions, participants were asked to use these notes when referring to workshop proceedings. Workshops 5a and 5b, the paired workshops on "Creating a Research Agenda for the Ecological Implications of Synthetic Biology," resulted in a formal report summarizing the discussion and synthesizing key points.[10] In addition, conveners and participants have produced papers using workshop findings, discussing both technical content and lessons about diverse participant involvement.[11, 12, 13]

Approach to Case Analysis

The present analysis examines the workshops for insights regarding participant contribution, exploring how the contributions may reflect participants' diverse backgrounds and affiliations as well as how the conversation among diverse parties may have affected contributions. It also seeks to discern practical considerations in convening diverse stakeholder processes, including challenges and ways in which PoET-Wilson workshop conveners prevented or addressed challenges.

The analysis relies primarily on the official notes produced following each workshop. It also uses the preparatory reading materials and reports of the workshop proceedings.

Personal notes and recollections from several of the workshops as well as communication with conveners and participants contribute to the analysis. The official notes summarize to varying degrees the discussion elements, and they vary in thoroughness and clarity. The notes are largely anonymized and typically omit speakers' affiliations. For analysis focusing on diverse stakeholder contributions, speakers' affiliations can sometimes be readily surmised, and the existence of a comment can often contribute to the analysis even if the speaker's affiliation is not known.

Participant Contribution

Consistent with and extending beyond Dana *et al.*'s findings, the PoET-Wilson workshops' diverse participants contributed information about the ecological and industrial systems and risks, system complexities affecting assessment, and participant groups' interests. They also encouraged broadening of assessment boundaries beyond considerations standard for environmental risk assessment, revealed a variety of approaches to testing and assessment, and revealed different underlying worldviews that may be valuable in conducting an assessment or a decision-making process. Participants also exchanged information about testing needs and capacities that could enable needed research to be conducted.

System and Risk Information

Participants contributed information about the technological, ecological, industrial, and other relevant systems. They identified hazards, identified possible concerns as being unlikely to present hazards, shared information regarding the state of relevant industries, pointed out system complexities that could affect assessment, and shared detailed knowledge about the current state of research and about resources that could benefit and models that could inform testing programs and other assessment efforts. While in many instances participants' contributions aligned with views that might be seen as stereotypical for the individual's affiliation, participants contributed broadly and at times crossed these "party lines," contributing based on their own knowledge and perceptions rather than only promoting their affiliation-based interests.

Hazards and Non-Hazards

As Dana *et al.* found in their paired workshop study, diverse participants identified hazards, system component interactions or possible occurrences that could result in harm, and they demonstrated different perceptions of system boundaries. Participants also contributed to an understanding of when system components or interactions do not constitute hazards or may present minimal concerns.

Ecologists contributed their perspective, as well as their knowledge of specific systems, to identifying hazards. For example, an ecologist provided insight on ecologists' way of perceiving systems that may inform their view of genetic alterations, commenting, "Physiology to populations to landscape – there is the potential for [genetically engineered organisms] to modify this..."[14] Training in ecology may encourage ready perception of how changes in an organism's physiology can result in changes to whole

populations and how these may in turn affect entire ecosystems.[15] The ecologist also described ways in which engineered organisms could affect ecosystem components of concern, citing examples of the occurrences in engineered crops.[16] In a discussion of algae engineered to produce sugars, to which a gene producing salinity tolerance had been added to enable release of the sugars, the technology developers focused on the point that the added genes would not improve the alga's fitness. An ecologist observed that many toxin-producing algae are limited by salinity, and pointed out that if the modified alga transferred its salinity tolerance gene to these freshwater algae, toxin producing algae could expand in range, a problem that he mentioned has analogues in existing ecological systems.[17] At another workshop, when a participant suggested that algae are distributed globally such that introduction of algae to a new environment should not arouse concern, an algal ecologist stated that this argument is true to a degree, but that some algae and other microbes live in restricted areas, or in broad but separated areas such as the southern rather than the northern hemisphere, and have not spread even though they may be capable of thriving in other locations.[18]

Other participants contributed to identifying hazards as well. Environmental organization members explained that production facilities sited near an endangered species' habitat would invite particular concern.[19] When some participants suggested brownfields as a good site for production facilities using engineered organisms because "The environmental effects have already happened,"[20] an environmental organization member responded that the site would still cause concern because the organism may disperse beyond this immediate environment.[21] This exchange may indicate differences in system boundaries considered. Participants also pointed out hazards not strictly of an ecological nature. For example, an environmental organization member noted that siting decisions could impinge on international treaties, explaining that "There are ducks regulated by treaty with Canada and Mexico that eat algae. They may want to know whether ... ponds [of engineered algae] are replacing ponds [where] ducks normally eat."[22] A lawyer expert in intellectual property expressed concern about recoded organisms that rely on a proprietary cocktail of small molecules, observing that

> In industrial biotechnology and even sometimes healthcare biotech where the culture is of trade secrets rather than patenting and openness, a problem arises when a release happens and no one, perhaps just the company and a regulatory agency, has the knowledge of what was there, which can make it hard to address problems. For recoded organisms, the small molecules they rely on could be the only secret, but those could be the key in a particular context.[23]

This observation represents a hazard that other parties could well have missed, but that was evident to the participant due to her distinctive knowledge-base and perspective.

Technology developers discussed potential hazards of their own and others' research. Discussing recoding that may prevent horizontal gene transfer and also reduces susceptibility to viruses, a researcher in other areas of bioengineering pointed out that viruses often control their host microbes' populations, such that a resistant microbe could spread by outcompeting wild types that are vulnerable to viruses.[24] A researcher working on recoding noted that recoding could inadvertently alter protein behavior due to differences in concentrations of tRNA molecules, codon-specific molecules needed for

DNA-to-protein translation, whose concentrations could affect protein assembly rate and thus folding patterns and function. The researcher suggested that choosing carefully among synonymous codons could help address this problem.[25]

In addition to identifying hazards, participants contributed information on system interactions that do not present hazards or when risk is likely small. In response to a question about whether the quantity of algae in production ponds affects the likelihood of survival in a receiving environment and ecosystem effects, an algal ecologist suggested that "It may affect dispersal events, but I would think that if they're local, if they can be in that environment they would be."[26] Several technologically-knowledgeable participants discussed engineering approaches that could reduce risk. For example, drawing from experience, a participant offered insights regarding methods of integration and horizontal gene transfer, stating that

> I've done a bunch of metabolic engineering in algae. ... chromosomal integration is highly stable, lasting decades in the lab. I've never experienced or heard of a reversion on a chromosomal integrant. Plasmids, however, get kicked out fast. This is not to say that chromosomal reversion doesn't occur, but it'll be tough to find.[27]

A regulatory official supported this position, indicating that the agency's review distinguishes between chromosomal integration and introduction on plasmids.[28] In another workshop, participants identified another transgenesis method as likely to be very stable as well as genomic site -specific, and mentioned that prey to predator transfer would not be expected with this method.[29] Discussing the possibility of reversion in a recoded organism, a biotechnology researcher mentioned steps that could be taken, such as rotating three codons and other approaches establishing selective pressures favoring the alternate code, to prevent reversion. Researchers also pointed out that changing the translation machinery in addition to the codons themselves contributes to preventing reversion.[30]

Complexities

Participants contributed insights regarding system complexities that could play a role in assessment. Environmental microbiologists discussed complexities associated with the concept of fitness, such as the possibility of an introduced organism's engaging in positive interactions that could enhance the fitness of organisms it encounters. They also offered simplified approaches that researchers in their field have developed to thinking about this complex concept.[31] Participants discussed ways that an introduced organism could affect an ecological community, and observed that scientific understanding of how ecological communities function is lacking, particularly regarding their response to exogenous organism introduction or their function under climate change.[32] Participants suggested that different applications may require different types of organismal behavior that could affect suitable evaluation schemes. For example, while some applications favor consistency and control over the organisms, others, such as pollutant degradation, may require the organism to evolve along with changes in the receiving environment to deliver the desired outcomes, potentially affecting assessment considerations and suitable approaches to preventing effects.[33]

Participants determined that directed evolution, in addition to genetic engineering as narrowly defined, warrants concern and scrutiny for environmental effects,[34] broadening the scope of the research and assessment consideration. The determination that products of directed evolution also warrant concern arose through the facilitator's prodding participants regarding differences among wild type algal strains, engineered strains, and current commercial production strains, many of which have been modified through directed evolution. The determination met some general agreement among participants, even though the groups represented who discuss risk concerns, such as environmental groups, regulatory officials, and ecologists, typically focus on genetic engineering, while industry typically does not focus publicly on environmental concerns. The determination may also represent a contribution developed through the facilitated workshop format.

State of Technologies and Industries

Throughout the workshops, technology developers provided detailed information about the existing technologies and current projects, including current shortfalls and areas in which they hoped to develop the technologies further, as well as design decisions still to be made. For example, recoding researchers explained that their current recoded organism was only altered through elimination of a single codon, and that they intended to recode a few more codons and expected substantial reduction in compatibility for viruses and gene transfer to result from the further changes.[35] A researcher working on nitrogen fixation for non-leguminous plants described his progress in the effort and also explained that he has not yet determined whether to locate the nitrogen fixation capability in microbes closely associated with plant roots, in soil microbes, or in the plants themselves.[36]

Industry members and academic applied biotechnology researchers provided insights regarding the current state of relevant industries. For example, a researcher discussed the field of algal biotechnology, including genetic alterations that have been made, types of algae currently used, and expected future applications.[37] Industry members discussed the shift in attention from freshwater to saltwater algae, the current state of work on applications other than biofuels, how strains are selected and modified, and details on location selection, confinement approaches, and other industrial practices.[38] One industry member mentioned that his company's facilities operate with closed loops and zero discharge, reducing concerns about by-products,[39] and perhaps suggesting practices that other companies could emulate. Companies and researchers also discussed cost considerations for facilities in developing countries, noting that in developing countries more enclosed photobioreactors' costs make them infeasible and open ponds should be expected.[40]

Existing Knowledge and Resources

Participants contributed substantial information about existing knowledge, resources, and models.

Participants contributed knowledge about research groups' activities and other resources. For example, some participants were members of a working group on algae, and participants mentioned its current and upcoming work, such as developing lists of algae with commercial potential, resources on all algal species,[41] and "sustainability indicators."[42] A participant mentioned that Australia has developed and Florida adopted an "invasiveness index," and wondered whether it might be helpful for consideration of engineered organisms,[43] and a participant mentioned a national lab's current study on siting for biofuels facilities.[44] A participant advised looking to other countries' research, as he was familiar with several countries' experiments investigating behavior and effects of engineered fish.[45] An algae industry member mentioned very early stage industry studies on algal invasiveness and on monitoring animals by algal ponds.[46]

Participants' diverse knowledge of existing research could enable useful connections. When a participant suggested studying the capabilities of directed evolution, particularly in the presence of other organisms, another participant was familiar with a lab conducting research on this particular subject.[47] When participants mentioned the need for technologies that could track engineered microbes, a participant mentioned a national lab's research against bioterrorism that he thought could be applied to this purpose.[48] In discussions of how to design testing systems, the need for guidance or standardization in good testing practices, and the availability of testing facilities, participants mentioned work at a national lab to develop flow-through aquatic testing systems,[49] and facilities with existing as well as proposed microcosm and mesocosm systems that could be accessible for studies.[50] In discussing existing groups that could partner to conduct monitoring for engineered organisms or ecological effects, one participant suggested various defense-related institutions, and another added a set of ecology-related institutions.[51]

Participants mentioned research studies and technologies that could address or be used to address questions arising in the discussions, as well as research findings that could be valuable for assessments. For example, participants were familiar with research observing a microbial strain's evolution on a daily timescale,[52] and with tools that could be used to detect phenotypic effects of genetic changes in individual strains and consortia.[53, 54] Participants mentioned a study apparently not broadly known in which inhibiting translation of a gene caused the organism to produce toxic compounds,[55] and a study identifying cellular mechanisms preventing rapid evolution.[56] While a narrow expert group would likely be aware of some existing resources and would conduct additional investigations, the participant diversity appears to have broadened the types of resources with which participants were familiar and facilitated inclusion of more new research or research known only in particular circles.

Participants referenced a range of existing programs and systems that they suggested could serve as models for accomplishing identified aims. For example, participants referenced a national lab's large program on plants for bioenergy as a model that could be applied to generating data needed for algae,[57] and cited an agency's approach to regulation of a particular organism as "a scheme that makes sense for both developers and regulators in helping everyone make the decisions they need to."[58] Discussing how to

encourage researchers to make research plans and results open, a participant cited an agreement in genetics research that achieved similar ends.[59] In advancing the need for an organization to advocate for the conduct of needed research, a participant described the advocacy that resulted in the EPA's producing research and better rules for air emissions.[60] Other participants as well suggested drawing from efforts with which they were familiar, potentially broadening the set of models and tools on which assessors or others using workshop results could draw.

In addition to existing knowledge and resources, participants also contributed information about knowledge gaps. For example, participants discussing algal engineering complained of a lack of information about algal strains, including commercial strains,[61] and a lack of research on introducing algae into new environments.[62] Industry members mentioned that their efforts to select strains carefully are challenged by a lack of information about strains other than those producing harmful blooms and those that have already been commercialized, and they generated a list of missing information.[63] Various participants, including regulatory officials, mentioned a lack of knowledge about horizontal gene transfer frequencies, particularly among particular types of organisms.[64, 65] Participants also mentioned gaps and flaws in research methodologies, noting that current thinking may be shaped by flawed earlier methodologies,[66] that work is needed on statistical methods and understanding how to draw predictions from controlled studies,[67] and that the field of ecological risk assessment struggles with incorporation of complexity and uncertainty.[68]

Diverse participants' knowledge about existing work and other resources can contribute directly to assessment content, increasing the information readily available to the assessment and enabling the assessment to access current information that may not yet be known beyond limited circles. Diverse participants' sharing information about work in their respective areas can also enable researchers in different fields to access each other and conduct research helpful to a particular assessment or, as the focus of the PoET-Wilson workshops, research that could contribute to many assessments and technology designs.

Information from Personal Experiences

Participants drew from their personal experiences to contribute to the discussions. For example, individuals with ecology experience shared practical challenges and considerations in conducting field studies, and regulatory officials shared challenges they encountered in reviewing submissions and compared applications being discussed with considerations that arose for submissions.

An ecologist shared an experience and advice on study design as well as insights into challenges of obtaining good information from field research:

> And replicate the hell out of [mesocosms], because you're going to have issues with some of them. For example, we were doing open mesocosms in Lake Erie that were two meters wide and four meters deep, and a great blue heron crapped in one and not in the other, and we didn't have enough replicates, and it threw the

> experiment way off. We wasted a whole summer's data. You need a lot of replicates.[69]

At another workshop, a participant experienced with models and field experiments for risk assessment also reflected on challenges in obtaining data:

> The model says it should go at this rate, and now we test in a mesocosm. That was a major undertaking. The complexity of these experiments just to determine if the transgene would behave in a model organism as the model says it would was all-consuming, and said little to nothing. You still can't make a prediction.[70]

Participants experienced in conducting and studying mesocosms mentioned components that they found were necessary to simulate environmental conditions for aquatic systems, mentioning how they take water samples, the need for flow-through and diurnal variations, and other considerations.[71] Insights into the real challenges of and approaches to conducting studies can be valuable in processes calling for or designing studies.

Regulatory officials described their experiences regarding problems and considerations they encountered in assessing organisms. For example, regulatory officials mentioned that they repeatedly encountered the problem that microbes can diminish to low population numbers while remaining viable and able to increase when conditions become favorable: "Organisms can be 'viable but not culturable.' Typical soil and marine microbes hunker down when conditions are unfavorable. They wait and seem to be dead, but when the right conditions occur the organism revives and there is something there."[72] This observation also contributed to advice regarding testing methods, as the officials also noted that new detection methods can be valuable for overcoming the problem.[73] Regulatory officials also compared elements of prompting cases or other examples to submissions they had reviewed.[74]

In discussing obtaining information about tests performed on engineered organisms belonging to companies, some participants referred to policies that should make information available, but another participant described his own experience attempting to obtain the information. He had found that while some labs and agencies make most of the information available, others redact nearly all of it.[75]

In these and other instances, participants' drawing from their personal experiences enabled them to contribute knowledge and insights that a group with less diversity of backgrounds may not have accessed as readily.

Contributions Arising from Diverse Exchange

Throughout the workshops, the diverse participation resulted in rich discussions in which participants heard each others' concerns and information and contributed their own knowledge and perspectives. While the workshops' diverse participants contributed based on their distinctive knowledge and perspectives, the opportunity for conversation among diverse parties itself gave rise to contributions.

New information that participants received often enabled them to contribute concerns or suggestions based on their own perspectives. For example, participants heard developers

of cyanobacteria modified to produce sugars complain that the organism is comparatively weak and that they need to worry about contamination of the culture, and they heard an ecologist introduce gene flow. A participant then suggested that if contamination is a concern, pesticide production or herbicide resistance genes could eventually be introduced to increase hardiness, and these added genes could be taken up by organisms in the receiving environment.[76]

Participants also contributed their knowledge in response to hearing other participants' concerns and perspectives. For example, participants suggested that the ability to track engineered microbes once they enter a receiving environment is needed, including the ability to distinguish engineered from wild populations, and that appropriate instrumentation and methods are needed. In response, other participants offered information about improvements in metagenomic analysis that could enable tracking, a particular national laboratory developing for other purposes DNA analysis capabilities that could be applied in this area, and the possibility of including genetic markers in engineered strains in order to distinguish engineered organisms within wild populations.[77]

Broader Consideration Boundaries

Participants frequently brought up considerations beyond areas typically considered in environmental or ecological risk assessment, suggesting interest in diverging from standard assessment models in considering implications and assessment.

Implications of and for Technology Development

Participants encouraged expanding consideration boundaries beyond the typical scope, including societal, ethical, and policy considerations. It may at times be impossible, or inadvisable, to divorce environmental assessment or standards design entirely from these other areas, which could affect decisions on a biotechnology application or how to conduct an assessment, or could inform an assessment itself. The research agenda report produced from Workshop 5 states that "a concomitant assessment of the economic and social implications of applications is necessary to provide context for the identified ecological impacts in order to develop sound public policies and regulatory structures governing the release of synthetic biology applications."[78] The report noted that a majority of participants identified societal, regulatory, and policy considerations even though these were not a direct focus of the workshops,[79] and that participants also brought up ethical, philosophical, public consent, and responsible science considerations.[80]

Acknowledging that the workshops focused exclusively on environmental effects, participants raised concerns about human health, particularly workers who may be exposed to engineered organisms.[81] Decisions must be made about where to draw assessment boundaries, and considering health along with environmental implications can be a useful approach. Even when these elements are considered separately, information about each may inform assessment of the other.

In discussing gene drives, a participant suggested that the importance of the ends pursued may challenge governance of the technology, explaining that "If you tell the world you

have the means for removing malaria, then there would be immense pressure to push through."[82] Another participant noted the financial incentives and other pressures to pursue applications suppressing particular agricultural pests.[83] A participant also pointed out that for some gene drive applications, even if one group decides that the application is too risky to pursue, others may still pursue it. The participant proposed acting based on the assumption that someone will develop the drive, including developing a monitoring program and preparing reversal drives.[84]

The discussion of gene drives also sparked identification of other socio-economic components that could affect how or whether a gene drive is used. A participant noted that use of a gene drive, such as one combatting malaria, could create changes outside of the narrow ecological system, such as, bluntly, "populations not being ready for their citizens not being dead," describing the problems as being of the "social-ecological system."[85] Participants discussed broader considerations for other applications as well. For example, in discussing technologies for nitrogen fixation, a participant urged consideration of consequences of not using the technologies, such as implications of synthetic fertilizer use.

Even when broader considerations must be temporarily set aside to focus on ecological effects, identification of these areas of consideration and delineation of an assessment's boundaries can be important areas for diverse stakeholder contribution.

Procedural Considerations

Participants discussed implications of proprietary industry information for risk assessment. They mentioned that industry maintaining information as proprietary, as well as controlling testing using intellectual property claims, has proven and remains a challenge for risk assessment.[86] Discussing safeguards, participants noted that patents are likely to provide the patent holder with power over studies of environmental implications. They mentioned that since some safeguards are also intended to help maintain company secrets, such as an organism's genetic composition or the combination of small molecules required to maintain it, details regarding the patented organism could be hidden as well as testing controlled.[87]

Other participants expressed concern about the implications of industry secrets for environmental assessment quality and acceptability. One environmental organization member stated that his organization would likely fight the biotechnology application under discussion "Unless it was shown to be safe with better testing that was public and not [Confidential Business Information]."[88] When a participant stated that except for certain proprietary data test information is made publicly available through the Freedom of Information Act, another participant responded that he had issued Freedom of Information Act requests with several agencies and obtained mixed results, with some tests nearly entirely public but others nearly entirely redacted.[89] These participants broadened the discussion from ecological hazards and testing methods to questions about how information-gathering and assessment occur and the procedures' influence on information trustworthiness and on trust. Positive public receipt is desirable for a

company seeking to use its technologies, particularly with the potential for or necessity of environmental release, and public sentiment can affect decision-making processes. Limiting access to assessment studies may also diminish the scientific quality of the study itself. When a participant suggested that "There are things that can be reported that are easily digestible without fully disclosing private work," a participant knowledgeable in risk assessment responded that "A phenomenological view is most important for the risk assessment model, so all the data need to be there. The original person may not ask all the questions eventually needed."[90]

Participants pointed out other components of information-gathering or decision-making that could affect assessment quality as well as trust. For example, a participant criticized a lack of opportunities for diverse input on specifics of an application or decision and for input earlier in a process, opining that Federal public comment periods occur too late in the development and decision-making process.[91] In addition, participants emphasized that public or public-private research consortia addressing general areas of uncertainty must be independent from economic interests.[92] These considerations, beyond the narrow scope of identifying and testing for ecological effects, are important for conducting sound studies, assessments, and decision processes, and participants' diverse backgrounds and experiences appear to have contributed to identifying these considerations and including them in the discussion.

Participant Interests

Diverse participants shared information about their interests and concerns based on their affiliations. Members of companies, environmental organizations, regulatory agencies, insurance companies, and others shared information about their interests. Insights from regulatory agencies and industry appeared prominently throughout the workshops.

Regulatory Agencies

Regulatory officials shared insights regarding their considerations when they review submissions, as well as other concerns and interests. Regulatory review considerations are important contributions in part because they play a role in shaping what applications are commercialized and under what conditions. In addition, regulatory officials develop substantial experience assessing organisms and applications, and their insights regarding important factors can be valuable, though their review also reflects their particular perspective and may be limited by the statutes under which they operate. Other stakeholder groups may similarly spend time considering risk and environmental implications from their own perspectives.

Regulatory officials discussed the types of questions they ask about a submission, emphasizing the importance of submitter familiarity with the organism and credible testing of claims. They also emphasized potential for gene transfer, mentioning that different insertion methods raise different levels of scrutiny, and the routes, volumes, and receiving environments of potential release.[93, 94] They listed other considerations, such as abiotic production inputs and factors related to human health.[95] Regulatory officials' considerations may provide insight regarding hazards and sound organism design. For

example, a participant asked whether officials regulate genes that already exist in nature, such as naturally-occurring antibiotic resistance genes, and whether these should be removed if added for production of the transgenic strain. A regulatory official explained that

> ... we do care about using naturally occurring genes. We do not want to add to an already existing problem of resistance development. Even though resistance genes occur in nature, they do not normally occur in such high concentrations. Using these genes in GMOs increases the likelihood of other organisms taking up the genes. So we are not only concerned just with artificial genes, but artificial concentrations of natural genes as well.[96]

Discussing their operations and operational concerns, regulatory officials mentioned that while they review submissions on a case-by-case basis, they seek ways to generalize, such as benefitting from their own familiarity if a given parental strain has already been reviewed with other modifications.[97] They stated their expectation that the technology's rapid advance will cause submissions soon to exceed review capacity and their desire to increase review efficiency and generalization. They also mentioned interest in making review more transparent, and the concern that intellectual property protections might hinder streamlining or transparency.[98]

Industry

Information on companies' operations and approaches to risk can provide insights regarding the production system and potential hazards. It can also provide insights on existing efforts to reduce risk, and on possibilities and hurdles to industry adoption of engineered safeguards and other risk reduction approaches.

Industry members provided information regarding how their companies choose, develop, and test organisms, including screening the organisms for toxicity and other undesired effects and efforts to make the organisms robust against contamination.[99] They described siting considerations, including characteristics they require in deciding where to locate facilities, the organism robustness needed for different types of production facilities, approaches to containment, and economically viable production scales.[100] An industry member explained that "Companies do their own risk-reward and environmental risk analysis, looking at safety of the exogenous materials, health and environmental effects."[101]

Participants discussed companies' economic motivations to ensure organism containment and genetic stability, mentioning that containment could enable a company proprietary access to its engineered strain,[102] as well as the existence of a litigation risk if an engineered organism contaminates another product.[103] A participant stated that "In reality, economics will drive stability. That's the biggest pressure to use genome insertion versus plasmids to convey genetic information – overall making sure your platform doesn't crash out of your strain,"[104] though the participant also admitted that competing interests may complicate the motive to ensure stability, explaining that "We still have to worry about consequences of stability. It's nice if your organism died if your gene wasn't stable,

but there is the danger of large financial losses if the organism dies due to contamination."

Industry members provided insights regarding factors affecting a company's interest in adopting engineered safeguards. An industry member pointed out that the molecules on which the organism is engineered to depend could affect the organism's desirability, explaining that

> Adoption will depend on the cost of the entire production process, as well as stability and availability of needed exogenous materials. IPTG is an exogenous substance very commonly used in labs. But to use it on industrial scale, there are market availability, impurity, cost, and disposal issues. Waste streams with exogenous materials are a factor.[105]

Discussing how regulation might affect adoption, an industry member stated that regulations have never been the factor preventing a product's commercialization.[106] An industry member explained that regulatory submissions include a history of safe use of the organism, which could challenge adoption of new recoded organisms.[107] An industry member stated that while some companies would be interested in participating in experimentation with engineered safeguards, incorporating information from the experimentation into company practice requires substantial effort and resources, and encouraging adoption across an industry without regulatory compulsion would present challenges.[108] An industry member suggested that political factors could also affect adoption, as companies may not wish to adopt measures, even safeguards, distinguishing them from the industry standard, due to concern about inviting negative public attention to themselves or their collaborators, or concern that they may lose collaborators if they seek to pressure them to adopt the safeguards.[109] These insights can be valuable to diverse groups considering how to design safeguards, assess their effectiveness, or encourage their adoption.

Specific Testing Needs

On a number of occasions, participants mentioned tests that they believed should be conducted to assess particular technologies or organisms. These exchanges may better enable knowledge available for assessments to keep pace with technology development because people able to conduct tests are made aware of testing needs and people desiring to conduct tests may be connected with needed resources.

Developer Testing Needs and Interests

Companies and technology developers articulated their needs for support in conducting tests. In these diverse participant contexts, these discussions had the potential to produce connections with the desired assistance.

In a discussion about whether experiment protocols or microcosm design can be improved, a participant described the challenges his company faces in attempting to determine how to conduct tests and indicated that the company desires guidance, stating that "We want to know what the appropriate tests are. We have phycologists on staff and we try to tap their expertise." The participant suggested that a coordinated effort, and

ideally standardization in testing protocols, would be much better than each company's attempting to design tests separately:

> ... we can't be the answer to all these questions on our own. A lot of companies are asking these questions. It would be reasonable to have national labs working on this, or sponsored academic research on these questions. I would love for you to come up with standard experimental conditions. I'll buy a dozen of those reactors if it'll help me standardize. As long as they're representative of real life.[110]

Participants discussed some details of how a microcosm should be designed and how it could be used and validated. Participants also asked a participant from a measurement devices company whether his company could produce items useful for the assessments, and shared knowledge about existing and proposed facilities suitable for the testing described.

At another workshop, researchers developing a confinement safeguard indicated that they would like to develop the technology to a level suitable for the scale associated with industrial production, but that they lack the facilities to test such large numbers of cells for escapes. The researchers indicated eagerness to partner with companies to conduct the tests using their facilities.[111] An industry member expressed that he may have suitable connections and these participants determined to speak further after the meeting.

Testing Recommendations

In discussing particular technologies and applications, participants indicated the types of tests they would desire to see, providing companies, technology developers, and others with insights into tests they should consider conducting to predict ecological outcomes or provide information desired by diverse parties.

Researchers developing recoding to prevent survival mentioned that the safeguard had worked on blood agar, chosen to suggest a medical setting, and soil extracts, chosen to suggest an outdoor setting.[112] When participants asked for details of the soil test, the researchers explained that they had used commercially available soil plates, and mentioned that "Some people in the lab did try to create their own ad hoc natural microcosms" through such efforts as collecting swamp water for experimentation.[113] Participants expressed great interest in hearing the results of those tests, even though the researchers had not pursued them further and had not published the results. Later, in discussing the recoding efforts applied to preventing gene flow, participants again emphasized a need for tests in more representative environments. They suggested several types of environments that could be represented by microcosms, and mentioned that these tests could be conducted within a lab and affordably, but bearing more weight of realism than a dish.[114]

Discussing a project, meant to be community-guided throughout, to explore introducing engineered mice to combat Lyme disease, a participant asked whether the researchers intend to experiment with ticks and mice in a lab-confined setting. When the researchers responded that they are considering doing so and that the communities might not care

whether or not they run these experiments, the participant urged the researchers to conduct these experiments even if the communities do not require them, because the communities may not know all the possible effects and if adverse events do occur, the researchers will have made that testing effort, as well as because the tests can provide insights as to potential environmental outcomes.[115]

The report describing Workshop 5 results includes a number of additional examples of participants' providing concerns and testing suggestions for specific technologies and applications in development.[116]

The exchanges also provided individuals requesting tests with information about what testing may or may not produce useful results. For example, in discussing recoding that could prevent horizontal gene transfer a participant asked whether studies have been conducted using naturally transformable bacteria to determine whether the recoded genetic material can be usefully transferred. The researchers explained that for the current state of the recoding efforts, the recipient bacteria would probably be able to express received genes, but that future recoding efforts are expected to produce genes that would not transfer functionally.[117] Input to technology developers and others on tests that would be valuable is important. It can also be important for those recommending or requiring tests to learn what information can be realistically obtained or what tests can provide useful results at a given stage of research.

Approaches to Testing and Assessment

Workshop participants revealed a variety of approaches to testing and assessment, generally and in particular areas. It appears likely that in many instances, balancing or incorporating elements of multiple approaches may benefit an assessment.

Test Components and Comparators

Participants contributed a variety of ideas regarding how organism behavior could be viewed in order to conduct tests predicting ecological effects. In doing so, participants drew from their own backgrounds and experiences in testing and in considering engineered organisms.

A number of ideas arose regarding what elements to include in testing fitness. While participants mostly discussed investigating the organism's survival under conditions meant to mimic potential receiving ecosystem types, primarily using soil or aquatic microcosms, and largely defaulted to comparison with wild type parental strains, several participants offered alternative perspectives. One participant emphasized competitiveness, rather than solely survival, as a primary concern, and also argued that it is necessary to analyze the entire ecological community, including grazers, which may often be omitted from microcosm studies.[118]

A participant experienced in bioprospecting explained the approach of learning about an organism's native conditions and behavior to help determine what behaviors to look for in microcosm studies of an engineered strain for whichever receiving environments it

may encounter. Revealing alternative perspectives on which comparators would yield the most useful information, a participant suggested testing the engineered strain under conditions mimicking the parent strain's native habitat: "Try to put it back in the original collection and see if it survives," while the bioprospector asked "Why do that at all, if I don't plan to grow it in Guam?"[119]

At another workshop, a participant suggested leveraging fitness's typical context specificity for prediction, asking "What is the niche within which our organism is the fittest, or set of niches where it is very fit?" and suggesting that "This offers a second way of mapping how this organism will behave in the natural environment."[120]

Even if not every approach is employed, considering a diversity of approaches may enrich testing and test analysis, and it could improve testing by enabling selection or design of the best approaches for a given scenario.

Questions for Testing

Participants articulated perspectives as to what questions should frame or motivate tests and studies and how questions should be identified.

Members of environmental organizations stated that tests of engineered organisms should include comparison between the proposed and existing methods of achieving the desired goal.[121] This perspective contrasts sharply with a more usual perspective in environmental risk assessment and regulation that identifies levels of risk and acceptable thresholds without comparing alternative methods of achieving the goal, and thus omits a component of evaluating potential benefits alongside risks. Kapuscinski *et al.*'s model for participatory risk assessment includes "Problem Formulation and Options Analysis," in which the goals meant to be achieved by use of the proposed engineered organism are articulated, alongside other options for achieving the same objectives.[122]

In discussing existing knowledge about gene transfer and testing to detect or predict transfer, a participant opined that "Solutions to prevent horizontal gene transfer are almost impossible. We need to focus on making sure that the genes are okay to transfer."[123] Throughout the workshops, some participants appeared most interested in methods of predicting whether or at what frequencies an organism will engage in useful gene flow or will survive in a receiving environment, and others maintained that gene flow and survival will eventually occur, and believed it most important to predict effects in order to ensure that these events will not cause adverse environmental consequences.

In response to a convener's asking what information is needed to conduct assessments, a participant emphasized the need for an overarching framework to organize existing information and identify topics for investigation:

> "... I'd grab [all the ideas] and relate them in a conceptual framework ... Everyone's laying out different couplings between something we care about and something that causes it. We have tremendous amounts of data coming in, and we can put that into this framework. Summarize all the things we've generated into a

> causal framework and identify the highest risk pathways. ... We can use these criteria to select the research..."[124]

Other participants supported the call for an integrated framework to identify concerns and research needs.

