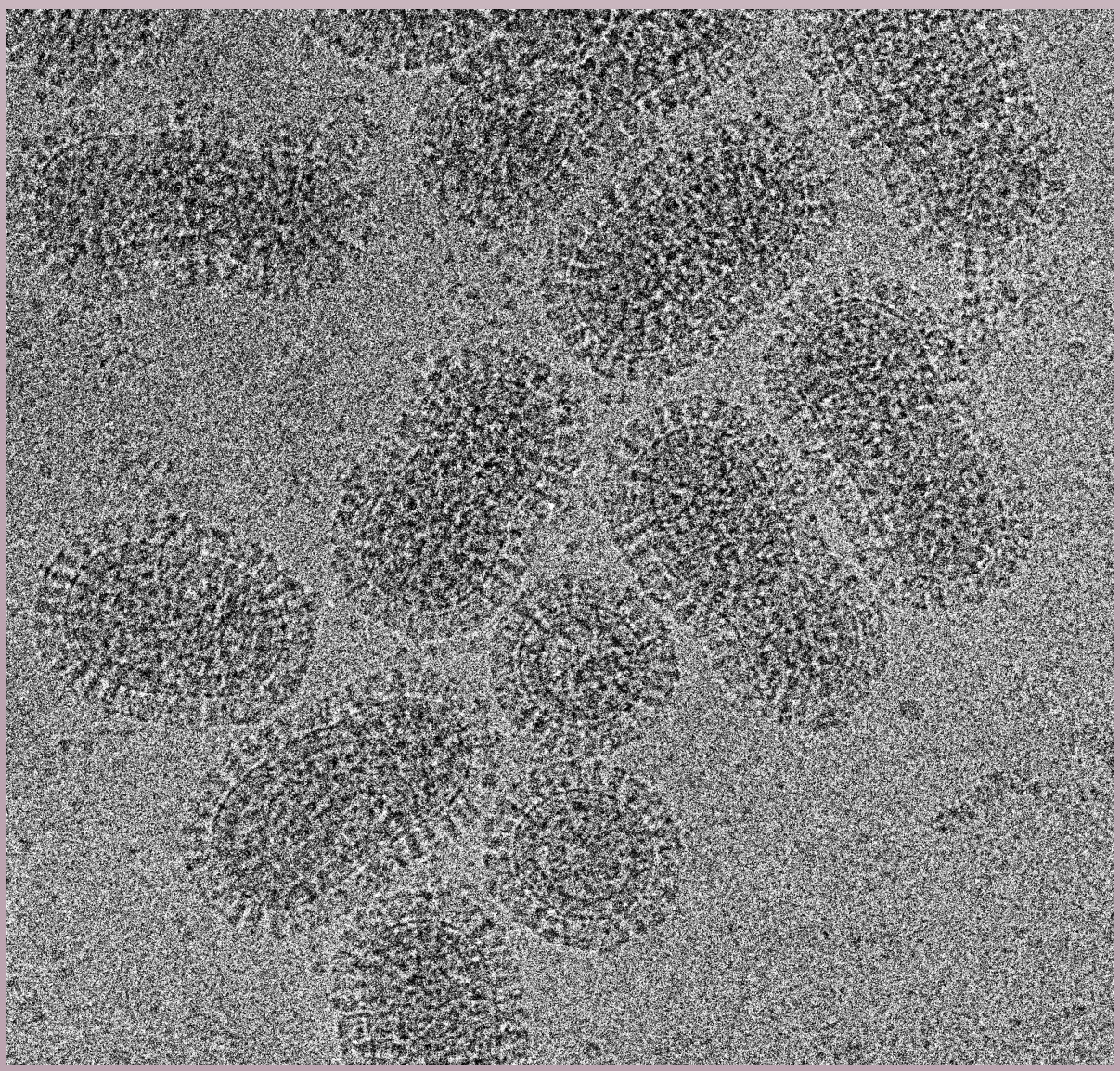
European Academies

easac

Science Advisory Council

Gain of function: experimental applications relating to potentially pandemic pathogens



EASAC policy report 27

October 2015

ISBN: 978-3-8047-3481-4

This report can be found at
www.easac.eu

building science into EU policy

EASAC

EASAC – the European Academies' Science Advisory Council – is formed by the national science academies of the EU Member States to enable them to collaborate with each other in giving advice to European policy-makers. It thus provides a means for the collective voice of European science to be heard. EASAC was founded in 2001 at the Royal Swedish Academy of Sciences.

Its mission reflects the view of academies that science is central to many aspects of modern life and that an appreciation of the scientific dimension is a pre-requisite to wise policy-making. This view already underpins the work of many academies at national level. With the growing importance of the European Union as an arena for policy, academies recognise that the scope of their advisory functions needs to extend beyond the national to cover also the European level. Here it is often the case that a trans-European grouping can be more effective than a body from a single country. The academies of Europe have therefore formed EASAC so that they can speak with a common voice with the goal of building science into policy at EU level.

Through EASAC, the academies work together to provide independent, expert, evidence-based advice about the scientific aspects of public policy to those who make or influence policy within the European institutions. Drawing on the memberships and networks of the academies, EASAC accesses the best of European science in carrying out its work. Its views are vigorously independent of commercial or political bias, and it is open and transparent in its processes. EASAC aims to deliver advice that is comprehensible, relevant and timely.

EASAC covers all scientific and technical disciplines, and its experts are drawn from all the countries of the European Union. It is funded by the member academies and by contracts with interested bodies. The expert members of EASAC's working groups give their time free of charge. EASAC has no commercial or business sponsors.

EASAC's activities include substantive studies of the scientific aspects of policy issues, reviews and advice about specific policy documents, workshops aimed at identifying current scientific thinking about major policy issues or at briefing policy-makers, and short, timely statements on topical subjects.

The EASAC Council has 29 individual members – highly experienced scientists nominated one each by the national science academies of EU Member States, by the Academia Europaea and by ALLEA. The national science academies of Norway and Switzerland are also represented. The Council is supported by a professional Secretariat based at the Leopoldina, the German National Academy of Sciences, in Halle (Saale) and by a Brussels Office at the Royal Academies for Science and the Arts of Belgium. The Council agrees the initiation of projects, appoints members of working groups, reviews drafts and approves reports for publication.

To find out more about EASAC, visit the website – www.easac.eu – or contact the EASAC Secretariat at secretariat@easac.eu

European Academies

Science Advisory Council

Gain of function: experimental applications relating to potentially pandemic pathogens

ISBN 978-3-8047-3481-4

EASAC Secretariat
Deutsche Akademie der Naturforscher Leopoldina
German National Academy of Sciences
Jägerberg 1
D-06108 Halle (Saale)
Germany
tel: +49 (0)345 4723 9833
fax: +49 (0)345 4723 9839
email: secretariat@easac.eu
web: www.easac.eu

Cover image: Cryomicroscopy image of influenza virus provided by Peter Rosenthal.

Copy-edited and typeset in Frutiger by The Clyvedon Press Ltd, Cardiff, United Kingdom

Printed by DVZ-Daten-Service GmbH, Halle/Saale, Germany

Contents

Foreword

In Gain of function (GoF) studies, genes are experimentally modified to study determinants of biological function. GoF research has been very helpful in microbiology to characterise pathogens, for example in support of therapeutic drug and vaccine selection and development.

However, recent GoF experiments to modify avian influenza of subtype H5N1, to help understand transmissibility, have been controversial, partly because of concerns about potential safety and security implications. In the USA there is a *de facto* moratorium on specific research and in the European Union (EU) members of the scientific community have expressed differing views about the value and desirability of GoF work to the European Commission.

It is the purpose of this report from the European Academies' Science Advisory Council (EASAC) to present the outputs from a project that brought together scientists with a range of views, to explore where there is consensus of opinion, to clarify what issues are still unresolved, and to advise on what additional analysis is needed to assess the future options for this research area. In advising on the priorities for action, we emphasise first the importance of understanding what existing regulations and procedures are in place in the EU and individual Member States to govern such research.

This report builds on the sustained interest by EASAC across a broad spectrum of infectious disease research, innovation and clinical practice topics and on our evaluation of modern developments in the biosciences, including synthetic biology, where wide-ranging matters for bioethics, biosafety and biosecurity have been explored in previous reports. The report takes account of the intense debate within the scientific community, expressed in several meetings in Europe and the USA, including those organised by academies of science, and has been prepared by consultation with a group of experts nominated by our member academies. I thank them and their Working Group chairman, Professor Volker ter Meulen, the EASAC Biosciences Programme Director, Dr Robin Fears, and our independent peer reviewers, for their commitment in evaluating the issues and supporting consensus recommendations. I also thank my colleagues in Council and the Biosciences Steering Panel for their guidance in defining the project, determining its objectives and scope, and for their continuing assistance in delivering our messages throughout Europe.

Among the critical issues covered are those for benefit–risk assessment, scientific responsibility and self-governance, research review and management frameworks, the roles of advisory bodies, and the publication of sensitive information. Our focus has been particularly on biosafety, where we recommend a layered approach with integration of responsibilities and action at researcher, research institution, research funder and national levels within the EU context. We are also very aware of potential biosecurity implications: although these are discussed in somewhat less detail in our report, we refer to other continuing collective academy initiatives, in particular the Biosecurity Working Group of the InterAcademy Partnership (IAP)[i].

In our recommendations, we have tried to clarify what is a Member State responsibility and what should be considered by European institutions at the EU level. In addition, we derive two other conclusions of great importance:

(1) There is considerable need for public engagement, to extend the debate, and for the scientific community to articulate the objectives of such research, the potential for benefit and the biorisk management practices and regulations already in place. EASAC will continue to support its academies in stimulating this further engagement across Europe.
(2) The issues are of global relevance. With this report, EASAC aims to support further discussion and action between the scientific community and policy-makers in the EU but also, through other international academy activity, to help inform further inquiry and debate worldwide.

We welcome discussion of any of the points that we have raised in this report or on any other points that require attention.

Jos WM van der Meer
EASAC President

[i] The IAP initiative reviews advances in science and technology, including GoF research, potentially relevant to biosecurity and the Biological Weapons Convention, with a view to advising the 8th Review Conference of the Convention in 2016 (www.interacademies.net/ProjectsAndActivities/10880/27693.aspx). GoF research can be seen to exemplify key themes from previous collective academy analysis identifying potential biosecurity implications of advances in science and technology, particularly with regard to the rapid pace of change in life sciences research and to the diffusion of knowledge as part of the globalisation of scientific effort.

Summary

Influenza outbreaks cause significant burden to public health. The inability to predict which specific virus subtypes will trigger the next influenza pandemic emphasizes the need to address gaps in the knowledge required to manage future pandemics. Research, including the study of virus transmissibility, host range, resistance, immunogenicity, pathogenicity and virulence, is critical to fill many of these knowledge gaps.

Gain of function (GoF) studies, experimentally modifying a virus and analysing the link between genotype and phenotype, have a long history of providing very useful information in virology. In the specific context initially considered in this report, GoF refers to those recent experimental manipulations of the influenza virus, particularly the H5N1 variant, to affect its transmission potential. Such research aims to understand the factors that determine the pandemic potential of an animal virus to spread to humans and between humans by an aerosol route.

Various concerns have been raised about the possible impact of this GoF research with regard to (1) biosafety, safeguarding researchers, the general public and the environment at large; and (2) biosecurity, safeguarding against intentional misuse. Experiments that are classified as dangerous because their products or processes have the potential to cause serious and sometimes transmissible disease require special consideration and precautions before they can be permitted. It is important to recognise that such studies are already subject to stringent European Union (EU) and national regulations applied to the handling of genetically modified organisms and to dealing with other biohazards.

In previous work, several EASAC member academies have examined specific issues for benefit and risk associated with GoF studies on potentially pandemic pathogens, together with broader considerations of biosafety and biosecurity in microbiology research at the national level. EASAC initiated the present project to explore whether there is need for further action by European institutions. These issues are relevant for all EU Member States, and varying views have already been expressed by the scientific community to the European Commission. Our work builds on the ongoing national academy activities and draws on the experience and advice of a Working Group of experts nominated by member academies. Our purpose is to determine whether there is consensus on key questions, identify where further assessment of issues is needed and clarify options for coherent policy development and action. With our report, we also aim to extend the debate within the broader life sciences community, highlight what good practice exists, determine what should be the responsibility of a Member State, support efforts to inform public engagement and contribute to the global debate on these matters.

