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COMMENTARY

European Academies Advise on Gain-of-Function Studies in Influenza Virus Research

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Gain-of-function (GoF) studies to understand factors affecting transmissibility of potentially pandemic pathogens are controversial. The European Academies Science Advisory Council (EASAC) recently published consensus recommendations relating to GoF research review and management on self-regulation and harmonization; bioethical considerations; benefit-risk assessment; biosafety, and biosecurity advisory options; and publication of sensitive information. A layered approach to integration of responsibilities must include conforming to the stringent rules and guidance already existing. Further commitment is essential to extend the debate on issues worldwide.

Results from gain-of-function (GoF) research may help in understanding the pandemic potential of the influenza virus and may yield health benefits, including the prioritization and development of prepandemic vaccines. Relevant research on fundamental biology of the influenza virus includes studies on transmissibility, host range, resistance, immunogenicity, pathogenicity, and virulence. However, experiments to modify the transmission potential of avian influenza and thereby to elucidate factors affecting animal virus spread by the aerosol route to humans and between humans have been controversial. Concerns have been expressed about the risk of GoF studies for researchers and the public with regard to biosafety (the accidental release of the pathogen from containment) and biosecurity (deliberate misuse). It should also be emphasized, however, that potentially dangerous research is already subject to stringent regulations and that biorisks associated with novel pathogens were reviewed in detail in previous investigations by U.S. national academies (1). It is critically important to be precise about terminology of GoF research so that attention is henceforth focused on those studies of greatest concern.

There is continuing robust debate among virology researchers (see, for example, references 2, 3, 4, and 5) about the conceivable benefits and risks of GoF research on potentially pandemic pathogens. In addition, however, it is also essential for researchers to articulate and debate their views in the wider scientific community and, through the activities of these larger communities, to policymakers and the public. The debate is widening as illustrated by recent publications from clinical practitioners (6) and the Infectious Diseases Society of America (7). As part of their ongoing activities, the U.S. National Academies organized a workshop on GoF research in 2014 (http://www.nap.edu/catalog/21666/potential-risks-and-benefits-of-gain-of-function-research), observing that the challenges were international, that researchers and their institutions must accept responsibility, and that risk-benefit calculation is not simple.

In Europe, the European Academies Science Advisory Council (EASAC) has recently published a report on GoF research issues and the options for management of such research and its outputs (8). EASAC is formed by the national science academies of European Union member states to enable them to collaborate in giving advice to European policymakers and has previously published extensively on public health and innovation issues relating to infectious disease (see, for example, reference 9). The EASAC report (8) brought together scientists with a wide range of expertise and views to advise on how to address some critical questions, including the following. Does GoF research raise new issues for biosafety and biosecurity procedures? Are there gaps in the current approaches to managing experiments of highest impact? If there are gaps, is there a need for more regulation, more ethical guidelines, or more communication about risks?

Various issues remain controversial, but the EASAC recommendations represent a consensus in the Working Group (see Acknowledgments for membership) and among EASAC member academies. Key topics, examined in detail in the report (8), are summarized here.

SELF-REGULATION AND HARMONIZATION

All scientists should acknowledge and accept responsibility for the safety of themselves, their colleagues, and the community at large. "Self-regulation" means that there are checks and balances within the scientific community, not that each researcher is free to decide unilaterally which procedure to follow. The EASAC report describes several examples of self-regulation and the options for harmonizing procedures to spread good practice in research design, review, and management across the European Union. Good practice requires conforming to established regulations, codes of conduct, and agreed procedures for biorisk management (see Fig. 1 for the current situation in the European Union).

Attention to key biosafety issues is imperative at all stages of the research endeavor from first formulating a research idea through to the publication of results. Grant applicants should discuss the

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Overarching EU legislation

(i) Research on contained use of GMOs is subject to Directive 2009/41/EC (formerly 90/2/219/EEC), which also describes criteria for performing a risk assessment.
(ii) Research which does not include genetic modification is regulated by Directive 2000/54/EC (formerly 90/679/EEC) on protection of workers from risks relating to exposure to biological agents at work, governing containment level 3 and 4 laboratories.
(iii) Publication of sensitive information in journals outside the EU is currently subject to EU Council Regulation 428/2009 on the control of export of dual-use technology.
EU legislation is implemented in respective Member State regulations with enforcement by local regulatory authorities.

Procedures for biorisk management

(i) European Committee for Standardisation (CEN) Workshop Agreement CWA 15793.2011 Biorisk management, in the process of being formulated as ISO standard ISO/AWI 35001 Laboratory biorisk management system.
(ii) WHO Laboratory Biosecurity Guidance
http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_EPR_2006_6.pdf
(iii) OECD Best Practice Guidelines for Biological Resource Laboratories
http://www.oecd.org/sti/biotech/oecdbestpracticeguidelinesforbiologicalresourcecentres.htm

Codes of conduct

Examples include:
(i) InterAcademyPanel with InterAcademy Council 2012 Report on Responsible conduct in the global research enterprise
(ii) DFG and Leopoldina German Academy of Sciences 2014 Report on Scientific freedom and scientific responsibility: Recommendations for handling security-relevant research

FIG 1 Components in the European Union framework governing GoF research. Further details are in EASAC 2015 (8).

potential risks involved in proposed experiments, and funders should consider, on a case-by-case basis, whether research proposals have scientific merit and whether the research can be safely conducted. Justification of the choice of biosafety category to be used in research should be an explicit part of the application for funding. Researchers also need to justify to funders and to their peers the claim that the information they need can be obtained only by doing GoF experiments in this way. Furthermore, part of the exercise of individual responsibility is the recognition that certain research can be conducted only in certain laboratories in certain countries with appropriate facilities. Academies of science, together with others in the scientific community, have a continuing role to play in promoting and increasing understanding of biosafety norms, which include, for example, the clarification of the level of biocontainment required.