Drawing on Existing Approaches

Several participants drew on their experience to mention existing approaches to testing and assessment in other fields and wondered how they could be applied to the needs at hand. For example, a participant familiar with human health risk assessment explained that human health risk assessment focuses on particular "red flags" most informative to the assessment, and asked whether similar red flags could be identified for synthetic biology.[125] Another participant suggested running toxicity tests "as you would for other substances" to determine whether secondary metabolites might present problems.[126] Participants familiar with chemical regulatory review suggested that helpful analogues might be found there, such as generating a synthetic biology analogue of the chemical structure-activity relationships database.[127]

A participant referenced risk analysis in the nuclear field, explaining that "the process involves assembling a group of people who are very knowledgeable about a process to systematically address these questions. It takes a group of a dozen people familiar with many different aspects of the total system, systematically working through combinations for a week or two." When the participant suggested that "If this hasn't already been done for synthetic biology, it might be a useful way to approach these issues, to determine which kinds of tests could or should be done," an industry member replied that "You've just described our normal process for evaluation of microorganisms subject to our rules."[128]

Participants also mentioned challenges in applying existing approaches. For example, participants criticized ecological risk assessment as struggling with employing "systems level" analysis. The participants suggested that the ecological risk assessment field retained a perspective drawn from general toxicity studies even though the former's subject matter is much more complex, and mentioned that it typically employs linear rather than systems models. The participants suggested that the increased complexity must be incorporated into risk assessment studies, including consideration of complex socio-economic systems and incorporation of uncertainty.[129]

Generalizability

Participants' perspectives on the extent to which testing needs and acceptable results might be standardized differed substantially. These perspectives appear at times to relate to participants' backgrounds or interests.

Many participants expressed the opinion that each engineered organism and application bears unique characteristics preventing sound generalization of assessment needs or standards, while others believed that standard testing needs could be generated. Some

participants believed that even if some aspects must be determined individually, efforts should be made to identify components that could be standardized.

For example, discussing approaches to streamlining regulatory review, participants suggested characterizing and approving particular known biological parts or standardizing genetically engineered containment. Another participant stated that the consequences of containment failure must be considered and that more scrutiny is needed when failure bears higher risks, and participants suggested that setting standards may not be appropriate at this time.[130] Discussing testing safeguard effectiveness, "Participants argued that one needs to know where the test is being applied, how the organism will be used, production volumes, and implications of escape before we know how safe is safe enough." Other participants, however, argued that "While it is not just one size fits all, for each application the nature of the hazard could be identified and thresholds determined."[131]

At another point, drawing from experience assessing submissions, a regulatory official suggested, "It's difficult to make assumptions, as it is often on a case-by-case basis. Each [genetic] construct will introduce questions that others may not." Other participants, including regulatory officials, argued that evaluating each genetic component separately does not scale up practically, asking what knowledge is needed in order to standardize some evaluation components or seeking a standard set of evaluation questions within which projects can be considered individually.[132] At another workshop, participants mentioned the limited resources available for research and risk assessment, and a participant stated, "From a regulatory perspective, the [agency] deals with companies and products on a case by case basis. There is no prescribed format for information required for approval. No checklist," then asked, "Should there be? What would this include?"[133]

In a number of instances workshop conveners expressed interest in identifying questions, tests, or other elements that could be standardized or generalized, while participants focused on the challenges to generalizability. At one workshop, when a convener suggested that the group discuss general areas to be examined and then narrow to specific examples, a regulatory official said that "This has been suggested before, but we really don't have the information to do it on a category basis," and another participant commented that "This is hard to think about without considering context."[134] At another point, a convener explained the basis for seeking safeguard standardization, suggesting it as a means for addressing both individual application concerns and the desire to streamline assessment:

> The concerns depend on the use of the organism, and the context, ... but reliance on chassis that have been orthogonalized would reduce the likelihood of gene transfer and improve safety irrespective of application. The effect on regulation would be that we could say we have a fixed review. Rather than making the determination for a specific organism with individualized testing, in general gene transfer would be reduced. By showing, testing, and standardizing, concerns would be addressed for whole classes of chassis that would not need to be taken case by case. That would be the dream on what this work might be able to do.[135]

Here too, however, participants had reservations, in this case regarding the potential for overprotection against risk. A participant stated that even if broadly reducing risk is theoretically desirable, at a practical level, "if the cases are those where risk is already far below a given threshold, it would be unfair to demand applying this kind of feature."[136]

Participants' perspectives regarding standardization desirability and feasibility aligned to a degree with their affiliations. Technology developers expressed interest in standards whereby they would know how their product needed to perform in order to achieve approval. For example, responding to a suggestion that teams be established to consider consequences and implications throughout a project, a technology developer commented that "'If you could show X, then it would be allowed' – that would be valuable."[137] Other participants expressed more hesitation regarding standards and emphasized the likely necessity of individual consideration, while a broad base of participants expressed concerns about regulatory review capacity and were interested in options for streamlining. Conveners expressed interest in exploring options for generalizing or standardizing some assessment components, while many participants appear to have been uncomfortable with pressure in this direction.

It appears that valid arguments exist both for attempting to standardize assessment elements and for exercising care against generalizing too extensively. It is likely that a range of decisions may be made regarding which testing or assessment elements may be standardized or should remain individual. Compared with narrow expert processes, diverse stakeholder processes bear increased potential for explicit deliberation about process decisions that might otherwise be assumed, potentially resulting in more careful decision-making and balance of competing valid considerations.

Remaining Uncertainty

Participants expressed perspectives regarding making decisions in the presence of uncertainty that remains in spite of testing.

A participant suggested that decisions can be made based on available information even without all the desired information. The participant, a regulatory official, stated that "We use information tools that will allow us to make do with the information resources we have."[138] Regulatory officials mentioned possible measures to limit risks in the absence of sufficient information,[139] though these measures may be flawed and limited in their applicability.[140]

At another workshop, participants discussed challenges of testing genetically engineered confinement strategies on sufficient scales to assure effectiveness at industrial-scale processing. A participant opined that

> We should not assume detection limits are a good basis for accepting a test. We may not be able to detect the level of safety that we need to put something in operation. If our testing ability is not yet sensitive enough for a sufficient safety level we should acknowledge that and think about improving but not having a useable technology at this point.[141]

These sentiments may reflect, and suggest present among participants, an overarching duality of perspectives regarding assessment limitations and decision-making under uncertainty: One perspective holds that once appropriate efforts have been made to obtain the desired information, the potentially risk-bearing activity could be undertaken even with insufficient information, with mitigation strategies employed as desired and available. In this perspective, a particular level of information is not imperative for approval, and the available information is thus taken as defining the boundaries of the inquiry, arguably substituting for a delineation of necessity. In the second perspective, the required level of information remains independent of information availability, and if available information does not meet the requirements, the activity is not undertaken. This duality is largely distinct from opinions about how much information is desired and from circumstances dictating whether a decision must be issued and within what timeframe, though statutory requirements related to approval criteria may affect the approach adopted in regulatory contexts.

This duality of perspectives is also evident in a discussion about the Glowing Plants project. A summary of participant questions includes:

> How will the impact of the bioluminescence from the plants on wild organisms be tracked across seed destinations? If this can't be tracked or known ahead of time, then how is the application ready for release?[142]

It appears that participants inquired about tracking impacts, and that while some participants, the Glowing Plant project members or others, felt that impossibility of tracking or prediction sufficed to permit release with neither, other participants felt that without appropriate tracking or prediction the organisms should not be released, even if release therefore does not occur.

It is unclear that one or the other perspective is always better, and intermediate approaches tuned to particular circumstances may exist. Many individuals may tend toward one perspective or the other, suggesting value in this duality and in others that may arise within diverse participant processes.

Decisions in Testing

While deliberating on test design, participants acknowledged that many decisions regarding test design are inherently subjective, and that they can systematically and sometimes predictably affect results.

In a discussion of how to design tests meant to predict organisms' behavior in receiving environments to be sufficiently realistic, sensitive, and controlled to reveal effects reliably, participants pointed out drawbacks to "trying to make things detectable, and have a sensitive assay to make the deleterious effect manifest." The participants linked test sensitivity to "trying to be conservative and precautionary," noting the politically charged nature of these terms.[143] They also pointed out that tests' being highly controlled, a design decision with benefits in effects detection as well as resources required, raises questions about their potential to predict effects in real receiving environments. A

participant explained the concern by commenting that "Many diseases require environmental messiness," drawing an analogy with lymphomas that do not manifest under lab conditions.[144]

In a discussion about test baselines and timescales, a topic that arose in several of the workshops, a participant pointed out, "This is highly subjective. It is different in the U.S. and the EU, for example,"[145] and participants mentioned that test duration can affect results regarding genetic stability and fitness. Participants noted that decisions about what elements to include in a trial "will affect the outcome, and you can game it if you know how to play to get the result you want."[146]

The observation that technical decisions about test design can be subjective and can affect study results and thus assessments suggests that diverse stakeholders should play a role throughout a research and assessment process, not just in later stages after information has been gathered. Workshop participants noted this value of broadly collaborative assessment work. In a discussion about model design, a participant pointed out that "A community model helps avoid issues of the model telling you what you want it to."[147]

Worldviews

Throughout the discussions, participants' statements reflected differences in worldviews or perspectives on overarching topics such as how risk or uncertainty should be approached or the rightful place of technology development in society. Many of the contributions did not directly contradict those reflecting other worldviews, but appear to reflect differences in emphasis. While in a number of instances the differences in underlying perspective appear directly to reflect the participants' affiliations, many participants contributed statements and perspectives not strictly aligning with the approaches typically associated with their affiliated groups.

Worldviews were not typically themselves central in the agendas or discussions. However, the differences in perspective can manifest practically within development of a research program or conduct of an environmental assessment.

Role of "Naturalness"

Throughout the workshops, participants pondered the relationship between engineered organisms and "natural" counterpart organisms or receiving environments. Even though participants often stated and appear largely to have agreed that the organism's actual behavior or environmental effects are the important characteristics, they repeatedly turned to comparisons with natural organisms or ecosystems in considering what triggers concern or is more likely or less likely to prove problematic. In one workshop, participants suggested that "The similarities of the GMO to the wild type are both good and bad. It's reassuring because the GMO is not that different from what already exists, but it's bad because this enables easy gene transfer."[148] In a discussion of recoding to prevent survival or gene flow, a few participants grappled with the suggestion, to them highly counter-intuitive, that increased artificiality could be used to reduce environmental

risk. Even though biofuels are produced using extensive synthetic inputs and artificial processing, one environmental organization member suggested that use of synthetic biology should be compared with other ways of making biofuels as "The equivalent of natural and organic vs. genetically engineered in this field,"[149] perhaps employing comparisons with other questions of naturalness and artificiality as a heuristic to consider the problem at hand. In discussing the potential for microbes to persist in dormant states, a participant wondered, "On a moral plane, do we object to the idea that something we've modified or 'created' may persist for a million years even if it is relatively innocuous?" suggesting that considerations of naturalness may underpin some concerns not explicitly treated in the discussion.

Some technology developers expressed discomfort with their work's being regarded as unnatural and with emphasis on the distinction. Citing research on extremophilic algae acquiring genes from bacteria and archaea through horizontal gene transfer, the researchers asked whether the transfer's having already occurred in nature makes their work "natural," and commented that "We're really more catalysts," engineering genetic events that could eventually occur unassisted.[150]

Some participants also invoked comparison with nature to suggest instances in which concern may be unwarranted. Technology developers and possibly other participants suggested that genes already prevalent or likely to occur in nature or similar to naturally occurring genes, or transfer events that "would have occurred anyway in nature" might not arouse concern or require further study.[151] Participants also suggested that some dangerous genes that already "exist in nature," such as some antibiotic resistance genes, might be acceptable for release and exemptible from regulation.[152] A participant proposed creating a "threshold of exoticism" to streamline review by differentiating between genes sufficiently prevalent that "we can assume they have been thoroughly sampled throughout evolution" and genes sufficiently rare "that we cannot be confident of how they will react in nature."[153] A participant suggested novelty as a rule of thumb for identifying the potential for risk: "What is the phylogenetic novelty of the function? That is to me the unknown risk. It may still be benign, but it's unknown. In contrast, if it's been out there in evolution it may be less of a risk."[154] Other participants disputed these suggestions, for example noting that scale of adding a gene to a receiving ecosystem affects risk and that the gene's product or the organism's behavior must be considered.[155]

Participants, including some regulatory officials, also realized that current regulatory structures incorporate views on the significance of naturalness and artificiality that may conflict with participants' own views and with views that they feel represent best governance based on where the science has gone or is heading. For example, discussing recoding efforts, participants observed that the increased artificiality would likely trigger more regulatory concern than organisms more minimally altered but without safeguards. Participants also noted that in some policies only interspecific or intergeneric transfer is subject to review due to perceptions of what could occur in nature or what is viewed as a "new" substance, even if these distinctions do not reflect the science.[156]

Uncertainty and Risk Pathways

Throughout the workshops, participants articulated sharply contrasting views regarding the nature of uncertainty and how to consider uncertainty and risk. Predominantly, members of environmental organizations and an ecologist expressed concerns with adverse effects that could not be anticipated or addressed through testing, while technology developers and perhaps industry members emphasized the point that survival and gene flow, called out for study or prevention due to prominence in risk pathways, are not themselves harmful and that the effects must be investigated.

In a discussion of research needs and protocols, an environmental organization member stated his perspective that many harms likely cannot be anticipated altogether, implicitly questioning the value of designing detailed research frameworks under those circumstances, or of focusing on identified unknowns while ignoring the existence of looming unanticipated potential harms. In a discussion of risks of introducing recoded genetic material, another environmental organization member mentioned that "Nature has gone in a particular way, but now we're raising supposedly first principles to simplify that. The big concern is that we really don't know."[157]

Discussing the need to consider an engineered organism's means of confinement, an ecologist suggested that an engineered organism in a receiving environment may be able to "evolve to persist even if we don't think it could."[158] This ecologist advocated for the pursuit of a robust research agenda regarding ecological risk, but still cautioned regarding limits of researchers' abilities to predict harms and regarding risks that cannot be addressed fully by conducting research. The ecologist also suggested that while confinement must be considered, "Any time you need confinement, it means you have doubts about safety, so maybe you should reconsider,"[159] a position further challenging the view that concerns can be fully addressed through testing.

Other participants, primarily technology developers and industry members, emphasized the point that horizontal gene transfer and survival in a receiving environment are not in themselves harmful, and expressed the perspective that it is most important to identify the consequences of these events in order to predict harm and dictate preventive measures. Participants asked such questions, apparently somewhat rhetorical, as "What is the actual problem with gene transfer?"[160] "What's the problem with persistence in the environment?"[161] and "What is the scientific concern about more DNA in the environment?"[162] They argued that because these events are not always harmful, it is necessary to determine the consequences of transfer or survival and differentiate among the consequences in considering risk.[163] One participant stated that "There is an implicit assumption that gene flow is negative, so it is actually valuable to frame the discussion in the context of how much do we know about the potential for deleterious effects."[164]

While these two perspectives do not directly contradict one another, they represent different views of risk. In the first perspective, key risk pathway components, such as escape, survival, and gene flow should themselves be avoided because fully predicting their consequences may be impossible. Occurrences that may not prove harmful still

warrant action due to challenges in prediction. This perspective may also incorporate concern that adverse events could long go undetected and could be irreversible. The second perspective lends substantially less gravity to risk pathway events that are not themselves harmful, instead emphasizing the need to determine what harm if any will result before deciding whether or to what degree to prevent the events. The first perspective may be aligned with the Precautionary Principle, advocating that when serious harm could reasonably result, cost-considerate action to prevent it should not require definitive proof of present or future harm,[165] while the second may reflect an alternative to the Precautionary Principle, sometimes referred to as "proof before action." Both perspectives contain strong elements of pragmatism: The first perspective acknowledges the difficulty in predicting adverse events and the likely irreversibility of harm, while the second acknowledges the burden of adopting measures to prevent categories of events, particularly the possibility that sufficient prevention could be achievable only through not advancing the technology.

Differences of opinion regarding underlying principles of risk, assessment, or decision-making appear to have manifested themselves to some degree even though the workshop agendas included no explicit discussion of these or other such areas.

Responsibility for Technology

Even though the discussion agendas did not include questions about the role of new technologies in society or the location of responsibility for outcomes, participants' perspectives in these areas occasionally surfaced. In a discussion of testing needs, one participant opined that "It's not just the demands on developers, but vice versa. They have a right to place demands back on the systems. You can't measure everything."[166] It appears that for this participant, technology developers have a right to develop their technology with reasonably minimal interference from parties desiring testing for safety or environmental effects, and developers have as much right to demand avoidance of burdensome testing, or perhaps to require clear and limited testing requirements, as others have to require tests. In other perspectives, technology developers or would-be deployers are seeking to impose their developments on the socio-ecological system and they have no inherent right to demand minimal or defined requirements to ensure that their technologies will not cause substantial harm.

At another workshop, a lawyer affiliated with an environmental organization suggested beginning with a strict liability standard, which refers to liability in case of harm regardless of intent or care, for harm from engineered organisms. The participant suggested that after beginning conceptually with this standard, one could then consider whether there may be circumstances to which strict liability should not apply, for example in association with contained systems.[167] Though not strictly conflicting, this view, suggesting that developers or deployers of an engineered organism are engaging in potentially hazardous behavior and arguably imposing their hazardous decision on the socio-ecological environment, contrasts sharply with the view that developers have a right to place demands on those who would require testing.

At both of these workshops, the points that these respective participants made were not pursued within the discussion. Conveners wished to focus on research needs and testing approaches as areas in which practical agreement could perhaps be reached even when disagreement persisted in such areas as the roles and responsibilities of technology and technology developers. Even though these points were not pursued, they indicate differences in underlying attitudes that could well emerge implicitly within discussions of testing needs and standards, needs for further research, or who should design, fund, conduct, or evaluate studies.

Insights into Participant Contributions

Participant contributions include sharing knowledge of the ecological and industrial systems that can be valuable for assessment. Participants contributed based on diverse conceptual models of the eco-industrial systems and the role of assessment, and based on distinctive values and priorities. They also contributed information and resources that may enable knowledge available to an assessment or research program to keep pace with needs generated by technological advance. In addition, participants challenged environmental assessment structures, questioning procedures and seeking to expand considerations beyond standard assessment boundaries. While participants' knowledge and perspectives often aligned with what might be expected based on affiliation, participants also crossed standard affiliation lines to explore problems together.

Process Observations

The PoET-Wilson workshops provide insight into strengths, challenges, and successful approaches in involving diverse stakeholders in assessment.

Access

Enabling individuals of diverse backgrounds, including individuals with limited technical knowledge of biological engineering or advanced biological concepts, to participate in the discussions required substantial effort, and may have remained a challenge. However, some of the efforts that appear to be oriented toward enabling broad participation would likely be needed even for participants of more uniform and technical knowledge, suggesting the possibility of a smaller added burden to enable broad participation than might be assumed.

Efforts to Provide Background

In advance of each workshop, conveners circulated preparatory reading materials to participants. These materials included background information about the prompting cases, and could also include information about workshop goals, risk assessment approaches to be employed, biological concepts likely relevant to the discussion, or results from previous workshops. For some workshops, published scientific papers provided the technical background on prompting cases or biological concepts; for others, convener staff members wrote literature reviews, paper summaries, or concept explanations; and for others, both were included.

Workshop sessions began with presentations. Typically, technology developers or company members working on the prompting case technologies presented their work. At a few sessions, conveners, ecologists, or regulatory officials presented assessment frameworks to be employed for the session, biological concepts, or existing regulatory frameworks, respectively.

Diverse and Narrow Participant Needs

Some of the background provided was distinctive to diverse groups, while other background would likely have been needed for any assessors. The nature of the process may also affect the needs for background information. For any assessment process, assessors require information about the application under consideration, and may require papers or other materials to become familiar with the technology or application. Whether presentations are arranged could depend on the assessment context. However, the need for explanations of biological concepts or paper summaries was likely distinctive to groups including individuals lacking technical background, and producing these materials required more convener effort than did assembling published papers.

Workshops employing unusual risk assessment methodologies, considering regulatory frameworks, or using other special models would likely require briefing in these approaches even for many narrow expert groups. Narrow expert assessments typically do not take place in an experimental workshop format. The assessors are likely familiar with the assessment methods they employ and any regulatory frameworks they are charged with upholding. Narrow expert processes' typically not requiring this additional briefing may therefore be in part an artifact of process differences rather than due strictly to the participant diversity.

Successes and Challenges in Access

Conveners learned over the course of the workshops about providing suitable background for participant access. For example, the second workshop's preparatory materials included a description of the workshop purpose, background on an assessment approach to be employed, and technical background on the prompting biotechnology and industry. At the workshop, in addition to the biotechnology presentation, an ecologist introduced gene flow. During the discussion, when the facilitator asked participants from an environmental organization whether they had anything to add, a participant responded that he did not feel he understood the scientific concepts, such as survivability, gene flow, and genetic stability, well enough to contribute.[168] The next workshop's preparatory materials included detailed introductions and literature reviews, written for non-technical readers, on these concepts.

Requests for clarification during the sessions were few, though they did occur.[169] It is difficult to be certain as to whether participants' not requesting clarification was due to their understanding or to their not wanting to interrupt to ask for background. At the start of one workshop, conveners reminded participants to be careful to use language clear to people outside their own fields of expertise.[170] This workshop was one in which

participants were largely individuals with scientific backgrounds but from disparate fields; conveners have noted participants' learning to dialogue with individuals from different scientific fields, not just engagement of individuals without technical background, as an important challenge and contribution of diverse participant exercises.[171]

Despite conveners' efforts to enable broad access, some discussions still consisted largely of participants possessing technical backgrounds, at times primarily technology developers and industry members, discussing scientific or technical details.[172] While full engagement of diverse participants may remain a challenge, the opportunity for biotechnology researchers from disparate fields or for other technically-trained individuals, who may not otherwise discuss risks together, to do so may be a strength of multi-stakeholder workshops. In the OPPT tier testing workshop, industry members and those with regulatory, ecological, or risk assessment experience were mixed in the work groups. The diverse participants may have helped one another to develop tier testing schemes, or the testing scheme details could have been crafted primarily by those with backgrounds most conducive to this task while other participants contributed based on their areas of knowledge. Specialized contribution based on distinctive expertise can be a strength, while maintaining access to the discussion content should be prioritized as well. Convener awareness of the level of access may be important for encouraging diverse participants' desired contributions.

Participant continuity may also play a role in access. Environmental organization members displayed and reported particular familiarity with technical concepts related to problems on which they had worked.[173] In addition, the ability to request background information enabled non-technical participants to receive the information they needed and utilize it at the next workshop.

Tasks and Structure

The workshops were carefully structured to obtain useful information and encourage participation while minimizing the potential for conflict. The workshop tasks and structure, including the level of flexibility in discussion topics and the use of prompting cases, experienced both benefits and challenges.

Task Specificity and Technicality

The workshop tasks were specific and technically focused, such as asking participants to construct event sequences that could lead to adverse outcomes, identify testing needs to predict ecological effects, or identify methodological or instrumentation challenges to testing. The workshops were also fairly tightly facilitated; a single facilitator led the group in discussion, with little or no opportunity for small group discussions or independent work. The facilitator typically identified beneficial topics and guided the conversation while also benefitting from participants' mentioning topics, by choosing when to permit wandering discussion and asking questions to pursue particular points.

The focus on technical tasks, in contrast, for example, with discussions explicitly concerning risk acceptance or the importance of caution, can yield information more readily applicable to assessment or testing schemes or application design. This approach can also serve to prevent some conflict. Tight facilitation can also encourage production of immediately useable results and reduce conflict. The tasks and facilitation may also reduce the space for expression or pursuit of broadly diverging perspectives. In a workshop focused on developing a research agenda for predicting or monitoring ecological effects, a participant diverged from the detailed technical discussion, suddenly listing several historical examples of new technologies' having ill effects that were not anticipated until substantial damage had occurred, and expressing doubt that any research agenda could capture all effects of concern. The participant appeared to harbor reservations about the workshop's overall premise, but the workshop structure did not enable full consideration of these concerns. The facilitator did not view the comment as helpful,[174] and immediately returned to the prior discussion. These perspectives represent real concerns and a potentially valuable type of stakeholder contribution, and discouraging these diverging discussions arguably circumscribes contribution and can make the discussion a less genuine reflection of participant perspectives. On the other hand, these broadly diverging perspectives can entirely shift a discussion and prevent pursuit of a valuable workshop agenda. Conveners must determine how strictly to pursue a particular agenda and to what extent to enable discussion of broadly diverging perspectives.

The workshops' focus on identifying knowledge gaps rather than engaging in later stages of assessment or decision-making may also serve to reduce conflict, enabling participants with diverse perspectives on risk acceptance or use of test results to find areas of agreement. Diverse participation may be valuable at later assessment stages as well, and these possibilities should be explored. PoET-Wilson workshop conveners hypothesize that processes including later or more controversial assessment components may benefit from beginning with less controversial questions like research needs to enable participants to develop relationships around areas of convergence.

Encouraging Participation

The conveners and facilitators utilized a number of approaches that may be valuable tools for encouraging candid participation.

Participants were asked to contribute based on their own personal perspectives rather than asked to represent a group, even while comments could be solicited to provide insight into what members of a participant's affiliated group might think. The facilitator used such phrasing as, "[Participants' names], what do you worry about when you hear this?" or "[Participants' names], what would you like to know more about?" In one workshop, the facilitator asked a regulatory official to describe an engineered organism that she would not like to see submitted due to its potential for environmental effects, and in subsequent discussion the facilitator nicknamed the invention "Gwen's monster" after the official. At another, the facilitator recounted a discussion from a previous workshop, stating, "Then Steve, not speaking as [company name], but just speaking as Steve, said ...

." Focusing on individuals and their own perspectives can reduce participants' concern for ensuring that their comments conform to their affiliated group's official or typical positions. This approach may encourage candid contribution, encourage participants to contribute based on their own knowledge and experiences that could extend beyond a current affiliation, and can enable participants to explore the merit of different perspectives and find common ground with participants from typically opposed groups.

Inquiring with individual participants, at times designating their affiliations, as to their perspectives also implied value in the contributions both for the technical content and for the information about what might concern a particular group, in effect reducing or erasing the distinction between the two. Thus, determining the value or validity of a particular concern or testing specification became secondary, as a particular person's voicing the matter served in itself as reason to regard it, an approach that elegantly broadens the view of desirable testing and assessment approaches beyond what a narrow expert group of scientists or risk assessors might prescribe while also creating an atmosphere conducive to participation.

The continuity among some participants across workshops may have enabled development of relationships that could have reduced hesitation to contribute. Similarly, the facilitator and other conveners developed or previously had personal relationships with many of the participants, and this familiarity could also have contributed to a relaxed atmosphere conducive to open discussion.

Conduct of the workshops under the Chatham House Rule requiring that statements be conveyed further only anonymously[175] was also meant to encourage candid participation. The extent to which these approaches contributed to candidness and to what extent participants may in fact have curtailed openness is unclear, but some level of candidness appears evident. For example, industry members spoke more candidly about their business considerations and particularly concerns about public relations than might be expected in a more public setting, and an environmental organization member working on biotechnology in his organization communicated that he did not feel he knew enough about some scientific concepts to evaluate other participants' statements and contribute to the discussion.

Prompting Cases and Concreteness

Workshop conveners utilized prompting cases to ground the discussion, while they also sought to generalize to hazards and research needs for synthetic biology applications more broadly.[176] Conveners chose cases that were sufficiently advanced in development or commercialization efforts for many technical details to be known, while sufficiently early that details remained open and feedback could contribute to the technological or application design. They also selected applications that might raise interesting considerations while many concerns would likely apply broadly.[177] The workshops overall included substantial discussion of details and considerations of the particular applications, including advice to developers, while they also generalized to hazards and particularly research needs for expected-release synthetic biology applications in general.

The prompting cases also served as a concrete handle whereby participants could identify and explore their perspectives. For example, when participants expressed differing perspectives regarding whether a particular prompting technology represents a "paradigm shift," they discussed the characteristics that they viewed as fundamentally similar to or different from existing technologies and as presenting or not presenting new concerns.[178]

Some participants felt that attaining sufficient specificity was difficult even with the prompting cases. Throughout the workshops, participants struggled with the difficulty of discussing considerations for technologies without more details about the intended applications. Participants, particularly environmental organization members, also expressed frustration with the divide between the workshops, identifying concerns and research needs, and assessments for applications actually undergoing decision-making processes for commercialization, but without meaningful diverse input. An environmental organization member complained that

> What we've talked about are generalizations and we have to realize that when we look at a specific organism it's very context-dependent. But although we may be getting better at getting a lot of parties in the room to talk about generalities there are not a lot of opportunities for other people to get a comment in, i.e. Federal Comment might come much later on [in a product development and approval process]. It would be good if there were a mechanism by which other concerned parties could be involved more and earlier on specifics instead of on generalities, which only gets us so far.[179]

The workshops obtained useful information and served as a proof-of-concept for diverse contribution to environmental assessment, and the use of prompting cases appears to have aided their doing so. Still, the lack of full application details as well as the workshops' limitations in real influence on decision-making appear to have bothered some participants.

Other participants expressed dissatisfaction with the level of concreteness as well, arguing that broader consideration of what system components are valued or what effects are to be avoided is needed before discussion of testing details. A participant complained that

> I'm perturbed by the structure of this portion of the agenda. It reminds me of grad students deciding on a dissertation topic. These are good questions, but there's no overarching framework. Are these the right questions? How do they fit together? ... someone who knows enough needs to make an intellectual framework from which will emerge an idea of which questions are most important and why. Only then do you want to go to measurement questions. We've bought into this at the wrong level.[180]

Participants further expressed the need for broader consideration:

> Which endpoints do we go after? Because we have limited resources. It's a strong value judgment: what do we care about protecting? ... You can put together something like a comprehensive environmental assessment framework to think about whether you have looked at the ethical, social, legal implications over the whole life cycle of your work. ... You can impose a lot more [analytical] structure to figure out what endpoints you care about and what society values.[181]

A participant outlined a discussion framework to focus in detail on particular organisms and applications while addressing questions of overall concerns and values:

> My desire for a next level of analysis would be to sit down and characterize two to three organisms really well, and then take them through the process from escape to bad things happening and possible endpoints. Figure out which organisms and endpoints you don't want. It would be a multi-stakeholder conversation. There are rigorous ways to drill down to identify specific endpoints, instead of vague statements like "we care about enhanced fitness." There are methods to do this work and we haven't used them.[182]

The facilitator addressed these concerns by focusing on areas of agreement about undesirable outcomes, such as toxicity and pathogenicity and "significant disruption of the composition of natural populations,"[183] mentioning that these areas of convergence could enable discussion of specific characteristics such as fitness, gene transfer, and stability. The facilitator also argued that participants may not agree on specifics of organisms or risk pathways, and that instead identifying information needed to perform such an assessment might result in more areas of agreement.

Dispute and Agreement

Participants appeared willing to engage with disagreement, though participants and facilitators also sought areas of convergence and avoided extended conflict. Participants identified areas of agreement that may be more challenging to find outside of multi-stakeholder workshop settings, suggesting that multi-stakeholder processes could enable typically opposed parties to find and act upon common ground.

Dispute and Conflict Avoidance

In several instances, participants voiced direct disagreement in areas in which the disagreement represented conflicting approaches or positions rather than merely correction of scientific facts. Participants and the facilitator also appear to have sought to avoid conflict. When participants identified a type of site as favorable for locating a production facility, a member of an environmental organization, asked whether he liked that site, responded, "Probably not. Ideally, it would be contained. If you can't do it contained, we would not be okay with it, and we would probably fight you along the way."[184] The participant also stated that existing testing and regulation are insufficient and that tests must be made public rather than permitted to remain Confidential Business Information. Other participants pushed back, arguing that testing is in fact made public. Participants also quickly sought areas of agreement, stating, "I think there's common ground there. We're all looking for a set of data and a process for determining safety."[185] In another instance, two participants reached a point of direct disagreement regarding the appropriate level of concern about a potential hazard. The facilitator halted the discussion by asking the participants whether the matter was "at least something that it would be good to learn more about." Though the participants did not appear satisfied, they expressed some agreement and acquiesced to the determination.

Conflict avoidance can be beneficial for pursuing a workshop agenda in a timely fashion as well as for building positive relationships among participants. It may also encourage

open participation, as in their study on social learning in Dana *et al.*'s workshops, Dana and Nelson found that some participants limited their participation due to "unfavourable attitudes by other participants."[186] However, dispute avoidance can also result in participants' not fully expressing their perspectives, and may therefore limit contribution and insights that could be gained. Furthermore, discussing points of disagreement may be necessary to enable further work together on concrete decisions, if desired.