Among the critical issues discussed are those for self-governance and scientific responsibility based on codes of conduct; benefit–risk assessment; EU consistency in research review and management systems; bioethics; research moratoria; biosecurity advisory bodies; publication of sensitive information; public engagement; and global consensus. Several of the points we address were raised in the US National Academies (Fink) report of 2004, and many of the present conclusions are compatible with the outputs from that previous analysis. EASAC emphasises a layered approach to biosafety with integration of responsibilities and action at researcher, research institution, research funder, national, EU and global levels. It is fundamentally important that Member States and their research institutions and researchers follow the rules and guidance already in place as a result of established EU legislation.

Our focus has been on GoF studies in virology but we advise that the recommendations that follow are also applicable more broadly in microbiology research. The main considerations in the report involve biosafety, but suboptimal biosafety practices also decrease biosecurity and we emphasise that it is a responsibility of researchers, research institutions and publishers to seek appropriate, specialist advice about biosecurity. There was consensus in the Working Group for the following recommendations.

Conclusions and recommendations
Self-regulation and harmonisation

- We endorse the commitment to good practice that is already in place in Member States, exemplified in our report, and which depends on (1) conforming with regulations and codes of conduct; (2) justification of research to funders and peers on a case-by-case basis; and (3) attention to safety conditions according to established procedures of biorisk management.

- Self-regulation means that there are checks and balances on research within the scientific community and does not mean that each researcher is free to decide for themselves what procedure to follow.

- Commitment to self-regulation for responsible science requires increasing effort to raise awareness of the issues for individual researchers and their research institutions; this includes education and training.

- There is also need for increasing commitment to sharing and spreading good practice to harmonise processes within and between countries.

- Attention to key biosafety issues is imperative at all stages of the research endeavour, from formulating the research idea through to publication of results. For example, justification of the choice of biosafety category to be used in proposed research should be an explicit part of the application for research funding. Grant applicants should discuss the potential risks involved in the proposed experimental approaches and funders should consider the potential value/benefits of the research in the context of those risks. Before awarding a grant, the funder must be confident that an effective regulatory framework is in place in the institution/ Member State to ensure adequate risk assessment and mitigation and if in doubt should seek further information and advice.

- Academies of science have a continuing role to play in promoting and increasing understanding of biosafety and biosecurity norms and in encouraging the auditing of research practices in terms of those norms.

Benefit–risk assessment

There are many uncertainties in the data available for evaluating benefit–risk of GoF studies on potentially pandemic pathogens, and differing value systems have also been applied in evaluating the data. Incommensurable parameters measured in risk and benefit do not allow a value-free determination to be made. There are varying views on whether benefit can be quantified in terms of prospective public health impact or described in terms of the generation of scientific knowledge. EASAC recommends that:

- Analysis of benefit–risk balance cannot be regarded as a 'once and for all' calculation but, rather, as a continuing, collective commitment to understand and communicate the issues, with particular regard to analysing, quantifying and reducing risk and to considering benefit.

- Academies and learned societies engage in a process to share data and perspectives and to promote discussion, across the scientific community and involving other stakeholders, to identify critical factors underpinning qualitative and quantitative assessment of risks and benefits.

- Opportunities for improving the capacity for public health preparedness and resilience to disease outbreaks generally should be considered.

Collating information on biosafety and biosecurity procedures already in place

EASAC recommends:

- Building commitment by researchers and their institutions to sharing information on the situation in all Member States to optimise EU value in spreading good practice. The European Commission's Health Security Committee under the auspices of DG Sante, with support from Directorate-General for Research and Innovation (DG Research) and the European Centre for Disease Prevention and Control (ECDC), will be invited to undertake the role to collate the information available.

Are new biosafety and biosecurity bodies required?

In the opinion of EASAC:

- There is no need for a new advisory body at the EU level. Nonetheless, the issues discussed in our report are highly significant for EU functions in various regards. In particular, with respect to European Commission funding of Horizon 2020, we bring to the attention of DG Research the importance of appropriate guidance on biosafety and biosecurity for research applications and evaluations.

- Taking account of subsidiarity, all Member States should have a clear national advisory approach. Clarification of practical options for advisory approaches will be aided by the research institutions' sharing of good practice. We emphasise throughout the report the importance of ensuring the assessment GoF study proposals on a case-by-case basis with thorough consideration of the issues for benefit–risk balance.

- Although new EU-level bodies are not required, it is imperative that all researchers and research institutions conform with the EU Directives and Regulations appertaining to biorisk management, as implemented in national legislation, guidance and procedures.

- It is important that the principle of a layered approach is adopted by Member States across the EU. Each Member State national mechanism responsible for governance should have statutory powers.

Publication of sensitive information

EASAC recommends:

- Ensuring that researchers and their institutions recognise their responsibility to make decisions about publishing sensitive information.

- Continuing the current procedure whereby many journals seek appropriate advice, including from security experts, since once released for publication in any country, the distribution of scientific information extends beyond that country. Those that do not are encouraged to do so.

- The scientific community should provide advice to DG Research on the revision of the European Commission's Export Control Regulation. We regard this Regulation as an inappropriate vehicle to block publication.

Public engagement

Trust, openness and public engagement are highly important for researchers and research institutions and it is recommended that:

- Academies and others in the scientific community should actively participate in public dialogue, articulating objectives for research, the potential for benefits, and the biorisk management practices adopted. EASAC will provide a lay summary of the present report to stimulate further debate.

Global context

EASAC advises:

- Further consideration should be given to the proposal in the Fink report for an international forum to sustain dialogue between the life sciences' and policy-making communities, and with other stakeholder involvement. This dialogue should cover biosafety and biosecurity, and the InterAcademy Partnership (IAP) should consider taking a prominent role in informing the global discussion.

1 Introduction

1.1 Public health and economic burden

Infectious diseases are responsible for a substantial proportion of deaths worldwide. The World Health Organization (WHO) has estimated that annual influenza epidemics account for 3 million to 5 million cases of severe illness and 250,000–500,000 deaths worldwide.[1] The burden of disease can increase dramatically during a pandemic. The 1997 H5N1 influenza outbreak in Hong Kong was the first documented incidence of an avian virus causing severe human disease and death. Over past decades there has been an increase in detection and reporting of avian influenza viruses crossing the species barrier to infect humans, that may result in severe disease (Schultz-Cherry et al., 2014)[2].

The total public health and economic burdens (health care costs plus indirect costs of lost work) of pandemics are difficult to quantify[3]. The US Centers for Disease Control and Prevention (CDC) has engaged in significant modelling work on pandemic mortality (for example Dawood et al 2012, and CDC discussion on http://www.cdc.gov/flu/spotlights/pandemic-global-estimates.htm). One UK modelling study indicated that, depending on severity, an influenza pandemic could result in losses of 0.5–4.3% of UK gross domestic product (GDP) (Smith et al., 2009). Preparedness against the threat of communicable disease has a high priority in the political agenda of the EU and its Member States.

The inability to predict which specific subtypes will cause the next influenza pandemic[4] demonstrates the need to address gaps in the knowledge required to manage more effectively future pandemics. H5N1 influenza viruses and other avian influenza strains represent a possible risk for causing a future pandemic but it is not well understood how these viruses might acquire airborne transmissibility between people. Research, including the study of transmissibility, host range, resistance, immunogenicity, pathogenicity and virulence, is critical to improving awareness of public health threats from pandemic influenza.

1.2 Gain of function studies

Gain of function studies, linking phenotype and genotype, have a long history of providing very useful information in virology, and microbiology more broadly. Their previous application in research on the biology of viruses includes the study of virus pathogenicity, the development of relevant animal models, antiviral drug design and vaccine development.

In the context initially considered here, GoF focuses on recent studies in which transmission of avian influenza viruses of subtype H5N1 has been experimentally modified with the aim of understanding the factors that increase the ability to spread in an animal model.

Experiments that are classified as dangerous, because the products or processes have the potential to cause serious and sometimes transmissible disease, require special considerations and precautions before they can be carried out. This assessment must be made on a case-by-case basis and take into account analysis of benefit–risk balance. These considerations are relevant to those GoF experiments that intend to alter virus transmission, host range, drug resistance, infectivity, immunity and virulence (Duprex and Casadevall, 2015). It is essential that widely considered and well-defined regulations and codes of practice are in place before such experiments are initiated.

GoF work can provide insight on the fundamental biology of the influenza virus, including virulence, immunogenicity, host range and transmissibility, and might help to drive health benefits, including the prioritisation and development of pre-pandemic vaccines. Various concerns have been expressed about the impact of these GoF experiments with regard to biosafety (that is, implementation of containment measures to avoid release of virus into the environment and protection measures to avoid exposure of personnel)—safeguarding researchers, the general public and the environment at large. There can also be legal implications for the liability of the research institution in such an eventuality, even if the

1 http://www.who.int/mediacentre/factsheets/fs211/en.

2 There may also be many more subclinical infections, for example with H5N1 influenza viruses, than the WHO numbers suggest (Wang et al., 2012).

3 Estimates and predictions may be controversial. WHO compiles numbers, for example for H5N1, http://www.who.int/influenza_animal_interface/EN_GIP_201503031CumulativeNumberH5N1cases.pdf?ua=1, but WHO also released a statement in 2015 that pandemics and the pandemic strain could not be predicted, http://www.who.int/influenza/publications/warningsignals201502/en.

4 http://www.who.int/medicines/areas/priority_medicines/Ch6_2Pandemic.pdf.

Box 1 Definitions associated with biorisk management (after WHO 2006)

Biosafety. Laboratory biosafety describes the containment principles, technologies and practices that are implemented to prevent the unintentional exposure to pathogens and toxins, or their accidental release.

Laboratory biosecurity. Laboratory biosecurity describes the protection, control and accountability for biological materials within laboratories to prevent their unauthorised access, loss, theft, misuse, diversion or intentional release. Biological materials in this definition include pathogens and toxins.

Dual-use. Initially used to refer to the aspects of certain materials, information and technologies that are useful in both military and civilian spheres. The expression is increasingly used to refer also to harmful misuse and peaceful activities.

Bioethics. The study of the ethical and moral implications of biological discoveries, biomedical advances and their applications as in the fields of genetic engineering.

Biorisk management. The analysis of ways and development of strategies to minimise the likelihood of the occurrence of biorisks. Biorisk is the probability or chance that a particular adverse event (including accidental infection or unauthorised access), possibly leading to harm, will occur. Biorisk management has three components: biosafety, laboratory biosecurity and bioethics.

researcher following established biosafety rules may not be personally liable. It must be borne in mind that safety breaches have resulted from neglect of safety procedures. Concerns about biosecurity (that is, implementation of protection measures against intentional misuse) have also been raised, with particular regard to the potential for dual use of modified pathogens. There is overlap between biosafety and biosecurity issues and WHO has used the term biorisk to cover both (see Box 1 for other commonly used definitions from WHO).

Bioethical considerations relate to the moral principles and duties that govern experimentation and include such issues as transparency of decision-making; public participation, confidence and trust; responsibility and vigilance in protecting society. Dual use and potentially dangerous research generally (as referred to in Box 1) raises issues about the limits of freedom of basic research. Ethical issues should be considered at all stages of GoF research (for example as reviewed by Resnik, 2013) – at the point of funding, during design and methodology development, and during publication – and are discussed further in Chapter 2.

Effective risk management underwrites public trust in the biological sciences (WHO, 2006). It is important to appreciate that in the EU, GoF studies are already subject to stringent GMO (genetically modified organism) regulations and other legislation. Laboratory design and personnel protection, well established by EU Directive in Member States[5], can be augmented by the availability of public health measures such as anti-viral drugs and vaccines. Furthermore, the CEN Workshop Agreement CWA 15793:2011 Biorisk Management currently in the process of being reformulated as an ISO Management System Standard is globally applicable for implementation of biosafety and biosecurity (see Chapter 2 and Appendix 4 for further discussion of EU and international frameworks).

EASAC initiated this project (section 1.5 and Appendix 1) to analyse the current situation and to formulate recommendations. Our focus is primarily on avian influenza A virology as this field has precipitated the current controversy, but our conclusions have broader connotations and are relevant to regulation of research on other microbes.

1.3 Broader contexts

Some of the concerns elicited by GoF studies on H5N1 or other avian influenza variants also apply to work on characterising or manipulating other pathogens. For example, the synthesis of poliovirus and the addition of an immune-modulatory gene into the mouse pox virus genome, rendering protection by vaccination ineffective, have provoked discussion in the past (see, for example, Gronvall, 2014).