BIOETHICAL CONSIDERATIONS

The moral principles and duties that govern experimentation are relevant to issues for transparency of decision-making, public participation, confidence and trust, responsibility, and vigilance in protecting society. GoF studies on potential pandemic pathogens require ethical scrutiny regarding the acceptability of risks of accidental or deliberate release and of global spread of pathogens. In the view of EASAC, ethical issues need to be considered at all stages of the research—from the point of funding through to preparation for publication. EASAC recommended that ethical review be part of the rigorous impartial assessment of proposed research at the institutional level.

BENEFIT-RISK ASSESSMENT

Evaluating benefit and risk is challenging because of the many uncertainties in the data available but also because of differing personal value systems applied in assessing the data. Incommensurable parameters measuring risk and benefit do not allow a value-free determination to be made. Whether benefits should be quantified in terms of prospective public health gains or described in terms of the generation of scientific knowledge is a matter for continuing debate.

EASAC suggested that analysis of the benefit-risk balance cannot be seen as a "once and for all" calculation but rather as a continuing effort to understand and communicate the issues. Academies and learned societies must engage in a process to share data and perspectives and to promote discussion, across the scientific community and involving all stakeholders, to identify and agree to the critical factors underpinning quantitative and qualitative assessment of risks and benefits. It is important to answer other related questions. For example, who should do the assessment, and how should subjectivity be acknowledged? How should the results of assessment be taken into account in informing policy development?

BIOSAFETY AND BIOSECURITY ADVISORY MECHANISMS

EASAC has suggested that there is no need for a new advisory body at the European Union level but has recommended that all European Union member states must have a clear national advisory approach to governance, with statutory powers. In sharing and implementing good practices, countries should adapt the principle of a layered approach so as to integrate responsibilities at the researcher, institution, funder, and national levels.

One concern raised related to the potential proliferation of technologies and information about pathogen sequences. Even if excellent biorisk management procedures are in place in the laboratory initiating GoF research, there can be no similar guarantee relating to the use of the research outputs in other settings with lower levels of regulation or skill. If potential risks are more widely distributed, should there be a higher threshold for delivery of benefits? In the view of EASAC, for such issues of competence and biosecurity, options should be explored by which sequences are made available only from restricted access sources, following permission to experiment provided by national regulatory authorities.

PUBLICATION OF SENSITIVE INFORMATION

Scientific freedom is not absolute, and the members of the scientific community realize that some information is sensitive. EASAC reaffirms the responsibility for researchers and their institutions to make decisions about publishing sensitive information and, together with funders, ethics committees, and others, to take account of these issues from the time of initiation of the research proposal. EASAC recommendations on early oversight of the implications for sensitive information are compatible with the one reached recently by U.S. journal editors (10).

EASAC also asserted that the European Commission's Export Control Regulation, designed to control the export of dual-use technology, is an inappropriate and ineffective vehicle with which to block scientific publication of sensitive information (see reference 2 for further discussion of how this regulation has been used to delay publication of GoF research).

PUBLIC ENGAGEMENT AND THE GLOBAL CONTEXT

The scientific community can do more to participate actively in public dialogue, communicating the objectives of GoF research, the potential benefits and risks, and the biorisk management practices adopted. Ethics review of research proposals should have lay involvement. Scientific accountability and public engagement need to extend worldwide.

In the global context, clarification of the opportunities and challenges for oversight and action by intergovernmental bodies

requires further attention. EASAC recommends that further consideration could also usefully be given to the 2004 recommendation by the U.S. National Academies (1) for an international forum to sustain dialogue between the life sciences and policymaking communities and with other stakeholder involvement. This dialogue will have to cover both biosafety and biosecurity issues and can capitalize on work already begun by the InterAcademy Partnership on the biosecurity implications of pathogen research (http://www.interacademies.net/ProjectsAndActivities/10880/27693.aspx).

Further information on all of the EASAC analysis and conclusions is in the EASAC report (8) and also in the summary of an event to launch the report, held in Brussels in October 2015 (http://www.easac.eu/home/easac-news/detail-view/article/summary-of-t.html). This launch summary also discusses how the European Commission has welcomed EASAC recommendations and how the European Union conclusions relate to the themes emerging from the interim National Science Advisory Board for Biosecurity (NSABB) conclusions (11).

There is much still to be done to sustain global discussion and to agree on standard setting and verification procedures: we hope that the EASAC report will serve as a resource to inform and stimulate debate and action, not just in the European Union but also more widely.

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