Areas of Agreement

Diverse participants voiced perspectives diverging from what might be regarded as typical for members of their affiliated groups. They also identified areas of agreement with participants from differing backgrounds. For example, environmental organization members, whose affiliated groups might typically be associated with attempting to block all biotechnology applications, discussed the complexities of biotechnologies and applications, and stated the need for research to enable better prediction of effects. Biotechnology industry members, whose affiliated groups might typically be associated with disinterest in testing or environmental assessment and avoidance of discussing risks, also expressed the need for better methodologies and more data to predict environmental effects. Participants from these typically opposed groups recognized their agreements. For example, when an industry member stated that groups independent of industry should fund and conduct the research because "No one would believe our research on environmental effects," an environmental organization member agreed genially that "You're right. We wouldn't believe the results if you did the tests."[187]

Participants' willingness to recognize areas of agreement and work together to identify research needs and testing considerations stands in contrast with many public occurrences. For example, the Sierra Club, an established environmental organization, has adopted a Biotechnology Policy describing the organization's stance toward biotechnology development, particularly release applications.[188] The policy aligns with PoET-Wilson workshop findings in a number of key respects. For example, several areas in which a broad array of participants indicated a need for further research, and in which industry members indicated a desire for better testing methods, align with areas in which the Sierra Club's policy calls for research in assessing an application, such as considering an organism's ecological role, the potential for gene flow, and effects of unintended or non-focal changes such as addition of antibiotic resistance genes. Other concerns expressed in the policy, such as the need for confined testing and careful controls to prevent premature releases, the need for public disclosure of testing, the importance of considering the release site in evaluating an application, the need to consider both short-term and long-term effects, and the need for post-release monitoring "through coordinated efforts of agencies, companies, and academic institutions in order to test predictions about the organisms' behavior, numbers, dispersal and environmental impact,"[189] also align with considerations raised by participants from a range of backgrounds. Despite these areas of overlap, biotechnology companies, environmental organizations like the Sierra Club, and other interested parties such as academic researchers developing biotechnologies, are engaged in little if any collaborative work to advance these apparent common interests. Environmental organizations are largely

viewed as opposing all biotechnology applications, industry is largely viewed as opposing all consideration of risk, neither is viewed as harboring interest in research to predict effects, and dialogue is largely absent. These observations suggest that multi-stakeholder processes hold the potential to enable typically opposed groups to identify areas of common ground and grounds for collaboration.

Challenges and Opportunities in Finding Common Ground

Despite the workshops' promise in enabling participants to identify areas of agreement and common goals, challenges in finding and acting on common ground remain. For example, agreeing that additional research would be beneficial, particularly in a workshop centered on identifying research needs, may be much easier than agreeing what studies are needed or sufficient when time and other resources are limited. Agreement regarding how to interpret study results to make decisions about biotechnology applications would likely pose additional challenges. Identifying areas of agreement in a workshop with protected anonymity may also be easier than collaborating with typically opposed groups, or diverging from one's own group's typical stances, in the more public settings in which decision-making processes are likely to occur.

Agreement among workshop participants, as well as between workshop findings and the Sierra Club's Biotechnology Policy, suggests that even if a multi-stakeholder workshop does not produce agreement on points of fundamental disagreement, the setting enables participants to identify common ground where it exists, perhaps more readily than in other settings. The findings also suggest that these common areas exist to be discovered. The workshops were designed to begin by discussing areas predicted to hold the most common ground in order to build relationships, a groundwork of agreement and collaboration, and a commonly-agreed-upon basis for proceeding with research, on the premise that this groundwork would facilitate subsequent efforts in more challenging areas. A report on two of the workshops explained that

> The project achieved two important outcomes. First, it strengthened the nascent, on-going collaboration between synthetic biology researchers and a wide range of evolutionary biologists, ecologists, and environmental scientists, ... Second, the project developed the beginnings of a research agenda for the ecological implications of synthetic biology ... with general agreement and support for the research from key stakeholder groups.[190]

Further work should test this design premise and advance these aims by advancing multi-stakeholder processes into further assessment stages, such as study design, interpretation, and decision-making, as well as incorporation of other areas that participants identified as important, such as philosophical and societal implications.

Continuity

Continuity over the workshop series appears to have benefitted workshop content and output by benefitting both participants' contribution and workshop design. The series may also have experienced some redundancy across sessions, which could present benefits but may also suggest missed potential for developing content.

Continuity for Participants

Each workshop included both new and continuing participants. Participant overlap across workshops appears to have benefitted participants' contributing and added to the workshop content. Participants lacking technical background had the opportunity to develop knowledge over multiple workshops, both through requesting additional background materials that were provided for the following workshop and through the discussions themselves. Participants also built on previous workshops' content in contributing; for example, developers of a technology used as a prompting case in both the second and third workshops brought to the third workshop more detailed responses to questions that had been raised at the second workshop.[191] In the fourth workshop, a participant suggested using an environmental assessment approach that conveners had piloted in the second workshop.[192]

Partial turnover may also present challenges. Findings from previous sessions as well as scientific information shared earlier must be conveyed to new participants sufficiently to enable full participation, particularly when participants benefit from developing scientific knowledge across sessions. Partial turnover could also result in returning participants' behaving to an extent as a social group, causing new participants to hesitate in contributing. At one workshop, several participants mentioned in their self-introductions that they had participated in previous workshops. Between sessions later, a new participant privately stated that he had not participated in any previous workshops and was therefore just watching to learn what was going on.

Continuity for Workshop Design

Continuity across workshops enabled conveners to build the approach and workshop details.

Ideas raised were further developed in subsequent workshops. For example, in the second and third workshops, participants mentioned challenges of instrumentation and metrology.[193] The fourth workshop included a member of a company specializing in instrumentation and measurement technologies, and both the fourth and fifth workshops' agendas included discussion of instrumentation and metrology needs. In the fourth workshop, a participant commented that "We don't have the right expertise in the room, and should bring in some evolutionary biologists, possibly for a separate exercise."[194] The next workshop included more participants with technical expertise, including in evolutionary biology. Diverse participation does not guarantee that all relevant parties or expertise are included, and holding multiple sessions can enable identification and gathering of desired participants or other resources.

Observing workshop results and external outcomes enabled conveners to tune subsequent workshops' goals. For example, when workshops effectively identified knowledge gaps and pointed to a need for a government-funded research program, sponsors expressed interest in work developing details of such a program, spurring a pair of workshops with more technically-trained participants to develop a more detailed research agenda. When the detailed agenda did not draw funder interest, instead of pursuing design of a still more

detailed research program along similar lines, conveners surmised that discerning risk may have lacked funder support and shifted the next workshop instead toward demonstration of safeguards to reduce risk.[195]

Redundancy

While each workshop included new considerations and information, substantial redundancy occurred among discussions in several of the workshops, particularly though not exclusively the first four. For example, participants repeatedly discussed challenges in determining elements to measure when testing fitness; the question of whether fitness incorporates considerations beyond whether or not an organism survives, such as relative ability to exploit resources; detection challenges in studying gene flow; the problem of how long a test for gene flow or survival should run; the potential for high-throughput sequencing technologies to aid in studies; the need to determine the ecological effects of gene flow or survival rather than just whether or not it occurs and the question of whether transfer or survival occurring should in itself be regarded as harm; the point that a level of absolutely no gene flow is unattainable; the need for well-designed micro- and meso-cosms; challenges of identifying unexpected phenotypic changes; and questions of whether general tests or criteria could be developed and how to address the complexity of each distinctive application. In these areas and others discussed repeatedly, participants did not make substantial progress in developing answers to the questions or in designing studies accounting for the difficulties.

Redundancy may be undesirable in some respects, but it may also be expected and acceptable. Some redundancy among conversations in ongoing periodic discussions may be unavoidable. In addition, covering particular topics multiple times, particularly areas of agreement, may aid participants in becoming oriented to new tasks or may help build rapport. In response to participant reservations about workshop structure, conveners commented, "The good news is ... every time there's overlap. We hear the same things and we move further forward. ... If there wasn't overlap I'd be worried. We reinforce main points and break new ground every time."[196] However, excessive redundancy can indicate that the conversations are not moving forward as rapidly or accomplishing as much as they could. Substantial redundancy could also cause participants to feel that their time is not being well spent. At one workshop, several participants complained about the lack of an overarching intellectual framework for the agenda or the use of established tools that could aid in organizing and moving forward the discussion.[197]

Several factors could have contributed to redundancy across workshops, and identifying these contributors may suggest ways to reduce redundancy and increase workshop progress. The overall workshop structures and events between workshops may have contributed to redundancy. The time-lag between workshops, which ranged from five to seventeen months and averaged about 10.5 months, as well as the incomplete overlap of participants, may have contributed. Little interaction among participants or between participants and conveners occurred between workshops; the circulation of draft and then final workshop notes may have been the only interaction between workshops. In addition, preparatory materials consisted largely of briefing on prompting cases or scientific

concepts; only two of the workshops' preparatory materials included very brief summaries of key outcomes from previous discussions. More extensive written summaries or presentations recalling previous workshops could have aided both returning and new participants in being aware of progress and moving the discussion forward.

In addition, few external events that might advance the discussion occurred between workshops. While new technologies were developed that were used to spur discussion, no substantive changes in areas that the workshops addressed, such as development of new ecological or risk information or testing capabilities, protocols, or standards, or regulatory frameworks, appear to have taken place over the course of the workshops. While these factors were beyond the control of workshop conveners, processes in which the multi-stakeholder workshops result in commission of research studies or in which participants are asked to investigate existing information or approaches and bring results to the subsequent discussion could see more development across sessions.

The agendas and discussion styles may also have played a role. While the agenda discussion questions were specific, they may also have left substantial room for overlap, particularly among the first four workshops. For example, the first workshop agenda included:

- What risks are associated with this early application of synthetic biology? How might risks be tested, reduced through redesign?
- Of issues not resolved in morning sessions, which disagreements on assessments of risks, design of tests, and redesign of devices are rooted in questions of values? Which disagreements are grounded in uncertainty over specific empirical issues? How might these issues be addressed?

The second workshop agenda included:

- What kind of effects might be important to investigate and at what organizational level?
- What external factors might influence the potential effects of [the organism]?
- What kinds of research questions would be important to answering [the above two questions]?

The third workshop agenda included:

- What is known about potential environmental risks of synthetic biology in general?
- What is known about potential environmental risks of our specific test objects? What additional work on potential risks of these applications needs to be done?

The fourth workshop agenda, which listed topics rather than posing questions, included under the heading "Identification of Ecological Endpoints to be Assessed":

- Defining endpoints within [identified receiving] environments
- Defining immediate vs. long-term data needs to assess endpoints

Multiple workshop agendas also asked participants to focus on fitness or survival, horizontal gene transfer, and genetic stability or evolvability in considering effects and research needs. Other questions in each of the agendas included overlap as well as more distinct areas. While each of these sets of questions was distinct and the discussions provided new information, they also allowed substantial space for overlap and re-

"discovery" of considerations articulated previously, particularly when generalizing from discussion of each workshop's prompting cases.

While the facilitation encouraged participants to move among topics to cover broad ground, the free-flowing discussion style may have hindered moving rapidly forward from points previously covered, particularly as steering away from participants' concerns or observations can negatively effect discussion. Participants' immediate awareness of previous discussions, as workshop summaries may have facilitated, could have aided in this area. In addition, broad workshop goals of developing an understanding of important factors to consider in assessment, areas in which more research is needed, and approaches to testing, as well as the use of different prompting cases across workshops, may have enabled overlap in a context of free-flowing discussion, in contrast with a process working toward producing an environmental assessment, written testing protocols, or a decision regarding a particular application, in which the objective itself may have provided more structure to ensure forward-moving discussion.

Insights from the PoET-Wilson Workshops

Examination of the PoET-Wilson workshops provides insights regarding how multi-stakeholder involvement can contribute to environmental assessment efforts, as well as practical considerations and practices for diverse-participant workshops.

In agreement with Dana *et al.*'s findings, participants contributed substantial information about the ecological, industrial, and technological systems, identifying hazards as well as pointing out considerations unlikely to represent hazards. They identified system aspects that could challenge assessment and drew from their distinctive knowledge-bases to discuss existing information and resources that could contribute to or serve as models for assessment or testing efforts. Diverse participants also provided insights directly from their personal experiences, sharing information that a narrow expert group might not have accessed as readily. Participants' sharing insights about their affiliated groups' approaches to biotechnology and assessment provided additional assessment-relevant information.

Participants articulated a variety of approaches to such aspects of testing and assessment as use of comparators, generalizability of results, and handling of uncertainty, and they revealed diverse underlying views in such areas as naturalness, uncertainty, and responsibility for technology. These disparate perspectives reflected diverse knowledge-bases, conceptual models, and values that should contribute to assessment. Participants also identified specific testing needs that could improve an assessment's scientific quality as well as its usefulness for decision-making. Participants shared insights beyond the environmental assessment agenda. Diverse participants' urging inclusion of broader philosophical, societal, and procedural considerations revealed interest in looking beyond standard environmental assessment boundaries and approaches. Throughout the workshops, participants contributed their own insights and also developed contributions through the diverse group conversation. Supporting the four hypothesized sources of stakeholder contribution, diverse participants contributed system knowledge as well as

information and resources that can enable available knowledge to keep pace with assessment needs, and they contributed based on diverse conceptual models and values.

Practical insights regarding multi-stakeholder processes emerge from the PoET-Wilson workshops. As other processes have indicated, substantial effort is needed to provide all participants, particularly those with non-technical knowledge-bases, with sufficient background to participate comfortably, though some background effort is likely needed for any assessment process. The workshops' tasks and structure, such as pursuit of specific and technically-oriented goals, use of concrete prompting cases, and facilitation-based as well as structural approaches to encouraging participation, appear to have experienced successes. The workshops suggest potential for multi-stakeholder processes to enable disparate groups to find common ground. The six-workshop series also reveals benefits of process continuity. Though challenges remain in each of these areas, the PoET-Wilson workshops provide practical insights and a working model for multi-stakeholder involvement in biotechnology assessment.

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Chapter 5

Salmon Environmental Assessment and Input

Examining an agency environmental assessment developed within regulatory review, as well as diverse stakeholder inputs and critiques, suggests insights into how stakeholders might contribute to assessment. The analysis considers differences in understanding regarding elements that the assessment should include, as well as other process aspects that could affect provision and incorporation of stakeholder input, particularly under existing governance.

Case Background

The first genetically engineered fish to receive United States regulatory review was the company AquaBounty's AquAdvantage Salmon, an Atlantic salmon engineered to grow more rapidly than the wild type. The Center for Veterinary Medicine (CVM) of the Food and Drug Administration (FDA) is regulating the fish. Due to regulation under the New Animal Drug provisions of the Federal Food, Drug, and Cosmetic Act, approval rested on determinations of the genetic alterations' safety and effectiveness. The Agency also produced an environmental assessment.[1] The present analysis focuses on the environmental assessment and on input and critiques pertaining to this assessment.

The review process included opportunities for public comment. Citizen groups also filed petitions with the Agency. The approval was controversial, and a group of organizations representing various stakeholders has filed a lawsuit objecting to the FDA's conclusions, including the environmental assessment findings.[2]

While they do not represent a participatory multi-stakeholder process, the public comments, petitions, and the legal complaint initiating the lawsuit[3] include detailed input into and critiques of the environmental assessment. These inputs could provide insight regarding information and perspectives that diverse stakeholders might contribute to an environmental assessment. The inputs and Agency responses also highlight the Agency's and inputting stakeholders' differences in understanding regarding elements that the assessment should include, providing insight into practical considerations for participatory processes, particularly as they relate to governance structures.

FDA Salmon Regulation and Environmental Assessment

While approval of the AquAdvantage Salmon application rested on determinations of the genetic construct's safety and effectiveness, statutes also called for assessment of environmental effects. The Agency determined that the conditions for approval were met, finding that the engineered construct was safe and effective. It also found that the approval would not significantly affect the environment. The process included opportunities for public comment, and a lawsuit initiated after the approval includes further stakeholder criticism.

Regulatory Context

The FDA is regulating the engineered salmon's added genetic construct as a new animal drug, and thus approval rested on a determination that the genetic alterations are safe for

the salmon and effective in their objective of growth enhancement, and that the engineered salmon are safe for human consumption.[4]

The Agency separately produced an Environmental Assessment under the National Environmental Policy Act of 1969 (NEPA). NEPA requires agencies to prepare an Environmental Impact Statement (EIS) for proposed "major Federal actions significantly affecting the quality of the human environment,"[5] assessing the action's environmental effects and evaluating alternatives. Under some circumstances, agencies may prepare a more limited Environmental Assessment (EA) to determine whether the action's environmental impacts warrant a full EIS.[6] Among other differences, while the EIS includes analysis of the action's social and economic effects as they relate to physical and environmental effects, the EA may require only a more strictly environmental assessment.[7] If the EA results in a Finding of No Significant Impact (FONSI), a full EIS is not required.

While NEPA is concerned with environmental effects within the United States, Executive Order 12114, "Environmental Effects Abroad of Major Federal Actions," requires that agencies "taking major Federal actions ... having significant effects on the environment outside the ... United States," specifically the "global commons outside the jurisdiction of any nation" and the environments of foreign nations not involved in the action, take environmental considerations into account in making decisions about the actions.[8] Actions that the agency has determined do not significantly affect these foreign environments are exempt from the Executive Order. The Executive Order does not address actions' effects on the environments of other countries participating in the action.

The Endangered Species Act requires Federal agencies to ensure, in consultation with the agencies administering the Act, that actions they undertake or authorize are not likely to jeopardize the existence of or damage a designated critical habitat of a listed threatened or endangered species.[9] According to the Environmental Assessment, the acting Agency, here the FDA, determines, typically through informal consultation with the administering Agencies, here the United States Fish and Wildlife Service (FWS) and the National Marine Fisheries Services (NMFS), whether the action "may affect" listed species or habitat. If the acting Agency determines that the action may have such effect, it may undertake a more formal consultation process.[10]

FDA Determinations

The FDA determined that the added genetic construct is safe for the fish and effective in its growth-enhancement objective and that the engineered fish are safe for human consumption, thus determining that the approval criteria were met.[11, 12]

The FDA completed an Environmental Assessment and concluded that the approval would not have a significant environmental impact.[13] Because the Agency had made a FONSI, it did not produce a full EIS. The approval, dated November 2015, specifies the locations and conditions under which the salmon may be reared,[14] with egg production at a facility in Prince Edward Island, Canada, and grow-out in a facility in Panama. The

FDA stated that its FONSI was based largely on AquaBounty's proposed physical and biological containment and the Agency's resultant determination that escape, survival, and interbreeding with wild Atlantic salmon is extremely unlikely.[15]

The FDA determined that the approval would have "no effect" on Endangered Species Act -listed Atlantic salmon Gulf of Maine Distinct Population Segment and that the approval would not jeopardize a listed species or damage critical habitat, which ended any informal consultation with the FWS and NMFS.[16] The Agency also determined that the approval would not significantly affect the global commons or non-participating foreign nations' environments, concluding that the approval action is exempt from Executive Order 12114.[17]

The present analysis focuses on the FDA's NEPA environmental assessment. The foreign environment analysis was comparatively limited and relied heavily on the environmental assessment findings. The public comments, the petition, and the complaint initiating the lawsuit challenging the approval focus on the environmental assessment, and they touch on the Endangered Species Act determination.

Environmental Assessment Process and Public Comment

AquaBounty submitted to the FDA an environmental assessment for the AquAdvantage Salmon. The FDA's Veterinary Medicine Advisory Committee (VMAC) held a public meeting about the salmon application in September 2010. The meeting included an orientation for the VMAC on genetic engineering technology and the FDA's regulatory process for engineered animals. The FDA's Center for Veterinary Medicine (CVM) also presented information relevant to evaluating the AquAdvantage Salmon's environmental, health, and safety implications. The meeting was open to the public, and members of the public presented information and views to the committee.[18, 19]

The CVM released its draft environmental assessment, with accompanying preliminary FONSI, in December 2012. The assessment was then open for public comment until April 2013.[20, 21] According to the Agency's response to public comments, commenters included "individual scientists, individual technology providers, trade and professional associations, individual consumers, consumer and environmental advocacy groups, foreign governments or regulatory agencies, and members of U.S. Congress and state legislatures."[22] In November 2015 the CVM issued its final environmental assessment and FONSI and approved the salmon for marketing as food in the United States.

The Center for Veterinary Medicine at the FDA prepared the environmental assessment, and the Agency states that AquaBounty submitted the initial draft.[23] According to an FDA official, the Agency's producing an environmental assessment is unusual; the Agency typically uses the submitting company's environmental assessment without producing its own.[24] The EA assesses environmental effects of approval of the AquAdvantage Salmon application as well as of the "no action alternative" of not approving the salmon. It also describes the Endangered Species Act evaluation process.

The CVM's assessment process also involved correspondence with and input from other government agencies, primarily the FWS and the NMFS, which possess specialized knowledge and distinctive perspectives related to environmental implications.

The CVM's process to determine that the engineered salmon are safe for human consumption, as well as decisions around labeling requirements, also included public comments and petitions.[25, 26, 27] The present analysis examines solely the environmental assessment and associated comments and critiques.

Additional Input: Petition and Lawsuit

In May 2011 several environmental and food safety organizations filed a Citizen Petition with the FDA requesting that the Agency not take final action regarding AquaBounty's application without a full EIS, as well as that the Agency amend its regulatory framework to account further for environmental considerations related to genetically engineered food animals and to increase review transparency and public involvement.[28] The petition critiques elements of AquaBounty's risk assessment and discussed other concerns. The Agency denied the petition, responding in detail to the petitioners' criticisms and requests, when it approved AquaBounty's application in November 2015.[29]

In March 2016, a coalition of organizations, including some of those that had filed the Citizen Petition, filed a lawsuit against the FDA regarding the approval. The plaintiffs are eleven organizations, including United States national environmental and consumer groups concerned with environmental conservation, food sustainability, genetically engineered organisms, and endangered species; wildlife, ecosystem, and marine resources advocacy groups from the United States' East and West coasts and Canada; and groups representing tribes, commercial, recreational, and subsistence salmon fishermen, and salmon businesses, restaurants, and consumers.[30]

The legal complaint, like some of the public comments and the petition, challenges the conduct of the FDA's environmental assessment and its conclusions' validity. It includes a detailed critique in such areas as information sources, assessment scope, and analysis methods. The complaint also challenges other aspects of the Agency's actions, such as procedural elements and the Agency's authority in regulating genetically engineered animals; the present analysis focuses on the environmental assessment critique and does not address these other challenges.

A committee of lawyers and other representatives of some of the plaintiff organizations prepared the complaint.[31] The plaintiff groups, which represent diverse stakeholders, contributed to its information and insights. The plaintiffs and other groups with relevant interests and expertise frequently share information through conference calls and an email listserve,[32] and knowledge arising from members' respective areas of expertise contributed to the complaint. For example, an individual who worked on the complaint stated that information about Canada or Panama came mostly from organizations based in those countries.[33] The legal case is currently pending.

Approach to Case Analysis

The public comments, petition, lawsuit, and the Agency's responses do not represent a participatory multi-stakeholder process. In such a process, diverse stakeholders, likely including participants from the FDA and AquaBounty, would work together to develop an environmental assessment or assessment components. Examining the inputs may still provide insights regarding how diverse stakeholders could contribute to an environmental assessment. It may also suggest differences between participatory processes and processes in which many stakeholders provide input through less interactive and possibly more limited avenues, and it could suggest practical considerations for multi-stakeholder processes.

Disagreement regarding whether a contribution positively affects an assessment may be expected, particularly when perspectives regarding assessment conduct differ. Identification of areas in which diverse stakeholders contribute new information or divergent perspectives does not imply that narrow expert assessors are remiss, but rather that broader participation could introduce or advance additional perspectives or information, particularly in processes designed to incorporate diverse inputs.

In the present case, diverse stakeholders offered input that the Agency declined or refuted. Whether inputs constitute new information or perspectives of which narrow expert assessors were unaware, or whether they reflect information or perspectives that the assessors chose to omit, may at times be unclear. Among inputs that assessors received but did not use, it may at times be unclear when disputes are best attributed to incomplete understanding of the input, to different estimations of what information is important or of how best to conduct an assessment, or to differences in statutory interpretation. Other explanations may also play a role, such as the possibility that input provided after an assessment has been completed is less likely to be incorporated than input contributed within the initial assessment process.

Enumerating Contributions

In the other cases examined, the multi-stakeholder processes and the analyses largely focus on the nature or number of elements that diverse participants contributed, rather than on the contributed elements' scientific value or whether they are eventually used in an assessment. The PoET-Wilson workshops and Dana *et al.*'s workshops each explicitly obviate the question of whether an assessment component is an important scientific contribution. In analyzing their workshops, Dana *et al.* use contribution as an endpoint metric in itself, comparing numbers of elements identified by the narrow expert and multi-stakeholder groups without evaluating the contributions' quality or seeking to predict whether the elements would likely be used to identify biodiversity risks.[34] In the PoET-Wilson workshops the facilitator frequently framed questions of what studies might be needed by asking individual participants what concerned or what would satisfy them personally, implicitly acknowledging that importance is often subject to individual perceptions. This approach appears to have helped participants communicate their perspectives and contribute to identifying considerations and developing a research agenda, though in a context of time and budget constraints differences of opinion

regarding elements' importance could still become relevant. The OPPT tier testing workshop report summarizes discussions. Participants selected among ideas to create testing schemes and some selection likely occurred in producing the summaries, but the report may to a degree represent a record of discussion about elements that might be valuable for consideration rather than decisions about criteria and their roles in assessment or in regulatory determinations.

In these cases as well as in the present case, diverse stakeholders may raise considerations that further deliberation could determine to be irrelevant or unnecessary, or that could be addressed without substantial changes to an assessment or decision.

The present analysis similarly seeks to identify stakeholder contributions without estimating their scientific merit or their likelihood of incorporation into or effect on an assessment. Broad consideration of contributed elements is appropriate, primarily because legitimate differences of opinion regarding particular contributions' merit are likely, and this fundamental subjectivity recommends caution in judgment. Furthermore, as environmental assessments are typically conducted by narrow experts and diverse stakeholders may offer fundamentally different views, judging stakeholder contributions based on likelihood of incorporation into a standard assessment process could unduly minimize stakeholder contribution and omit important ways in which stakeholder involvement could enrich assessments meant to integrate diverse perspectives. In addition, many points raised may not eventually be included in or substantially affect any given assessment, and the present analysis examines individual contributions to discern larger sources or types of contribution to environmental assessment generally, rather than to trace individual contributions' outcomes in a particular assessment.

Calibrating Contributions

In addition to enabling observation of stakeholder contributions, the present case offers an opportunity to examine diverse stakeholder input within a narrow expert assessment process. This investigation may illuminate what contributions broader input may uniquely introduce. A view of which contributions the narrow expert assessors view as valuable additions may also provide insights into diverse participant contribution.

Stark differences between the present case and participatory processes may affect narrow expert assessor estimation of stakeholder contributions. A participatory process should begin from early assessment stages, enabling stakeholders to collaborate in developing a problem formulation and identifying assessment components or needed information.[35] In the present case, diverse stakeholders commented on an assessment developed by the submitting company and on a draft assessment developed by the Agency. A completed, even draft, assessment reflects deliberation, decisions regarding assessment conduct, and research such that those creating or presenting the assessment may view input less openly than they might if it were provided at earlier stages, and it could also affect the types of input offered.

The lack of collaborative interaction may challenge participants' learning from one another's views. The PoET-Wilson workshops' structure was based in part on the premise that collaboration on assessment tasks would enable individuals with divergent perspectives to identify areas of common ground.[36] Researchers Dana and Nelson argue that social learning, which includes participants' "work[ing] to create a joint foundation for collective action," requires participatory processes and may be important to environmental risk analysis success, particularly as participant diversity is broadened.[37] In the present case, Agency or other stakeholders' perspectives on matters of disagreement might have shifted with opportunities for discussion and collaboration.

Divergence between the diverse stakeholders and the Agency may be particularly pronounced in the lawsuit complaint, because the plaintiff stakeholders are seeking to demonstrate insufficiencies in the Agency's environmental assessment while the Agency is seeking to defend its assessment as conducted. However, many of the items mentioned in the complaint are also reflected elsewhere in stakeholder input, where comments advised rather than challenged a decision legally.

Despite differences from participatory processes, the present case can provide insights into stakeholder contribution, and the Agency's perspective regarding some contributions can enable helpful calibration. Differences between the regulatory process and typical participatory multi-stakeholder assessments may further suggest practical considerations for multi-stakeholder processes, including within existing governance structures.

Contribution and Dispute

The diverse stakeholders' inputs, as well as the FDA's responses, suggest that some of the inputs may represent new information that the Agency incorporated into its assessment, or that the Agency may well have found valuable had the information been introduced before the assessment was finalized. These inputs represent the clearest instances of stakeholder contribution that could positively affect assessment.

Some of the inputs may represent stakeholders' perspectives regarding scientific substance. These inputs may reflect different judgments regarding best or appropriate assessment conduct, including needed or suitable information, levels or types of evidence necessary to support conclusions, or approaches to uncertainty. Even though the Agency largely maintained its initial positions, the inputs still represent types of stakeholder contribution that could positively affect an assessment. Judgment contributions and differences regarding aspects of assessment conduct appear in other cases as well. For example, the OPPT tier testing workshop participants appear to have disagreed regarding microcosms' suitability as simulations as well as regarding whether or not organisms should be tested under both anthropogenically stressed and healthy non-stressed conditions. PoET-Wilson workshop participants articulated diverse approaches to testing fitness as well as varying opinions regarding under what circumstances an application could move forward when desired information was unavailable. Dana *et al.* describe that while a few participants worked to define and categorize particular system elements in detail, others felt this effort unnecessary and tedious, opining that a more general

approach or other focus would better serve the expressed needs.[38] In a participatory multi-stakeholder process, the agency, the company, and other stakeholders would deliberate together to produce an assessment, and diverse perspectives regarding assessment conduct may enrich a discussion and could improve assessment quality or validity.

In some instances, an input to the FDA assessment is framed as addressing assessment substance while the Agency expresses that the recommendation falls outside of statutory scope. These contributions, and input expressly addressing statutory requirements on which the commenter and the Agency disagree, may reflect differences in interpretation of statute. In a participatory process beginning early in a review, the regulating agency or other decision-makers could provide the statutory framework. Alternatively, diverse stakeholders could work together in interpreting statute, or diverse considerations or underlying differences in perspective that could contribute to statutory interpretation could be revealed and discussed. The present analysis focuses on input and disputes agreed to center on scientific or assessment substance. Contributions that may fall outside of the assessment's statutory scope are less likely to represent substantive contributions to the particular assessment, and they may also more likely represent elements that the narrow expert assessors would have included on their own had the statute or their interpretation of it been different.

The FDA also received public comments that do not address the assessment or that fall more roundly outside of the assessment's and the FONSI's statutory scope, such as comments advising the Agency to focus on encouraging commercialization of fast-growing non-engineered salmon or expressing general concerns about the approval[39] or other concerns about biotechnology industries.[40] While researchers argue that broader considerations[41] and alternative actions[42] should play a role in assessment, assessors cannot explicitly incorporate these contributions into assessments constrained otherwise by statute, so these comments do not readily represent contributions that a multi-stakeholder process might have added to the AquAdvantage Salmon assessment. The present analysis does not focus on these contributions.

An input may represent a contribution that could positively affect assessment even if some participants or narrow expert assessors do not agree that it is valuable. Diverse stakeholders may offer differing perspectives or urge incorporation of considerations that could enrich or improve an assessment. At the same time, as in any assessment, not every contribution necessarily represents improvement. A participatory process could enable diverse individuals to understand each others' perspectives and reach agreement regarding what elements should be included.

Examining diverse inputs may also provide insights into stakeholder contributions that could contribute to the process's or results' perceived validity or acceptability. Researchers point out that a key purpose of risk assessment is to protect stakeholder values.[43] Similarly, the PoET-Wilson workshop facilitation suggested that whether a given component improves an assessment's scientific quality or only its acceptability to diverse parties may be a matter of opinion, and implied that contributions improving perceived validity or acceptability may be valuable for doing so.

Identification of areas of dispute or of areas in which a multi-stakeholder process may contribute to assessment does not suggest that narrow experts' approach is lacking. It suggests that diverse perspectives and knowledge-bases, particularly within a participatory process designed to enable incorporation of diverse stakeholder information and considerations, could enrich an assessment beyond that which narrow experts would likely produce on their own. Furthermore, in addition to challenges in determining what contributions represent improvement, in the present case what suggested elements a participatory process would have chosen to incorporate is unknown.

Present Analysis

The present analysis examines diverse stakeholder inputs to identify elements that could represent areas of stakeholder contribution to an assessment. It compares identified elements with the types of contributions found in other multi-stakeholder processes examined, to validate results while enabling identification of additional areas of potential contribution. The analysis further attempts to discern whether a contribution may represent information or perspectives that the Agency incorporated or would have incorporated had the input been available, whether it may reflect differences in perspective regarding scientific substance or assessment conduct, or whether it may imply differences in statutory interpretation. These categories do not necessarily imply a contribution's merit, but they may suggest insights regarding the nature of diverse stakeholder input and the input's relationship with assessment processes. The analysis also examines other aspects of the case assessment and inputs in order to discern further practical considerations for stakeholder involvement.

The sources of diverse stakeholder input examined overlap in the points they mention, and they draw from each other. The FDA responses similarly overlap in content. The present discussion draws from these sources without exhaustively describing how each source reflects each contribution. In addition, as in analyzing the other cases, the present discussion does not seek to describe stakeholder inputs exhaustively.

Stakeholder Contributions

The public comments, petition, legal complaint, and other inputs describe a number of additions or considerations that the commenters felt should be reflected in the environmental assessment or the Agency's determinations, which could suggest contributions that diverse stakeholders could make in an assessment process. Many of the contributions align closely with areas of discussion or contribution observed in other cases, while others extend beyond contributions already identified.

Calls for Information and Analysis

Inputting stakeholders recommended a number of types of research and analysis that they felt could have improved the assessment, including studies investigating potential consequences of salmon escape and survival, studies relevant to escape and survival likelihoods, a monitoring and enforcement plan, and more extensive analysis of

alternatives to the approval action. In each of these areas, the FDA explained its position that the EA as written sufficed to evaluate risks and determine no significant impact. A portion of the disagreement may stem from differing degrees of willingness to rely on containment and differing levels of comfort with legal compliance and inspection assurances. Statutory frameworks or interpretation may also have affected the parties' considerations. The FDA and the inputting stakeholders also expressed opinions regarding how particular types of studies may be used in assessment and how to treat uncertainty.