Concerns for safety have to a significant extent been exacerbated by reports of accidental releases of highly infectious agents and toxins from high containment laboratories in the USA. The recent incidents involving

[5] For example EC Directive 2000/54/EC biosafety legislation governing containment level 3 and 4 laboratories, http://www.biosafety-europe.en/d20public_300309.pdf. Annex III of Directive 2009/41/EC and guidance notes published in European Commission Decision 2000/608/EC describe, in general terms, the elements considered for performing a risk assessment of genetically modified organisms. Further detail on the current situation in the EU is provided in Appendix 4.

live anthrax bacteria and avian influenza viruses at the US Centers for Disease Control and Prevention (CDC) highlights the importance of rigorous audit of procedures used in biocontainment laboratories working on dangerous pathogens. Laboratory accidents happen: a CDC analysis reports 727 incidents of theft, loss or release of select agents and toxins in the USA between 2004 and 2010, and 11 laboratory-acquired infections (Henkel et al., 2012). For potentially pandemic pathogens the biosafety issues are especially important for public health as well as occupational health.

Following the recent US incidents (including laboratory samples of smallpox), there have been renewed calls for further strengthening the culture of biosafety (for example, Butler, 2014). The concerns emphasise the need to use high-containment facilities appropriately and to ensure that inspection and audit of the facilities and of the procedures used in them are maintained at the highest levels. They also emphasise the requirement for scientists at all levels of seniority to recognise and accept responsibility for the safety of themselves, their colleagues and the community at large.

Consideration of GoF studies on potentially pandemic pathogens raises issues for ethics in science, openness and sharing outputs, and questions of whether these issues are in conflict with the requirements for safety and security. It is also important to emphasise, however, that the general issues associated with the creation of novel pathogens with unique properties have already been explored in detail in previous wide-ranging reviews, most notably the US National Academies Fink report[6] on research standards and practices to prevent the destructive application of biotechnology. The recommendations from the Fink report are listed in Appendix 2 of the present report and they will be discussed further (Chapters 2 and 3).

1.4 What is the EU relevance?

Various issues relating to GoF experiments have already been emphasised in letters to the President of the European Commission and other senior policy makers from the European Society of Virology (October 2013)[7] and the Foundation for Vaccine Research (December 2013, see also Wain-Hobson 2013, 2014a, b)[8], setting out different views on the prospective benefits and risks of H5N1 research (see Appendix 4 for details). A debate between the principal authors of these two letters was organised by the Koninklijke Nederlandse Academie van Wetenschappen (KNAW: Royal Netherlands Academy of Arts and Sciences) in June 2014 (Table 1 in Appendix 1) to help clarify differing views on risk–benefit balance of these GoF experiments and of related matters that will be discussed throughout the present report. The European Commission is also reflecting how best to address matters related to GoF research: in particular, in view of the potential for accidental release and misuse, there is a need to improve awareness among members of the scientific community of these issues, and to promote an underlying culture of responsibility.

The accelerating pace of biological research is likely to stimulate further controversy relating to both biosafety and biosecurity. These matters are relevant to EU as well as to Member State policy in several respects. For example, who decides the following:

- How to define benefit and risk in a research proposal? How to take account of ethical issues?
- Advising with regard to biosecurity implications?
- Setting the appropriate balance between statutory regulation (and perhaps restriction) of research and scientific self-governance?
- International sharing of sensitive research methods and results, including publication in scientific journals?

It is essential to ensure public engagement about these issues. These questions merit the attention of EASAC because they should be of interest to all Member States, because some of the options for action (for example review of research, regulation and possible provision of shared pathogen containment facilities) involve EU-wide strategy, and because of the previous and ongoing work by European academies (listed in Appendix 3).

1.5 EASAC objectives for this work

The purpose of this report is to explore where there is consensus on key questions, to identify where further assessment of the issues is required and to clarify options for policy development. EASAC is drawing on the previous work by individual academies and expert group discussion in order to:

- Help extend the debate with the broader life sciences community and academies across Europe. Our aim is to contribute to a framework of analysis on key issues relevant to potential bioethical, biosafety, biosecurity and biorisk management aspects of the GoF studies associated with the experimental manipulation of potentially pandemic pathogens: these challenges

[6] Committee on research standards and practices to prevent the destructive application of biotechnology, Biotechnology research in an age of terrorism, 2004, http://www.nap.edu/openbook.php?record_id=10827.
[7] http://www.eusv.eu/pdf/ESV%20letter%20on%20Gain%20of%20function_GOF_research%20in%20Virology.pdf.
[8] http://news.sciencemag.org/sites/default/files/media/Letter%20to%20Barroso_0.pdf.

pervade the funding of the research, its design and conduct and the publication of its outputs.

- Identify what is good practice and share that good practice on current approaches to defining, assessing and resolving issues associated with the questions asked in the previous section: to mitigate risks while continuing to ensure scientific discovery and innovation.

- Clarify what is a Member State responsibility and what might be addressed at the EU level, so as to provide recommendations for policy makers in the EU institutions and in Member State governments.

- Support efforts to improve openness and inform public engagement.

The issues are of global concern and it is hoped that the present report will also serve as a resource to inform other inquiry globally and provide a basis for the EU to be involved in those discussions worldwide between policy makers and academies of science.

EASAC messages will be directed to:

- Academies of science in other regions, outside the EU, and all who are interested in the global context of these issues.

- Those who make or influence policy in the European Commission, European Parliament and Council of Ministers. The issues for GoF studies may be of particular relevance to DG Research and Innovation (relating to research review and management), DG Trade (relating to scientific publishing in the context of export controls, under Council Regulation EC428/2009), DG Agri (plant health) and DG Sante (human, animal and plant health).

- Those who make or influence policy at the EU Member State level.

- Research funding bodies.

- Regulatory authorities.

- Professional societies and others in the scientific community, including individual researchers.

- The lay public.

The next chapter describes some of the critical issues considered by the Working Group: further information on the science and the present regulatory frameworks are in Appendix 4, with a country case study in Appendix 5. EASAC conclusions and recommendations are presented in Chapter 4.

2 What are the critical issues and are they specific for these GoF studies?

In this chapter, we aim to clarify and address some key questions that have been raised in previous scientific discussions and commentary about GoF work. In the following chapter we present our recommendations. Do these GoF experiments raise new issues for biosafety and biosecurity procedures? Are there gaps in our current approaches to managing these sorts of experiments within the EU or globally? If so, what are the new issues and what are these gaps: is there need for ethical guidelines, or more regulation, or better communication about risk between researchers and the community-at-large?

There were meetings in late 2014 in Europe and the USA (Table 1) to discuss the issues and the EASAC report draws on these open discussions as well as our Working Group deliberations. Significant concerns have been articulated within the scientific community about the risks of research on respiratory-transmissible highly pathogenic viruses. However, understanding and combating potentially pathogenic viruses is vitally important for public health, and this requires research. What then should be done about identifying and addressing the risks of those experimental studies of highest impact?

2.1 Self-governance and scientific responsibility based on codes of conduct

Self-regulation is a necessary first step, as emphasised in the work of KNAW and others (Appendix 3). The scientist's moral duty to do no harm includes not just intentional harmful acts but also acts that impose risks of harm (Relman, 2013). If it is possible to obtain the information in a safer way, then that is what should be done. As noted at the Royal Society meeting in 2013, scientists are accountable to society; therefore personal responsibility for compliance with regulations is essential. The Working Group emphasised that researchers must exercise individual responsibility based on a full understanding of the issues. Part of this exercise of individual responsibility will be the recognition that certain research on potentially pathogenic agents can only be conducted in those countries with stringent regulations and appropriate facilities.

Inculcating scientific responsibility requires education, training and awareness raising. Awareness must include familiarity with relevant legislation and codes of conduct, and of when and how to seek guidance from expert advisory groups. There may need to be external evaluation procedures put in place to assess awareness. Teaching in the undergraduate curriculum as well as training as part of continuing personal development should include information on principles and regulations pertaining to biosafety practices as well as the issues for exercising scientific responsibility. The work of the European Biosafety Association could be valuable in this regard and their current strategic plan[9] includes efforts to promote and secure implementation of best practice, to raise awareness and understanding in biosafety and to advocate high standards in competency. The wider international connections of the European Biosafety Association are also an important resource to promote global coherence in biosafety.

Significant work in developing broad codes of conduct has already been accomplished by individual academies and when working together within InterAcademy Council (IAC) and InterAcademy Panel (IAP: InterAcademy Partnership from 2014) (Appendix 3). Furthermore, the code of conduct published by the Max Planck Society in 2010[10] has been a very valuable initiative in promoting self-regulation for dual use research of concern: in providing for broad interdisciplinary coverage, distinguishing legal and ethical norms and supporting researchers. The work of the Max Planck Society also helped to provide input for the report (Appendix 3) from the German National Academy of Sciences Leopoldina together with DFG, which explicitly covers GoF research and provides several recommendations for:

(1) Individual responsibility—promoting awareness of the danger of misused research requires actions for risk analysis, measures for reducing risk, evaluating timing and content of publication and, as a last resort, abstaining from research.

(2) Research institutions—raising awareness of problems and legal constraints on research, supporting training, developing ethics rules that go beyond compliance with legal regulations, and constituting committees on research ethics to implement rules and advise scientists.

As emphasised in the next chapter, EASAC strongly endorses this necessary focus on both individual and institutional responsibility with regard to use and misuse of research.

[9] European Biosafety Association Strategic Plan is on http://www.ebsaweb.eu/ebsa_media/EBSA+Strategy+Paper.pdf.
[10] Guidelines and rules of the Max Planck Society on a responsible approach to freedom of research and research risks, 2010, on http://www.mpikg.mpg.de/2441420/Freedon-of-research.pdf.

2.2 Benefit–risk analysis

In benefit–risk assessment, there are two dimensions that need to be separated: (1) the nature of the outcome, which is harm and benefit, and (2) the likelihood of the outcome. Both dimensions can be graded. There can be a low probability for a serious negative outcome, as well as a high probability for a negative outcome that is not serious. If the outcome is harm, the word 'risk' is used for the likelihood; if the outcome is benefit, 'chance' is used.

The 'risk–benefit' terminology does not separate these two dimensions clearly; 'risk' is sometimes used synonymously with 'negative outcome', sometimes for 'the likelihood of a negative outcome'. A problem with this terminology, well established though it is, is that it suggests that negative outcomes are uncertain but benefits are certain. Research is needed to determine the outcome, that is the consequences, of various options and actions; and explicit value premises are needed to determine the nature of the outcome: as harm or benefit. Research is also needed to distinguish between outcomes that are possible, probable or documented

If chances for benefits of various kinds are compared with risks of adverse events, when GoF research is carried out by competent researchers in laboratories of a certain kind, it is clear that this comparison involves many steps and elements that are incommensurate. There are also many uncertainties and gaps in our knowledge. This means that there is a danger in pretending that these comparisons are more exact than the foundations allow; mathematical models can convey a sense of false exactness, since the figures used in the calculations tend to be somewhat arbitrary. This does not mean that making approximate estimates should be avoided.

A multi-stakeholder dialogue could be one way of assessing the risks and benefits and decide whether the benefits in a particular case or type of research are such that they outweigh the risks. It should be noted that values change over time and within as well as between groups in society. Moreover, new technology may reduce risks and make methods previously used less dangerous. The obvious conclusion is that risk–benefit assessments should not be made once and for all; we must be prepared to revise them when the evidence and values change.

Decisions about which level of risk is safe, given the probable or expected benefits, are ultimately based on values, on what the stakeholders involved want to achieve and avoid. To say this is not to say or suggest that these decisions are arbitrary; it is possible to argue for or against such decisions by exploring their relations to, for instance, human rights, to principles of fairness, and human health and wellbeing.

The current deliberative phase in the USA (see Appendix 4 for details) encompasses efforts[11] by the US national academies to promote dialogue and commissioned work to assess the issues involved in conducting benefit–risk analysis on GoF studies (details are provided in the webcast and summary from the meeting in December 2014; see Table 1 in Appendix 1). While the goals are for such analysis to be objective, robust and quantitative there are potential problems to achieving these goals—particularly in respect to understanding the nature of harms and benefits as discussed above, weighing one against the other, and then communicating the assessment[12].

It is critically important to be precise about terminology of GoF research, so that attention is focused on those studies of greatest concern. There are multiple uncertainties in the evidence available relating to probability and impact of risk, exposure assessment and dose–response. Assessment of risk and its attribution is particularly challenging for those risks that will be very rare but of potentially wide-ranging impact. Risk assessment should take into account those biosafety measures and public health defences that are already in place and, ideally, should be based on a probability that represents actual laboratory experience of the viruses under consideration.

One of the other problems for risk–benefit assessment in this area is that benefits are difficult to quantify. There are also differing perspectives, assumptions and value systems for defining benefit, for example relating to innovation and how to value fundamental knowledge as an outcome. The difficulty is highlighted by the differing opinions that have been expressed in the scientific literature (see Appendix 4 for reference to key literature).