Study of Release Consequences

The EA focuses primarily on the likelihood of fish escape from the facilities, as well as on likelihood of survival and establishment in receiving environments. Many stakeholders expressed the opinion that the EA's analysis is insufficient to support a finding of no significant impact. They emphasized the perspective that the assessment should also analyze how the engineered salmon could affect the environment if they were to escape and survive, rather than relying on determinations of unlikely escape and survival to find that there would not be significant environmental effects and therefore omitting this analysis.[44, 45, 46] In her comments at the VMAC meeting, Dr. Kapuscinski stated that

> ... the Environmental Assessment ... stops at estimating that the likelihood of escape is 'extremely small' due to multiple confinement ... . But ... even with actual exposure very close to zero, it is necessary to assess ecological consequences and then estimate the overall risk ...[47]

The petition references "the dearth of information relating to how transgenic salmon will behave in the wild, including how they will interact with native salmon,"[48] citing scientists mentioning high uncertainty or calling for more studies regarding the engineered salmons' fitness under wild conditions.[49] It also cites studies suggesting increased competitive behaviors in growth-enhanced salmon and studies finding that engineered fish can sometimes outcompete wild type fish.[50] The complaint notes that the EA did not study the potential fitness of the GE salmon directly, instead extrapolating from studies of other GE fishes' fitness.[51]

In its response to the petition, the FDA emphasizes the containment measures as key to the assessment, stating that "The analysis in the EA focuses first and foremost on the adequacy and redundancy of containment, as the conditions specified in the approval require extensive and redundant physical and biological containment."[52] It also states that some uncertainty is inevitable, and that addressing all uncertainty is unnecessary to determine that the approval will not have a significant environmental impact:

> ... there will always be some level of uncertainty surrounding any risk estimation... .
>
> Further, because to date, there have been no approvals for AquAdvantage Salmon, or free releases of AquAdvantage Salmon into the environment, risk assessors and regulators must extrapolate outcomes from studies conducted under laboratory or simulated natural conditions ... . Generating additional data in

> laboratory studies or even mesocosms could somewhat reduce but not eliminate uncertainty ... .
>
> Thus, although the scientists cited ... may have identified additional research that could add to the general knowledge base concerning the behavior of GE fish in the wild, ... such research is not necessary to determine that there is no significant impact on the environment under the particular conditions specified in the NADA for AquAdvantage Salmon because [of the containment methods and lack of nearby conspecifics].[53]

The FDA also responded to the petitioners' cited studies, stating that the referenced studies use mathematical models rather than environmental studies.[54] The petitioners and the Agency mention additional details to support their respective arguments that the studies suggest or do not suggest a need for a more comprehensive environmental assessment. The Agency also emphasized that for fitness to be relevant, the engineered salmon must escape confinement, and that escape and establishment are highly unlikely for the conditions specified in the approval.[55]

Types of studies needed and when it is appropriate to extrapolate from studies to a given real-world scenario are important questions in conducting an assessment, as is how to treat uncertainty. Diverse stakeholders offered their perspectives in these areas in the present case, as they did in the OPPT tier testing workshop and the PoET-Wilson workshops. The disagreement between the FDA and the stakeholders requesting further analysis of effects in the event of escape and establishment may also stem from differences in estimation of whether the containment is sufficiently reliable to obviate concerns about further effects.

Studies Related to Escape Likelihood

Stakeholders suggested a number of types of analysis or research, including studies related to the likelihood of escape and establishment. For example, fisheries and engineered fish experts Anne Kapuscinski and Fredrik Sundström and other commenters recommended a particular type of failure analysis for the facilities.[56, 57] They and other commenters, citing research finding that some fish engineered for growth display increased thermal tolerance compared to wild types or changed characteristics in high temperatures, also called for study of AquAdvantage Salmon tolerance of warmer waters as in Panama.[58, 59] The EA cites Panamanian waters' high temperatures as a component of containment.[60] For each of these offered studies and others, the FDA provided reasons that it did not believe such studies were needed. For example, regarding thermal tolerance, the FDA stated that there is no information to suggest that AquAdvantage Salmon would have greater tolerance than wild type Atlantic salmon, and it cited studies finding that some related triploid fishes have reduced thermal tolerance compared with diploids.[61] In the PoET-Wilson workshops as well as the OPPT tier testing workshop, diverse participants contributed their expertise and perspectives regarding what types of tests are appropriate for determining risk posed by engineered organisms. Despite the disagreements, it appears that diverse stakeholders may contribute study needs and designs that could, under some circumstances, benefit an assessment.

Monitoring and Enforcement Policy

According to the complaint, a number of stakeholder groups had requested that the Agency establish regulations requiring monitoring, reporting, and inspection procedures for engineered fish producers.[62] The complaint states that the containment measures are solely under AquaBounty's control and that the FDA has not explained how it will monitor compliance,[63] and it mentions that government scientists expressed concern about the lack of a monitoring and enforcement policy regarding facility operations and escape.[64] Other stakeholders also mentioned concerns about monitoring and enforcement.[65]

The FDA's approval letter includes recordkeeping and reporting requirements for the company, including requirements for reporting fish escapes.[66] The approval also specifies that the company must allow FDA officers to inspect the facilities. It does not mention enforcement measures. The EA specifies points of automated or staff monitoring of the facilities and mentions inspections and audits by United States and Canadian or Panamanian officials.[67] It does not describe or assess an independent monitoring plan or enforcement measures. Responding to public comments expressing concern about monitoring and enforcement, the FDA states,

> Under the [Federal Food, Drug, and Cosmetic] Act, a new animal drug that does not comply with its approved application is "unsafe" and an unsafe new animal drug is "adulterated." ... FDA may take enforcement action against adulterated drugs and foods, including refusing admission ... . If AquAdvantage Salmon were not in compliance with the conditions under the approved [application] it would be adulterated under these provisions and subject to FDA's enforcement action. FDA will monitor for compliance ...[68]

Remaining concerns about monitoring and enforcement may stem in part from differences between internal and external trust in the Agency's inspection and enforcement practices or in the company's legal compliance and good faith. For individuals closely connected to the Agency, knowledge of legal specifications and of the FDA's option of conducting inspections may suffice. These individuals may also be most familiar with the Agency's intentions or typical actions regarding inspections. In addition, Agency officials have inspected the facilities and reviewed the company's records, and their findings may lend the Agency confidence in the company's future practices. For those more distant from the Agency, including those less confident in the Agency's concern about environmental effects or in the company's vigilance, knowledge of company reporting requirements or of the FDA's inspection option or intention, or even knowledge of Agency inspection practices, may not suffice to alleviate concerns that the conditions will not be rigorously upheld or to remove desire for a more specific written plan or reduced reliance on self-reporting. In addition to legal requirements and the possibility of inspections and enforcement, the Agency may regard unofficial considerations, such as reputational damage that the company would suffer if violations were found, as an important deterrent, while some stakeholders may not regard these deterrents as sufficient, as they also appear to believe that under the approved conditions

violations could too easily go undetected. In a participatory multi-stakeholder process, participants may exchange knowledge and perspectives, discussing together to determine whether specifications beyond the existing legal framework are needed and to design a plan.

Alternatives

NEPA requires Federal agencies to "Use the NEPA process to identify and assess the reasonable alternatives to proposed actions that will avoid or minimize adverse effects of these actions upon the quality of the human environment."[69] In an EA, agencies are required briefly to discuss alternatives as well as the proposed action's and alternatives' environmental impacts.[70] The more detailed description of EIS requirements, which may help in identifying the types of alternatives to be discussed, specifies exploration of "reasonable alternatives," including alternatives outside the agency's jurisdiction, the no-action alternative, and appropriate mitigation measures.[71]

The EA considers the approval action and the no-action alternative of not approving AquaBounty's application, and it briefly discusses three other alternatives: rearing in net pens; rearing in closed, water-based systems such as fiberglass tanks; and rearing in land-based, closed recirculation systems in contrast with the flow-through systems described in the approval.[72]

The complaint suggests a number of other alternative regulatory actions to reduce environmental effects, including conditions that the FDA could impose, such as "limiting the volume of GE fish that could be grown at once; imposing more stringent monitoring, recordkeeping, or reporting requirements; requiring additional training or qualifications for workers; ... or granting only a limited, pilot project," and others, as well as alternatives requiring review or restrictions set by other agencies, such as NMFS or FWS.[73] In discussing the action's "purpose and need," to which an agency is responding in proposing alternatives,[74] the EA emphasizes the New Animal Drug Application for the AquAdvantage Salmon.[75] The complaint states that based on the EA's framing, the purpose and need may include addressing the global overfishing crisis, decline in wild fish stocks, and meeting increasing demand for fish protein,[76] and it cites alternatives submitted as public comments, including development of projects and policies meant to support sustainable fishing and aquaculture, actions to protect and restore salmon populations, and approaches to developing faster growing salmon without genetic engineering technologies.[77]

Responding to public comments regarding alternatives, the FDA states that the NEPA regulation says that an agency "must evaluate all reasonable alternatives," and then that "Under the Food, Drug, and Cosmetic Act ..., sponsors may submit [New Animal Drug Applications] to FDA ..., and FDA must approve the [application] unless there are specific grounds under the [Food, Drug, and Cosmetic] Act to deny approval ... ."[78] This statement may be suggesting that the Agency cannot regard alternatives departing from the Food, Drug, and Cosmetic Act's specifications as "reasonable." The Agency goes on to state that

> Alternatives suggested by the commenters are not "reasonable" or feasible given that other agencies do not have the authority to review for approval a[New Animal Drug Application] under the [Food, Drug, and Cosmetic] Act and given that the application before FDA was for approval of a specific article in AquAdvantage Salmon and not for the development of fast-growing salmon by any possible method, many of which may not ... be within FDA's jurisdiction.[79]

It appears that diverse stakeholders contributed specific alternatives to the approval action, but that the FDA did not determine many of the alternatives to be reasonable or feasible based on the Agency's statutory requirements and perhaps the nature of other governance structures. Identification of alternative courses of action, both mitigation approaches for a particular application and broader alternatives, may be an area in which diverse stakeholders could contribute within decision-making structures designed to use such information. According to Kapuscinski and colleagues, identification and assessment of alternative actions, and of the problems use of an engineered organism may address, should be components of an environmental assessment process and are important areas for stakeholder contribution in processes structured accordingly.[80]

Assessment Scope – Cumulative Impacts

The inputting stakeholders' and the FDA's perspectives differed regarding whether particular related activities, including AquaBounty's expansion plans, should be included in the assessment as "cumulative impacts." These differences may stem from interpretation of statute, though differences in understanding of appropriate assessment scope, how to address uncertainty, or containment reliability, as well as differing views of the regulatory system itself, may also play a role.

Expansion Plans

The EA discusses the Agency's consideration of "cumulative impacts," which NEPA defines as "the impact on the environment which results from the incremental impact of the action when added to other past, present, and reasonably foreseeable future actions... ."[81] The EA states that there is no cumulative impact because "this would be the first [New Animal Drug Application] approval for AquAdvantage Salmon, and FDA is not aware of any specific, reasonably foreseeable future actions on [New Animal Drug Applications] for GE fish at this time."[82] The EA further notes that "With regard to AquaAdvantage [sic] Salmon, at the present time, FDA has no other applications or proposals from [AquaBounty] to develop and grow AquAdvantage Salmon anywhere but in the Canadian and Panamanian facilities covered by the current [application],"[83] and says that it is not aware of any specific reasonably foreseeable future actions on AquAdvantage Salmon applications.

The petition cites AquaBounty public statements by AquaBounty's Chief Executive Officer, including statements at the VMAC meeting, indicating the company's intentions to increase AquAdvantage Salmon production throughout the United States and the world.[84] It also cites correspondence between a former AquaBounty executive and the Maine Department of Environmental Protection discussing raising the engineered fish in

Maine, in a facility that would discharge wastewaters into the marine environment.[85] It cites AquaBounty financial statements stating that "Plans to expand capacity for the production of eggs for sale are in place and will be implemented as soon as approval is granted," and indicating that developers in the United States and elsewhere had expressed interest in raising the salmon.[86] The legal complaint also notes public statements and financial disclosures demonstrating that AquaBounty intends to expand production,[87] stating that at least since 2010, AquaBounty has told investors of plans to raise GE salmon in other locations, including in the United States.[88] The complaint notes that in 2014 the company stated in financial disclosures that "we currently plan to apply for regulatory approval of a second hatchery that would likely be located in the United States."[89]

Mentioning NEPA's requirement that in determining EIS scope an agency must consider

> [c]umulative actions, which when viewed with other proposed actions have cumulatively significant impacts and should therefore be discussed in the same impact statement, [and s]imilar actions, which when viewed with other reasonably foreseeable or proposed agency actions, have similarities that provide a basis for evaluating their environmental consequences together...[90]

The petition argues that the FDA must consider AquaBounty's expansion plans.[91] The complaint also challenges the FDA's limiting the scope of the assessment to the two production facilities indicated in AquaBounty's application, considering the company's stated plans to expand production, as well as the EA's discussion of AquAdvantage egg production for commercial sale,[92] which the complaint notes[93] would be unnecessary if only two facilities, both owned by AquaBounty, were involved. It expresses that the analysis should have included effects of the possibility of future marketing of AquAdvantage Salmon eggs as well as AquaBounty expansion.[94]

Suggesting that the dispute is at least in part one of difference in statutory interpretation, the FDA's petition response points out that the requirement to consider cumulative impacts is only one component of determining whether an action may have a significant impact,[95] as well as that the cited requirements to consider cumulative actions and similar actions refer to determining an EIS's scope.[96] The Agency also states that any other facilities are not within the scope of the current application, and that they "are not part of the action FDA is taking in approving this [application]."[97]

The Agency further states that discussions of possible production facilities in the United States "are purely speculative,"[98] and that possible future FDA actions regarding such applications are not reasonably foreseeable, and are therefore not cumulative impacts as defined by the statute. The response cites legal cases indicating that hypothetical projects or future planned development need not be considered in an EA or EIS, including quoting a court case that "an EIS need not delve into possible effects of a hypothetical project, but need only focus on the impact of the particular proposal at issue and other pending or recently approved proposals that might be connected to or act cumulatively with the proposal at issue."[99] The FDA also states that it cannot reasonably analyze the environmental impacts of possible future facilities without specific information about their locations and proposed containment measures.[100] In discussing the conclusion that

the action has no cumulative impacts, the EA also emphasizes the many possible future growing conditions and states,

> Because production of AquAdvantage Salmon would be possible at any number of locations worldwide or within the United States, potentially under different containment conditions and within areas where native Atlantic salmon or other salmonid species are present, there are far too many variables and unknowns in relation to the conditions of use and potentially affected environment(s) for the agency to determine at the present time what might be a reasonable foreseeable action(s) in terms of a future [application](s) for AquAdvantage Salmon. Thus, it is not possible to perform an accurate, comprehensive cumulative impacts assessment taking into account these potential future actions.[101]

Within the discussion of whether expansion plans should be considered, the petitioners and the FDA also discuss the degree to which the approval could enable expansion. The EA and the petition response state that the EA addresses only a particular set of conditions, and that if AquaBounty were to propose additional facilities, a supplemental New Animal Drug Application would be required, and it would trigger a separate NEPA analysis, which would consider the additional facility's cumulative impact.[102] The petition cites VMAC meeting discussions as well as the FDA's regulations for supplemental New Animal Drug Applications to support the position that the review standards for a supplemental application could well be substantially weaker than those for the initial application. For example, the petition argues that some changes require preliminary approval only if they adversely affect the drug's identity, strength, quality, purity, or potency, and thus that AquaBounty could argue that Agency approval is not needed for changes to containment measures with environmental implications.[103] The FDA responded that new facilities' water quality, air temperature, and triploidy-induction controls could affect product identity or quality, as well as that submission of a supplemental application for manufacturing facility changes is a condition of the present approval. The EA and the approval emphasize the point that the approval only permits the production facilities and rearing conditions specified in AquaBounty's application and in the Agency's approval letter, and that any significant changes would require separate approval.[104, 105]

The petition refers to temporary VMAC member Dr. Gregory Jaffe's statement of concern that

> ... this EA is very limited. It is limited to two facilities and there was discussion about supplemental applications if they have new facilities coming on ... . And there is a concern here that there are going to be ... multiple, many, many little EAs ... . And I worry that there is not a cumulative impacts analysis. And that this is a way to sort of get around doing an environmental impact statement about the fact that this salmon could be grown in multiple locations ... . And so I think there is a concern here that the process that is being set up may in fact avoid a full environmental impact statement or a full assessment under NEPA as this moves along, if this moves along, as the business plan of the sponsor suggests.[106]

The petition also cites AquaBounty's Chief Executive Officer as stating that a supplemental application and EA would be merely a "technicality," "posing no barrier to

raising AquAdvantage Salmon in the United States."[107] The complaint cites the FWS as speculating that the company's seeking approval for only the Prince Edward Island and Panama facilities may have been an attempt to enable more ready regulatory approval for more actions.[108]

The difference between the diverse stakeholders' and the Agency's perspectives regarding whether or not to consider the expansion plans in assessing effects or in determining what type of assessment is needed may stem purely from differences in interpretation of the statute. It could also indicate different approaches regarding system boundaries, types of information sufficient for consideration, or how to address uncertainty, each of which appear in other cases as areas of stakeholder contribution. Differing expectations or trust regarding the regulatory system's likely treatment of future applications may also in part underlie differing estimations of the imperative to consider future expansion, though these expectations may arguably not affect statutory interpretation or other approaches to determining assessment scope.

Other Actions

The complaint argues that the EA should have considered additional "actions" or events that could contribute to cumulative environmental impacts of the engineered salmon approval. According to NEPA, a cumulative impact is the "incremental impact of the action when added to other past, present, and reasonably foreseeable future actions regardless of what agency ... or person undertakes such other actions. Cumulative impacts can result from individually minor but collectively significant actions taking place over a period of time."[109] The EA states that

> FDA has not considered any cumulative impacts for this action because FDA believes there are no other past, present, or reasonably foreseeable future actions. ... There would be no 'incremental impact' because this would be the first [New Animal Drug Application] approval for AquAdvantage Salmon and FDA is not aware of any specific reasonably foreseeable future actions on [applications] for GE fish at this time.[110]

The complaint argues that in addition to AquaBounty's expansion plans, the EA should have analyzed such actions or events as other genetically engineered fish in development, other actions potentially affecting the aquatic environments affected by the approval, other existing threats to wild salmon stocks, and habitat changes due to climate change.[111]

The dispute may be one of statutory interpretation. In response to the complaint's points, the FDA could point out, as it did regarding the petitioners' arguments about the planned expansion, that NEPA specifies consideration of cumulative impacts only as part of an EIS scope or as one, perhaps optional, component of determining whether or not there may be a significant impact. It could argue that these additional impacts therefore need not be considered, particularly if for other reasons there will not be a significant impact.

The plaintiff stakeholders may believe consideration of the additional actions or events to be required or at least necessary for sound assessment, even though cumulative impacts

are only one component of determining whether there will be effects, because they believe these components likely to affect whether significant impact is found.

The dispute regarding whether or not cumulative impacts must be considered may represent a difference in statutory interpretation. It could also in part reflect disagreement regarding the likelihood that consideration of the cumulative impacts may affect the finding; other differences in understanding of appropriate assessment scope; different estimations of containment reliability, on which the EA and FONSI determination focus; or different understandings of how focus on containment should affect assessment.

Interpretation of Information

The input indicates areas in which diverse stakeholders may contribute different perspectives regarding interpretation of established information. This area has limited analogues in other cases, which largely did not extend to the point of interpreting implications of study results or data. It may suggest ways in which stakeholders could contribute to these later stages of an environmental assessment.

Implications of Reduced Fitness

Both the EA and the complaint discuss the potential fitness of the engineered salmon compared with wild type salmon. The EA determines that the engineered salmon are less fit than wild types and concludes that the reduced fitness results in reduced risk, because even in the event of survival and reproduction in the receiving environment, the engineered organisms' genes would disappear from the population due to natural selection.[112] While it challenges the data whereby the EA concludes that fitness would be reduced,[113] the complaint also points out a different potential environmental implication of reduced fitness, stating that if less fit engineered salmon interbreed with wild type salmon, the offspring may carry the engineered parents' less fit genes, reducing survival in the salmon population overall, with potentially particularly damaging effects for small, fragile populations such as endangered salmon.[114] Here, the plaintiff stakeholders have a different scientific perspective on implications of a finding of reduced fitness, an additional insight regarding potential effects that could under some circumstances contribute to an assessment.

The difference in perspective could also relate to differences in estimation of the containment methods. Reduced fitness' causing a genotype to diminish in the population without causing other negative effects could be more likely if the genotype is introduced in low numbers, while other adverse effects could be more likely in the event of larger-scale release.[115] A difference in imagined escape numbers may or may not be playing a role in this difference in scientific perspective.

Assurance of Genetic Containment

The EA's conclusion that the engineered salmon as approved would not significantly affect the environment is based in part on genetic containment, the determination that due to being sterile and all female, in the event of escape the fish would be unable to

interbreed with wild fish or to form an ongoing population. Even when they use the same data, the FDA and some stakeholders reach different conclusions regarding whether the genetic containment is sufficiently reliable.

The EA states that besides the broodstock, the fish would be sterilized through induction of triploidy, as well as that chances of breeding in the event of escape would be reduced or eliminated by the production of only female fish.

The EA states that the salmon eggs would undergo a treatment to render them triploid, possessing three sets of chromosomes rather than the usual two. The EA states that "... there are no specific data demonstrating that triploid AquAdvantage Salmon are indeed sterile, that is, incapable of producing viable offspring; however, as discussed below, there are several reasons why this is believed to be the case."[116] The petition[117] as well as the complaint[118] assert that the EA provides insufficient evidence of triploid sterility. The FDA's response to the petition notes that the EA describes evidence that triploidy does result in sterility in Atlantic salmon and other fish, and it also encourages viewing the various containment methods together, rather than focusing on the effectiveness of any one method in isolation.[119] It states that the containment methods support the conclusion that escape is very unlikely, and that even if diploid fish did escape, survival and establishment are similarly extremely unlikely.[120]

The EA provides evidence of severely reduced, though not entirely absent, reproductive potential among triploid fish.[121] The EA includes a footnote that "Although almost all of the AquAdvantage Salmon being cultured for retail sale as food would have no reproductive capacity, triploidy is not 100% effective in producing infertility ..., and reference to 'sterile' AquAdvantage Salmon in this document should be interpreted in that context."[122] The EA describes triploid salmon as sterile, and it references this sterility to indicate that the engineered salmon would be unable to contribute their genes to wild populations.[123]

The EA notes that one of the post-approval quality control conditions is demonstration of the effectiveness of triploidy induction using samples of eggs, and it states that the criterion for releasing a batch of eggs for shipment is that the probability is less than 0.05 that the eggs are not at least 95% triploid. The EA also notes that AquaBounty had in studies achieved an average of 99.8% triploidy induction (range 98.9 to 100% for batches tested).[124] A scientist at the VMAC meeting explained that the 95% limit is a statistical artifact and that triploidy induction is actually higher,[125] and the petition response notes that it "is consistently, on average, 99.8% effective for AquAdvantage Salmon."[126] The EA states that the production process "ensures" triploidy and results in a population that is "entirely" triploid, and thus effectively sterile.[127]

The EA mentions that the entire population would be female, including some of the broodstock that would be "neomales," or genetic females with artificially induced male characteristics, including sperm production.[128] The EA notes that neomales are "in general" unable to release sperm, and that the sperm would be extracted by first killing the fish.[129] The EA states that "The combination of triploidy and an all-female population

is expected to render AquAdvantage Salmon effectively and functionally sterile resulting in complete reproductive containment."[130] The EA also indicates that the breeding facility would include some true males and quantifies them as "relatively few," equal to the number of neomales.[131]

Stakeholder inputs dispute the EA's assumption of sterility. For example, the complaint notes that the EA acknowledges that up to five percent of the engineered salmon may not be successfully made triploid, and states that evidence is insufficient that triploidy results in sterility. The Citizen Petition further notes that triploid sterility has not been demonstrated for AquAdvantage Salmon specifically.[132] In questioning triploid sterility, the petition references the VMAC meeting briefing packet, which states that "Although adequate demonstration of triploidy has been provided, [AquaBounty] has not submitted any specific data to show whether or not AquAdvantage Salmon are indeed sterile. Although perhaps not completely sterile, the fertility of triploid females is expected to be greatly reduced by the procedure ..."[133] The complaint also challenges the EA's assertion of sterility for genetic confinement considering the presence of fertile engineered salmon broodstock, including males, at the Canadian facility.[134]

FDA responses to sterility concerns[135, 136, 137] describe research finding high levels of triploid sterility in Atlantic salmon other fish, even though it has not been shown in AquAdvantage Salmon themselves. They also emphasize the point that triploid sterility is only one form of confinement to be viewed together with other forms, particularly, for biological or reproductive containment, an all-female population, which according to the petition response "is 100% effective in preventing reproduction."[138]

The FDA responded to concerns about the fertile broodstock at the Canadian facility by stating that "It is correct that there is no biological containment for the AquAdvantage Salmon broodstock in the PEI egg production facility ... these diploid GE Atlantic salmon ... broodstock represent the greatest potential risk to the environment in the unlikely event of an escape."[139] The response then states that the FDA has determined reproduction and establishment in the event of escape to be unlikely due to: the facility's only maintaining several thousand adult broodstock fish at a time, negating the potential for the much larger releases that can occur in other fish farming; about half of the adult "males'" actually being neomales that "generally cannot spawn on their own"; AquAdvantage Salmon showing reduced fitness and largely poorer reproductive performance than wild types; and the absence of Atlantic salmon in watersheds near the facility despite stocking efforts.

Here, the FDA and other stakeholders appear to be using the same information and interpreting its implications differently, differing regarding whether or to what extent an approximation that largely ignores a small measure of fertility among the engineered fish is appropriate. Differences may include dispute regarding when studies are needed on the particular engineered organism in question and when studies using other species or varieties suffice. Both the FDA and inputting stakeholders at times cite studies using proxy organisms, and at times discount or dismiss studies using proxy organisms and criticize the other's use of proxy organisms.[140] Assessors must make judgment

determinations regarding many assessment details, including for what purposes proxy organism studies are suitable. These judgments may be an area in which diverse stakeholders can contribute perspectives.

Differing levels of willingness to accept the genetic containment assurances could also reflect differing estimations of other containment measures' reliabilities. The FDA emphasizes that the containment measures should be considered together. In responding to concerns about triploidy effectiveness, the petition response states that "... your focus on triploidy in isolation gives an incomplete picture of the containment measures ... ."[141] It emphasizes the "numerous biological, physical, and geographical/geophysical methods of containment," and notes, quoting the EA, that

> No single containment measure will be completely effective at all times and should not be considered to exist outside the context of multiple, independent and complementary measures in series. ... By combining containment measures with different stringencies, attributes, and modes-of-action, the compromise of aggregate containment by the failure of a single measure becomes increasingly unlikely.[142]

The EA also cites recommendations of multiple, redundant, and independent containment measures.[143] Expressing a contrasting view, a plaintiff organization member stated that biological, physical, and geographical containment are regarded as necessary components in genetically engineered organism containment. He argued that for AquaBounty's Canadian facility each of these elements is addressed insufficiently, because "Good physical containment fails because you've got people working in that facility who are just normal guys who might want to take some of the eggs out and use them to go fishing," and due to occasional hurricanes on Prince Edward Island; because Prince Edward Island, overall an area with breeding populations of Atlantic salmon, is "absolutely the wrong place if you're going to do geographical containment at all"; and because "Their sterilization technique fails because it's not 100%." The stakeholder summarized that "Containment really relies on having all three working. [They have a] bad location, bad assumptions about their physical containment, and not complete biological containment."[144] The FDA's and the organization member's statements suggest some agreement regarding containment principles, but possibly differing estimations of various containment elements' reliabilities. They may also suggest differences regarding how sets of assurances or hazards should be considered together in assessment.

PEI Salmon Proximity

The FDA and some inputting stakeholders appear to have disagreed regarding whether or not Atlantic salmon live near AquaBounty's Prince Edward Island (PEI), Canada facility. The groups may have been using similar information but interpreting it differently.

The FDA emphasizes the absence of Atlantic salmon near the PEI facility, both in determining that any escaping engineered salmon would have no conspecifics with which to mate[145] and in determining, particularly considering past stocking efforts, that the local environment is unconducive to Atlantic salmon and thus that escaping engineered fish are unlikely to be able to establish a population.[146] The EA states that "Atlantic salmon are

not currently present in the Fortune River watershed [where the PEI facility is located] or any nearby watersheds... ."[147] The FDA's response to the Citizen Petition similarly states that "any possibility of establishment either near the broodstock or grow-out facilities is precluded because there are no wild Atlantic salmon populations nearby in Panama or in any of the watersheds near the PEI facility ... ."[148]

Some inputting stakeholders disputed the determination that Atlantic salmon are absent from nearby waters, stating that even though they are not located in the river by the PEI facility, they are found in rivers that the stakeholders regard as sufficiently near for concern.[149]

The FDA and the stakeholders may be using similar information but interpreting it differently. The Agency's sources for Atlantic salmon absence[150, 151] and a stakeholder organization member's cited sources for Atlantic salmon presence[152] both find no salmon in the Fortune River watershed itself or in the two nearest watersheds.[i] Both find the nearest watershed, by sea travel, having Atlantic salmon to be the Cardigan River watershed, located approximately thirteen kilometers (eight miles) down the coast from the Fortune River watershed. None of the cited sources finds salmon in the other watersheds along the same stretch of coast, except that one of the FDA's sources finds salmon in the Brudenell River watershed immediately adjacent to the Cardigan River watershed.[153] The sources find salmon in several adjacent watersheds on the northern coast of the same end of the island, rather than on the southeastern coast where Fortune River is located;[154, 155, 156] the nearest of these watersheds is located approximately 26 kilometers (16 miles) from the Fortune River watershed by sea travel.

A PEI fisheries biologist expressed concern that while salmon normally migrate over sea and then return to their natal river, fish hatched in a hatchery and then released may not necessarily enter their nearest natal or release river upon return, such that they could move into other nearby rivers,[157] and the inputting stakeholders also mentioned the long distances over which Atlantic salmon migrate.[158] The EA states,

> There is no reason to expect any escaped/released AquAdvantage Salmon or diploid [AquaBounty] salmon to undertake a migration to waters of the United States given that these fish are produced from domesticated hatchery stocks, ... In general, as they mature, escaped farmed Atlantic salmon of hatchery origin show a strong tendency to migrate into rivers in the vicinity of the site of escape ... . If AquAdvantage Salmon and broodstock behave similarly, ... [they] should remain in the general vicinity of the PEI broodstock facility in the event of an escape or release ...[159]

The source that the EA cites regarding migration, or return, to rivers in the vicinity of the escape site mentions substantial homing variability depending on escape life stage, time

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[i] Stakeholders also cited surveys finding small numbers of Atlantic salmon nests in Fortune River in 2015 and in Souris River, the nearest river to Fortune to the northeast, in 2014 (See "Atlantic Salmon Redd Surveys," Souris and Area Branch of the PEI Wildlife Federation. Available at http://www.souriswl.com/atlantic-salmon-redd-surveys.html (accessed June 21, 2017).) These survey findings are not directly relevant to the present analysis because the findings or their publication likely post-date the approval or most of the EA development.

of year, whether release occurred into a marine site or a river, and the strain's degree of domestication. It appears that escaped Atlantic salmon homing can be much lower than that of wild Atlantic salmon.[160]

While the contrasting perspectives could represent possessing or accepting different information, they may also further suggest different views regarding what distances should be seen as close to the facility or to its watershed. Distances regarded as proximate for farmed salmon return to nearby rivers may be ambiguous. The FDA's source for the finding that domesticated, hatchery-origin Atlantic salmon tend to migrate into rivers close to the escape site uses for this information research that appears to regard return to rivers within 100 kilometers (60 miles), such as averaging rivers 50-76 kilometers (31-47 miles), from the release site as return to the release area, and return migration to rivers over 200-500 kilometers (100-300 miles) from the release site as straying.[161] Researchers discussing establishment of zones between fish farms and important river populations and migratory routes to prevent both disease transmission and farm escapees' moving into rivers state that "Exactly what distances should be chosen is not clear... ."[162]

Possibly implying different system boundaries or different perceptions of distances to be regarded as notable, inputting stakeholders also mentioned Nova Scotia and New Brunswick as being close to PEI and as also having Atlantic salmon populations.[163] Considering the distances of watersheds on PEI that the FDA did not regard as proximate to the facility, the Agency may well have regarded Nova Scotia and New Brunswick to be too distant for detailed consideration. The Agency could also have limited its investigation of adjacent Canadian areas, and perhaps even its investigation of whether engineered salmon are likely to move into other PEI rivers, due to limiting assessment to events it considered likely to affect the United States' environment.

The FDA and the inputting stakeholders could also be employing different conceptual models regarding how engineered salmon could come to contact wild Atlantic salmon. The EA appears to emphasize the conclusion that eggs and young fish would not survive the immediate conditions to reach other areas, while the inputting stakeholders mention that engineered salmon released as adults or having grown to adulthood outside the facility could migrate and then return to other rivers.[164] The stakeholders appear to believe that fish could enter the waterways at any life stage, mentioning the occurrence of weather events and the possibility of deliberate release. The stakeholders and the FDA could also understand differently the reliability or value of the Cardigan River watershed population, which one stakeholder mentioned is "not a particularly healthy salmon population, but it is more than none."[165] Another stakeholder stated that "There are definitely salmon all over the area,"[166] while the EA references numerous hindrances to the establishment of healthy salmon populations in the area.

The FDA and the inputting stakeholders may also be seeing broader trends differently, placing different emphasis on trends, or considering different timeframes. The EA emphasizes the absence of Atlantic salmon in the Fortune River watershed despite past stocking efforts and describes the largely anthropogenically-induced conditions making the waterway unconducive to salmon, as well as area fish population declines and salmon

fishery closures for conservation.[167] One source that the EA cites also suggests many, though not exclusively, declining trends for salmon fishing in many PEI rivers over the years 1995 to 2009.[168] A local community leader, by contrast, stated that "They are coming back, and the river down Bay Fortune is a potential river for a comeback ... the whole area is seeing a revitalization of the Atlantic salmon."[169] Another inputting stakeholder stated that

> ... the big thing that has changed over the last ten years is they've cleaned up a lot of the streams that were getting silted in from the potato farms. It's the farms that have been damaging the habitat. If this keeps up they're going to have a good salmon fishery soon ... . It's a wonderful story of things coming back.[170]

While several stakeholders involved in the case mentioned PEI salmon proximity as an important concern, it does not appear to have been discussed substantially in either the public comments or in the other input avenues, possibly suggesting that a participatory process could reveal information or perspectives not articulated through the input mechanisms employed.

Significance of Harms and Guarantee of Containment

Many of the disputes between the FDA and inputting stakeholders regarding needed studies or appropriate assessment scope appear to be rooted in differences regarding whether the containment is sufficiently reliable to obviate further concerns. Differences in estimation of likely effect in the event of escape may also affect the level of analysis seen as needed and even the level of reliability ascribed to the containment measures.

The EA largely relies on containment methods and resultant low likelihoods of escape, survival, and establishment to determine that further examination of potential effects is unnecessary.[171] Discussing effects on the United States environment in the event of escape,[172] the EA further emphasizes low likelihood of escape and the biological, geographic, and geophysical containment, as well as the influence of escape scale and frequency on ecological risk. In addition, mentioning studies on related transgenic fish, the EA states that "Collectively, these results suggest that in the event of an escape, AquAdvantage broodstock would have compromised reproductive performance, that is, reduced fitness compared to wild Atlantic salmon."[173] Emphasizing "the lack of wild Atlantic salmon anywhere nearby,"[174] the EA also cites a model for gene flow potential and AquAdvantage Salmon data to suggest that gene flow would be compromised, and it cites other research and researchers suggesting low risk of harm from gene flow. The section also presents other information to support the position that escape and survival would not result in environmental effects, as well as that the fish would be unlikely to migrate to the United States at all or in large numbers.

Other points within the EA further suggest that the FDA believes effects in the event of escape and establishment to be of relative unconcern. For example, in an appendix on "Background on the Biology of the Atlantic Salmon," a discussion of genetic disturbance in interactions between non-engineered domesticated and wild salmon[175] mentions the presence of many anthropogenic selection pressures on Atlantic salmon, and states that

genetically-differentiated population structuring is still evident. The EA states that farmed salmon are typically genetically distinct from local wild populations and that farmed strains can escape and interbreed with local populations. It concludes that

> The persistence of genetic population structuring, even in the extreme circumstance of low population abundance and significant management intervention, indicates a degree of genetic resilience in locally-adapted wild populations ... . Evidence of such persistence ... raises doubt about the capacity of cultured salmon ... to undermine even small populations of wild salmon over time through genetic introgression...[176]

The EA here presents information suggesting, though not systematically analyzing, genetic resilience in native salmon populations, a discussion that could contribute to or reflect lack of concern about effects in the event of interbreeding.

Inputting stakeholders expressed concern about effects that could result from escape and establishment,[177] and they also indicated the perspective that the likelihood of escape was too high not to examine these potential effects. The legal complaint cites fish and environment experts as saying that "it must be assumed that escape will ... occur," as well as that "any interaction between wild and [engineered] salmon must be considered a serious threat," arguing that the EA presents insufficient evidence to conclude that risks to native salmon populations are negligible.[178] The complaint also cites fish and environment experts as expressing concerns about the potential for escape and reproduction, and concerns that escaped fish "could catastrophically harm native salmon populations."[179] Stating that "[t]he environmental risks of GE fish are both very real and potentially disastrous," the complaint references data suggesting a possibility of effects in the event of escape, such as studies finding engineered fish to be more competitive and less discriminatory in food sources than wild type fish.[180] It emphasizes that various mechanisms of effect in the event of escape and survival, such as predation, competition, introduction of pathogens, and altered behavior due to gene flow, may be expected to produce "significant and irreversible" environmental impacts.[181]

The complaint also mentions salmon populations' economic, cultural, social, and aesthetic value for various United States communities.[182] While the EA does not consider these aspects, stating that NEPA calls for inclusion of these considerations only if it were determined that the action significantly affects the environment,[183] these aspects could still inform the degree of harm that might be perceived as potentially resulting from engineered salmon escape or establishment. They could thus implicitly affect willingness to rely on the confinement measures. Understanding and valuing of these factors may be contributions that diverse stakeholders could make to engineered organism assessments able to incorporate them.

While stakeholders may diverge regarding the numerical likelihood of escape, survival, and establishment, some differences regarding whether the likelihood is sufficiently low to rely on containment may be due in part to a difference in estimation of the effects' gravity were escape and establishment or gene flow to occur. This difference may suggest an area in which diverse participant deliberation could enrich an assessment.

System Information

Although they do not appear to have contributed large amounts of new system information to the EA, diverse stakeholders may have contributed, and in a participatory process could perhaps further have contributed, system information.

Infectious Salmon Anemia Virus

An outbreak of infectious salmon anemia virus (ISAV), a severe and contagious disease affecting salmon, occurred at AquaBounty's Prince Edward Island, Canada facility in 2009. The EA discusses the outbreak,[184] mentioning the company's response when the outbreak occurred and the prevention measures it implemented. AquaBounty's 2010 environmental assessment does not mention the outbreak.[185]

The FDA may have found out about the ISAV outbreak through lawsuit plaintiff organizations and their allies. According to an organization member,[186] in 2011 a Canadian organization that works with the plaintiff groups in a "GE fish coalition" inquired with the Canadian government regarding ISAV, through which it discovered the 2009 ISAV occurrence at AquaBounty's Canadian facility. The organization informed other coalition members about the outbreak and publicized the findings on its web site in December 2011. Several coalition members, including plaintiff groups, then contacted government offices, including the FDA and the White House Council on Environmental Quality, to inform them of the incident, referencing the Canadian organization's posted materials. FDA and Council on Environmental Quality emails dated December 16, 2011 suggest that the FDA found out about the ISAV outbreak at that time and point to the Canadian organization's online posting.[187] A letter from the CVM to AquaBounty dated December 21, 2011 states, "It has come to our attention that AquaBounty Technology's Facility at Prince Edward Island, Canada, has tested positive for the presence of Infectious Salmon Anemia (ISA) virus" and requests information about testing, remediation, and prevention plans.[188]

The 2012 draft EA and the final EA discuss the outbreak. The EA includes the statement that Canadian authorities were notified, discusses an FDA inspection of the facility in June, 2012 "with one of its primary goals to examine facility records, [Standard Operating Procedures], and responses ... in relation to the outbreak of ISA that occurred in the fall of 2009," and states that were AquaBounty's application to be approved, the company would be required to inform the FDA of any disease occurrence.[189]

Diverse stakeholders may have contributed knowledge, which the FDA incorporated into its EA, of the ISAV outbreak, suggesting that, as found in other cases, stakeholders may contribute system information to an environmental assessment, including information that narrow experts involved in the assessment view as valuable.

Escape Mechanism

For each of AquaBounty's facilities, the FDA considered two scenarios whereby the engineered salmon could enter a local receiving environment: a catastrophic weather

event causing failure of all of the facility's containment mechanisms, and vandalism or "eco-terrorism" resulting in intentional malicious release.[190] The EA concluded that these scenarios are "extremely unlikely" or "improbable" due to redundant containment measures, infrequency of catastrophic weather events, surveillance and security measures, and other elements. Any other scenarios resulting in escape or release were considered to be much less likely than these, and were not specifically listed.[191]

The security measures described in the EA are designed against outside intruders.[192] The EA does not mention the possibility of employees' taking fish or eggs. At the 2010 VMAC meeting, a temporary Committee member asked about the possibility of employees' stealing engineered salmon eggs,[193] and another meeting participant responded that employee theft of a substantial number of eggs is possible,[194] though the FDA does not appear to have pursued the question in its assessment.

Drawing from personal experience, stakeholders familiar with fisheries expressed the concern that salmon would enter receiving environments through employees' taking fish or eggs home with them. A plaintiff organization member stated, "AquaBounty says groups like Greenpeace will sabotage it. And I say, your employees will want to go fishing, and take out a jar of eggs because salmon are good for fishing. And dump the jar out. That's how they'll get into the wild."[195] Drawing from his own experience, the organization member said that

> Anyone who has ever worked around a fish farm, and this is a fish farm, knows that they're not particularly secure facilities. My uncle worked for a [state-owned] fish hatchery, and when we visited we'd always have trout for breakfast, courtesy of [the state]. The people who are actually doing the work are pretty relaxed about it.[196]

A fisheries biologist local to AquaBounty's Canadian facility commented that

> They can build it as bulletproof as you like, but you can't stop deliberate release, and that could be anywhere. Someone working there could take a plastic baggy, put in some small fish, bring it to their cottage at the other end of the island, where the river could be full of salmon. ... It's human nature to take things out. I built a fish facility in a maximum security prison, people were always smuggling drugs and other things. If they can do that at a maximum security prison, they can do it in other places. I've seen it happen in fisheries all the time, people sneaking live fish home.[197]

As the EA discusses escape mechanisms and the FONSI relies heavily on containment, stakeholders' experiential knowledge regarding aquaculture facility security could represent a valuable contribution to environmental assessment, though the FDA, had it been presented with the information, may also not have found it relevant or within EA scope. Regarding other concerns based on evidence about engineered fish in general, the petition response emphasizes the importance of using information directly addressing the specified facilities and conditions,[198] so personal experience with other aquaculture facilities may not have been viewed as relevant.

Political considerations or perceptions of legal enforcement or incentives could also have prevented examination of theft as a release mechanism. Responding to a public comment concerned about egg theft, the FDA stated:

> ... in order for the eggs to survive it would be necessary to remove them in special containers (e.g., coolers) and transfer them to husbandry condition [sic] that maintain the tightly controlled conditions for survival; this would be difficult for an individual to accomplish surrepetitiously [sic]. Further, there are significant disincentives for employees who would wish to steal the eggs for purposes of release or unauthorized sale, as both would be offenses that would be punishable by civil or criminal penalties.[199]

In addition to viewing the scenario as unlikely, the Agency may be acting on an understanding that the EA need not assess company or employee actions constituting legal violations, including violations of the approval conditions, as a component of environmental risk. The Agency could also be legally or politically constrained not to consider violation of the approval conditions. Still, if the possibility of violation and its leading to release is real, inputting stakeholders' wishing for it to be considered appears understandable as well. The fisheries biologist commented, "It's illegal, but people are willing to do illegal things. If people take them out, that's where the [environmental] impact comes from."[200] The Agency has inspected AquaBounty's facilities and reviewed its records, and its confidence in future maintenance of approval conditions could also arise in part from its experience with the company's practices or from other considerations, such as the company's reputational concerns were violations to be found.

Some individuals believe that employees may have removed engineered fish from the facility. Discussing the possibility of employees taking eggs or fish, the fisheries biologist mentioned having seen salmon that he thought could be from AquaBounty's facility, being reared in a pond in the area. He stated that

> I did see fish in a pond up there years ago, they certainly had all the characteristics of a very fat bodied salmon. They are very distinct, very chubby, very abnormal fish. It could be just a genetic fluke, but it looked exactly like what [AquaBounty] produced. I've seen a lot of fish. ... I've been in their facility, and these had the physical characteristics of their fish.[201]

The plaintiff organization member similarly mentioned that he had been given photographs of fish being reared in ponds and was told that community members who worked in the facility had taken eggs from the facility and were rearing them in ponds. According to the organization member, a former AquaBounty scientist had later confirmed based on the images that the fish indeed appeared to be AquaBounty's engineered salmon.[202] A removal that occurred years before the FDA's approval could be viewed as irrelevant, or the FDA could find such information valuable for assessment or for designing requirements or inspections.

Diverse Stakeholder Contribution

The public comments and critiques of the AquAdvantage Salmon environmental assessment suggest a number of types of contribution that diverse stakeholders could make to environmental assessment. As in other cases examined, diverse stakeholders

offered their perspectives regarding research needed, including areas of inquiry and specific studies, as well as sources of information. They also contributed their delineation of system boundaries and their conceptual models of the system, such as concern regarding monitoring and enforcement, and they provided information about the aquaculture systems.

The present case also suggests areas of potential stakeholder contribution beyond those observed in other cases. Here, stakeholders contributed practical, scenario-specific information and considerations, while other cases did not offer this opportunity because they largely discussed hypothetical or generalized applications. Researchers have argued that multi-stakeholder process participants should be presented with specific scenarios and real details in order to enable meaningful deliberation.[203, 204] The contribution of situation-specific information and considerations supports this position while further suggesting that unanticipated specifics may arise in every scenario, such that stakeholders may contribute to assessment for each organism and application. Stakeholders also offered their perspectives regarding interpretation of study results and other information, and they contributed more extensively than in other cases regarding acceptability of various types or sources of evidence. The other cases focused on early assessment stages such as identifying system components or areas for research, and did not progress to the point of interpreting information to inform decision-making. The present case suggests that stakeholders could contribute in these areas as well.

In most if not all instances the FDA declined or refuted inputting stakeholders' contributions or critiques. In some instances, the Agency based responses on scientific and assessment methods, such as differing determinations of when reliance on an approximating assumption or proxy studies is appropriate. In these instances, for any given divergence it may be impossible to predict how a group collaboratively producing an assessment would have proceeded, though it is likely that overall, diverse stakeholders' perspectives could contribute to assessment. In some instances, the Agency's responses cited statutory constraints. These occurrences suggest challenges in integrating stakeholder input into existing governance.

Process Observations

The case suggests a number of observations that may be informative in considering multi-stakeholder processes. It provides insights regarding challenges of integrating diverse stakeholder input with existing governance structures, suggests that apparent concerns about diverse involvement may also stem from dissatisfaction regarding substance, indicates an important role for diverse experts in addition to non-technical stakeholders, and provides views of how values can manifest in assessment, including how they may be expressed through technical assessment decisions and treatment of uncertainty.

Multi-Stakeholder Processes and Existing Governance

Although government agencies may receive diverse stakeholders' input through public comments and other avenues, existing governance structures do not typically include

participatory multi-stakeholder processes, in which diverse stakeholders work together to develop an assessment or other product to inform assessment or decision-making. In such a process, the regulatory agency or other decision-maker could participate as a member of the group, or its decision-making could be otherwise informed by the deliberation products or outcomes.[205] While diverse stakeholder involvement may contribute to assessment, inclusion within existing governance structures presents challenges.

Mismatches

A number of mismatches exist between existing governance and conditions identified as ideal for stakeholder contribution, including ways in which governance structures may be challenged in incorporating stakeholder input. The AquAdvantage Salmon regulation process may experience some of these mismatches.

Some rules governing regulatory agencies' conduct do not permit involvement of diverse parties in agency review or decision-making details. Even when involvement is permitted, an agency may be concerned about political implications of appearing to consult with interested parties regarding a decision, even if the group's composition is designed for balance in perspectives. Existing statutes may include other practical hindrances to broader involvement, such as trade secret protections. In its response to the Citizen Petition, the FDA states that it limits public participation when so required under laws prohibiting disclosure of confidential commercial information.[206] The Agency also notes that AquaBounty gave the FDA permission to make publicly available information that the Agency would otherwise not be permitted to release.[207]

Many regulatory processes' application submission procedures may hinder incorporation of diverse stakeholder input, in part because the input likely comes after an assessment has been drafted. In many United States regulatory agency procedures, an application sponsor, such as a company seeking manufacture or marketing approval, submits data to support the application, and if an environmental assessment is needed, the sponsor includes an environmental assessment with the supporting information. If the agency then produces an assessment, the company's already having submitted an assessment could frame or otherwise affect the considerations. In addition, when broader stakeholders submit input after a draft assessment has been produced, incorporating the input may be more difficult than when the diverse stakeholders are involved from earlier stages, because when considering reasonable alternatives, one may be more likely to maintain an existing decision than to make changes, whereas input may be more readily incorporated if it is discussed before decisions are made. In addition, once a draft has been produced and preliminary conclusions drawn, the assessors have an interest in maintaining and perhaps defending their work, particularly if suggestions appear to represent reasonable alternatives that some individuals may prefer rather than corrections without which the assessment is indefensible.

As typically conceived, participatory stakeholder processes require substantial time and resources. An agency or other decision-maker must decide that the benefits of broader involvement are worth the expenditure. Some researchers have cited a moral imperative

to involve stakeholders in decisions that could affect them.[208] If diverse stakeholders are involved to contribute to an assessment's scientific quality, the decision-maker or other authority must believe that the expected improvement is worth the time and resources needed to involve diverse participants.

Researchers discussing transgenic organism assessment and governance have noted that diverse involvement could reduce conflict and increase societal confidence in decisions.[209] The reduced conflict could ultimately conserve decision-maker time and resources. Most of the stakeholders submitting public comments or petitions regarding the salmon assessment expressed concerns. This predominance may be expected because the assessment found no significant impact and the preliminary determinations on which comments were submitted included a FONSI and an application approval, so stakeholders supporting approval may have felt less imperative to offer input. However, some public comments did "express[] a favorable opinion about the AquAdvantage Salmon application noting the thoroughness of the scientific, risk-based review and the benefits of AquAdvantage Salmon for sustainable aquaculture."[210] The company submitted the initial environmental assessment and interacted directly with the Agency in other ways. In a participatory multi-stakeholder process all of the parties would work together, which could enable parties to address disagreements directly and produce a broadly suitable assessment or other product, which could reduce decision-maker time and effort in seeking to prevent and then addressing dispute. Observers of the FDA's process have suggested that the AquAdvantage Salmon review was substantially lengthened by the Agency's efforts to reduce negative public reaction through such avenues as holding the public VMAC meeting, producing its own environmental assessment, and responding to public comments more extensively than may be usual. A decision-maker may consider how a participatory multi-stakeholder process may compare with these efforts, combined with post hoc efforts to explain or defend the decision, in resources required. However, a participatory process does not guarantee lack of conflict, and the effort required may deter decision-makers from involving stakeholders directly in the assessment process.

While diverse stakeholders are able to contribute information aligning with assessment scope as defined by the governance structures, some ways in which stakeholders may contribute may not accord with existing governance. Kapuscinski *et al.* emphasize that diverse stakeholders can contribute to an assessment process involving articulating a problem that a biotechnology application may contribute to solving, determining whether it is a substantial problem, identifying other approaches to addressing the problem, and evaluating the alternatives, including the biotechnology application.[211] Many governance structures, such as those calling for approval upon satisfaction of certain criteria such as safety and effectiveness and even those framing decisions in terms of costs and benefits of the application alone, cannot readily incorporate this approach. In the present case diverse stakeholders offered alternative courses of action that could address fish supply problems, though the Agency did not find consideration of these alternatives to fall within its scope directed by statute. Researchers have also stated that broader considerations, such as ethical and societal implications, should be incorporated into assessment,[212] but many existing governance structures are not designed to include them.[213] PoET-Wilson workshop participants raised human health, philosophical,

political, and other considerations outside of that workshop's scope of identifying research needs for ecological implications.[214] In the present case, public comments argued that the EA should have considered economic, social, and cultural effects, though the Agency had found these considerations to be outside of EA scope.[215]

Approaches

Government decision-makers or others could consider various approaches to addressing challenges of incorporating diverse stakeholder processes into governance.

Decision-makers may choose not to include diverse stakeholders in any participatory process directly tied to governance or regulatory decision-making. They could determine that broader involvement should be limited to public comments and other non-participatory input avenues commonly utilized in United States regulatory processes. In this event, and because most governance does not now incorporate diverse participant processes, it may be desirable to consider whether and how diverse stakeholders' information and perspectives could access decision-making avenues, such as through advisory relationships with biotechnology labs or companies or through other alternative means. Policy researchers found that synthetic biology researchers developing technologies for eventual commercial application benefitted from diverse participant workshops identifying regulatory, environmental, and other considerations for their technologies.[216] The National Science Foundation's Synthetic Biology Engineering Research Center (NSF SynBERC), which supported some of the scientists' work, co-sponsored these workshops and encouraged scientist participation.

Decision-makers could conduct highly structured processes in which diverse stakeholders are asked to contribute particular types of input according with the decision-maker's perceived needs and constraints. The OPPT tier testing workshops may have adopted this type of approach, providing diverse participants with discussion questions and example tier testing schemes and guiding them through tasks to provide the desired information and schemes. The participants provided information and developed schemes largely as desired, and regulatory officials convening the workshop viewed it as successful. However, some stakeholders may not find this type of framework appropriate or satisfactory. In controversial areas it may not serve to reduce conflict or to increase societal confidence. This structured approach would likely largely prevent receipt of input falling outside of decision-makers' perceived scope, a limitation that the decision-maker may desire, and it may well prevent receipt of alternative views that could fall within scope, a limitation that the decision-maker may or may not desire.

Decision-makers could explore integrating stakeholders into governance in ways that provide them with responsibility for the legal and political implications of the decisions in which they are involved. As typically conceived, multi-stakeholder processes may advise an agency or other decision-maker, but the agency is responsible for decision-making and for decisions' legal and political ramifications, as is the FDA regarding the AquAdvantage Salmon approval. An advising body's not bearing responsibility for the decision, or, if the agency participates, only one participant's bearing responsibility, can

create or exacerbate differences in motivations, concerns, or statutory interpretation, which may increase likelihood of the stakeholders' offering advice that is not politically or legally practical and of the decision-maker's not acting on the advice. Integration faces practical challenges, but it may warrant exploration.

Diverse stakeholder groups could be involved with decision-makers on an ongoing basis. Ongoing involvement could result in stakeholders' better understanding governance structures, enable avenues for stakeholders to share responsibility for decision ramifications, or help enable provision of application information regarded as confidential. On the other hand, ongoing involvement could limit participation, such as to individuals with the time to participate on an ongoing basis. Conflicts of interest could arise, and it is unclear how broader stakeholders whom the participants may be meant to represent would respond to an ongoing committee structure; attention to independence and other political considerations would be needed. Ongoing involvement may also limit representation of individuals distinctly relevant to each assessment, such as local residents. If participation distinctive to each assessment were desired, special efforts would be needed to integrate these individuals for each process.

Governance structures themselves could be changed to enable their incorporation of diverse stakeholder contributions. Governance changes could include procedural changes that would facilitate diverse stakeholder involvement and inclusion of contributions, as well as changes in approval criteria or other aspects of decision-making that could enable incorporation of contributions more broadly challenging typical assessment or regulatory scopes. In the present case, criteria established in the 1938 Food, Drug, and Cosmetic Act underpinned the FDA's overall review framework and may have constrained the environmental assessment. Though existing governance may not readily change to enable incorporation of stakeholder considerations, exploration in this area may prove beneficial.

The AquAdvantage Salmon assessment process reveals tensions between stakeholder involvement and existing governance. Work is needed to explore how and when to integrate participatory multi-stakeholder processes with governance, and exploration is also needed of how stakeholder knowledge and considerations can contribute to decision-making when governance capacity to receive and incorporate diverse input is limited.

Substance and Acceptance

In addition to substantive contribution to assessment, another often-cited reason for stakeholder inclusion is to garner acceptance of a technology or a decision.[217] However, nominal inclusion simply to gain acceptance may not be effective. Kapuscinski and colleagues state that in order for a multi-stakeholder process to be viewed as legitimate, decision-makers must use the results to inform their decisions.[218] The present case suggests that stakeholder concerns articulated or understood as desire for involvement may in fact be substantive, and as such, involvement may not in itself produce acceptance. In addition, when stakeholders are excluded, they may be more likely to object to the process or the outcomes for substantive reasons.

Although the FDA's process included more opportunities for input than a New Animal Drug Application review might typically involve,[219] various stakeholders criticized the FDA as ignoring stakeholder input regarding both regulatory mechanisms and environmental assessment specifics. These criticisms suggest that the process, which many stakeholders viewed as closed or unresponsive, caused discontent. However, this discontent may have been based in concerns about substance rather than only in dissatisfaction with the process.

The legal complaint states that the FDA did not take scientific experts' and others' concerns and recommendations into account in preparing drafts or the final environmental assessment.[220] It also mentions that many stakeholders, including scientists, legislators, and plaintiff organizations raised concerns about the sufficiency of the environmental review and called on the FDA to prepare a full EIS rather than merely an EA,[221] and it charges that the 2012 draft EA and the final EA are very similar to the 2010 environmental assessment that AquaBounty had prepared.[222]

Any of the points that the complaint frames as problems of responsiveness are also, or primarily, substantive. For example, the complaint states that "Comments on FDA's 2012 draft EA from Drs. Kapuscinski and Sundström explained that FDA continued to ignore their 2010 recommendations for conducting an adequate risk assessment that is consistent with current science, a failure that rendered the draft EA 'weak and scientifically unacceptable.'"[223] The complaint's mention of stakeholders' calling for a full EIS is also substantively based: The plaintiffs believe that an Environmental Assessment is insufficient to assess the salmon's environmental impacts and that the problem requires an EIS.[224]

It is unclear to what extent perceived unresponsiveness itself caused discontent and to what extent the plaintiffs were unsatisfied with the assessment itself, and further disgruntled that contributions to improve it were not incorporated. Although many stakeholders likely felt that the process still involved too little public or stakeholder involvement, the FDA's indications that the AquAdvantage Salmon review process involved more input opportunities than most Agency review processes may further suggest that inputting stakeholders were concerned with substance rather than entirely with involvement. While incorporation of stakeholder input could garner acceptance because of the responsiveness itself, it appears more likely that acceptance would be generated because the assessment is thereby improved according to stakeholders' views of what it should include. Accordingly, processes nominally including stakeholders but not substantively incorporating their views, as may occur with many multi-stakeholder deliberation workshops for new technologies,[225] may not garner the acceptance they expect.

Diverse Expert Participants

The Citizen Petition and the lawsuit complaint reference many points to scientists expert in such areas as genetically engineered fish and risk assessment; fish biology, ecology, and gene flow; and fish conservation genetics, and to FWS and NMFS scientists.

Similarly, public comment contributors include scientists, regulatory officials from other countries, and other subject area experts. In the OPPT tier testing workshops, the PoET-Wilson workshops, and Dana *et al.*'s diverse participant workshop as well, many participants possessed extensive scientific and technical expertise in relevant areas and might easily be construed as "narrow experts."

These experts represent diversity that may contribute to environmental assessment. One may conclude that rather than including only an extremely limited group of scientific or risk assessment experts to conduct an environmental assessment, participation should be broadened to include larger numbers and larger diversity of experts, such as experts in different areas of ecology, biology, genetics, and risk. It appears that even such diversity of experts is often omitted from risk assessment processes, and that it may contribute positively to assessments. Diversifying participation and expertise beyond a small group of experts who may typically conduct an assessment may be particularly valuable for emerging technologies, in which the precise expertise needs may be less clear and in which individuals typically conducting assessments may be less familiar with the technologies and applications and the questions they raise. In addition, researchers have identified mismatches between existing governance mechanisms and emerging technologies,[226] such that regulatory officials may be faced with assessment tasks for which their experience is not ideally suited. Regular inclusion of diverse participants may help mitigate the effects of such mismatches.

Each case also involved individuals with expertise in areas beyond ecology, genetics, and risk, such as in farming and conservation in Dana *et al.*'s workshops, and in such areas as law, insurance, and conservation in the PoET-Wilson workshops. In the present case many public comments and complaint contributions came from individuals and organizations not regarded as scientific or technical experts. These individuals also made potentially valuable contributions to their respective processes.

An expert in multi-stakeholder deliberation for risk assessment has discussed the question of whether stakeholders in the narrow sense of parties potentially affected by an action must themselves participate in an assessment process, or whether experts representing stakeholders' interests suffice. One perspective is that experts are sufficient because a broad enough suite of experts will think of every point that the stakeholders they represent may raise. The alternate perspective is that expert representation is different from the stakeholders' own voices, and that the stakeholders themselves are needed to speak from their own point of view.[227]

Whether diverse stakeholders themselves must be included may depend in part on the purpose of including stakeholders, as well as, if stakeholders are included in part for their knowledge- or perspective- based contributions, on the types of contributions desired and who might possess the needed knowledge.

The present case suggests that if participant involvement is sought in part for diverse knowledge or for knowledge representing diverse interests, rather than simply to gain acceptance, including experts who reflect disparate interests may be important, as

stakeholders in the narrow sense may lack the knowledge to support rigorously even their own interests. For example, stakeholders from fishing communities or tribes to which salmon are central may be able to express the importance of unadulterated wild salmon stocks, while experts like Kapuscinski and Sundström may be better able to advance scientifically an assertion that the approval could result in adulteration of wild salmon populations. By the same token, a biotechnology company employee knowledgeable in the technology and perhaps in environmental or regulatory considerations is more likely to be invited to participate in a multi-stakeholder deliberation than is, for example, an employee from the financial office who can speak primarily about the company's interest in making money.

Although diverse scientific experts, or scientific experts possessing diverse perspectives, may be important participants in multi-stakeholder processes, diverse stakeholders in the narrow sense, and individuals lacking scientific or technical background, may contribute valuably as well. The present case reveals an important role for non-technical knowledge. For example, non-technical stakeholders contributed an escape mechanism, employees' removing eggs for their personal use, and knowledge that such removal may have occurred. Stakeholders in the narrow sense, or other participants who may lack scientific background, may also contribute values or perspectives that they may be better able to articulate than may experts who do not share the stakeholders' experiences or potential to be affected.

Values and Perspectives

Disagreements between the EA and the diverse stakeholders' comments may in part reflect differences in underlying values and priorities. These values and priorities could have contributed both to the assessment and to the inputs, including on points articulated as predominantly technical. Influence of values is inevitable in scientific risk assessment, and it may also be inherent in statutes or other components of governance that can influence or constrain assessment conduct. Examining the AquAdvantage Salmon review, researchers have argued that the influence of values, or bias, in any regulatory assessment indicates a need for diverse stakeholder involvement.[228]

Governance and Values

Individual assessors bring their values to bear in decisions regarding assessment conduct. Statutes or other components of governance calling for or otherwise relating to an assessment or decision may also incorporate values or priorities that can influence the assessment.

For example, Congress frames the NEPA statute by saying in part:

> In order to carry out the policy set forth in this Act, it is the continuing responsibility of the federal government to use all practicable means, consistent with other essential considerations of national policy, to improve and coordinate federal plans, functions, programs, and resources to the end that the Nation may –
>
> ... fulfill the responsibilities of each generation as trustee of the environment for succeeding generations; ... attain the widest range of beneficial uses of the

> environment without degradation, risk to health or safety, or other undesirable and unintended consequences; ... preserve important historic, cultural, and natural aspects of our national heritage, and maintain, wherever possible, an environment which supports diversity, and variety of individual choice; ...[229]

This articulation advances values and instructs the government to direct efforts toward upholding them.

The NEPA regulations also imply and thus dictate values when they define "effects" and "impacts" as including "ecological ..., aesthetic, historic, cultural, economic, social, or health, whether direct, indirect, or cumulative."[230] They may also do so in stating that

> ... economic or social effects are not intended by themselves to require preparation of an environmental impact statement. When an environmental impact statement is prepared and economic or social and natural or physical environmental effects are interrelated, then the environmental impact statement will discuss all of these effects on the human environment.[231]

The EA understands this provision as omitting from EA requirements considerations beyond effects on the physical environment and requiring these broader considerations only if the agency determines the action to have a significant effect on the physical environment.[232]

The Federal Food, Drug, and Cosmetic Act may practically impose values on a review by calling for approval if a drug is found to be safe and effective for the drug's users, or, for animal drugs, the animals and people consuming it, without calling for consideration of environmental or other broader effects. Some current practical ramifications of the Act's basing approval on safety and effectiveness without considering environmental or other effects may have arisen long after the statute's 1938 origin, for example through changes in drug production processes, types of products regarded as drugs, or environmental awareness, but the statutory language still affects review and decision-making.

The statutory framework in effect isolates consideration of drugs' effects on their users from broader environmental or societal implications. While mismatches between regulatory frameworks and governance needs or considerations that some regard as important may be particularly acute for emerging technologies, standard pharmaceuticals also raise concerns regarding environmental effects, such as effects of synthetic hormones, antibiotics, and other drugs on aquatic life.[233, 234] Researchers investigating pharmaceuticals' environmental effects have complained that

> Regulations associated with drugs are generally overseen by human health agencies, which usually have limited experience in environmental issues and until recently pharmaceuticals were not seen as potentially toxic substances. Therefore, ... they have not been subjected to detailed research regarding their possible environmental effects.[235]

This segregation of environmental effects, which are assessed, if at all, through statutes that may not directly affect approval, from effects on intended users, itself implies and imposes values that are actualized within regulatory review.

Framing

The EA and the legal complaint frame strikingly differently the context in which the AquAdvantage Salmon was developed and reviewed for approval. In a section providing background for the development of the salmon,[236] the EA describes increasing global demand for fish protein, the importance of fish protein in human diets, the United States government's recommendation that Americans consume more seafood-based protein sources, and health findings regarding fish in contrast with other protein sources. It discusses the global problem of overfishing, mentioning that overfishing contributed to the Gulf of Maine Atlantic salmon's being listed as an endangered species, and describes current and projected increases in commercial aquaculture to meet increasing demand for fish protein in a context of declining wild fish stocks. The discussion also emphasizes the point that demand for seafood is expected to continue to increase.

The complaint, by contrast, describes[237] the present vulnerability of wild fish populations, including Atlantic and Pacific salmon and closely related species, and mentions the point that anthropogenic pressures have decimated and continue to threaten these populations. It discusses the salmon's ecological importance, as well as its economic and cultural importance for coastal communities and tribes and recreational, commercial, and subsistence fishermen. The complaint also mentions the ecological and economic value of the integrity of individual salmon populations and runs.