Expert peer review is essential in devising robust estimates of benefit and risk. The current US initiative

[11] http://osp.od.nih.gov/sites/default/files/14_Stanley-Addressing%20the%20Charge%20to%20NSABB%20508%20SB%20CSL.pdf.

[12] These issues are broadly relevant to the consideration of research and innovation in many sectors. A recent report from the UK Government's Chief Scientific Adviser discusses the challenges for clarifying and addressing hazard, risk, exposure, vulnerability and uncertainty drawing on evidence from social sciences research and other disciplines in a wide range of case studies (Government Office for Science (2014) *Innovation: managing risk , not avoiding it,* on https://www.gov.uk/government/publications/innovation-managing-risk-not-avoiding-it).

is important in helping to understand the principles involved and clarify key considerations – both quantitative and qualitative – for the design of risk and benefit analyses in the global context[13]. However, while awaiting the outcome of this analysis, it is important to continue generating wider awareness of all the issues relating to GoF studies, as outlined in the present report.

The challenges in performing risk–benefit analysis in this area are illustrated by the controversy surrounding initial calculations to assess risk as the sum of probability and consequence, on the basis of limited data[14]. In addition to uncertainties about the data available, there are other points of contention. For example, should biosecurity risk as well as biosafety risk be included, to cover intentional as well as accidental releases of pathogen? This may be particularly difficult in view of the uncertain and likely varying nature of the biosecurity threat.

If it were possible to develop a robust benefit–risk assessment template, questions would remain: who should do the assessment, how should subjectivity be acknowledged and how should the results of that assessment be taken into account in informing policy development? That is, who decides whether a particular level of risk is acceptable or not? The EASAC recommendation (Chapter 3) is that these are ultimately responsibilities of national regulatory authorities, fulfilled with the best scientific advice available.

To reiterate, analysis of benefit–risk balance cannot be regarded as a 'once and for all' calculation but rather as an ongoing, collective commitment to understand and communicate the issues.

2.3 Present research review and management systems

The National Academy of Sciences (NAS) and Hannover meetings in December 2014 discussed whether attention should focus on those viruses perceived to be the most dangerous—combining properties of high virulence, transmissibility and not amenable to control measures . Would this represent a class of research that is not acceptable because the risks are too high, or is it possible to apply the highest safety controls to allow even this research? Is it already the case that such research would not be proposed by responsible scientists, not supported by responsible funders nor allowed by responsible research institutions?

As noted in Chapter 1, there have been extensive previous deliberations in the biosciences that are relevant to the further consideration of GoF studies. In particular, these include the work that led to the seven categories of concern (and the criteria for defining them) in the US National Academies Fink report (see Appendix 2)[6]. It is feasible to fit current GoF studies into this existing taxonomy of concern. Is more required to maintain/increase the appropriate level of oversight and encourage public trust while avoiding hindering research?

Biorisk management in the laboratory has important technical considerations, for example establishing the level of biological containment and other safety procedures that are required (Duprex et al., 2015). It is not the purpose of the present report to be prescriptive but rather to emphasise principles for good practice: general recommendations on biorisk management have previously been published by WHO (Box 2). As discussed in the meeting at the Royal Society in 2013 (Table 1 in Appendix 1), such management must take into account the availability of experimental options that carry lesser risk (and see discussion in Box 4 in Appendix 4).

Modern practices of biorisk management can learn from the safety culture introduced into other sectors. The provisions for laboratory risk management comprehensively described in the European document CWA 15793[15] cover important principles and actions for safety management systems, infrastructure, risk assessment, auditing and approval of actions (see also Appendix 4).

Another concern has been raised recently in the context of the potential proliferation of technologies and information on 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 use of those research outputs in other, less well regulated/less-skilled settings. If potential risks are more widely distributed, should

---

[13] This work on benefit-risk assessment may also usefully draw on lessons learnt in other sectors. For example the FDA Framework 2013 recognises there is scientific and policy judgement involved in all analyses, recommends quantifying what can be quantifiable without ignoring other elements and highlights ethical issues: Structured approach to benefit-risk assessment in drug regulatory decision-making, http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf.

[14] Lipsitch M, Risks and alternatives to gain-of-function studies, presented to National Science Advisory Board for Biosecurity (NSABB) meeting, 22 October 2014, see http://osp.od.nih.gov/sites/default/files/4_Lipsitch_508.pdf. Recent publications in mBio (Fouchier, 2015; Lipsitch and Inglesby, 2015) have provided detailed accounts, drawing very different conclusions, on public health risks.

[15] Laboratory risk management, CEN workshop agreement, European Committee for Standardisation, Brussels 2011, on http://www.uab.cat/doc/CWA15793_2011. In addition to the WHO and CWA documents, there is national guidance on biorisk management available from the USA (Centers for Disease Control and Prevention (CDC) and from the National Institutes of Health (NIH) regarding recombinant or synthetic DNA) and Canada.

Box 2 Essential components in biorisk management programmes (WHO 2006)

1. Identify biological materials (see Box 1) that require protection.
2. Establish clear guidelines, roles, responsibilities and authorities for those who work with or have access to the facilities.
3. Promote a culture of awareness, shared sense of responsibility, ethics, and respect for codes of conduct within the international scientific community.
4. Develop policies that do not hinder efficient sharing of reference material and scientific data and do not impede conduct of legitimate research.
5. Strengthen collaboration between the scientific, technical and security sectors.
6. Provide appropriate training and protection to laboratory staff.
7. Strengthen emergency response and recovery plans because '*biorisk management can never really eliminate every conceivable threat*' and commit to continuously improve biorisk management plans.

there be a much higher threshold for delivery of benefits? In the view of EASAC, where such issues of competence or biosecurity are concerned, procedures should be devised by which sequences are made available from restricted access sources, following permission to experiment from national regulatory authorities (see Chapter 3.)

2.4 Harmonising good practice

The Working Group emphasised the critical importance of ensuring that present good practice in developing a layered approach to biosafety and biosecurity is shared and harmonised between Member States and at EU level (for example in Horizon 2020). One example of the procedures currently in place in a Member State is provided in Appendix 5[16]. Although the practical organisation of a layered approach, to include governance at the national level, may vary between Member States, it is vitally important that the principle of layering is adopted across the EU—to ensure accountability and public trust as well as the spread of good practice.

This sharing and harmonisation of experience must encompass the procedures for early review of research protocols, research practices and their monitoring, to build the culture of biosafety. Review must apply not just to individual research proposals but also to performance at the institutional level and, as noted previously, to the awareness of individual researchers.

As proposed by the KNAW report on biosecurity (Appendix 3) there may be need for external evaluation to ensure the maintenance and spread of good practice across institutions, but it is important to avoid duplication of functions between different bodies. If Member States can deal with the issues in the same way, reflecting best practice, then there is no need for an additional EU body, but Member States may have much to do to work together to ensure the necessary consistency in procedures. It is also important, as emphasised for example in the KNAW debate (Table 1 in Appendix 1), that the system is sufficiently credible to build public trust. This will require participation in the oversight mechanisms from those outside the scientific community, including the security services.

Careful scientific and ethical review of relevant research and its management on a case-by-case basis requires a mechanism for collective learning from cases and this might entail some sort of inventory of relevant experiments, to construct the evidence base for audit, analysis and debate. Disclosure of detail on experiments should include information on how risk was assessed, managed and monitored. Academies of science should consider further how they can assist in helping to evaluate this shared resource.

Assessing considerations of benefit–risk early in project development is a responsibility for the researchers and their institutions as described in section 2.1, but also for research-funding bodies whether at Member State or EU level[17]. Broad recommendations for the funders and others involved in research are described in the IAP global work on scientific responsibility (Appendix 3). Funders must require that researchers agree to comply with an established Code of practice.

2.5 Bioethics

GoF experiments on novel potential pandemic pathogens require ethical scrutiny regarding the acceptability of risks of accidental or deliberate release and of global spread. Ethical analysis is also required to help address issues that may not be covered by current legal frameworks. The Working Group concluded that there should be ethical review of those scientific laboratory protocols that potentially pose risks to

[16] The USA also has a layered approach to biosafety, encompassing the institutional, local (for example, some city committees), national (for example the Select Agent Regulations), research funder (NIH) and NSABB.
[17] The process for EU Horizon 2020 project proposal appraisal includes ethical review and, if needed, additional security scrutiny.

humans but they did not identify new and unique ethical aspects of GoF research. Ethics scrutiny should be part of the rigorous, impartial assessment of pathogen GoF studies at the institutional level.

The ethical principles involved and need for scrutiny as part of protocol review are not matters that are unique for GoF studies. The US Presidential Commission for Study of Bioethical Issues (focusing on synthetic biology, Gutmann, 2011) made broad examination of various relevant points, including: public beneficence (maximise public benefits, minimise public harms); responsible stewardship (and the duty owed to future generations); intellectual freedom and responsibility; democratic deliberation (involving stakeholder collaboration and iteration); and justice and fairness (global distribution of effects).

The German Ethics Council's Ethikrat report[18] also provides extensive discussion of ethical issues and it emphasises the importance of the precautionary principle, distinguishing between different interpretations of the principle. As observed by EASAC in other areas (EASAC, 2013), when applying the precautionary principle to emerging technologies it is equally necessary to consider the risks of not embarking on new work, namely the benefits that may be lost to society by deterring research and innovation. An alternative case has been made to apply the proportionality principle to GoF research, rather than the precautionary principle, to resolve conflicts (reviewed in Rath, 2014). The importance of applying the principle of proportionality, and its relation to the precautionary principle, when considering emerging technologies and research ethics, has been discussed in detail by Hermeren (2012).

The Ethikrat report also discusses how central elements of a science ethos based on accountability and self-regulation have formed the basis of the confidence that the public has placed in scientists. In a context of uncertainty and inequality, from the Ethikrat perspective, codes of conduct are useful but not sufficient because they are not legally binding, they are limited to particular groups, and they may have little democratic legitimacy. However, it should be added that codes of practice accepted by national regulatory authorities can be considered to have this legitimacy.

The EASAC Working Group agreed that it is important to engage with all relevant interests in the deliberative process, securing public trust through ongoing involvement and accountability.

2.6 Addressing the scientific concerns

Several groups have formed to debate issues of risk and benefit of experiments generally (see also Wain-Hobson 2013, 2014a, b). For example, an international statement in favour of curtailing all such GoF experiments until risks have been more clearly assessed was published by the Cambridge Working Group in 2014[19]. This Statement notes that recent incidents involving smallpox, anthrax and avian flu in top US laboratories reinforce the urgent need for thorough reassessment of biosafety: '*Accident risks with newly created potential pandemic pathogens raise grave new concerns … Experiments involving the creation of potential pandemic pathogens should be curtailed until there has been a quantitative, objective and credible assessment of the risks, potential benefits, and opportunities for risk mitigation, as well as comparison against safer experimental approaches … Whenever possible, safer approaches should be pursued in preference to any approach that risks an accidental pandemic.*'

Following this statement, alternative views have been expressed by another international group, Scientists for Science (http://www.scientistsforscience.org), expressing confidence that biomedical research on potentially dangerous pathogens can be performed safely.

The current US pause on new funding for GoF studies, together with voluntary desistance from other research is a *de facto* moratorium. This can only be useful as part of a clear strategy to provide time for the National Science Advisory Board for Biosecurity (NSABB) to provide its recommendations to the US Government. It is important to be clear about what issues need to be addressed specifically relating to GoF experiments and to resist conflating the issues with other concerns raised in consequence of the recent US laboratory incidents relating to other pathogens. There will be valuable lessons for the operation of NSABB from its current initiative and other countries will also need to take note of what is decided as the eventual brief of the NSABB. There have been some calls for a European Advisory Board for Biosecurity, to involve scientists (including those in public health), policy makers, biosecurity and biosafety experts and civil society (footnote 7, Palu 2014, and discussion in KNAW debate and Brissago Island meeting, Table 1 in Appendix 1).

Does the *status quo* in the EU need to change and, if so, how? Does there need to be an analogue of NSABB in the EU, or might the functions be satisfied

[18] Biosecurity – freedom and responsibility of research, May 2014, http://www.ethikrat.org/publications/opinions/biosicherheit.
[19] Cambridge Working Group Consensus Statement on the Creation of Potential Pandemic Pathogens, http://www.cambridgeworkinggroup.org.

by a national biosecurity committee as proposed by Ethikrat[18], or would effective institutional review committees be adequate? Although the focus of the Ethikrat report was described as biosecurity, it was recognised that there is a lot of overlap with biosafety in terms of measures that might need to be taken. Therefore, it might be difficult to define inclusion criteria for the research to be covered by the Ethikrat-proposed biosecurity national commission and to ensure that it did not duplicate the functions of the existing German Central Commission for Biological Safety, ZKBS[20].