Both of these sets of points may formally fall outside of the scope of elements that the EA considers, but the FDA and the plaintiffs included them as background for framing the problem or explaining the context. These framing differences may relate to different underlying priorities or concerns that can affect the conduct of an environmental assessment.

Technical Points

The diverse stakeholders' comments discuss a number of technical points that the EA also treats. It is likely that in some of these, the parties' different underlying perspectives affected how each viewed the technical points.

The EA relies heavily on data suggesting low likelihoods of escape, survival, and interbreeding or establishment in its determination that pathways to environmental effects would not occur, while many stakeholders believed the risks to be too high to determine no significant effects based on these low likelihoods. It appears that the inputting stakeholders may have viewed the potential results in the event of escape and establishment with more concern than did the FDA, and this difference may have contributed to the parties' respective perspectives on whether the effects' likelihood could be regarded as negligible.

Differences in willingness to accept approximating assumptions regarding sterility could also reflect differences in underlying concerns. The FDA largely accepted the sterility measures, particularly combined with the all-female population, as sufficient basis to approximate sterility or reproductive containment, despite noting that the process of

triploidy induction is not 100% effective, that triploidy does not guarantee sterility, and that one of the facilities would contain fertile broodstock, including some males. Many stakeholders viewed the assurances as insufficient to assume sterility or reproductive containment. This technical dispute regarding when an approximating assumption is appropriate and the types of evidence needed or the combinations of containment mechanisms needed may well stem in part from underlying differences in concern about the engineered salmon's effects or from other differences in priorities or perspective.

The inputs indicate a number of other points regarding which stakeholders felt that evidence or analysis insufficiently supports the EA's conclusions. Each of these disagreements may have scientific basis and substance, while for any of them the differences could also relate to underlying differences in perspective or priorities. Researchers have argued that a reason to include diverse stakeholders within technical assessment processes is so that the narrow expert assessors' values or perspectives not be the sole perspectives underlying the assessment.

Uncertainty

The EA and the complaint attach uncertainty to different components of the analysis, and they use the concept in overlapping as well as opposing ways that further their respective conclusions and may reflect underlying values. Other diverse stakeholder inputs such as the public comments generally resemble the complaint in their use of uncertainty.

The EA references uncertainty primarily in order to indicate that further investigation or analysis would be fruitless, and to suggest that it is therefore unnecessary or will not be undertaken. It also references uncertainty to dismiss or cast doubt on information, as well as to suggest why a containment or mitigation measure should not be relied upon. The complaint references uncertainty to indicate potential unforeseen magnitude of effect and suggest the need for caution, as well as for the EA's latter reason, to indicate that a containment or mitigation measure should not be relied upon.

In discussing environmental implications of the "no action alternative," the EA states that if the salmon were not approved for marketing in the United States, AquaBounty could cease production, or it could continue production without intending to market the salmon in the United States. Though it mentions that production under less stringent containment or regulatory oversight would more likely result in effects due to higher likelihood of escape and establishment, the EA states that assessment of environmental impacts for the no action scenario is "highly uncertain" because the rearing locations and conditions are not foreseeable, and therefore that "... it is not possible to perform an accurate, comprehensive cumulative impacts assessment ... ."[238]

In discussing environmental implications were the engineered salmon to escape and survive, the EA states that "there is considerable uncertainty associated with predicting or quantifying any particular outcome."[239] The subsequent discussion mentions the possibilities of resource competition or interbreeding, while emphasizing engineered salmon's poor competitive performance and the low likelihoods of survival and

establishment. In introducing the discussion, the EA also cites scholarly discussion of uncertainty in engineered Atlantic salmon risk assessments. The scholarly discussion as cited indicates that variations in characteristics are strongly influenced by background genetics, environment, and age rather than only by the presence of the transgene. The EA's discussion does not directly address or analyze the uncertainties. Overall, it implies that uncertainty suggests that further investigation or attempts to establish risk information would be fruitless and that any need for concern likely cannot reasonably be established.

In describing AquAdvantage Salmon behavior, the EA mentions studies finding coho salmon engineered for growth to be more competitive, less discriminating in choice of food sources, and better at using lower quality food than non-engineered coho salmon. While it mentions that these characteristics could result in ecological effects, the EA concludes that "The extent to which this information on GE coho salmon can predict the behavior of GE Atlantic salmon is ... unknown."[240]

By contrast, the complaint refers to uncertainty primarily to suggest that lack of full understanding of risks implies a need for caution and for fuller scientific assessment. For example, the complaint states that "Independent, expert scientists have made clear that the kind and extent of harm escaped or released GE salmon may impose on natural environments and ecosystems are unique and extremely uncertain. These scientists have warned... that FDA must utilize additional, more comprehensive studies and up-to-date scientific methods to assess risks."[241] The complaint notes that an agency must consider the degree to which effects are uncertain or unknown in determining an action's significance under NEPA.[242] It also states that the Endangered Species Act "requires federal agencies to give the benefit of the doubt to listed species and places the burden of risk and uncertainty on the proposed action."[243] Furthering its apparent view of uncertainty as often representing areas in which further investigation would be fruitless, the FDA responded to calls for further studies to address uncertainty in part by pointing out that some uncertainty will always exist and that further studies may reduce but will not eliminate uncertainty.[244]

The EA and the complaint attach uncertainty and thus unreliability to different confinement measures. The EA mentions that the Agency considered alternative types of enclosures for rearing the engineered salmon, including net pens and closed, water-based systems such as floating tanks. The EA states that net pens have not proven reliable in preventing escapes while the water-based tanks are new and their ensuring containment has not been sufficiently documented, and determines that uncertainty associated with these alternatives is too high.[245] Particularly regarding the net pens, the EA indicates not that the pens themselves have uncertain performance, but rather that the increased chance of escape increases uncertainty, stating that "... these would be significant increases in the uncertainty associated with possible outcomes should AquAdvantage Salmon escape from ocean net pens in significant numbers."[246] The EA appears to be suggesting that a higher chance of escape would increase the relevance of or need to consider the resulting uncertain situation, or that due to uncertainty regarding results of escape, a higher chance of escape increases overall uncertainty. The complaint attaches uncertainty to the

containment system that the Agency chose, arguing that the FDA should have prepared an EIS rather than relying on mitigation strategies the complaint describes as "uncertain, unanalyzed, and unenforced" to prepare only an Environmental Assessment.[247] It appears that the Agency sought to reduce uncertainty by specifying containment measures that it viewed as sufficient to prevent escape and establishment, and to which in combination it ascribed little uncertainty as to reliability. The inputting stakeholders, by contrast, did not ascribe the same level of reliability to the containment measures and did not view the measures as negating the need to address uncertainties associated with escape and establishment. Unlike the Agency, inputting stakeholders also do not hold the authority to impose conditions that they believe would reduce uncertainty. In urging further alternatives analysis they suggested measures, such as granting a smaller project or particular reporting requirements, that they may have felt would reduce uncertainty, even though they did not frame the suggestions in these terms.

Overall, the EA appears to reference uncertainty largely to suggest that further investigation would not be valuable or to cast doubt on concerns, while the complaint and other inputs reference uncertainty to suggest a need for further investigation or for cautious avoidance of actions that could cause harm. When the FDA and the inputting stakeholders agree on uncertainty's implications, such as in confinement mechanism reliabilities, they differ in where they identify uncertainty. Each of these perspectives may have some validity, and each may stem in part from the parties' underlying perspectives rather than from purely scientific evaluations of evidence. Determining how to treat uncertainty is important in risk assessment, and multiple valid approaches may exist for any particular instance. A participatory multi-stakeholder process could include discussion of implications and handling of uncertainty, as well as of where uncertainty exists, and diverse stakeholders may contribute their perspectives in this area.

Diverse Contribution of Values

Any scientific assessment must incorporate decisions regarding what types of information are reliable or sufficient, when approximating assumptions are appropriate, and how to treat uncertainty, and judgments can stem from values along with scientific understandings. Narrow expert assessments are not devoid of values' influence; they may accept the assessors' values and priorities as those that should shape the assessment, and in processes constrained by statute, values incorporated into the statute have influence as well. Involving diverse stakeholders in an assessment can enable consideration and influence of diverse perspectives throughout the process. By contrast, processes entirely conducted by narrow experts or those in which a few experts conduct the assessment and present results to diverse stakeholders to choose among options ignore the role that values can play in how an assessment is conducted.

This case suggests that differences in values, perspectives, and priorities can manifest through discussion of technical points. Explicit discussion of values in a multi-stakeholder process may be beneficial, or the best approach may be to allow perspectives to manifest through practical discussion. It is possible that for individuals with technical expertise, putting values into practice through completing a task, such as components of

an environmental assessment, is the best approach, while citizens lacking technical background may lack the knowledge needed to complete the task based on their values and may better influence a process through direct articulation of values and concerns, or other approaches may be most appropriate. This area remains to be explored.

Insights from the Salmon Assessment and Input

Examining the FDA's environmental assessment for the first genetically engineered salmon to receive United States regulatory review, along with diverse stakeholder comments and criticism, reveals a number of types of contribution that stakeholders may make to an environmental assessment. Inputting stakeholders offered contributions of types that appeared in other cases, such as suggesting system components and boundaries, identifying research that could contribute to assessment, and offering perspectives regarding appropriate information sources. They also contributed in additional ways, such as by offering interpretation of study results, calling for additional analyses, and introducing new information uniquely pertinent to the scenario. These findings suggest further how stakeholders may contribute to assessment, particularly to processes including data analysis and decision-making stages for a particular biotechnology application. Diverse stakeholders appear to have offered contributions reflecting each of the four hypothesized sources of stakeholder contribution to environmental assessment: They offered knowledge of the ecological and aquaculture systems; brought to bear different conceptual models of the system, including boundaries; contributed in ways that could enable available knowledge to keep pace with assessment needs, such as by offering study approaches, research needs, and information that might not otherwise be readily available; and they brought their values to bear in their recommendations.

The Agency declined or refuted most or all of the inputting stakeholders' suggestions and criticisms. It is impossible to know what contributions a collaborative multi-stakeholder group would have incorporated. Several aspects of the process, including when in the assessment process broader input is introduced and statutory constraints on the review, may affect what contributions are adopted.

The case suggests additional insights regarding multi-stakeholder process conduct. Integration of participatory stakeholder processes with existing governance presents a number of challenges, and approaches to integration as well as alternative avenues for stakeholder contribution to decision-making should be explored. Including in multi-stakeholder processes scientific and technical experts diverse both in areas of expertise and in underlying perspectives or values, as well as non-technical stakeholders, may be important. Values, perspectives, and priorities appear to play a role in both the diverse stakeholder input and the Agency's environmental assessment, including on points articulated in technical terms. Statutes and other governance elements may also impose values and priorities on an assessment.

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Chapter 6

Findings and Extensions to Societal Processes

Findings from the cases support the hypothesis that diverse stakeholders may contribute to environmental assessment for biotechnologies in ways that could aid assessment quality as well as integrity and functionality. Alongside interest in stakeholder involvement, researchers and practitioners are increasingly interested in broad societal involvement in environmental assessment. The cases suggest a role for such involvement and provide some indications regarding likely societal participant characteristics and needs. It appears that broader societal involvement could contribute to assessment quality as well. The cases reveal practical considerations that may be of value in enabling multi-stakeholder and societal contribution.

Findings: Diverse Stakeholder Contribution

The cases indicate that diverse participants contribute to assessment through the four mechanisms hypothesized from single workshop observations and theoretical suggestions, as well as through an additional mechanism (Figure 2). Diverse participants contribute system knowledge, employ diverse conceptual models, enable knowledge available to the assessment to keep pace with technology development and assessment needs, and contribute based on their values, suggesting avenues for positively affecting assessment content. They also exhibit interest in challenging conventional assessment approaches. As researchers have suggested that typical methods are insufficient, particularly for emerging technologies, such challenges may contribute to the conduct of effective assessments.

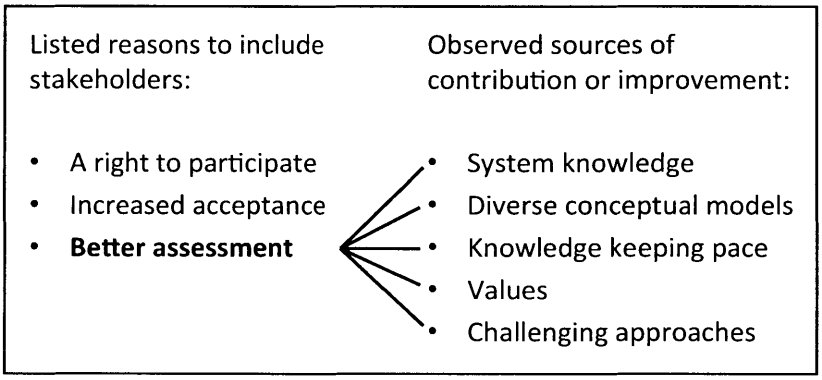

Figure 2. Listed reasons to include stakeholders and observed sources of contribution, including the four hypothesized sources and challenging established assessment approaches.

System Knowledge

In each of the multi-stakeholder cases, participants contributed knowledge of systems relevant to the assessment, including information to which narrow expert assessors might have limited access.

In the OPPT tier testing workshop, industry members contributed information about industries in which microbial biotechnology applications were expected, including detailed accounts of industry practices, organism characteristics that may be desired, and modifications that could be performed for each use. Participants also generated lists of possible release and dispersal mechanisms, pathogenic organisms, and characteristics

associated with pathogenicity, and they contributed other information based on knowledge of particular systems.

In the PoET-Wilson workshops, industry members provided information about industrial systems, ecologists provided information about likely receiving environments and identified mechanisms whereby engineered organisms could affect them, technology developers contributed information about their technologies, and others contributed system information as well. Participants also contributed insights from their personal experiences, such as experience conducting ecological research studies.

In the salmon case, inputting stakeholders may have introduced knowledge of a disease outbreak in the Canadian facility, indicated information about an escape mechanism, and advised based on their expertise regarding particular analyses that could be conducted.

Diverse Conceptual Models

Participants appear to have contributed based on diverse conceptual models of the systems. Unlike in Dana *et al.*'s workshops,[1] participants did not draw or describe their conceptual models explicitly, but underlying differences in system perceptions are evidenced. Diverse stakeholders' conceptual models are not necessarily more correct or more complete than those of narrow experts. Diverse conceptual models are valuable in enabling assessors to consider the systems from a variety of perspectives to gain insight into system functioning and potential effects that would not be evident from viewing the system using a single conceptual model. In discussing participatory risk assessment approaches, Kapuscinski and colleagues explain that

> It is not necessary, and often inadvisable, to agree on a single conceptual model. If divergent opinions within stakeholder and expert groups result in two or more different conceptual models, and all are consistent with existing scientific information, then analysts ... should consider whether or not all models need to be carried through the risk assessment and analysed as model uncertainty...[2]

In the OPPT workshop, participants may have implied different conceptual models when they described a variety of mechanisms whereby an engineered microbe could come to affect a receiving environment and when they incorporated consideration of a broad set of potential exposure sites and dispersal mechanisms. These perceptions carry practical implications for testing and assessment. Participants also likely implied different conceptual models when they differed regarding necessary test conditions, suitability of microcosms, and escape likelihoods.

In the PoET-Wilson workshops, participants offered a variety of perspectives regarding conditions and comparators for testing organism behavior. While many participants suggested testing under conditions meant to mimic potential receiving environments, a participant suggested instead testing an engineered strain in the parental strain's native conditions to compare fitness. Many participants recommended microcosms, but a participant suggested the importance of analyzing the engineered strain in the presence of a broader representation of the ecological community, including grazers, which may

often be omitted from microcosm studies. Offering another conceptual model, a participant suggested that fitness's typical context-specificity could be leveraged for prediction, suggesting that considering in which niches the organism is most fit could aid in mapping its behavior in receiving environments. Participants also implied diverse conceptual models when their perspectives differed regarding whether testing needs and acceptable results could be standardized, and regarding the location of responsibility for new technology and the acceptability of imposing testing burdens on developers.

In the salmon case, inputting stakeholders and FDA assessors may have exhibited different conceptual models when they differed regarding whether or not containment may obviate detailed examination of environmental effects in the event of escape and establishment. The FDA and inputting stakeholders may also have exhibited different system conceptual models when they appear to have differed in their willingness to rely on the existence of legal penalties and the potential for FDA inspections to ensure maintenance of containment conditions. They also appear to have differed regarding types of alternative actions that should be examined as "reasonable." The environmental assessment regarded reduced fitness among the engineered fish as indicating that they would not negatively affect receiving ecosystems, while the plaintiff stakeholders argued that wild type salmon interbreeding with less fit engineered strains could reduce the population's overall fitness and increase vulnerability, a difference in perspective that could also imply different conceptual models.

Knowledge Keeping Pace

Participation of and exchange among diverse participants produced contributions that could enable knowledge available to an assessment effort to keep pace with developing technology and assessment needs. Contributions can enable knowledge to keep pace by introducing information that might not be otherwise available and by facilitating generation of new knowledge.

In the OPPT workshop, participants contributed detailed information about industries that were not yet employing technologies requiring OPPT regulatory review but were expected to do so, including information regarding likely upcoming technological developments. Participants also offered information available within their specialties, such as their offering to consult sources available at their institutions in order to develop a pathogen list. A participant who had recently published research on detection and assessment of engineered microbes' environmental effects shared insights from his work, indicating that broad involvement can also enable use of the most current research methods.

In the PoET-Wilson workshops, participants drew from and described new research, research still in progress, and other research that was apparently not widely known outside of the participants' own circles. Participants also enabled generation of needed knowledge by indicating to technology developers what studies would be useful and by exchanging information about existing and planned testing facilities, including helping to

connect developers desiring to conduct tests with companies possessing suitable facilities.

In the salmon case, the involvement of diverse groups, each with its own goals and angles of perception, may have enabled the revelation of the disease outbreak, which an organization allied with the plaintiffs discovered upon inquiring with the Canadian government regarding the illness for other purposes. In addition, various stakeholders proposed particular studies and analyses. Had these studies been conducted, the suggestions might have contributed to knowledge generation for the assessment.

Values

Both narrow experts and diverse stakeholders inevitably manifest their values through decisions in many assessment aspects, such as problem framing, breadth of inquiry or system boundaries, standards for inclusion of a research study, level of evidence needed to draw a conclusion, or response to uncertainty. One argument favoring diverse stakeholders' contributing their values to assessment is that narrow experts, who are engaged for their scientific or risk assessment expertise, do not possess values intrinsically superior to those of other stakeholders, and therefore that narrow experts' values should not be privileged as being the ones to drive an assessment's conduct. A second argument is that diverse stakeholders are more likely than are like-minded or similarly-trained experts to reveal differences in values and to challenge one another's values-based assumptions or approaches, enabling the assessors to reach more nuanced or better approaches than might be likely when a single set of values prevails without question.

OPPT workshop participants diverged regarding how extensively an engineered microbe should be tested for ecological effects in different environments, such as whether testing in environments stressed by other anthropogenic pressures is necessary. They also diverged regarding whether microcosms are sufficient or sufficiently reliable for testing and whether organism release and other hazards such as horizontal gene transfer are highly unlikely or nearly inevitable, and they may have diverged regarding whether information requirements should be flexible based on information already available in a given industry. Each of these differences of opinion may arise as much from values-rooted differences in concern about negative effects or in aversion to imposing testing burden on submitters as from differences in calculated risk levels or estimated likelihoods that lower but not higher levels of testing would miss adverse effects.

PoET-Wilson workshop participants expressed differing opinions regarding the desirability of attempting to prevent organism survival or gene flow upon release generally versus seeking to predict whether or not the occurrence will cause adverse environmental effects before determining whether to try to prevent it, perspectives that may reflect different underlying levels of concern and of aversion to prevention burden. Participants also revealed differing opinions regarding whether to move forward with an application in the presence of information initially deemed insufficient or to insist that information requirements be maintained and applications declined until information

standards are met, in part a values-based judgment with important implications for testing and decision-making. Participants also revealed differing levels of concern regarding unanticipated risks as well as diverse perspectives regarding how "naturalness" should affect concern, perspectives that may also stem in part from underlying values.

In the salmon case, the FDA and the plaintiff stakeholders articulate starkly different context framings. In providing background, the FDA's environmental assessment describes increasing demand for fish protein, the importance of fish protein in human diets, the problem of overfishing, and projected need for increases in commercial aquaculture. The complaint discusses wild fish populations' vulnerability, the continuous threats from anthropogenic pressures, and the salmon's ecological, economic, and cultural importance for coastal communities, tribes, and fishermen. The two sets of framing facts could both be true, but they may reflect different values or underlying perspectives that could affect risk assessment and decision-making. The environmental assessment and the stakeholder critiques, such as the complaint and the Citizen Petition, also make different assessment decisions that could stem in part from underlying perspectives. For example, they differ regarding when a related species may be used as a research proxy and in whether the sterility assurance suffices considering high but imperfect procedure success rates and considerable but imperfect data regarding sterility's resulting from the procedures. Differing treatments of uncertainty may also reflect underlying perspectives. The environmental assessment references uncertainty largely to suggest that further investigation would be fruitless or in suggesting doubt regarding a concern, while the complaint references uncertainty to indicate a potential unforeseen substantial effect and in suggesting a need for caution. The case also suggests that statutes or other governance constraining an assessment or decision may also incorporate values or priorities that can affect an assessment.

Observations from across the cases indicate that values-influenced judgments occur throughout an assessment process, including in designing research needs and testing schemes as well as in identifying suitable studies or study designs and interpreting results. This observation supports arguments that diverse stakeholders should be included throughout assessment processes rather than offered options or provided with input opportunities after tests and analyses are complete.

In the cases, participants largely did not discuss the underlying values explicitly. Instead, values manifested through opinions regarding technical questions of study design and analysis. Articulating underlying values through these actionable discussions, rather than explicitly in ways that do not immediately delineate their application, may be most productive. However, individuals lacking technical knowledge may possess values no less valid for incorporation into assessment and decision-making, while these individuals may be less capable of articulating their values in terms immediately actionable within technical assessment details. In these scenarios, discussion of values in themselves may be appropriate, with subsequent work on incorporating the values concretely, or support to participants in translating values into actionable perspectives may be most effective.

Challenging Typical Assessment Approaches

In addition to the four contribution sources hypothesized, the diverse participant groups appear to have displayed an interest in or willingness to challenge typical environmental assessment approaches, while these challenges appear not to have prevented workshop participants from completing assessment tasks as designed. These challenges may be particularly valuable for producing more effective assessment of emerging technologies, though they appear to present challenges in interfacing with existing governance.

Challenges in the Cases

The diverse stakeholder groups appear to have challenged typical assessment approaches across the cases.

In the OPPT workshop, some participants suggested that the standard formula expressing risk as the product of hazard and exposure, or of magnitude and likelihood of harm, may not be appropriate for determining ecological risk associated with uncontained microbe applications. Some participants created a tier testing scheme that changed the role of field testing: While the provided models included field testing as an upper tier used when prior testing suggests harm, these participants included field testing only when other testing points away from harm. Though they note the problem that for microbes, field testing in the event of predicted harm could result in irreversible release and thus environmental damage, the Subdivision M guidelines retain the standard scheme while indicating that field testing should be undertaken only when the Agency is confident in containment capabilities. Practical or political considerations could work against divergence from established frameworks, presenting challenges in how to solicit and integrate diverse stakeholder input.

In the PoET-Wilson workshops, participants raised and to an extent sought to include considerations not normally incorporated into environmental assessment, such as worker health, philosophical, and societal implications. They also mentioned how broader ramifications could affect assessment itself, such as how pressure to move forward with a potentially life-saving technology could affect assessment conduct, and they made procedural suggestions related to assessment integrity, such as emphasizing the need for openness of test results. When participants noted that technical decisions in test or model design could predictably affect results, a participant advised that "a community model helps avoid issues of the model telling you what you want it to."[3] Participants also appear to have considered assessment frameworks broadly, offering suggestions from their own backgrounds regarding how to conduct an assessment, drawing from human health, chemical, and nuclear risk assessment, and an environmental assessor noted her own field's struggles and failures in addressing complexity and uncertainty.

Diverse stakeholders' challenging established assessment approaches may be less evident in the salmon case, and it would likely not be expected in inputs seeking to advise or critique an agency within the terms of the statute and standard sound assessment as inputters perceive them. However, many of the public comments submitted do not directly address the assessment or they appear to fall outside of the assessment's statutory

scope, such as comments advising the Agency to focus on encouraging other types of aquaculture development[4] or expressing other concerns about biotechnology industries.[5] These comments may suggest stakeholder interest in broadening the scope of review or assessment consideration beyond elements typically included. Here as well, stakeholder perceptions of assessment needs or challenging of established frameworks may present challenges in diverse inputs' relationship with existing governance.

Challenging Approaches as a Contribution

Researchers have discussed flaws in standard risk assessment approaches and have suggested that these approaches may be particularly imperfect for emerging technologies. For example, assessment boundaries, such as the implications, contributing factors, or alternative decisions considered, are typically established more by convention, convenience, or political forces such as regulatory mandates than by scientific rigor. Research has found that altering assessment boundaries can improve scientific defensibility and bear important analytical and policy implications.[6] Researchers also point out that

> Confirming the results of risk assessments can be extremely difficult, in particular when cause-effect relationships are hard to establish, when they are instable due to variations in both causes and effects and when effects are both scarce and difficult to understand.[7]

Challenging standard assessment approaches and seeking alternatives could thus be an important contribution that could improve assessment and eventual decision-making.

In their paired ecological risk analysis workshops, Dana *et al.* found that the diverse group, unlike the narrow expert group, was unable to complete the hazard prioritization step, as well as that the diverse group had more trouble generating consistent risk assessment values, instead generating values that were scattered and not conducive to drawing conclusions. The researchers attribute these difficulties both to the diverse participants' lack of knowledge on the matters in question and to lack of scientific information on these points. If the diverse group's difficulty was indeed due in part to lack of existing information then the narrow group may have been making predictions based on too little information or ignoring uncertainty, in which case even though the narrow expert group was able to develop hazard prioritization and consistent risk assessment numbers where the diverse group was not, the narrow group's results were not necessarily more valid, and could lead to false assurance or to failure to pursue needed information. The researchers also commented about the hazard prioritization step:

> Further compounding the[diverse participants'] frustration was the fact that the prioritization process was not built to incorporate uncertainty; each participant had to provide a binary, Yes/No answer to the criteria. Many participants felt there was too much uncertainty about the hazards to choose either answer with confidence.[8]

Not incorporating uncertainty appears to have bothered the diverse participants more than it did the narrow expert group. As recognizing and incorporating uncertainty is increasingly seen as important for assessment, the diverse group's frustration, if

recognized as pointing out a possible flaw in the method, may represent a contribution to assessment quality or validity.

Researchers have also argued that assessments should include broader sets of considerations than are conventionally incorporated. For example, while environmental risk assessments often focus solely on data traditionally viewed as "scientific,"[9] the National Academies of Sciences, Engineering, and Medicine panel on gene drives as well as the International Risk Governance Council advise that other types of data, such as information on a decision's ethical, legal, social, cultural, and economic implications, must be incorporated into assessment.[10, 11] While one could argue that these components should be included in some consideration but not in an environmental assessment, serious consideration and assessment in these areas are normally absent from decision-making about biotechnology applications. In addition to being areas in which diverse stakeholders may be well positioned to offer information and insight, workshop participants urged consideration of these areas in assessing applications, further suggesting that diverse stakeholders' questioning of standard approaches and boundaries could improve assessment and decision-making.

Emerging technologies are marked by high levels of uncertainty, which challenges standard assessment approaches, and by lack of prior information on which to base assessment decisions and risk estimates. Approaches established for particular types of risks may also fit poorly with new technologies for which suitable methods are not yet available, as suggested by the possible misfits observed in the OPPT and OPP microbes case in applying testing scheme approaches from chemical risks to microbes. Thus, challenging existing approaches may be particularly important for assessing emerging technologies.

Multi-Stakeholder Contribution to Assessment Quality

The present findings support and extend Dana *et al.*'s and other researchers' and conveners' findings and hypotheses regarding sources of multi-stakeholder contribution to assessment processes. Diverse participants' consistent contribution in key ways bearing potential to aid assessment scientific quality and validity strongly suggests that diverse involvement should be sought, and that conveners and others should pursue approaches to enabling diverse participants to contribute and to ensuring that their contributions can be incorporated into assessment and decision-making.

Broader Societal Involvement

In addition to interest in involving diverse stakeholders in assessment and decision-making for emerging technologies or other actions, researchers and practitioners are increasingly interested in involving "ordinary citizens" or "broader society" in related efforts. Some evidence from the cases points to a role for such involvement, and it appears likely that broader societal involvement could contribute to assessments in the five core ways observed in the multi-stakeholder cases, suggesting that such involvement too could aid assessment quality, integrity, or scientific validity. While controversy exists around defining characteristics of broader societal participants, comparison with the

multi-stakeholder cases may help to identify some likely characteristics that could help predict participant needs and potential sources of contribution.

Interest in Societal Involvement

Recent interest in broader societal involvement has focused on nanotechnologies, but it has also included other emerging technologies[12, 13] and other decisions with complex scientific components.[14] Goals of such engagements have varied, including goals largely of conveying messages to citizens and encouraging acceptance of new technologies as well as of understanding citizen perspectives or conveying citizen opinions to decision-makers.[15, 16, 17] Researchers have emphasized the importance of substantive stakeholder participation. For example, the International Risk Governance Council argues that

> ... the governance process ... is seen as a necessary... prerequisite for tackling risks in both a sustainable and acceptable manner and, consequently, imposes an obligation to ensure the early and meaningful involvement of all stakeholders and, in particular, civil society.[18]

The Lyme Project: A Citizen Involvement Experiment

Citizen involvement efforts have predominantly focused on broad categories of technology, such as nanotechnology or biotechnology, or on overarching issues or application categories such as nanotechnology in consumer products, rather than on specific products or applications. A few efforts have begun involving citizens in deliberation around particular technologies and applications.[19]

The Lyme Project, spearheaded by biotechnology researchers at MIT, aims to experiment with and serve as a model of community involvement and decision-making regarding assessment and use of emerging technologies.[20] The project centers on the possibility of using genetic engineering to immunize wild mouse populations against tick-borne disease such as Lyme, an endeavor the researchers propose be initially limited to Massachusetts islands and possibly eventually expanded using gene drive. The project aims to engage citizens of the islands to develop assessment and decision-making protocols and to decide whether and how the project will proceed through various stages.

In presentations on the islands, the biotechnology researchers are seeking to avoid overly grand reference to the technology's possibilities or emphasizing the gravity of the Lyme disease problem.[21] They are requiring that committees or other governance processes be formally independent of the researchers.[22] The Lyme Project as currently conceived appears to push farther than many societal engagement efforts in promoting full community involvement and decision-making. With preliminary project design and early findings available but many details still open, the Lyme Project may serve as a societal involvement effort to which the present findings and recommendations may be compared.

Suggestion from the Cases

Examination of the cases reveals evidence of the potential for societal participants to contribute valuably to assessment processes.

The first PoET-Wilson workshop included discussion of environmental implications of an arsenic biosensor meant for use in developing countries with high levels of arsenic contamination. Participants determined that product use and disposal practices that might occur in such contexts could substantially affect environmental implications, and that insights into expected practices were needed to assess implications. The participants also realized that the assembled group, which included an expert in environmental assessment of genetically engineered organisms as well as a science and technology official from a relevant developing country, did not possess the needed knowledge of likely real use and disposal practices.[23] A process more broadly including members of potentially affected communities could include individuals with the needed knowledge. The small group of experts participating in the first of Dana *et al.*'s paired workshops similarly determined that information on farmer practices was needed for an assessment. In the second, diverse, workshop, participants with farming experience helped the group develop a matrix of farmer practices and aided in illuminating how different types of farmers' practices in such areas as irrigation, storage, and disposal could affect environmental implications.[24]

In the salmon case, a local resident who knows employees at AquaBounty's Canadian facility provided the information that employees may have taken eggs or fish from the facility to rear, transmitting the information to a plaintiff organization member whom he knew. In this instance, neither the narrow expert assessors nor individuals involved in the stakeholder lawsuit appear to have anticipated a need for such information or for information from these parties. A broad-involvement process can reveal information that conveners or narrow experts do not think to pursue. In the salmon case more generally, a broad, largely self-selected array of interested individuals and groups provided information and input that under some circumstances might prove valuable for assessment.

At several points in the PoET-Wilson workshops, participants voiced what they believed "the public" would desire or accept in monitoring, testing, or safety standards, or how they believed the public perceived a particular level of risk or assurance.[25] These points suggest that participants felt public perception or demands to be an important consideration in designing testing or organisms. If public perception indeed constitutes an important consideration, opportunities for members of the public to contribute their own perceptions could be valuable. The facilitator often asked participants what they personally cared about or how they felt about a piece of the discussion, implying importance in stakeholders' own concerns and those of their affiliated groups. In light of this effective facilitation approach, participants' postulating what members of the public might desire or perceive bolsters the suggestion that the public's participation could contribute desirable insights.

Participants in the pair of PoET-Wilson workshops on Creating a Research Agenda appear to have believed public input to be an important component of a research effort for synthetic biology. The report on findings from these workshops states that

> ... institutions, regulators, and researchers should be prepared to respond to rapidly changing situations in a timely way. Democratic, deliberative processes ... should have a strong role, not just for the public to be informed, but consulted. Careful consideration should be dedicated to promoting and ensuring outlets are available for public input ...[26]

It appears that the cases, which largely involved "professional stakeholders" rather than broader society, reveal important roles for additionally broad participation, and that societal participants' absence from the deliberations was sometimes directly felt.

Potential Contributions

Diverse societal participants may be able to realize sources of contribution similar to those of the cases' "professional stakeholder" participants.