It would also be necessary to decide if the recommendations from new EU or national bodies would be advisory or obligatory, *ad hoc* or permanent, and how the impact of these recommendations on researchers and their institutions would be monitored. In the UK, for example, the work of the Health and Safety Executive (Appendix 5) is statutory. EASAC concludes that each Member State national mechanism responsible for governance should have statutory powers. Academies need to have a continuing role in monitoring the impact of these governance mechanisms.

EU-level policy can be useful in standard-setting, exemplified by previous work on setting minimum standards for Member State laboratories to work on foot and mouth disease virus[21] that, thereby, restricts research on a highly pathogenic and transmissible virus to certain laboratories.

In the view of the Working Group, there is less need for an overarching EU body if the good practice in place in some Member States (as exemplified in Appendix 5, and subject to EU Directives and Regulations) is harmonised across the EU (section 2.4). It is likely that some Member States would view the EU as lacking the legal competence to provide a new layer of oversight in this area and that, under subsidiarity, these matters should be reserved as a national responsibility. Thus, the preferred EASAC option is to work at the national level to build strong governance and harmonised practice rather than create new EU bodies with increasing likelihood of bureaucracy, duplication of functions, and inappropriate curtailment of innovation.

A moratorium, as implemented in the USA for GoF research, requires a specified reason (in that case, in support of the functions of the NSABB) and a specified goal which, when achieved, defines the end of the moratorium. In the absence of need for a new EU body, analogous to the NSABB, an EU moratorium would be impractical. The issues for a moratorium in individual EU Member States can only be decided at the national level according to national procedures.

2.7 Global regulation

As the issues are not only national and regional, but global, what should be done to establish global understanding, standards and procedures?

To an extent, current national concerns about safety are assuaged by the operating standards in those laboratories which first worked on H5N1 GoF—they have high levels of biosafety, training and controls, high-quality equipment and health monitoring of researchers and the work is conducted in a public health environment where plans are in place for control of outbreaks and pandemics.

Would the same standards apply elsewhere? Some countries have national guidelines and legal frameworks, others may not. Relatively few countries have national oversight organisations. Some countries are weaker in biocontainment, personnel protection, other infrastructure and in a culture of biosafety. How should the rigorous oversight be agreed so that work is done only at facilities with the highest standards of biosafety (Anon, 2014)? Some of the issues for biosafety and biosecurity of biomaterials in resource-poor environments are being examined in detail in work by the UK Royal Institute of International Affairs[22].

Even if it proved possible to harmonise biosafety standards, how might different national perspectives on the significance of benefit–risk analysis be accommodated—is there potential for some experiments to be judged acceptable in some countries and not in others? Agreement on international standard setting may be easier to achieve than international verification of procedures but the issues are not unique for GoF studies. The opportunities for oversight and action by intergovernmental bodies require further consideration.

It is worth noting that the discussions on the issues relating to GoF studies have also drawn attention to broader unmet global public health needs: (1) how to do better disease surveillance and using surveillance data in modelling and as a resource for innovation in candidate vaccine development; (2) how to develop coherent strategies to tackle global priorities rather than limiting attention to local/national issues.

---

[20] http://www.bvl.bund.de.

[21] Council Directive 2003/85/EC on Community measures for control of foot-and-mouth disease. Further information on minimum standards for laboratories working with FMDV in vitro/in vivo is on http://www.fao.org/ag/againfo/commissions/docs/genses38/Appendix_10.pdf.

[22] http://www.chathamhouse.org/about/structure/global-health-security/biosecurity-project.

2.8 Dissemination of results

EU Council Regulation 428/2009[23] was designed to control the export of dual-use technology, but is not ordinarily applied to basic research, export control policy being the responsibility of DG Trade. Concerns about the requirement to obtain an export licence according to this Regulation before publishing sensitive results from GoF experiments from a Member State in an international journal have been articulated in the letter from the European Society of Virology[7] (and see also Palu, 2014). Application of the Export Control Regulation has been perceived as a disproportionate (and probably ineffective) measure (as discussed by Rath, 2014).Under the present rules, an export permit might be required for publication of results on approximately 90 viruses or other microbes[7]—the issue is how to share sensitive data in a way that does not compromise biosecurity.

In 2011, the European Commission launched a Green Paper for public consultation to review the export control regime. The European Commission Communication COM 2014 (244) sets out options for revision of the legislation to clarify control of dual use research and, following impact assessment, action by DG Trade is expected in 2015.

The risk inherent in not publishing data must also be taken into account. This includes the risk of forgoing potential benefits and the risk of causing unnecessary duplication of research as well as the scientific need for verification and reproducibility. Considerations on publication can be part of biorisk management and ethical issues arising during publication and associated with potentially dangerous experiments have been reviewed in detail elsewhere (for example, Resnik, 2013). Discussion in the Working Group noted that there are contradictory trends within the European Commission—acting to encourage data sharing and openness yet concealing certain data because of perceived danger. These contradictory tendencies need to be reconciled by good governance in support of openness.

The Working Group concluded that an export ban on publications is unlikely to be effective in blocking communication as well as being disproportionate and not necessary, because of the other approaches that are in use in managing sensitive research. As stated in the Wellcome Trust Position Statement on Bioterrorism and Biomedical Research (see Appendix 4 for further discussion), '*the dissemination of research results in the context of scientific publication should be based on the voluntary self-governance of the scientific community and not be subject to formal regulation by governments.*' A similar view was taken in the Fink report (see Appendix 2). The oversight within the scientific community must involve journal publishers and editors, and professional societies as well as researchers, their funders and institutions (Duprex et al., 2015) with the objective that as much data as possible should be published. In complex cases, national advisory bodies can play a role.

2.9 Other considerations regarding biosecurity

Research is usually considered to be outside the limits of the Biological Weapons Convention (BWC), whose text does not mention research or experimentation, but the outcomes from GoF studies may be relevant to the BWC. The Working Group agreed that there is need for international action to improve the processes of control and implementation within the BWC. These are outside the scope of this EASAC project but EASAC takes this opportunity to reaffirm that biosecurity issues should be considered on a case-by-case basis; addressing particular issues with particular experts and on the advice of national authorities.

Relevant work on biosecurity issues has been conducted by other individual academy members of EASAC as mentioned elsewhere in this report (for example the UK Royal Society, KNAW and the German National Academy of Sciences Leopoldina with DFG, see Appendix 3), by EASAC in its work on synthetic biology (EASAC, 2010) and in the report by the German ethics group Ethikrat[18], that discusses ethical issues in detail with respect to the responsibilities of the scientific community for the possible misuse of its research outputs.

2.10 Public debate and engagement

Public trust requires openness (Yarborough, 2014), credible regulatory systems and monitoring. Therefore, progress in engaging with the public depends on progress in addressing the points raised in previous sections. The Working Group strongly endorsed the objectives to generate effective and sustained debate with the public, to ensure a culture of greater openness within research institutions, and for researchers and their institutions to accept that they must hold themselves to standards of accountability. The scientific community has a responsibility to participate in dialogue in an accurate and timely way (Duprex et al., 2015), explaining objectives, the potential for benefits and biorisk management practices. Because some of these issues are controversial – within the scientific community and in public discourse – engagement should be based on science not speculation (Palese and Wang, 2012).

[23] http://ec.europa.eu/trade/import-and-export-rules/export-from-eu/dual-use-control.

As described in the Hannover and NAS December 2014 meetings, engagement with public interests can be considered at three levels: (1) global interests, where there may be issues for public health and health equity associated with innovation; (2) national interests, where the taxpayer is acting to fund research and seeks for justification of the expenditure; and (3) local interests, where the issues may primarily relate to risk to the neighbours of research institutions, although also potentially global in reach and significance.

3 EASAC conclusions and recommendations

The discussion in the preceding chapter emphasises the importance of a layered approach to biosafety with the integration of responsibility for action at various levels, including research funding agencies, and with due regard to regional (EU) and global contexts. We have also emphasised throughout this report that relevant regulations already exist in the EU—and it is critically important that Member States and their research institutions follow the rules and guidelines. There was consensus in the Working Group relating to the points discussed in the following sections.

3.1 Scope

The focus of our report has been on those GoF studies relating to the manipulation of potential pathogens. Concerns about such experiments were clearly articulated in 2004 in the Fink report (see Appendix 2 of our report, categories 1–5 are particularly relevant to the present focus) and the more recent discussions (for example those listed in Table 1 in Appendix 1) substantiate many of the conclusions and recommendations in the Fink report.

The evidence considered in our report has focused on virology but in the view of EASAC the general principles espoused in the preceding chapter and the recommendations that follow here are applicable more broadly in microbiology.

The present focus has been mainly on biosafety but we recognise that related biosecurity implications can also be very important. As noted elsewhere in our report, it is a responsibility for researchers, their institutions, regulators, funders and publishers to seek appropriate specialist advice on biosecurity on a case-by-case basis; these issues have been discussed in detail in the previous work by individual academies (for example KNAW and the German academies, Appendix 3).

3.2 Self-regulation and harmonisation

Self-regulation means that there are checks and balances on research agreed within the scientific community and does not mean that each researcher is free to decide for themselves what procedures to follow. Experience in Member States has been presented to exemplify the rigorous approaches that are taken within the scientific community: combining the principle of self-regulation and the existing legislative framework created by the EU for research on GMOs and biohazards.

EASAC endorses this commitment to good practice that depends on: (1) conforming with regulations and codes of conduct; (2) justification of research (to funders and peers) on a case-by-case basis; and (3) attention to safety conditions entailing a properly run laboratory, according to established principles of biorisk management (see previous chapters).

To ensure that good practice is harmonised across the EU, EASAC recommends:

- Ensuring that the appropriate checks and balances on research are agreed within the scientific community to support the culture of self-regulation.

- Increasing effort to raise awareness of the issues for individual researchers and for research institutions. As discussed in the previous chapter, raising awareness requires education and ongoing training for all scientists and for others, on issues associated with scientific responsibility, relevant legislation, biosafety and biosecurity practices.

- Increasing commitment to sharing and spreading good practice, to harmonise processes within and between countries, to inculcate a positive approach to collective learning. EASAC considers that the previous recommendations to researchers and their institutions, for example in the work of the German National Academy of Sciences Leopoldina with the DFG (section 2.1), are relevant for all Member States.

- Raising awareness and ensuring good practice should be initiated in the research institutions within the layered framework rather than 'top-down' from the European Commission.

- Recognition of the issues is important at all stages of the research endeavour: when formulating the research study, proposing and evaluating a grant application, during conduct of the study and when preparing to publish results. In particular, it is recommended – to researchers and research funders – that consideration of the biosafety category employed, with justification of the hazard group rating (with consideration of raising the rating for altered viruses if justification is insufficient), should be an explicit part of the grant application. Grant applicants should discuss the potential risks involved in the proposed experimental approaches and funders should consider the potential value/benefits of the research in the context of those risks. Before awarding a grant the funder must be confident that an effective regulatory framework is in place in the institution/Member State to ensure adequate risk assessment and mitigation and if in doubt should seek further information and advice.

- Academies of science, together with others in the scientific community, have a continuing role to play in promoting and increasing understanding of biosafety norms. These norms will include, for example, clarification of the level of biocontainment required. Academies must also encourage the idea of auditing research practice in terms of these norms.

3.3 Societal and scientific benefits and risk assessment

There are many uncertainties in the data available for calculating risk and benefit and, as discussed previously, the assessment may be subject to varying value systems – based on personal and public interests – as well as to the evidence accrued. We agree that it is important to continue to work to understand specific elements of the likelihood of a harmful outcome (risk), to reduce the margins of error in the calculation, and there is reasonable prospect of making progress in quantifying a range of risks associated with GoF experiments (see section 2.2).

Quantifying the likelihood and nature of potential benefits is more challenging and there are differing views on whether benefit can and should be quantified in terms of public health benefit or – because possible benefits may not be foreseen – should be described in terms of the generation of scientific knowledge. Prospective benefits arising from scientific knowledge obtained in GoF experiments are likely to be the most useful if relevant questions originated from epidemiology in natural systems, including those of related viruses, for example the possibility of respiratory transmission of the pathogen under study.

Quantifying the benefit–risk balance is difficult if the metrics for assessing risk and benefit are not commensurate. EASAC recommends that:

- Analysis of benefit–risk cannot be regarded as a 'once and for all' calculation but rather as a continuing, collective commitment to understand and communicate the issues involved, with particular regard to analysing, quantifying and reducing risk.

- Academies and learned societies engage in an ongoing process to share data and perspectives and to catalyse discussion across the broader scientific community and involving other stakeholders, to identify the critical factors involved in attempting quantitative assessment. One option is to organise a series of workshops across the EU.

- Opportunities for improving preparedness and resilience to respond should be considered. These include addressing specific issues for biosafety and biosecurity in laboratory research, as described previously, but also ensuring that the public health surveillance and risk management infrastructure is in place, should there be any adverse event. This has implications for the institutions in public health.

3.4 Collating information on biosafety and biosecurity procedures already in place in Member States

Our case study from the UK (Appendix 5) illustrates what is already standard practice but there is need to share equivalent information on the situation in all Member States so as to optimise EU value in spreading good practice.
EASAC recommends:

- This information on procedures already in place in Member States should be collected and collated by the European Commission. We propose that the Health Security Committee[24], which has representation from all Member States, under the auspices of DG Sante, should take a lead in initiating this collection of information, with support from DG Research and ECDC.

3.5 Are new biosafety and biosecurity bodies required?

EASAC recommends that:

- There is no need for a new advisory body at the EU level. The issues discussed in our report are, of course, highly significant for EU functions in various respects. In particular, in the context of the major commitment made by the European Commission to research funding in Horizon 2020, we bring to the attention of DG Research the importance of appropriate guidance for research applications and evaluations. As discussed earlier in this chapter, such guidance should include advice on appropriate containment level and the possible specification of upgrading containment according to experimental objectives.

- Taking account of subsidiarity, all Member States should have a clear national advisory approach. EASAC urges the scientific community to share information on regulations and procedures between Member States and to consult on biosecurity issues where appropriate.

[24] See http://ec.europa.eu/health/preparedness_response/risk_management/hsc/index_en.htm. The Commission Staff Working Document, SEC(2009) 1622 final, 'Health Security in the European Union and Internationally', reviews the various roles of the Health Security Committee in threat and risk assessment, preparedness, scientific advice, communication and global cooperation.

- Although no new EU-level body is proposed, it is imperative that all researchers and research institutions conform to EU Directives and Regulations appertaining to biorisk management, as implemented in national legislation, guidelines and procedures.

- It is important that the principle of a layered approach is adopted by Member States across the EU. Each Member State national mechanism responsible for governance should have statutory powers.

3.6 Should there be a repository of data on key studies for collective learning?

The notion of a collective repository (the evidence base to help in evaluating experience, section 2.4) is interesting, but there are practical problems. For example, it may be difficult to define the limits on the scope of studies to include in the repository. There may be reluctance to disclose some biosecurity issues, although for the experiments in the highest risk category a reluctance to discuss studies should be deemed unacceptable by the scientific community. We have already recommended the sharing of good practice to aid collective learning for assessment of risk and benefit and the organisation of activities to enable this by academies and others may well serve in place of constructing and managing a dedicated repository of evidence. We also now recommend that Member States encourage their regulators to come together to discuss these issues, and to involve their scientific advisory committees to ensure the connection with the wider scientific community.

3.7 Publication of sensitive information

Scientific freedom is not absolute and the scientific community recognises that some information is sensitive. With regard to making rational decisions to publish, EASAC:

- Reiterates the responsibility for researchers and their institutions in making decisions about publishing sensitive information.

- Endorses the current procedure where many journals seek appropriate advice, including from security experts.

- Advises that the European Commission's Export Control Regulation is an inappropriate vehicle to block publication (for various reasons, as discussed in section 2.8, but also because in practical terms it does not block publication in the country of origin of the research). EASAC welcomes the current attempt by DG Research to raise awareness about the revision of the Export Control Regulation and encourages the scientific community to provide advice to DG Research on the revision (see http://www.easac.eu/home/easac-news/detail-view/article/gain-of-func.html for further details).

3.8 Public engagement

Trust, openness and ongoing public engagement are crucial for researchers and research institutions (section 2.10). Academies of science have an important role to play in public engagement; for example, the Royal Society published the outputs from its 2012 meeting (Appendix 3) on its website. EASAC will produce a short lay summary of the present report as a resource for its member academies to engage more broadly. We recommend that:

- Academies and others in the scientific community actively participate in ongoing public dialogue, articulating objectives for this research, the potential for benefits and the biorisk management practices adopted. Stakeholders must be involved in the proposed discussions on issues for assessing benefit–risk and ethics review of research proposals must include lay involvement.

The importance of public engagement has also recently been emphasised in the US discussions on GoF research (Fineberg, 2015), '*The benefits and risks of doing such research do not apply equally to all people, institutions or countries, and a rigorous risk/benefit analysis will have to be mindful of these inequities and hear from various stakeholders.*'

3.9 Global context

The Fink report (Appendix 2) called for the creation of an International Forum on Biosecurity to sustain dialogue between the life sciences' and policy-making communities, including issues for: education; international jurisdiction; control of pathogen handling within and between laboratories; development of systems of review to provide oversight of research, including international norms for managing 'experiments of concern' and dissemination of 'sensitive information'. The Fink report suggested that sponsors of this international forum could include IAP and IAC, as well as United Nations Educational, Scientific and Cultural Organization (UNESCO) and WHO. EASAC recommends that:

- This proposal should be given further attention, and that international discussion must cover biosafety as well as biosecurity.

- The IAP Biosecurity group[25] may wish to consider further the biosecurity implications of GoF studies as part of their global efforts to raise awareness of pathogen research issues.

Thus, in addition to recommending EU countries to harmonise approaches based on shared principles, we urge other countries worldwide to spread and implement good practice.

[25] The IAP Biosecurity group, led by the Polish Academy of Sciences, organised an event before the meeting of BWC experts in August 2014 on the subject of advances in understanding pathogenicity and the relevance to biosecurity and the BWC. The work of this group is likely to be of continuing value with regard to efforts to support education in biosecurity, to communicate about responsible conduct of science in the research community, and to promote cooperation between the public health and security sectors. For further details, see IAP Annual Report 2013, Raising awareness on dual-use issues; details of IAP Biosecurity Programme are on http://www.interacademies.net/ProjectsandActivities/Projects/23017.aspx.

Appendix 1 Working Group and sources

The report was prepared by consultation with a Working Group of experts acting in an individual capacity, nominated by member academies of EASAC:
Volker ter Meulen (Chair, Germany)
Goran Hermeren (ALLEA)
Ursula Jenal (Switzerland)
Hans Klenk (Germany)
André Knottnerus (The Netherlands)
Maria Masucci (Sweden)
John McCauley (UK)
Thomas Mettenleiter (Germany)
Giorgio Palu (Italy)
Gyorgy Posfai (Hungary)
Bert Rima (Ireland)
John Skehel (UK)
Simon Wain-Hobson (France)
Robin Fears (secretariat, UK)

The Working Group met in November 2014 (Frankfurt), and January and March 2015 (Brussels). At the January meeting, the Working Group met with external guests from ECDC (Mike Catchpole), DG Research and Innovation (Cornelius Schmaltz and Irene Plank) and the European Group on Ethics (Pere Puigdomenech). EASAC thanks the Working Group members for their insight, commitment and support and thanks members of the EASAC Biosciences Steering Panel for their advice and guidance.

The project was announced on www.easac.eu with a call for evidence in December 2014.

As well as the Working Group inputs and the publications cited in the References, the report draws on discussion from other meetings in Europe and the USA (Table 1).

Table 1: Recent discussions about GoF experiments

Organiser and venue	Date and link
Royal Society, London, UK: Gain of function meeting	An open discussion meeting in 2012 was organised by Skehel and Wain-Hobson on H5N1 research: biosafety, biosecurity and bioethics, https://royalsociety.org/event/2012/viruses. In December 2013 a European discussion meeting was organised.
KNAW, Amsterdam, The Netherlands: Debate on gain-of-function research	June 2014, Palu and Wain-Hobson, chaired by Knottnerus, http://www.knaw.nl/shared/resources/actueel/bestanden/Reportdebategainof functionresearch25June2014.pdf
European Society for Virology, Brissago Island, Switzerland: Early events in virus infection	August 2014, discussion initiated by Palu and Wain-Hobson, http://events.mnf.uzh.ch/fileadmin/Events/2014/MteVerita/Program_short.pdf
Volkswagen Foundation, Hannover, Germany: Dual use research on microbes: biosafety, biosecurity, responsibility	December 2014, the Summary report is on http://www.volkswagenstiftung.de/en/dualuseresearch.html. Skehel and Wain-Hobson were members of the scientific organising committee.
National Academy of Sciences, Washington, DC, USA: Risks and benefits of gain-of-function research	December 2014, http://dels.nas.edu/resources/static-assets/bis/miscellaneous/GOF_Agenda_Draft.pdf; the webcast is on http://www.youtube.com/playlist?list=PLuTGMA3A-16HWJ6smsx4w1Bh_2TKf4OV and slides presented are on https://www.scribd.com/collections/11133114/Gain-of-Function-Symposium-Slides. Skehel was a member of the scientific organising committee. A summary of the meeting was published in January 2015 on http://www.nap.edu/21666/potential-risks-and-benefits-of-gain-of-function-research-summary.

Appendix 2 Recommendations from the National Academies (Fink) report, 2004

The detailed recommendations from the report *Biotechnology research in an age of terrorism* addressed main areas including educating the scientific community, review of plans for experiments, publication of results, creation of a national science advisory board, global context and issues relating to biosecurity and deliberate misuse. The report specifically proposes seven classes of experiments (Box 3), which (although they were clarified mostly with using experiments from bacteriology) can be used to define GoF experiments of concern.

Box 3 Proposed seven classes of experiments

These would require review and discussion by informed members of the scientific and medical community before they are carried out.

These classes include experiments that:

1. Would demonstrate how to render a vaccine ineffective.
2. Would confer resistance to therapeutically useful antibiotics or antiviral agents.
3. Would enhance the virulence of a pathogen or render a non-pathogen virulent.
4. Would increase transmissibility of a pathogen.
5. Would alter the host range of a pathogen.
6. Would enable the evasion of diagnostic/detection modalities.
7. Would enable the weaponisation of a biological agent or toxin.

Appendix 3 Other previous work by academies

(1) KNAW

A code of conduct for biosecurity, 2008. Report focusing on prevention of biological weapons or other misuse of biological agents. Addressed primarily to researchers, their institutions and those involved with publishing. Covers issues for: raising awareness; research and publication policy; accountability and oversight; internal and external communication; screening of staff and visitors to facilities; and transport of biological materials.

Improving biosecurity: assessment of dual-use research, 2013. Report considering how dual-use research should be assessed and by whom: based on principles of guided self-regulation. Stimulated by the H5N1 research, threat analysis was deemed relevant with regard to dual-use aspects of research and publication. It was observed that none of the existing committees or institutions in the Netherlands were sufficiently equipped for the task of assessing potential cases of dual-use research and KNAW recommended establishing a Biosecurity Advisory Committee for Research in the Life Sciences, under the statutory authority of the Health Council of the Netherlands (Gezondheidsraad) .Starting from self-regulation within the scientific community, this committee would advise researchers and institutions where needed. If there is concern that important advice is repeatedly ignored, the committee should be able to take action with various degrees of rigour, and with informing the government as ultimate option.

Debate on Gain of Function, June 2014. Meeting organised to provide insight into the scientific arguments for and against GoF research (Table 1). Points are incorporated into the EASAC work.

(2) Royal Society

H5N1 research, biosafety, biosecurity and ethics, 2012. Meeting discussed virus research from the perspectives of researchers, publishers, policy makers and funders.

Gain of function, December 2013. Meeting to review and extend debate on GoF experiments stimulated by concerns about engineering of transmissible influenza H5N1 viruses (Table 1). This meeting advised that the term GoF is potentially misleading; and there is need for more discussion within the scientific community about the risks of such experiments, the availability and suitability of existing regulations, the role of self-regulation, issues for containment and security, awareness-raising and education of the next generation of researchers and sustained engagement with the public. It was concluded that '… *Europe has an opportunity to lead in developing regulations for gain of function experiments …*'

(3) Leopoldina with DFG

Scientific responsibility: recommendations for handling security-relevant research, 2014. Report addressed to researchers and their institutions, referring to experiments on avian flu viruses and to the broader debate on developing ethical principles and mechanisms for a responsible approach to research and its risks. Covers issues for risk analysis, minimising risk, evaluating and communicating research, potentially forgoing research, training, legal provisions and ethical review. Proposes that each research institution should set up committee on research ethics to implement rules and advise scientists.