Societal participants may contribute system information that could aid assessment and would not be readily available to either narrow expert or professional stakeholder assessors. For example, they could contribute information about the ecology or human uses of a proposed application site; about human activities relevant to use, disposal, or movement of a genetically engineered organism; about individuals' or communities' need for a proposed application; and in many other areas of knowledge. Societal participants may contribute based on diverse conceptual models, including their perceptions of problem boundaries or system elements to be included or omitted and other aspects of how to view the systems or considerations. They may contribute to knowledge's keeping pace with assessment needs, through contributing otherwise-unavailable system information, examining relevant literatures on their own, enacting "citizen science" efforts to gather needed data, or identifying research needed.

Societal participants may also contribute based on their values. In advancing a broadly participatory assessment process, Kapuscinski *et al.* recall that protecting values constitutes a core purpose of risk assessment, noting that their method "emphasizes stakeholder participation as well as communication because risk assessment should be designed to protect inter alia stakeholder values ... ."[27] They also explain that the method "generates a shared understanding of adverse effects and system dynamics based on scientific data, as well as values and ethics."[28]

Societal participants may also challenge established assessment approaches. For example, researchers have pointed out that lay citizens often "question[] ... the status quo—for example, ... they raise concerns about ethical issues, social disparities, or environmental and health risks related to technologies... ."[29] Initiatives that, like the Lyme Project, involve societal participants' developing their own assessment processes or decision-making criteria may see the development of non-standard approaches for elements of the process.

Who Are Societal Stakeholders?

Initiatives to involve broader society in assessment processes vary in the types of individuals whom they wish to engage and in mechanisms of invitation. Some conveners seek individuals with little prior knowledge and no prior opinions regarding the matters under deliberation,[30] while others engage diverse stakeholders, including representatives of interest groups on subjects related to the technology or application.[31]

Criticizing recent efforts to engage in deliberations about emerging technologies particularly citizens lacking prior knowledge or interest, researchers have contrasted these efforts with participatory approaches in other fields, including other fora addressing complex problems with environmental or health components such as the AIDS crisis, environmental toxins, nuclear waste disposal, or water management. These researchers suggest that in recent efforts around emerging technologies, conveners' interest is largely focused toward conveying messages to citizens and garnering acceptance for the technology, whereas in the other areas, participants' knowledge and perspectives are valued as assets for understanding the problems.[32]

Lines are not clearly defined between societal deliberations, particularly those including interested and knowledgeable participants, and those involving only a broad array of professional expertise and interest. Both may be termed multi-stakeholder processes. Overlap and some differences are likely between participants in societal multi-stakeholder and in professional multi-stakeholder deliberations like those occurring in the cases. Comparison with case participants may help in identifying likely societal participant characteristics, particularly for processes that do not require individuals lacking prior interest, and may help identify ways in which societal participants could contribute and considerations for conveners in enabling contribution.

It appears that societal processes could involve broader arrays of expertise, including more expertise that conveners did not anticipate as relevant, as well as interested individuals lacking particularly relevant knowledge-bases. Societal processes may also be more likely to include individuals who have not formed opinions on the assessment subject, though conveners of any process should assume participant openness and changeability. More societal participants may lack scientific backgrounds, though the cases' workshops included diverse levels of scientific background as well. Societal processes may be more likely to include individuals with a heightened personal stake in process outcomes. As in the workshops examined as cases, participant identification mechanisms and process practicalities such as timing may affect participation. Decisions regarding how broadly to seek participants are challenging, and may themselves be appropriate subjects of inclusive discussion.

Case Participants

The multi-stakeholder cases, particularly the OPPT tier testing workshop and the PoET-Wilson workshops, involved participants whom the conveners had invited due to their knowledge or affiliations in areas that conveners deemed relevant to the questions at hand. Many participants were employed at high levels in their institutions, for example as

professors, research Principal Investigators, heads of units within their companies, or heads of biotechnology campaigns in their organizations.

Dana *et al.*'s multi-stakeholder workshop may contrast somewhat with the cases by including farmers and wildlife rangers, but in this workshop as well, most if not all participants had substantial academic training and operated at high levels in their institutions.[33] Of the 22 participants, eleven had earned Ph.D.'s, four had earned Masters degrees, and the remaining seven had earned Honors one-year post-baccalaureate degrees, all in relevant fields. Several of the participants listed as having farming experience are noted as "work[ing] with farmers," and the two noted as being farmers themselves were also a government researcher with a Ph.D. in plant pathology and an environmental organization member with a Ph.D. in botany.

Societal Participants

A number of characteristics may distinguish societal stakeholder participants from narrow expert assessors as well as from professional stakeholder participants as in the workshops examined as cases, and these characteristics may suggest societal processes' needs and strengths.

Some societal engagement efforts include only invited participants, while others, like the Lyme Project, may be open to all interested participants. In the latter instance, individuals may identify their own knowledge as relevant or they may participate due to interest, such as residence near a proposed application, even with no identified relevant knowledge. Processes involving invited participants may face more public or political pressure than did conveners in the cases to include members of broader swaths of society or representatives of particular interest groups.[34]

Participants in societal processes may thus be more likely to include individuals possessing distinct areas of expertise, including areas of expertise that conveners do not anticipate. They may possess substantial local knowledge of a proposed application site's ecology, agriculture, or socio-cultural context, practical experience working for a biotechnology company, experience or expertise with an illness or other societal problem the technology seeks to address, knowledge of regulation or outcomes of a similar technology in another country, expertise in an alternative technology aiming to achieve similar ends, or any of many other areas of knowledge. Societal participants' inclusion, particularly along with individuals typically conducting narrow expert assessments or chosen to represent stakeholder groups or knowledge-bases previously identified as relevant, could substantially expand the areas of knowledge and perspectives represented.

While a number of the workshop participants lacked relevant scientific background and many societal participants may be expected to possess substantial scientific knowledge, in many societal processes more participants lacking scientific knowledge may be expected. OPPT workshop, PoET-Wilson workshop, and Dana *et al.*'s workshop conveners each provided participants with preparatory materials including background on scientific concepts. In the PoET-Wilson workshops, providing adequate background

information was an ongoing learning process. Mentioning the importance of providing "adequate education and access to information before and during the process," Dana and Nelson, discussing Dana *et al.*'s workshops, mention that the unfamiliarity of some technical concepts impeded some participants' ability to participate fully, "even though preparatory readings were provided and experts in the field explained some new concepts."[35] Societal processes may require careful efforts to enable participants lacking scientific background to participate and to enable the process to benefit from their contributions. In addition to provision of information, consideration of continuing difficulty with scientific concepts may be needed.

Some societal participants may be less likely than participants in the cases, who were selected in part for their affiliations, to have previously formed opinions related to assessment subjects. Many societal participants may join due to affiliation with interest groups or may enter the process with ideas or opinions regarding the questions at hand, but others may merely wish to understand the considerations and provide their knowledge or opinions as they learn.[36] For example, a production facility proposed for siting could garner interest from residents curious as to how the facility might affect their town's employment, taxes, air or water quality, nearby farmland, or protected natural spaces, and desiring to contribute their values and considerations to the discussion. Local residents may also be as concerned as others about a proposed application's positive or negative implications for broader society. In early meetings, the Lyme Project appears to be garnering interest from citizens desiring a solution to Lyme disease in their communities, interested in making sure that undesirable outcomes will not overshadow positive effects, wishing to ensure that decisions remain in the communities' hands, and curious about how the project may develop.[37, 38] These early findings contrast with common conceptions among scientists of citizens as categorically fearful of or averse to new technologies. In the cases, even participants whose affiliations associated them with strong perspectives on the topics demonstrated some departure from their affiliations' typical stances. For example, in the PoET-Wilson workshops, industry members discussed the importance of studying risks, environmental organization members indicated the need to learn more and to approach biotechnology applications on an individual basis, and biotechnology researchers identified hazards of the technologies. Describing their participatory method, Kapuscinski *et al.* state that "Unlike public debates where the positions of advocates and opponents of a technology are often simply reinforced, participants in [this process] often adapt their views as their understanding of the issue deepens."[39] Conveners should remain aware that participants' considerations and opinions may not be predictable and that many participants may not initially have formed opinions regarding desired deliberation outcomes or may learn and change their opinions through the deliberation. Discouraging participants' assuming the nature of others' opinions may also aid open and productive deliberation.

Participants' personal stake in process or decision outcomes may be heightened in some societal processes. In multi-stakeholder processes like the cases' workshops, company representatives and others interested in development likely care about companies' reputations and opportunities, environmental organization members, ecologists, or others may be personally concerned about environmental damage, and participants may

personally wish to see a technology's intended societal benefit. However, the personal stake or interests may be higher for societal processes. More participants may, for example, be personally affected by an illness or other problem the technology seeks to address or may be concerned about the technology's effects on their own family's water quality, food safety, or employment possibilities. Considerations could conflict both among participants and for individual participants. Conveners should recognize that personal experiences and stakes can benefit an assessment. They should also maintain sensitive awareness of the deliberation subject's potential for personal significance or effects.

Process Effects on Who Participates

The technological application, deliberation process, or participant selection mechanism may affect the types of expertise represented. For example, a process focused on a decision to apply a biotechnology or site a manufacturing facility in a particular location may garner interest from local residents, while deliberation regarding general siting considerations or applications with immediate national implications may draw individuals with other types of expertise. A self-selected participant group may include more expertise that conveners had not realized is relevant, as participants identify their own knowledge or perspectives as valuable to the deliberation.

Processes with less convener control over participant composition may be more likely to experience challenges in participants' working together. In addition to including only invited participants, the workshops examined as cases had conveners already working in the area addressed in the workshop. Particularly in the PoET-Wilson workshops, many participants were identified through conveners' existing networks. Conveners could thus select participants whom they expected to work well together in a workshop setting. Societal process conveners may be less likely to be able to select participants in this way. Even processes including only invited participants may be politically constrained to include broader sets of individuals or representatives of particular groups. Discussing a method for diverse involvement in environmental assessment, Kapuscinski *et al.* acknowledge behavior concerns, advising that

> Disruptive participants, who lack sincerity in their deliberation, may use the meetings to create extreme conflict and block action. Operating rules and tools for assessing and managing potentially disruptive behaviour will have to be developed so that everyone can have voice and influence. Representatives must express interest in the deliberative process in preliminary interviews and agree upon ground rules of civil behaviour, with the final recourse of expulsion if the group agrees that the representative is not deliberating in good faith.[40]

Practical aspects of a process can affect participation. Processes convening during working hours, during the harvest season, without providing childcare, or in areas not accessible by public transportation may exclude potentially valuable participants. While process continuity bears substantial benefits, processes requiring substantial time commitments may also be prohibitive for some participants. In the PoET-Wilson workshops, participants' time constraints limited process duration, and competing events

limited both scheduling and participation. Conveners should seek to learn what selection they risk imposing in a particular scenario and secure guidance in designing appropriately.

Identifying Stakeholders and Lyme Project Participation

Introducing their proposed participatory assessment process, Kapuscinski *et al.* explain that

> An essential element of the ... process is the involvement of a broad spectrum of stakeholders ... . The identification and selection of the relevant stakeholders ... is particularly important for maintaining the public legitimacy of the proposed ... process. All interested and affected stakeholders ... need to be included in the deliberation process.[41]

The researchers suggest questions that could aid in identifying stakeholders:

- Who can provide knowledge or information about [the technology]?
- Who makes decisions on the use of [the technology]?
- Who is most likely to be affected by [use of the technology]?
- Who is troubled about [the technology]?
- Who has a stake in the successful adoption of [the technology]?
- Who can disseminate information regarding [the technology]?[42]

Detailed guidelines for identifying and selecting stakeholders have been published.[43, 44]

The Lyme project plans an open-participation process in which any resident of target communities may choose to become involved, at least through attending public meetings and voting, though particular steering or guidance committees may be limited in participation.[45] In addition, outside individuals with related expertise have been asked to participate in particular advisory capacities.[46] This open approach reduces the challenge of selecting individual participants or participant groups within the community, though many types of processes, particularly those considering applications not centered on defined and politically organized communities, may find open inclusion unwieldy.

It appears that for the project stages centering on particular communities, outside of these communities only standard regulatory approval will be sought; while the application is meant to affect only the targeted communities' ecosystems and disease rates, individuals concerned about engineered mice moving to the mainland or viewing broadly the project's societal, ecological, or ethical implications may object to the communities' being consulted as the sole stakeholders. Determinations of how broadly to view potential stakeholders may be important and challenging decisions in diverse participant processes. Deliberate and perhaps inclusive decision-making mechanisms for these determinations could be appropriate for some processes.

Societal Participation and Contribution

The cases and other literature suggest that broader societal participation in assessment processes could contribute to assessment as could more professional multi-stakeholder involvement. No clear lines distinguish professional multi-stakeholder processes of the

sort reflected in the cases from broader societal processes. Still, examination of the cases helps discern how societal participants' characteristics and needs may align with and how they may differ from those of the types of stakeholders participating in the cases, providing possible insights into opportunities and challenges in enabling societal contribution.

Process Considerations

Several key considerations in convening multi-stakeholder assessment processes, including considerations of continuity, process authority, and structure and flexibility, arise across the cases. Each of these areas includes elements that are typically inherent in narrow expert processes but are often absent from diverse participant processes, where they may be at least as important. Observations from the cases point to practices that could contribute to process effectiveness, both for professional multi-stakeholder processes like those examined and for broader societal processes.

Continuity

Continuity over time appears to have carried benefits in the cases, both for participants' abilities to contribute and for conveners' designing efforts, though challenges in enabling continuity also arose. Continuity may be even more beneficial in other types of processes, and the cases may provide insights into approaches to achieving continuity.

Continuity in the Cases

Continuity contributed positively in each of the cases, and it appears that further continuity could have produced further positive results. Challenges also exist in achieving continuity and these must sometimes be weighed against its benefits.

The OPPT tier testing workshop took place as a single, three-day workshop with minimal contact after the meeting. Even the limited continuity inherent in a multiple-day workshop may have been beneficial in enabling participants to consider topics over the course of the workshop, including during breaks and overnight. It appears that more continuity, such as conveners' working with participants following the workshop, could readily have enabled more contribution. Participants with expertise in microbial pathogenicity and toxicity created a list of some pathogenic species, and they described gaps in available lists and noted that literature searches would be necessary to secure the information conveners had requested. The participants offered to help expand the list using information sources available at their offices and institutions.[47] These offers suggest the potential value of ongoing interaction and of opportunities for participants to undertake their own investigation over the course of a process.

The Subdivision M Guidelines, which were developed over years by a group of officials within a single agency office, show positive effects of continuity. For example, the Guidelines reference the Agency's experience gained over time and they incorporate considerations arising as a result of the officials' earlier testimony before Congress, further indicating that insights can arise through circumstances that emerge over time.

Many narrow expert processes, including regulatory processes, include continuity in that the assessors work together on the assessment, and often on related types of assessments, over time, and may benefit from the knowledge and experience generated thereby.

Continuity also presents challenges that depending on conveners' goals may not be worth its benefits. In the tier testing workshop, arranging ongoing interactions or even substantial further work with the participants who had offered additional assistance would have required substantial convener effort. The conveners, who judged the workshop successful, appear to have determined that their goals were sufficiently met within the single meeting. It appears that they did not wish to expend the effort to follow up, even if the further interaction could result in additional useful information. It is also unclear how many of the participants beyond those offering particular additional resources would have been interested in ongoing interactions had the conveners wished to engage in subsequent activities.

The PoET-Wilson workshops, which consisted of a series of workshops over several years with partial participant overlap, benefitted substantially from continuity. Technology developers presenting their work at two consecutive workshops brought to the latter workshop further answers to questions that participants had posed at the former. Participants referred to approaches and observations made during previous workshops. Participants with limited scientific background appear to have developed their knowledge over time. Furthermore, conveners incorporated their learning from earlier workshops into later ones: Points raised regarding important considerations or needed expertise affected subsequent workshop agendas and participant compositions, and conveners responded to participant feedback regarding needed background information.

In these workshops as well, additional continuity could have been beneficial. Some of the redundancy observed across workshops may be due to elements of a lack of continuity. Most of the workshops were broadly spaced in time with little contact between them; little summary was provided to remind continuing or to inform new participants of earlier discussion content; and at each workshop, conveners and participants did not know whether or when a subsequent workshop would occur. In addition, most of the workshops were only one day long, and some included working sessions during lunch, providing little opportunity for reflection that may have enhanced participant contribution.

Although the PoET-Wilson workshops achieved substantial continuity, conveners faced challenges in this area. Conveners needed to balance participant continuity with a desire to invite the most suitable participants for each workshop's unique agenda, resulting in partial continuity among participants. Participants' professional moves at times prevented individuals' continuing participation. In addition, uncertainty in funding may have necessitated each workshop's being organized to stand alone and appears to have prevented assuring participants of future sessions or developing an ongoing agenda. According to conveners, workshops' limitation to single-day or occasionally 1.5-day formats was largely due to participants' schedules.[48]

Stakeholders developing the salmon legal complaint benefitted from continuity both over time and in participants across the project and related efforts. Participants had worked over years on matters related to AquaBounty's facilities and regulatory submission, enabling them to become familiar with both scientific details and the regulatory processes, and enabling them to gather information over time. Participants were also members of a group of plaintiff organizations and other stakeholder groups interested in engineered fish. The coalition members knew each other and exchanged information relevant to each other's interests, and some of this information, such as notification of the illness outbreak, contributed to the complaint.

Continuity Beyond the Cases

While continuity appears to have been beneficial in the cases, it may be even more important in other types of assessment processes.

The cases involved participants' identifying considerations and developing testing schemes, research agendas, and critiques of existing assessments. When a process seeks to produce a full environmental assessment or an assessment and decision for a particular biotechnology application, continuity may be particularly crucial. When professional assessors conduct an assessment, they are expected to take time to gather information and to incorporate new information as it arises. They may also experiment with assessment approaches, consult with outside parties on a one-time or ongoing basis, or seek the generation of new information, all activities requiring involvement over time. When diverse stakeholders or broader society are engaged in a real assessment process, isolated meetings may similarly not suffice.

Continuity may also be particularly important when more participants lack scientific background, as in many multi-stakeholder and particularly societal processes. Engagement over time may enable participants to develop knowledge of and comfort with technical concepts, furthering their ability to contribute. In the PoET-Wilson workshops and the salmon case, environmental organization members with little scientific background displayed and reported deep familiarity with technical concepts relevant to problems on which they had worked.[49] In addition to requesting background information that was provided for subsequent workshops, PoET-Wilson workshop participants also sought information on scientific concepts through other avenues,[50] as many participants in ongoing processes may be expected to do. Research has found that members of society lacking technical background can, and often do, develop substantial scientific knowledge for engagement on matters of concern to them. Scholar Sheila Jasanoff writes that "Many studies of community responses to risk have shown that citizens are capable of learning extraordinary amounts of technical information, and indeed of participating actively in creating relevant new knowledge, when the stakes are high enough."[51] Researchers discussing diverse participant processes mention the importance of providing participants with balanced technical background information.[52] Balance of information may well present smaller concern when participants have opportunities, such as over the course of an ongoing process, to investigate the topics themselves. Narrow experts approaching a new assessment project are expected to

develop their own knowledge as needed for the task. At least as much opportunity should be afforded to broader participants.

Any effort involving cross-disciplinary collaboration may benefit from continuity to enable participants from different disciplines to learn how to understand each other. The workshop report on "Developing a Research Agenda for the Ecological Effects of Synthetic Biology" finds that

> ... a conscientious effort should be made to establish and sustain multidisciplinary research groups to address priority research areas. ... because these complex questions introduce communication barriers across disciplines, they should take place over the long term to ensure a favorable outcome from the effort.[53]

In addition, participants from technical fields are likely to be as unfamiliar with many societal participants' languages as societal participants may be with scientific concepts and language, and ongoing interactions can enable understanding and productive deliberation.

Continuity may be particularly important for multi-stakeholder or societal processes because it can enable participants with diverse perspectives or opinions to develop relationships and to find and develop common ground. The PoET-Wilson workshops sought to enable diverse participants, including those from typically-opposed groups, to work together on specific tasks and thereby identify areas of agreement, from which they could eventually build to work in more controversial areas. Processes involving additional stages of an assessment process, such as deciding what studies are needed, interpreting results, analyzing evidence, and making decisions about a biotechnology application, are likely to involve more areas of disagreement than are efforts to identify hazards and research needs. Diverse individuals' finding common ground and developing an assessment together may well require participant continuity over time.

Researchers have advocated multi-stakeholder or societal groups' working with academic or industry researchers in order to identify considerations and aid the researchers in guiding their work toward beneficial ends. This type of involvement would also benefit substantially from continuity due to research projects' ongoing nature, the likely need for participants to become familiar with specialized technical concepts, the importance of personal relationships, and the likely need to gather outside information over time.

Enabling Continuity

Examination of the cases suggests several process design decisions that could promote continuity. Processes' taking place over multiple separate sessions and possibly also as multiple-day sessions appears to promote continuity. Opportunities for communication between sessions, particularly if sessions are widely spaced in time, may be beneficial. Participant overlap across sessions appears to be important. Some attrition or turnover is inevitable, so efforts to ensure that new participants are comfortable in the group and knowledgeable as to background information and progress may aid continuity. Distributing discussion summaries and progress records may remind continuing participants of previous progress and enable new participants to join confidently and

efficiently. Continuity may also benefit from early development of a plan outlining the overall process, projected meeting frequency and format, and the expected nature of continuity or changes in the participant body. While encouraging participants to investigate background knowledge or needed information between sessions could prove beneficial, the cases suggest that participants may conduct this investigation without convener urging.

Measures to promote continuity bear challenges and hurdles. For example, convener or participant time or project funding may limit session frequency or length, and maintaining detailed records requires resources as well. Conveners, and perhaps participants, must consider process goals and decide what efforts are worth the benefits derived from continuity.

When ideal process continuity is impossible, conveners may consider what if any extended engagement to enable and how to maximize participants' abilities to contribute even in a contained setting. In addition to being particularly careful to include relevant background knowledge in materials distributed in advance, conveners could design the materials to convey a detailed understanding of the types of knowledge or information sought, in order to enable participants to come equipped with relevant resources and perhaps to obtain additional background knowledge in advance if needed. Conveners could also endeavor to distribute materials sufficiently far in advance to enable such preparation. Inclusion as participants of individuals engaged with the topics on a longer-term basis and soliciting their insights could help other participants extend their perspectives and increase their ability to contribute. Conveners could also request limited follow-up with particular participants to obtain additional insights or information.

Influence or Authority

The literature and evidence from the cases suggest importance in multi-stakeholder and societal processes' having authority or credible expectations of influence in eventual decision-making. While garnering acceptance of controversial decisions may be a key motivation behind some diverse participant processes, real influence could be necessary to garner acceptance. Creativity may be needed to lend diverse participant processes credible authority under existing governance frameworks.

Need for Influence

Societal deliberation processes for new technologies often lack real influence, though influence is desired and may be important for sustaining diverse participant processes. Researchers comment that "Unfortunately, engagement forums are rarely connected to actual policy discussions or public input processes in meaningful ways."[54] Researchers discussing a series of citizen consultation workshops observe that

> ... average citizens very much want to be involved in the decisions that shape technologies that, in turn, shape their lives. ... average people are able to ... generate thoughtful, informed, deliberative recommendations. They also fully expect governmental and private sector decision-makers to listen to their ideas.[55]

Introducing their participatory assessment method, Kapuscinski *et al.* mention the importance of credible influence, commenting that "In order for [the process] to be viewed as legitimate, regulators will have to accept [the process] as part of a risk assessment at a government level ... ."[56] They warn that "If leaders do not provide legitimacy for the outcomes of [the process] by using the reports to inform their ... decisions, the public will see [the process] as a pretence and not participate."[57] Narrow expert assessments are normally expected to have some influence in decision-making, and expert assessors would likely be less interested in conducting assessments if they expected their input to be ignored.

Several indications in the cases suggest a desire for processes that are responsive to or that lend real influence to broad input. Each of the cases involved participants' expecting some degree of influence on policy outcomes. In the OPPT workshops, participants contributed to the formation of guidance and testing schemes for regulatory officials to use for reference. The salmon public input was submitted with the desire to affect the environmental assessment or the regulatory decision, while the lawsuit was launched with the hope of changing the regulatory decision and larger aspects of the Agency's policy. The PoET-Wilson workshops sought to identify research needs with the hopes of instigating launch of and informing a research program to address those needs. In addition to this chance for influence, a PoET-Wilson workshop convener suggested that the opportunity to talk with regulatory officials may have attracted industry members to participate, while the presence of industry members and regulators together may have attracted environmental organization members to participate in order to ensure that they too had a role in the discussion.[58] Even though the convener suggested that the industry members' postulated interest in interacting with regulatory officials was due to hope of learning from rather than influencing the officials, practical benefit was still suggested to serve as the motivating attractor.

Other observations from the cases further suggest a desire for real influence. Some PoET-Wilson workshop participants, particularly environmental organization members, expressed frustration at the workshops' lack of real authority, complaining as well about the lack of influence in input avenues in processes that do hold authority, such as regulatory review. A participant commented that

> What we've talked about are generalizations .... But although we may be getting better at getting a lot of parties in the room to talk about generalities there are not a lot of opportunities for other people to get a comment in, i.e. Federal Comment might come much later on [in a product development or commercialization process]. It would be good if there were a mechanism by which other concerned parties could be involved more and earlier on specifics instead of on generalities, which only gets us so far.[59]

At another workshop, participants praised a particular facility siting idea, but an environmental organization member said that he would oppose the site unless better and publicly available testing took place, and added that "We need a better tool than [the governing statute] for regulating these things."[60] While another participant offered that "I think there's common ground there. We're all looking for a set of data and a process for determining safety,"[61] the organization member's comment appears to reflect frustration

that the workshop, despite its participants' seeking a sound process for determining safety, has no authority or direct influence within existing governance.

In the salmon case, participants are directly seeking influence through public comment mechanisms or a lawsuit. In addition, the legal complaint frequently complains of the Agency's in its view having ignored stakeholder petitions and not having heeded public comments. These statements suggest among these stakeholders, like the environmental organization member in the PoET-Wilson workshops, frustration with a perceived lack of real influence in decision-making processes.

PoET-Wilson workshop participants also appear to have discussed the importance of societal input about synthetic biology governance. The report summarizing findings from two of the workshops emphasizes the need to ensure that societal processes include avenues for influence, advising that "Democratic, deliberative processes ... should have a strong role, not just for the public to be informed, but consulted."[62]

Influence could also aid continuity. While many participants may be willing to engage in a workshop or other short-term process for scientific discussions or to air and explore views, real influence could be needed to sustain interest in a process requiring larger time commitments.

Acceptance and Acceptability

A reason frequently cited for seeking broad or societal involvement in deliberation around new technologies is to promote acceptance of the technology. Researchers comment that public engagement initiatives often "reflect a desire to reduce conflict, help (re)build trust, and smooth the way for new innovations."[63] Other researchers note that

> Some critics ... suggest that exercises intended to engage people upstream in scientific and technological issues, particularly those organized by large institutions and other powerful sponsors, may not really be intended to stimulate meaningful dialogues or to genuinely include laypeople in decision-making, but instead are essentially public relations mechanisms to help assure public acceptance for the technologies ...[64]

The cases do not make clear that broader engagement efforts produce acceptance without outcomes that are acceptable to participants. PoET-Wilson workshop participants expressed frustration with lack of opportunity for input on regulatory decisions and with much testing data's being kept confidential, complaints that appear primarily related to process and inclusion. However, these complaints also carry substance. Participants argued that better testing is needed, suggested that public oversight would result in better testing, and explained how public availability of data would result in higher quality assessments. Salmon lawsuit plaintiffs' complaints about the Agency's perceived unresponsiveness appear to have been substantive as well. For example, the stakeholders' complaint of the Agency's not heeding calls for a full Environmental Impact Statement rather than a more limited Environmental Assessment appears to be due at least as much to their genuinely believing an Environmental Assessment to be insufficient as to their

dissatisfaction at not having been heeded. Criticisms of the Agency's not having incorporated recommended assessment methods were due at least as much to the position that the resultant assessment was not scientifically sound as to a desire for incorporation of recommendations.[65] In both the PoET-Wilson workshops and the salmon case, participants interested in more public involvement and decision-maker responsiveness appeared to view these elements as likely important for acceptable assessments and decision-making to occur. They may also have viewed testing data availability as being at times necessary for acceptance because a controversial decision may not be accepted without sufficient information on its basis. However, these participants do not appear to have viewed involvement or data availability as in themselves producing acceptance.

Even though diverse participant processes may not garner acceptance of a decision through their occurrence in itself and may not create acceptance in the presence of genuine disagreement, they could induce acceptance through several mechanisms, including enabling communication of assessment or design recommendations that can then be heeded, encouraging concrete identification of concerns, and enabling discussion of concerns and alternative actions. Each of these mechanisms may produce acceptance only if the process bears potential for real influence on assessment and decision-making.

Diverse participant processes could enable participants to communicate their concerns and desires regarding testing and assessment, and companies' and decision-makers' then incorporating these considerations could thereby garner acceptance. Environmental organization members participating in the PoET-Wilson workshops indicated that appropriate testing sufficiently demonstrating absence of adverse environmental effects and other effects of concern could or would result in their acceptance of an application. A salmon plaintiff organization member, discussing his organization's successful fight against another engineered organism application for which his organization believed the environmental assessment insufficient, commented, "We're expecting the company to come back with an environmental assessment for a new [location]. We will review their assessment; they should be able to read our stuff and do better next time. We're not saying don't do it, we're saying do it right."[66] Participants may also recommend courses of action other than assessment, such as in organism design or engineered safeguards, containment or facility design, facility location, or uses of the technology, that they find acceptable, and action upon these options could result in acceptance. Identification of and action upon such alternative recommendations may be most possible when discussions occur during technology development or application design rather than for post hoc assessment.

Multi-stakeholder processes can encourage participants to identify and explain their concerns, perspectives, and information standards, and the processes may bring to light courses of action of which some participants may not otherwise be aware. Individuals acting within their institutional or local contexts may not be forced to explain, defend, or even entirely identify their concerns, assumptions, or standards for acceptance, and identifying as well as challenging these elements can open avenues toward acceptance, such as by aiding participants in recognizing acceptable options. Both communication and identification of concerns, information standards, and courses of action may require

responsiveness. If participants are asked about their concerns but these are not incorporated into assessment or decision-making processes acceptance is unlikely to result. In addition, if participants do not expect their points to be heeded they may be unlikely to invest effort in defining concern boundaries, information requirements, or acceptable courses of action.

Diverse participant processes can also encourage acceptance through enabling participants to explore each other's views. A goal of the PoET-Wilson workshops was for participants to develop an ability to work together across affiliation boundaries, explore the merits of each other's views, and identify common ground and areas of agreement. Through learning about, challenging, and discussing each other's views, participants could find that they sympathize with views previously held in distain, enabling more acceptance of actions driven by others' views. They may also learn more details about one another's proposed actions and discover areas of acceptability. For example, an industry member could come to appreciate an environmental organization member's concerns, an environmental organization member could learn more about industry testing or safety measures and decide that they are in fact acceptable, or the two could identify sufficient common ground to develop an acceptable course of action together. The Sierra Club's Biotechnology Policy[67] includes many elements that align with perspectives that industry members expressed during the PoET-Wilson workshops, but outside of a multi-stakeholder process, industry members are unlikely to read the Sierra Club's Biotechnology Policy and declare areas of alignment, while Sierra Club officials are similarly unlikely to approach biotechnology companies to identify common interests. While exploring diverse views and discovering areas of agreement does not inherently require decision-making authority, processes meant to encourage some participants to align their views with particular perspectives and processes with no avenue to influence decision-making are unlikely to garner the same earnest and collaborative engagement as mutual processes with potential for influence.

Framing processes as seeking acceptance may inherently conflict with other diverse process goals. When conveners or researchers hypothesize that involvement in a deliberative process can produce acceptance of otherwise distasteful decisions, they typically[68] refer only to concerned or objecting citizens' accepting the new technology. They do not, for example, mean that through participating in a deliberative process a company will accept a decision rejecting its technology or a facility location. This observation is inherent in the point that many public engagement initiatives "reflect a desire to ... smooth the way for new innovations."[69] A formulation around acceptance may thus be inherently biased toward promoting a technology or application or condescending toward or dismissive of concern about adverse effects. Acceptance thus invoked also assumes power differentials. No one would speak of a regulatory official, due to participating in a deliberative process, coming to accept the need for more information before issuing a decision, or accepting that an application should or should not be approved, because the official chooses what information is required and decides upon approval. It is possible that processes genuinely meant to develop collaborative relationships and gather diverse participants' knowledge and insights cannot be framed as seeking acceptance.

Participation Under Existing Governance

Even when a multi-stakeholder process is meant to learn from and lend influence to diverse participants, overarching governance structures may be hindered in incorporating input. Existing governance's being unable to incorporate diverse input may negatively affect participants' abilities to contribute in multi-stakeholder processes.

Diverse participant processes take place in contexts also including existing governance frameworks, such as companies' submitting proposed biotechnology applications to a regulatory agency and the agency's approving or denying the application based on statute-constrained criteria and standards. Under existing frameworks, authority over decisions and over decision-making criteria typically rests outside of the diverse participant group. Space for broader input within these frameworks is limited. Public comment processes enable submission of input and may require decision-maker response, but they do not mandate particular incorporation of input into assessments or decisions. When regulatory officials are not prohibited from convening diverse participatory processes, soliciting such input is still not mandated. Apparent lack of governance constitutes a framework as well. For example, academic and industry labs are free to conduct most biotechnology research and development as they see fit as long as lab safety protocols are followed and the work does not violate rules in particular governed categories such as Dual Use or human subjects research. In this free context, a participatory process's advising researchers regarding research areas or methods constitutes an imposition that the researchers are under no legal obligation to heed.