(4) EASAC

Previous reports on infectious diseases cover issues for the impact of pandemic flu. A previous report on synthetic biology covers related issues for assuring biosafety and biosecurity, developing codes of conduct for self-regulation, and public engagement.

(5) NAS

Perspectives on research with H5N1 avian influenza: issues raised, lessons learned, and paths forward for dual-use research in the life sciences. Report (Matchett et al., 2013) based on meetings in 2012. The goals were: '*to look forward to the future and consider new paradigms for the evaluation, oversight and communication of research warranting special consideration; to evaluate the potential need for enhanced biosafety and biosecurity oversight; and to reflect on how a new mechanism might be structured and implemented.*' The NAS discussion covers key issues for identifying how general a regulatory mechanism would need to be; who should be involved in decisions about risk and benefit; what constitutes risk; possible mechanism for regulating research and the role of researchers; how to ensure inclusive (lay) participation in development of oversight mechanisms; what is needed to improve education of the next generation of scientists, in particular regarding ethics, sharing of data, disclosure of conflict of interest; and conduct of risk–benefit estimations.

Meeting on potential risks and benefits of GoF research (December 2014) (Table 1) feeding into the US deliberative phase.

(6) IAP

Statement on biosecurity in 2005 and on Responsible conduct in the global research enterprise (with IAC) in 2012.

Appendix 4 Synopsis of initial scientific and regulatory developments

Research findings

In 2011, research groups led by Fouchier of the Erasmus Medical Center in Rotterdam, the Netherlands, and Kawaoka of the University of Wisconsin-Madison, USA, both funded by the US NIH (and Professor Fouchier also by the EU under the 7th Framework Programme for Health Research), generated controversy when they artificially engineered aerosol-transmissible forms of the H5N1 avian influenza virus in ferrets, used as the standard mammalian model to evaluate the potential pandemic spread of strains of influenza (Box 4).

Self-regulation and governance mechanisms

A voluntary moratorium on research was declared following these initial GoF studies, which involved only a small number of groups. Although this initial moratorium ended in 2013, it was deemed to have provided some valuable time to begin discussion of possible public health benefits and to elucidate necessary biosafety and biosecurity precautions (Anon, 2013). Thus, in 2013, the US introduced guidelines governing the framework for research involving GoF studies on H5N1[30]. The NIH guidelines operated within a broader US context that has also included, during the past decade, the NSABB, reporting to the NIH and the Department of Health and Human Services. The NSABB is a federal advisory committee that provides guidance and leadership regarding biosecurity oversight to all federal departments and agencies with an interest in life sciences research[31].

Triggered at least in part by the laboratory incidents described in section 1.3, which had renewed generic

Box 4 Controversial scientific advances

Varying views on the potential benefits of this H5N1 GoF research have been expressed in the letters to the European Commission[7,8] and in the scientific literature (for example, Wain-Hobson 2013, 2014a, b; Palu 2014; Linster et al., 2014; Lipsitch and Galvani, 2014; Russell et al., 2014; Duprex et al., 2015). The contrasting views on the potential benefits arising from the science, for example to improve disease surveillance capacity and as a resource for candidate vaccine selection[26], will not be reviewed in detail here. However, it is worth noting that much of this debate has concentrated on the present or early use of such information. It is also necessary to plan for, and take account of, how data can be generated and better used in the future for public health preparedness.

The research groups of Fouchier and Kawaoka (2013) also proposed to perform experiments that may result in GoF of H7N9, research that could potentially modify immunogenicity, adaptation to mammals, drug resistance, transmission and pathogenicity. H7N9 may be of particular concern regarding future pandemics in that it already contains some of the adaptive mutations associated with transmissibility between ferrets through the air (Klenk, 2014).

The US group have also recently published on work to generate a virus composed of avian influenza segments with high homology to the 1918 virus and with pandemic potential (Watanabe et al., 2014). Nonetheless the whole process is probably more complex than has been discovered so far from the ferret model and great caution has been advised (Klenk, 2014) in making pandemic predictions (see also the WHO report cited in footnote 2).

With the benefit of hindsight, various views may be taken of the claims from published experiments, but outcomes may not be predictable in advance of the research. New knowledge generation may have subsequent, unforeseen, value and as observed in the Wellcome Trust policy position[27], '*creation and dissemination of scientific knowledge is a tangible public good, which needs to be set against risks that may sometimes be hypothetical and hard to quantify.*'

There are also varying views on the potential risks[7,8,28] and some have suggested (for example, Wain-Hobson, 2013) that there might be substantial risks even if it is assumed there is low probability that a pandemic would ensue from a laboratory accident. It is also posited that alternative approaches[29] would be safer and more effective at improving surveillance, and in vaccine design, such as using viral components rather than the entire infectious virus (Anon, 2014; Lipsitch and Galvani, 2014).

A recent series of editorials in mBio by Casadevall and colleagues (Casadevall et al., 2014a, b; Casadevall and Imperiale, 2014) reviews the scientific controversy and calls for reasoned discussion to find a way to allow GoF research to go forward with minimal risk and maximal benefit.

---

26 Examples of where some GoF studies have previously been useful in informing the scientific community about factors involved in vaccine virus selection and the preparation of pre-pandemic flu vaccines are reviewed by Schultz-Cherry et al. (2014).

27 Wellcome Trust Position Statement on bioterrorism and biomedical research: the scope of this Statement includes experiments to increase transmissibility of a pathogen. Available on http://www.wellcome.ac.uk/About-us/Policy/Policy-and-position-statements/WTD002767.htm.

28 See section for 2.2 further discussion of risk assessment.

29 Potential alternative scientific approaches (and information that it may not be possible to generate using alternative approaches) were discussed in some detail in the Herrenhausen and Washington, DC meetings (Table 1 in Appendix 1).

30 "A framework for guiding US Department of Health and Human Services funding decisions about research proposals with the potential for generating highly pathogenic avian influenza H5N1 viruses that are transmissible among mammals by respiratory droplets", February 2013.

31 http://osp.od.nih.gov/office-biotechnology-activities/biosecurity/nsabb.

concerns about biosafety and biosecurity, in October 2014 the US Government launched a further deliberative process to assess the potential risks and benefits associated with GoF studies and to determine what special standards should be applied to that research.[32] During this period of deliberation about policy and practice, the US Government has initiated a pause on funding for new studies on respiratory pathogens of pandemic potential that include certain GoF experiments involving influenza, SARS and MERS viruses. Researchers currently conducting this type of work are also encouraged – whether federally funded or not – to voluntarily pause their research while risks and benefits are reassessed. The National Research Council (NRC) is convening scientific meetings to discuss the issues involved (Table 1 in Appendix 1) and the NSABB will provide recommendations on oversight of this area. At the first NSABB deliberative meeting, some researchers regarded the new moratorium as too broad, with potential public health consequences for surveillance and seasonal vaccine supply (Reardon, 2014). Because of these concerns expressed by the research community, the NSABB has asked for government clarification on what types of experiment are affected by the research funding pause and deliberative process[33].

Until now, the assessment of the relative risks and benefits of GoF research has remained largely qualitative. But whatever the individual views on risks and benefits, there should be consensus that the process for assessment – of both biosafety and biosecurity – is transparent and effective. At the global level, WHO released a report (WHO, 2012) on issues relating to publication of experiments and the safety of research with laboratory-modified viruses, while the initial moratorium was in place, and concluded that the moratorium should continue ' … *at least until the conditions under which such research can take place safely have been determined.*' There is still controversy as to whether these conditions have been satisfied and, if so, where. WHO called for further discussion of the scientific and social issues raised by this kind of research, to increase awareness of the nature and objectives of this research, and to define essential biosafety and laboratory biosecurity standards and practices to be observed. Although there is support for the WHO guidelines that such work should conform to international risk management standards so as to encourage a culture of safety, it was noted that there is no international means of enforcement and that facilities that could not identify and control risks should refrain from such work (Anon, 2013).

In the EU, there have been various discussions about the issues (for example, see the discussions referred to in Table 1 in Appendix 1). The ECDC also hosted a recent meeting to involve the community of public health scientists[34] and in an earlier comment on the work of Watanabe et al. (2014) observed,[35] '*It is important to ask what this type of result adds to the field of pandemic influenza preparedness and how the prediction of efficacy of influenza vaccines or antivirals against influenza viruses is improved based on these results … A forum of public health discussion around dual-use research of concern topics is not yet available at European level. ECDC advocates for open discussion about studies where potential pandemic threats are created. The research community should in all their work apply the medical ethical principle of first do no harm.*'

As discussed by the EASAC Working Group in the preceding chapters, there must be procedures for assessing benefit–risk in place before these GoF studies can be justified. There are precedents in the EU for restricting research on a highly pathogenic and transmissible virus to certain laboratories, for example for research on foot-and-mouth disease virus[19] and the broader legislative background for the EU is described below. There must also be appropriate ethical review of all GoF research proposals submitted to the European Commission for funding.

Regulatory background in Europe

Critical issues related to GoF experiments (Chapters 2 and 3) have been discussed against the background of existing EU Directives and guidelines covering biosafety and biosecurity. Biological risk assessment which can be applied to GoF research and subsequent determination of biorisk management practices and containment facilities has been regulated since 1990 by Directive 2009/41/

[32] Office of Science and Technology Policy, USA, 17 October 2014, Doing diligence to assess the risks and benefits of life sciences gain-of-function research, http://www.whitehouse.gov.

[33] Statement 25 November 2014 on http://osp.od.nih.gov/office-biotechnology-activites/biosecurity/nsabb/reports-and-recommendations.

[34] In this meeting, organised by the ECDC in November 2014, a survey of the audience found a majority in favour of: an EU pause on GoF research until clearer policies are in place; more involvement of the public health sector in risk–benefit analysis of GoF research; and the proposition that the EU should have a dedicated body to manage biosafety and biosecurity issues around dual use "research of concern". See http://ecdc.europa.eu/en/ESCAIDE/Documents/ESCAIDE14-survey-Dual-research.pdf.

[35] http://www.ecdc.europa.eu/en/healthtopics/avian_influenza/Pages/index.aspx.

EC, formerly 90/219/EEC[36] on the contained use of genetically modified organisms. Research which does not include genetic modification is regulated by the Directive 2000/54/EC, formerly 90/679/EEC, on the protection of workers from risks related to exposure to biological agents at work[37]. These Directives have been implemented in respective country regulation and enforcement mechanisms by local regulatory authorities are in place. In particular, high risk research with biological agents is subject to authorisation and facilities and work practices can be inspected for adequate, risk-based containment and implementation of safety measures. Thus, surveillance of biosafety issues related to GoF dealt within the EU and in countries who have adopted these EC Directives is in place, as has been illustrated by different reviews[38,39]. However, these reviews demonstrate that biosecurity regulation, in the sense of laboratory biosecurity as defined by the WHO Laboratory biosecurity guidance[40], is much more limited. In fact, this guidance together with the OECD Best Practice Guidelines for Biological Resource Centres[41] and the CWA15793(2011) on Biorisk Management are the first and foremost encompassing reference documents for laboratory biosecurity risk assessment and management. However, they have mostly not been converted into country-specific regulatory requirements in Europe. CWA15793:2001 Biorisk Management is in the process of being transformed into an ISO Standard, ISO/AWI 35001 Laboratory biorisk management system, by the ISO-TC212_JWG5, and it will be supporting implementation of biosecurity requirements on a more international scale.

Currently, the EU CBRN Risk Mitigation Centres of Excellence Initiative addresses the mitigation of and preparedness against risks related to CBRN material and agents, where CBRN refers to both weaponised and non-weaponised chemical, biological, radiological and nuclear material. The origin of these risks can be criminal (proliferation, theft, sabotage and illicit trafficking), accidental (industrial catastrophes, in particular chemical or nuclear, waste treatment and transport) or natural (mainly pandemics but also be the consequence of natural hazards on CBRN material and facilities)[42]. The CBRN action plan and projects related to it, however, do not focus on Europe and only very few projects deal with laboratory biosecurity. None of the above regulatory requirements and guidelines deal with risk of information transfer.

36 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:125:0075:0097:EN:PDF.
37 http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32000L0054.
38 Biosafety – Europe, Containment level 3 and 4 laboratories: legislative and regulatory framework which was prepared under FP6, http://www.biosafety-europe.eu/d20public_300309.pdf.
39 State-of-the-Art in Biosafety and Biosecurity in European Countries, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4024129/.
40 Biorisk management, Laboratory biosecurity guidance, http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_EPR_2006_6.pdf.
41 http://www.oecd.org/sti/biotech/oecdbestpracticeguidelinesforbiologicalresourcecentres.htm.
42 http://ec.europa.eu/dgs/home-affairs/what-we-do/policies/crisis-and-terrorism/securing-dangerous-material/index_en.htm.