Under existing governance, decision-makers seeking input from diverse participants may be prevented from lending them authority. The officials convening the OPPT tier testing workshop carefully avoided any appearance of lending the workshops authority to create regulatory requirements or formal considerations, instead seeking to make clear that the workshops were meant purely as informational meetings. Regulatory agencies and other decision-making bodies may well prefer, or be required, to avoid scenarios in which stakeholders are lent influence in regulatory activities.

Regulatory assessment boundaries or approaches may often be constrained by statute, as occurred in the salmon case, limiting though not eliminating diverse participants' abilities to contribute and governance's ability to incorporate contributions, particularly as strengths of diverse participant contribution include employing diverse conceptual models and challenging established assessment approaches. In the salmon case, in addition to offering perspectives regarding the assessment's scientific substance, stakeholders urged further consideration of alternative actions and other considerations that the Agency determined to fall outside of its scope as mandated by statute. A portion of the discrepancy may have arisen from the Federal Food, Drug, and Cosmetic Act's specification, separate from the National Environmental Policy Act's environmental assessment requirement, that the Agency approve submissions of animal drugs deemed safe and effective. This specification may have precluded, or the Agency may have determined that it precluded, incorporation of some environmental, ethical, or other

considerations into decision-making. This specification appears to have constrained the FDA's environmental assessment's alternatives analysis, and it could have constrained the overall environmental assessment or the regulatory review in ways that diverse stakeholders may have wished to challenge.

Effects on Deliberation

Decision-making authority's lying elsewhere could affect deliberation itself. For example, concerned citizen groups may need to decide whether to spend limited resources participating in a process in which their input may well have no real effect or instead to spend those resources organizing protest, litigation, or other means of pursuing their aims. Groups and individuals that do participate may still contribute differently if they perceive no authority or influence in the process. For example, they could maintain extreme and uncompromising positions in order to "make their voices heard" representing and promoting official stances; they could contribute their true knowledge and perspectives minimally, meekly hoping to "move the needle" slightly or to raise some awareness of their considerations in hopes of eventual benefit in other contexts; or they could remain quiet once they learn that the process has no real influence. Whatever the response, a process's lacking authority or influence may distort the interpersonal dynamic and diminish some participants' contribution.

Any diverse process may be expected to include participants holding unequal power within the society,[70] and conveners and participants must be careful regarding how these power differentials may affect participants' abilities to contribute.[71] The existing governance may create or exacerbate power differentials that can affect the deliberation. For example, the participation of regulatory officials or other government officials with whom power over the final decision actually rests could affect participants' responses. Participant knowledge, based on statute or precedent, of a particular decision's likelihood may lend implicit power to those favoring the likely decision or place those not desiring this outcome into a defensive position. In the PoET-Wilson workshops, even though participants were working together to identify research needs in order to ensure safety, environmental organization members were keenly aware that in the real governance structure outside the workshops standards were in their view lax, perceived secrecy of test results was permitted, and their input was unlikely to influence decisions. The resultant implicit power differential may have manifested when, asked whether he liked a proposed facility location that others had favored, an environmental organization member, instead of merely explaining his concerns, first stated that "we would not be okay with it, and we would probably fight you along the way."[72] This response suggests that power differentials generated from existing governance can affect deliberation, perhaps particularly when the process does not directly affect real decisions or governance.

Influence Decisions and Credible Commitments

Determination of how a process will contribute to an assessment or decision and credible commitment regarding the authority or influence may be needed. Kapuscinski *et al.* advise that "regulators will have to accept [the process] as part of a risk assessment at a

government level,"[73] and they suggest leaders' "using the reports to inform their ... decisions."[74] How the results are to contribute to assessment or decision-making remains to be determined. The importance of process influence in affecting whether and how participants contribute and the challenges of assuring influence under governance structures that place decision-making power elsewhere suggest that some credible commitment to using results in specified ways may be appropriate for some or many processes.

Establishing the nature of process influence on decision-making is likely to present challenges. As existing regulatory structures may preclude guaranteeing a particular level of influence, let alone decision-making authority, to a diverse participant group, other entities holding power may be better positioned to lend the process needed authority. For example, a company could decide that it will not move forward with an application or a facility location unless an independently convened diverse participant process approves the action. Because the company would be choosing to constrain its operations beyond legal boundaries, some demonstration of credibility and development of trust may be needed, if participation or other aspects of the process indeed hinge on the promised level of authority. In such a scenario, the company's keeping its word regarding the authority lent to the process would be of utmost importance to avoid damaging credibility for future processes, and adherence would likely contribute substantially to trust in the company's intentions and integrity.

Determining the nature of results or outcomes in a diverse participant process and making these useable to decision-makers who have committed to them presents additional challenges. For example, processes seeking to identify hazards or areas for investigation may be heeded through the conduct of studies or assessment incorporating these considerations, but questions may still arise regarding how sincerely the diverse process's recommendations were used. Indisputable commitments may be most possible for processes designed to reach a final decision rather than to identify considerations or help design inquiries. Tight integration between diverse participant processes and decision-making bodies or processes may help to build trust and make decision-makers' level of commitment to the diverse input evident. More work is needed regarding how credibly to integrate diverse participant processes with decision-making.

The Lyme Project is engaging with lending societal processes authority over biotechnology endeavors. The project seeks to place decision-making authority with the targeted communities, in part through encouraging communities in which citizens are already engaged with governance through town hall meetings and related mechanisms to develop assessment and decision-making procedures. The researchers stated that they would not move forward even with lab research without the community's expressing interest, and they have presented project plans indicating community decision points at several stages. To date, the communities' Boards of Health have determined to create Steering Committees to guide the project, with each Committee to include at least one individual skeptical of the project. The organizers hope that the skeptical individuals will convey perspectives of other skeptical citizens who may hesitate to voice their perspectives.[75] The specific natures of the assessment and decision-making processes

remain to be seen, and while initial response appears positive, eventual community response to the researchers' stated commitments to community governance will be of interest as well. While the project may come to serve as a model for community guidance and decision-making for biotechnology endeavors, such an approach may be received differently for projects, such as many typical commercial applications, that are not viewed as seeking to address important societal or community problems, though community guidance may be appropriate and effective for these types of applications as well.

Diverse participants could potentially be involved in processes providing a variety of types of input on different stages or components of a biotechnology endeavor. For example, in addition to assessment and decisions for applications, diverse groups could advise labs or companies on desirable technologies to pursue, societal problems to seek to address, or assessment needs,[76] or they could advise grant-making or investing bodies on their decisions or help guide projects they fund. For each role, determinations regarding the diverse participant group's authority or influence and perhaps according credible commitments or process designs that encourage and reveal commitment may be needed. Close or ongoing relationships with the input's recipients could aid in establishing both influence and its credibility.

Structure, Flexibility, and Access

Diverse participant assessment processes appear to benefit from structure and from working to accomplish specific, often technically-oriented, tasks. However, adherence to predetermined structures and seeking to accomplish established assessment steps can curtail important contributions. Balance between structure and flexibility, determining when to invite or enable consideration of fundamentally diverging views, and designing processes to enable individuals with diverse knowledge and languages to contribute fully may aid multi-stakeholder and broader societal processes.

Structure Strengths – Useable Outputs

Predefined structures, such as active facilitation, discussion questions, and specific tasks, particularly adhering to existing assessment approaches, may enable participants to produce results that are readily useable and that can contribute within existing governance and decision-making structures.

In the OPPT tier testing workshop, regulatory officials desired tier testing schemes and particular information. The listed questions, sessions organized around specific tasks, extensive description of the desired output, and facilitators aiding participants in creating a product adhering to the charge appear to have enabled participants to produce testing schemes and convey information useful to regulatory officials.

It is likely that had the conveners left the structure much more open, participants would not have conveyed as precisely the information in which the officials were interested, nor produced tier testing schemes according with regulatory needs, making the process less useful to conveners and thereby reducing participants' contribution to real assessment

and decision processes. A PoET-Wilson workshop convener familiar with the OPPT workshop's tier testing schemes but less familiar with the workshop's structure and preparatory materials privately expressed that the PoET-Wilson participants might arrive through discussion at a testing scheme concept along the lines of the OPPT's schemes. PoET-Wilson workshop conveners did not provide or suggest this model, and participants did not arrive at this idea on their own, suggesting that detailed instructions may be needed if particular outcomes are sought.

The PoET-Wilson workshops were also structured, through descriptions of workshop goals, printed discussion questions, active facilitation, and occasional activities. These approaches appear to have aided participants in achieving workshop goals, including developing a research agenda that could form the basis for a larger research program. Dana *et al.*'s workshops similarly included structure to enable participants to produce the desired ecological risk analysis. Conveners divided the risk analysis task into discrete steps, and the facilitator described each activity and guided participants in completing the tasks. Even though the process did not result in a completed risk analysis, the defined structure enabled participants to move toward a full risk analysis and to produce information that could be useful for a risk analysis or for developing a monitoring program as the South African government had purposed.

The salmon public comments, petition, and lawsuit complaint were constrained in structure based on their regulatory and legal functions. Addressing the particular statutory and risk assessment considerations binding the FDA may have enabled these inputs the possibility of influence. As occurred for the many public comments addressing considerations beyond the Agency's assessment and decision scope, inputs diverging from established protocols or primarily challenging underlying legal foundations or assessment concepts do not have the same possibility of influence.

While in each of the cases participants challenged established assessment approaches and convener assumptions, divergent points were not substantially pursued. Pursuing fundamental challenges could well have negatively affected participants' producing useable results. In the OPPT workshop, time limits constrained participants' addressing the listed questions, so taking time to discuss fundamental challenges would likely have further curtailed the desired outputs. Furthermore, even had participants reached valuable conclusions regarding fundamental points of established assessment approaches, the officials convening the workshop may be constrained by statute and other procedural considerations and could have been largely unable to put these findings into practice. In the PoET-Wilson workshops, the salmon complaint development and public comments, and Dana *et al.*'s workshops as well, pursuing fundamentally divergent perspectives could have sufficiently diverted the discussion as to curtail producing the desired outputs, and the governance structures with which conveners designed the processes to interact might lack authority to or interest in incorporating fundamental challenges. Thus, while exploring and incorporating broadly diverging perspectives could result in better assessments and decisions, governance that is unable to use this input may make adhering to existing structures the most reliable means of contributing to assessment and decision-making.

Adherence to established structures and assessment approaches appears to aid the creation of defined, readily useable products; a process that is too open or pursues every divergent perspective may result in valuable exchanges but may be challenged in producing an output for practical further use. Adherence to established structures can also enable outputs of types possessing defined roles within existing governance, giving diverse participants' knowledge and perspectives, even if somewhat curtailed, the possibility of contributing to real outcomes.

Structure Strengths – Working Together

Predefined structures and specific, often technical tasks may aid diverse participants in working together. In introducing their proposed diverse deliberation process, Kapuscinski *et al.* suggest that structure and scientific focus can enable participants to learn from each other and identify areas of agreement, explaining that

> As a structured, deliberative process, [the method] allows stakeholders with different views to learn about the current state of scientific information, hear each other's ideas, identify points where they agree and disagree, and understand the rationale behind each other's perspectives. Unlike public debates where the positions of advocates and opponents of a technology are often simply reinforced, participants in a [process using this method] often adapt their views as their understanding of the issue deepens.[77]

PoET-Wilson workshop convener Kenneth Oye has similarly suggested that participants who likely disagree in many underlying areas such as in how risk should be viewed or assessed or how much risk should be tolerated, and who may encounter large disagreements in free-flowing discussion or in discussion of underlying principles, may be able to work together to complete specific, technically-oriented assessment tasks. The PoET-Wilson workshops used and tested this hypothesis to a degree, finding diverse participants able to agree on areas in which more information would be helpful, but also that other questions, such as whether or what types of actions should be taken to reduce even uncertain risk, did not develop agreement. Diverse participants were able to work together in discussing the questions posed. These workshops primarily addressed early and general assessment stages, including general information needs and research study considerations. The hypothesis remains to be tested in later stages, settings in which time or budget to commission studies is constrained, or other areas likely to prove more controversial.

Structure Failings – Broadly Divergent Views

Processes' utilizing predefined structures and adhering to existing assessment frameworks can curtail important contributions, including by curtailing participants' abilities to identify, express, and pursue broadly divergent views or fundamental challenges, such as questioning assessment approaches or consideration boundaries. Challenging established assessment approaches and convener assumptions may be an important way in which diverse participation may aid assessment quality, integrity, or validity, so careful process design, perhaps itself incorporating diverse input, is needed.

Although practical considerations may counterbalance, changes to the governance structures with which diverse participant processes interact may be indicated as well.

Even processes seeking diverse perspectives likely curtail the expression of diverging views to some degree, even if only by framing a problem, agenda, and approach that shape the discussion and through active facilitation. Researchers convening and facilitating online discussions about controversial biomedical topics observed that

> ... we were unable to remain neutral mediators. By selecting the medium and writing the opening article, and by inviting and informing the experts, we had framed the original topic. Our framing work continued when we responded to questions about the purpose of the discussion or summarized arguments to regain focus.[78]

Researchers discussing multi-stakeholder processes have observed that structured exercises may present the appearance of enabling fully participatory articulation of views, while their structures omit consideration of larger questions that challenge existing risk assessment frameworks.[79] Investigating Dana *et al.*'s multi-stakeholder workshop, Dana and Nelson note that most participants found the workshops' structured process restrictive and not conducive to "unrestrained thinking," which the researchers view as an important component of a multi-stakeholder process.[80]

A workshop's framing and task can affect discussion nature or range. The OPPT tier testing workshop report[81] assumes throughout that the submitter of the engineered microbial product conducts and reports on the tests. In the PoET-Wilson workshops, participants discussed who should conduct tests to assess possible ecological effects, and industry members and environmental group members agreed that if the companies were to conduct the tests, other concerned parties would not trust the results, and thus that testing must be independently funded and conducted. In the OPPT workshop, the assumption that submitters would conduct the tests was appropriate. This assumption accords with the convening Agencies' operating frameworks, and the workshop was meant to gather information about industries and applications, identify ecological considerations, and structure tier testing schemes, not to challenge the Agencies' underlying approaches. However, the contrast with the PoET-Wilson discussion suggests that a workshop's overarching structure or assumptions can limit the types of considerations a participant may voice or fully explore. An industry member participating in the OPPT workshop and concerned not just with identifying potential ecological effects but also with public response to new products might have harbored concern about companies' being expected to conduct the tests. However, the industry member likely would not have believed it appropriate to express this concern, and had it been expressed, the perspective likely could not have been fully incorporated into the discussion nor affected the workshop outcomes.

More broadly, each of the workshops was structured around discussion questions and established assessment processes, and this direction in itself, as well as time limitations, likely curtailed some discussion because participants likely did not wish to divert the discussion more than conveners desired or to detract from achievement of workshop goals. In the OPPT tier testing workshop, participants challenged standard assessment

approaches as well as convener assumptions, but they also responded to the charge and questions and did not pursue the alternative perspectives. In a PoET-Wilson workshop discussion of testing needs, a participant expressed concern about adverse effects that could not be anticipated, suggesting that improved testing in areas of anticipated harm is of limited value. The comment was not taken up in discussion and the participant did not pursue it further. At other points in the PoET-Wilson workshops, participants largely adhered to the agenda questions and discussion topics. Occasionally they expressed doubts about the underlying value or efficacy of the conveners' approach, and they raised human health, ethical, and other considerations that conveners regarded as being out of scope, but they do not appear to have pursued these topics to the point of curtailing the planned agenda. Participants also likely did not choose to mention every misgiving. Discussing Dana *et al.*'s diverse participant workshop, Dana and Nelson note that some participants afterwards stated that they limited their contributions in order to save time or avoid criticizing others.[82] It is difficult to ascertain where and to what degree participants curtailed or directed their contributions, but the cases each suggest that the framings elicited particular contributions and that participants largely sought to adhere to convener guidance. The structures could thus have prevented participants from expressing views or questions less convenient for the established agendas but that could contribute to assessment quality or integrity.

Addressing Challenges – Broadly Divergent Views

It is not obvious how to conduct a process that encourages participants to contribute based on their values and perspectives, including identifying, voicing, and productively pursuing unanticipated or divergent perspectives. Discerning the ideal degree of divergence for each process is also not trivial. Even the lightest structure could prevent some pursuit of divergent views that could prove beneficial, while some structure is likely necessary for any process and adhering to a provided structure may enable productive contribution and outputs useful for decision-making. Conveners should seek to be aware of ways in which their assumptions and the workshop structure may affect deliberations even when participants appear free to voice diverging perspectives, so that they may decide what types of contributions to enable or curtail.

Researchers have noted the importance of ensuring that participants in risk assessment processes share particular goals and understandings. For example, the International Risk Governance Council states,

> The first step ... places particular importance on the need for all interested parties to share a common understanding of the risk issue(s) being addressed or, otherwise, to raise awareness amongst those parties of the differences in what is perceived as a risk. For a common understanding to be achieved, actors need both to agree with the underlying goal of the activity or event generating the risk and be willing to accept the risk's foreseeable implications on that very goal.[83]

It is unclear what to do when these understandings or objectives are not shared or in the event of other fundamental divergences, though the researchers appear to suggest that awareness or clear acknowledgement of divergences can help in lieu of agreement. Thus,

discussion of participants' perspectives in some fundamental areas may at times be needed even in highly structured processes.

Some scholars have suggested that other types of spaces or processes for discussing fundamental perspectives related to the nature of risk, interaction between technology and society, ethical technological development, or other broader considerations for new technologies may be needed outside of risk assessment or other processes designed to align with existing scientific or governance structures. While separate discussions may be valuable, they may face even more challenges than do typical diverse participant processes in obtaining influence under current governance. Even though established assessment approaches may lack ready avenues for incorporating fundamentally diverging perspectives, they are also most connected to existing governance structures. Diverting discussion of broader challenges to other fora may reduce these diverging perspectives' and their proponents' access to decision-making processes and reduce decision-making processes' exposure to these perspectives. Alternative fora also do not substitute for a role for broader considerations or challenges within standard assessment processes. The proposed fora would enable more extensive discussion of important considerations, but diverting these discussions to separate spaces could deprive more standard assessment processes of the input, including the pressure and challenges, that could benefit their validity and integrity. PoET-Wilson workshop participants raised challenges regarding assessment approaches and boundaries as considerations that should be incorporated into the research and assessment processes that the workshops sought to inform. Hearing broadly divergent views is arguably important even if they cannot yet be fully incorporated, and pressure to learn how to incorporate these views may remain keenest when they are expressed within established assessment contexts. In addition, many concerns that do not fit well into established environmental assessment frameworks may also not fit well in other, much broader frameworks. For example, a process convened to discuss the roles of technology and risk in society as an alternative to a concurrent standard environmental assessment process leaves little platform for concerns about transparency regarding worker health.

Work on pursuing and incorporating broadly divergent views and fundamental challenges within assessment processes is needed. Among other efforts, researchers and conveners should explore involving diverse stakeholders in designing processes, rather than entirely as participants in processes that conveners have designed. Work is also needed on how broadly divergent views may be incorporated within governance and decision-making. Changes in governance structures, rather than only in diverse participant processes, are likely needed in order to achieve these aims.[84]

Structure Failings – Non-Technical Participants and Contributions

Focusing a process around technical tasks bears benefits, but it may also curtail contribution by participants lacking technical backgrounds, and it may distort or curtail contributions not readily articulated in technical terms. A technical focus could also increase technically-trained conveners' and participants' difficulties in recognizing and

appreciating contributions expressed in language differing from that typical in scientific discourse. These challenges may be particularly acute for broad societal processes.

Each of the cases involved participants' undertaking technical tasks such as identifying system components and hazards, identifying research needs and testing considerations, or designing testing schemes, as well as addressing often technical discussion questions. Inclusion of technically-oriented tasks carries benefits, such as enabling diverse participants to contribute their knowledge and considerations to a scientific process; enabling participants to provide input in formats that could readily integrate into existing assessment and decision-making frameworks; and directing focus toward technical points on which diverse participants may agree or whose merits could be discussed from technical angles.

A focus on technical tasks may also challenge diverse participants' abilities to contribute their knowledge and perspectives. Technical tasks provide an avenue whereby underlying values and perspectives in such areas as caution and risk acceptance may be applicably articulated through practical discussions of system components and testing needs. However, this type of process can require participants to express their perspectives and values in these technical terms, such as through identifying unanticipated hazards, explaining why a process is unlikely to pose a hazard, or explaining why a test regime is methodologically or statistically suitable or is insufficient. Participants who are not proficient in the scientific details and are thus unable to express their considerations in these terms may be unable to contribute their views and values.

The cases and other descriptions of diverse participant processes emphasize the need for efforts to educate non-technical participants regarding the technologies and scientific concepts in order to enable participation. Even with preparatory materials and briefing presentations, participants without prior technical backgrounds are likely often insufficiently comfortable and facile with the technical content to contribute fully to the tasks and to integrate their knowledge and perspectives into the technical discourse. In the PoET-Wilson workshops, some environmental organization members, who largely lacked extensive technical backgrounds, expressed technical concerns based on their prior knowledge or attempted to use the new technical information to identify hazards, but in most instances they did not contribute substantially to the technical discussions. Discussing participant experiences in Dana *et al.*'s diverse participant workshop, Dana and Nelson note that "... the topic of GM crops and risk was very new for some participants, impeding their ability to fully participate in the [environmental risk analysis], which in turn influenced their satisfaction and capacity to learn more than the basics. ... even though preparatory readings were provided and experts in the field explained some new concepts."[85]

In addition to hindering non-technical individuals' participation, focus on technical tasks may curtail the types of contributions offered. Valuable considerations such as system components exceeding established assessment boundaries or the possibility of unanticipated harms may not readily fit within technical tasks' charges. In the PoET-Wilson workshops, participants consistently raised broader concerns or concerns outside

of the agenda's boundaries, such as transparency, worker health, or unanticipated risks. The facilitator acknowledged these contributions and some reports mentioned them, but they could not readily be integrated into the workshop framework. Dana *et al.* relate that when participants were asked for "ecologically-relevant elements comprising the agro-ecological system,"[86] biotechnology industry representatives added such positive phrases as "full tummies," "educated children," and "happy farmers."[87] It appears that although these items are not the type of system elements that conveners were seeking, these participants felt it important that these considerations be included, and they may have perceived the request for ecologically-relevant elements to be the best opening for voicing them. Stakeholders lacking technical background may be more likely than stakeholders participating largely due to their technical work to harbor concerns that do not fit into technical frameworks. They may also be less able than technical participants to articulate these concerns in the terms of the discussion tasks.

While articulating considerations in terms of technical tasks and assessment steps may facilitate actionable outputs, a need to articulate considerations and objectives in these terms could also hinder honest discussion for technical or non-technical participants. For example, if concerns about unknowable risks must be expressed as a desire for perhaps unnecessarily elaborate testing requirements, or if interest in pursuing an application even if local ecosystem damage is manifest results in advocating unreasonably low testing requirements, participants may experience confusion, frustration, and dispute that open discussion of true considerations could prevent.

In addition to challenges articulating non-technical considerations in technical terms, elements falling within technical tasks, such as identifying system components and hazards or determining how to address uncertainty, could also prove challenging for non-technical individuals who find themselves inside a technical discourse, even if they could contribute in these areas if discussed in more familiar terms.

A process's technical orientation could also favor language and discourse styles that hinder non-technical participants' contribution by inhibiting conveners' and technical participants' recognition of the value of their contributions due to their discourse style. Throughout the PoET-Wilson workshops, participants lacking technical backgrounds articulated concerns in terms that may well not be taken seriously within technical circles. For example, one environmental organization member responded to a request to explain his concerns by stating,

> The totally engineered organism is the concern. Nature has been forced to go certain ways, and there is a history. We are eliminating that. And then the question is – are we going to create a superbug? Nature has gone in a particular way, but now we're raising supposedly first principles to simplify that. The big concern is that we really don't know.[88]

Although more technically-trained participants had expressed similar concerns, such phrases as "Are we going to create a superbug?" are unlikely to lend the arguments credibility within scientific risk discourse. At other points, environmental organization members referred to ecological risks as "what makes the environment sick,"[89] and identified a hazard noting that its actualization would result in a "nightmare scenario."[90]

Delivering a public comment at an FDA meeting about the AquAdvantage Salmon, a resident local to the Canadian facility raised scientific and regulatory points, but then concluded that "... we do not want to become known as the home of the frankensalmon."[91] In describing their concerns, environmental organization members participating in the PoET-Wilson workshops often raised known examples of occurrences that they viewed as similar. For example, in attempting to raise the problem of unanticipated risks, a participant listed several historical examples of unanticipated harms' manifesting after a product or technology was deemed safe. At another point an environmental organization member raising concerns about worker health and the need for appropriate review and governance stated, "There was a genetic engineer working for Pfizer who got a 1.4 million settlement for infection by lentivirus but didn't get any medical records."[92] These statements represent types of phrasing and rhetorical devices normal in civil society such as environmental organizations, but participants and conveners embedded in technical risk discourse may have trouble viewing the points as scientifically based and integrating them into their discussion or technical outputs, despite their validity. In the PoET-Wilson workshops the atmosphere was respectful of diverse discourse styles, but the examples still illustrate a problem that could arise in many technically oriented discussions, particularly less genial ones, and in efforts to incorporate comments into technical outputs. This language problem may be particularly acute in broad societal processes, in which participants may possess more diverse and less technical backgrounds than professional stakeholders such as environmental organization members and may be less likely than professional stakeholders to have previously interacted with scientific risk discourse.

If technically-oriented tasks and discourse hinder diverse participants' abilities to contribute and conveners' and other participants' abilities to recognize and value contributions, these structures can produce imbalance among participants. Kapuscinski *et al.* mention the high likelihood of power imbalances among process participants and the importance of seeking to minimize these imbalances' effects.[93] Conveners may seek to include participants from a broad range of backgrounds and interests or to balance numbers of participants expected to have opposing interests, and differences in ability to participate in a technically-focused discussion may also produce power differentials of which conveners should be aware as they design processes.

Addressing Challenges – Non-Technical Participants and Contributions

Diverse participants should be involved in technically-oriented processes, and methods or approaches for incorporating non-technical inputs into assessment processes are needed. Integration of diverse technically-trained participants with non-technical or societal participants could further aid the incorporation of diverse perspectives into technical processes. Work in helping technical participants understand and appreciate other participants' languages may prove beneficial. Process continuity may aid in these areas.

Forcing articulation of considerations as points that may be readily acted upon or included in an assessment carries benefits. However, seeking and incorporating inputs that have not been or cannot be articulated within established assessment terms may

enable broader inputs that could improve an assessment, and may facilitate incorporation of insights from individuals lacking technical backgrounds. Researchers are exploring approaches to incorporating broader types of inputs,[94] and more work is needed.

Non-technical participants may also articulate contributions using language and devices unusual to conveners and technical participants, even if the contributions themselves may be readily utilized within the technical framework. Conveners should seek to recognize participants' different languages and to aid in integrating contributions articulated through non-technical languages and devices. In addition to introducing non-technical participants to scientific and technological concepts, encouraging diverse participants to learn and appreciate each other's languages and styles of contribution may prove beneficial.

Continuity over time may aid in each of these areas. In addition to enabling non-technical participants to become familiar with technical concepts and language and learn how to articulate their considerations in technical terms, continuity may aid conveners and technical participants in understanding and appreciating diverse input types and contribution styles. Continuity could also provide conveners and participants with the time, comfort, and outside investigation opportunities needed to explore how to incorporate input exceeding established frameworks.

Participation of technically-trained individuals of diverse backgrounds and orientations may prove valuable as well. Many societal processes seek as participants only citizens lacking technical background, while involving scientists only as educators to inform the citizens on technical topics.[95, 96, 97, 98] Evidence from the cases suggests that integration of diverse technically-trained and diverse non-technical participants may enable increased incorporation of diverse considerations, and this benefit may be even more prominent in broader societal processes. In the PoET-Wilson workshops, participants lacking technical backgrounds made several points that individuals possessing technical backgrounds also articulated or directly echoed. The technical participants expressed the points in more scientific language, lending credence to the considerations. For example, an ecologist expressed concerns about unanticipated risks[99] that non-technical participants also mentioned. A political scientist echoed and provided details to support other participants' emphasis of the importance and frequent absence of transparency in testing,[100] and a risk assessment expert supported and further explained in technical terms a non-technical participant's call for openness in all information contributing to an assessment rather than merely in results or conclusions.[101] Biotechnology researchers also explored new technologies' safety weaknesses that less technical participants likely could not have identified, enriching the discussions beyond what would be possible by involving only societal or non-technical participants. In the salmon case, petitioners and plaintiffs cited statements made by biotechnology risk assessment, fisheries, and wildlife experts whose views lent credence and technical specificity to their own.

When considerations or perspectives must be articulated in technical terms, scientists may aid in translating non-technical participants' considerations into terms accessible to the discourse. Inclusion of technical participants with diverse perspectives may be

needed. However, inclusion of technically-trained participants who can formulate arguments and considerations in the assessment framework terms does not substitute for process structures and cultures that value and incorporate contributions made in diverse participants' own languages, including inherently non-technical contributions.

Processes to Enable Contribution

Elements of process design and interface with governance structures emerge from the cases and the literature as potentially key in enabling participant contribution in both professional stakeholder and broader societal processes. Process continuity; authority or influence; and balances of structure with flexibility and of technical tasks with welcoming non-technical input each bear opportunities to enable valuable contribution as well as challenges in conception and execution. Substantial aspects of each of these elements are inherent in narrow expert but typically absent from diverse participant processes. Investigation and development are needed in each of these areas, as well as in process interaction with governance, to ensure that valuable contributions are made, received, and used to aid assessment and decision-making.

Lessons and Further Work

Across the cases, stakeholders contributed in each of the four ways hypothesized from the literature. They (1) contributed relevant system knowledge; (2) employed diverse conceptual models; (3) helped available knowledge keep pace with assessment needs; and (4) contributed based on their values as do narrow expert assessors. These findings suggest that diverse involvement could regularly contribute to assessment scientific quality and validity. In addition to these hypothesized mechanisms, diverse participants also (5) displayed willingness to challenge established assessment approaches and convener assumptions, challenges that may also contribute to assessment quality, integrity, and validity, perhaps especially for emerging technologies.

Researchers and practitioners are increasingly interested in broader societal as well as professional multi-stakeholder involvement in assessment processes. Evidence from the cases suggests a role for broader societal involvement, and it appears that societal participants could contribute to assessments through the same five key mechanisms, suggesting that societal involvement could also contribute to assessment quality. Comparison with participants in the cases suggests several likely characteristics of societal stakeholder participants, including diversity of knowledge, lack in some instances of scientific backgrounds or of preformed opinions about assessment subjects, and heightened personal stake in process outcomes. Aspects of the assessment topic and process may affect participant composition, and inclusion breadth may warrant careful consideration.

The Lyme Project, engaging in community governance for a possible biotechnology application on Massachusetts islands, is experimenting intensively with lending communities authority in an ongoing research and assessment process. Early results are positive, and the project may eventually become a model for credible societal guidance of technology endeavors.

A few aspects of process design and conduct that may affect diverse participant contribution emerge across the cases. Process continuity; authority or influence; and navigation between predefined structure and openness and between technical tasks and enabling non-technical input may be key. Attention to these areas may be particularly important for encouraging valuable societal contribution.

Examination of the cases suggests that involvement in a process over time can facilitate contribution, for example by enabling participants to access outside resources and to develop relationships and by enabling conveners to incorporate new information into the process. Continuity may be even more important in processes assessing a particular application or including larger numbers of individuals lacking technical backgrounds. While most narrow expert processes inherently take place over time, diverse participant processes often lack continuity, for example occurring as single workshops. Continuing diverse processes over time presents challenges, and conveners should explore when and how continuity can be achieved.

Unlike typical narrow expert processes, diverse participant processes often do not carry authority or credible expectations of influence on decision-making. Lack of real influence or authority may negatively affect participants' desires or abilities to contribute. In addition, though some process conveners appear to be motivated at least in part by a desire to garner acceptance of a new technology, it is unclear that diverse processes result in acceptance when they do not carry real influence. Creative approaches to lending diverse participant processes authority under existing governance, including through alternative decision-making avenues, should be explored.

Predetermined structures and a focus on technical tasks may play important roles in process execution and in enabling links to real decision-making. However, these structures may also curtail valuable contributions. They may prevent participants from offering fundamental challenges or broadly divergent views, prevent participants lacking technical backgrounds from fully contributing, and curtail contribution of considerations not readily expressed in the assessment's technical terms. These structures may also challenge conveners in incorporating broadly diverging contributions or contributions not expressed within the assessment framework. More work is needed on incorporating non-technical considerations and fundamental challenges into assessment, including work on using these types of inputs within existing governance and perhaps exploration of how governance systems would need to change in order to benefit from these contributions. Integration of non-technical with technically-trained participants with diverse perspectives may also aid incorporation of diverse contributions.

Multi-stakeholder and societal involvement in assessment and decision-making for biotechnologies, as well as for other emerging technologies and broad or complex -effect decisions, appears ripe to aid assessment and decision quality, integrity, and acceptability. Practitioners and scholars should enthusiastically pursue engagement and exploration in this area. More work is particularly needed on developing and conducting processes encompassing later assessment stages such as research study analysis,

assessment production, and eventual decision-making; on processes continuing over time; on incorporating non-technical inputs into assessments; and on integrating diverse participant processes with governance systems. Involving diverse participants in other aspects of technology development and execution, such as in advising labs or companies, should be explored. Ideally, both those developing diverse participant processes and those making decisions about biotechnology development and use will involve stakeholders in ways that leverage their potential to contribute substantively to assessment and decision-making. These efforts can, through stakeholder contributions to both substantive content and incorporation of values, result in assessments that best direct technology development and use to benefit society.

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