Appendix 5 Member State case study: the situation in the UK

In general, scientists must assess the risks of their experiments being dangerous to themselves, to their contacts and to the environment. They must ensure that they and any others directly involved, have had training and have the equipment and facilities suitable for safe experimentation[43]. For work with dangerous pathogens this would include containment facilities of a sufficiently high standard that are inspected regularly, and assessed to be properly operational by responsible inspectors. They must submit their proposals for research to the local Biological Safety Committee, ensuring that they include justification for the experiments, detail of the potential outcomes, and indicate that they have thoroughly considered less dangerous alternatives and compared the potential risks and benefits.

The Biological Safety Committee must have members with appropriate knowledge, expertise, and experience to assess the proposal, or it must obtain expert advice. For work requiring highly secure facilities, at Containment Levels 3 or 4, the proposal, with the recommendations of the Biological Safety Committee, must be submitted to the senior management of the establishment. At this stage, if the proposal is acceptable, the requirement for additional ethical review must be considered and overall responsibility for the work must be accepted.

With these initial procedures responsibly undertaken at the research establishment, an acceptable proposal would then be submitted formally to the Health and Safety Executive (HSE)[44] by the establishment's Biological Safety Officer, as a 'Notification of Intention to Conduct Individual Contained Use Activities.'

The HSE, consulting when necessary its scientific advisors, reviews the application and returns comments and questions that arise to the establishment's Biological Safety Officer, to whom it eventually communicates its decision. Permission to proceed must be received from HSE before any of the notified experiments begin.

The experiments themselves must be done by experienced scientists, trained for work in the facilities and adhering strictly to the established safety procedures. If possible, vaccination should be considered and available therapies should be made accessible. Observation of Containment 4 laboratories using CCTV is continuous and records are kept of all procedures used and times of access.

---

43 Research in the UK is subject to biosafety legislation in the following respects:

- Control of Substances Hazardous to Health (COSHH).
- GMOs (Contained Use).
- GMOs (Deliberate Release).
- Specified Animal Pathogens Order.
- Importation of Animal Pathogens Order.
- Antiterrorism Crime and Security act (schedule 5 of this Act covers activities with pathogens).

Further information is on http://www.bbsrc.ac.uk/organisation/policies/employment/code/health/a9-13/a9-13i.aspx. The UK Research Councils joint security policy is on http://www.bbsrc.ac.uk/organisation/policies/employment/code/health/a9-5/a9-5-main.aspx and further information on the biosafety policy with regard to COSSH is on http://www.bbsrc.ac.uk/organisation/policies/employment/code/health/a9-8.aspx.

44 Health and Safety Executive information on the contained use of GMOs is on http://www.hse.gov.uk/biosafety/gmo/index.htm.

List of abbreviations

BWC	Biological Weapons Convention
CDC	US Centers for Disease Control and Prevention
CEN	European Committee for Standardisation
COSHH	Control of Substances Hazardous to Health
CWA	CEN Workshop Agreement
DG Research	Directorate-General for Research and Innovation
DFG	Deutsche Forschungsgemeinschaft
EASAC	European Academies Science Advisory Council
ECDC	European Centre for Disease Prevention and Control
EU	European Union
GDP	Gross domestic product
GMOs	Genetically modified organisms
GoF	Gain of function
HSE	Health and Safety Executive
IAC	InterAcademy Council
IAP	InterAcademy Panel (InterAcademy Partnership from 2014)
KNAW	Koninklijke Nederlandse Academie van Wetenschappen (Royal Netherlands Academy of Arts and Sciences)
NAS	National Academy of Sciences
NIH	National Institutes of Health
NSABB	National Science Advisory Board for Biosecurity
OECD	Organisation for Economic Co-operation and Development
RNA	Ribonucleic acid
SARS	Severe Acute Respiratory Syndrome
MERS	Middle East Respiratory Syndrome
UNESCO	United Nations Educational, Scientific and Cultural Organization
WHO	World Health Organization

References

Anon (2013). *Vigilance needed: experiments that make deadly pathogens more dangerous demand the utmost scrutiny.* Nature **493**, 460

Anon (2014). *Biosafety in the balance.* Nature **510**, doi: 10.1038/510443a

Butler D (2014). *Biosafety controls come under fire.* Nature **511**, 515–516

Butler D and Maher B (2014). *Risk of flu work underrated.* Nature **511**, 13–14

Casadevall A and Howard D (2014). *Risks and benefits of gain-of-function experiments with pathogens of pandemic potential, such as influenza virus: a call for a science-based discussion.* mBio doi: 10.1128/mBio01730-14

Casadevall A, Howard D and Imperiale MJ (2014a). *An epistemological perspective on the value of gain-of-function experiments involving pathogens with pandemic potential.* mBio doi: 10.1128/mBio01875-16

Casadevall A, Howard D and Imperiale MJ (2014b). *The apocalypse as a rhetorical device in the influenza virus gain-of-function debate.* mBio doi: 10.1128/mBio02062-14

Dawood FS et al. (2012). *Estimated global mortality associate with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study.* Lancet Infectious Diseases **12**, 687–695

DFG and Leopoldina (2014). *Scientific freedom and scientific responsibility. Recommendations for handling security-relevant research.*

Duprex WP and Casadevall A (2015). *Falling down the rabbit hole: aTRIP towards lexiconic precision in the "gain of function" (GOF) debate.* mBio In Press

Duprex WP, Fouchier RAM, Imperiale MJ, Lipsitch M and Relman DA (2015). *Gain-of-function experiments: time for a real debate.* Nature Reviews Microbiology **13**, 58–64

EASAC (2010). *Realising European potential in synthetic biology: scientific opportunities and good governance.*

EASAC (2011). *European public health and innovation policy for infectious disease: the view from EASAC.*

EASAC (2013). *Planting the future: opportunities and challenges for using crop genetic improvement technologies for sustainable agriculture.*

Fineberg H (2015). *Wider attention for GOF science.* Science **347**, 929

Fouchier RAM and Kawaoka Y (2013). *Gain-of-function experiments on H7N9.* Nature **500**, 150–151

Fouchier RAM (2015). *Studies on influenza transmission between ferrets; the public health risks revisited.* MBio doi: 10.1128/mBio.02560-14

Gronvall GK (2014). *National-level biosafety norms needed for dual-use research.* Frontiers in Public Health **2**, doi: 10.3389/fpubh.2014.00084

Gutmann A (2011). *The ethics of synthetic biology: guiding principles for emerging technologies.* Hastings Center Report **41**, 17–22

Henkel RD, Miller T and Weyant RS (2012). *Monitoring select agent theft, loss and release reports in the United States – 2004-2010.* Applied Biosafety **17**, 171–180

Hermeren G (2012). *The principle of proportionality revisited: interpretations and applications.* Medicine, Health Care and Philosophy **15**, 373–382

IAP (2005). *Statement on biosecurity.*

IAP with IAC (2012). *Responsible conduct in the global research enterprise.*

Jaffe HW, Patterson AP and Lurie N (2013). *Extra oversight for H7N9 experiments.* Nature **500**, 151

Klenk HD (2014). *Influenza virus en route from birds to man.* Cell, Host and Microbe **15**, 653–654

KNAW (2008). *A code of conduct for biosecurity.*

KNAW (2013). *Improving biosecurity. Assessment of dual-use research.*

KNAW (2014). *Report of a debate on gain-of-function research between Professor Giorgio Palu and Professor Simon Wain-Hobson.*

Linster M et al. (2014). *Identification, characterization and natural selection of mutations driving airborne transmission of A/H5N1 virus.* Cell **157**, 329–339

Lipsitch M and Galvani AP (2014). *Ethical alternatives to experiments with novel potential pandemic pathogens.* PLoS Medicine doi: 10.1371/journal.pmed.1001646

Lipsitch M and Inglesby TV (2015). *Reply to Studies on influenza transmission between ferrets; the public health risks revisited.* mBio doi: 10.1128/mBio.00041-15

Matchett K, Mazza A-M and Kendall S (2013). *Perspectives on research with H5N1 avian influenza.* The National Academies Press

Palese P and Wang TT (2012). *H5N1 influenza viruses: facts not fear.* Proc. Natl Acad. Sci. USA **109**, 2211–2213

Palu G (2014). *Regulating dual-use research in Europe.* Science **343**, 368–369

Rath J (2014). *Rules of engagement: Restricting security-sensitive research data – a European view.* EMBO Report **15**, 1119–1122

Reardon S (2014). *Viral-research research moratorium called too broad.* Nature News http://www.nature.com/news/viral-research-moratorium-called-too-broad-1.16211

Relman DA (2013). *The increasingly compeling moral responsibilities of life scientists.* Hastings Center Report **43**, 34–35

Resnik HB (2013). *H5N1 avian flu research and the ethics of knowledge.* Hastings Center Report **43**, 22–33

Russell CA et al. (2014). *Improving pandemic influenza risk assessment.* eLife doi: 10.7554/eLife03883

Schultz-Cherry S et al. (2014). *Influenza gain-of-function experiments: their role in vaccine virus recommendation and pandemic preparedness.* mBio **5**, e02430-14

Smith RD, Keogh-Brown MR, Barnett T and Tait J (2009). *The economy-wide impact of pandemic influenza on the UK: a computable general equilibrium modelling experiment.* British Medical Journal **339**, 1298

Wain-Hobson S (2013). *H5N1 viral-engineering dangers will not go away.* Nature **495**, 411

Wain-Hobson S (2014a). *The irrationality of GOF avian influenza virus research.* Frontiers in Public Health doi: 10.3389/fpubh.2014.00077

Wain-Hobson s (2014b). *An avian H7N1 gain-of-function experiment of great concern.* mBio doi: 10.1128/mBio.01882-14

Wang TT, Parides MK and Palese P (2012). *Seroevidence for H5N1 influenza infections in humans: Meta-analysis.* Science **335**, 1463

Watanabe T et al. (2014). *Circulating avian influenza viruses closely related to the 1918 virus have pandemic potential.* Cell, Host and Microbe **15**, 692–705

WHO (2006). *Biorisk management – laboratory biosecurity guidance.* WHO/CDS/EPR/2006.6, http:///www.who.int/ihr/biosafety/publications_WHO_CDS_EPR_2006_6/en

WHO (2012). *Controversial research modifying A (H5N1) influenza viruses in the laboratory – Formal report of WHO technical consultation.* http://www.who.int/influenza/human_animal_interface/mtg_report_h5n1.pdf

Yarborough M (2014). *Openness in science is key to keeping public trust.* Nature **515**, 313

EASAC, the European Academies' Science Advisory Council, consists of representatives of the following European national academies and academic bodies who have issued this report:

Academia Europaea
All European Academies (ALLEA)
The Austrian Academy of Sciences
The Royal Academies for Science and the Arts of Belgium
The Bulgarian Academy of Sciences
The Croatian Academy of Sciences and Arts
The Czech Academy of Sciences
The Royal Danish Academy of Sciences and Letters
The Estonian Academy of Sciences
The Council of Finnish Academies
The Académie des sciences (France)
The German National Academy of Sciences Leopoldina
The Academy of Athens
The Hungarian Academy of Sciences
The Royal Irish Academy
The Accademia Nazionale dei Lincei (Italy)
The Latvian Academy of Sciences
The Lithuanian Academy of Sciences
The Royal Netherlands Academy of Arts and Sciences
The Polish Academy of Sciences
The Academy of Sciences of Lisbon
The Romanian Academy
The Slovak Academy of Sciences
The Slovenian Academy of Arts and Science
The Spanish Royal Academy of Sciences
The Royal Swedish Academy of Sciences
The Royal Society (United Kingdom)

The Norwegian Academy of Science and Letters
The Swiss Academies of Arts and Sciences

For further information:

EASAC Secretariat
Deutsche Akademie der Naturforscher Leopoldina
German National Academy of Sciences
Postfach 110543
06019 Halle (Saale)
Germany

tel +49 (0)345 4723 9833
fax +49 (0)345 4723 9839
email secretariat@easac.eu

EASAC Brussels Office
Royal Academies for Science and the
Arts of Belgium (RASAB)
Hertogsstraat 1 Rue Ducale
1000 Brussels
Belgium

tel +32 (2) 550 23 32
fax +32 (2) 550 23 78
email brusselsoffice@easac.eu

The affiliated network for Europe of
iap
the global network of science academies

Printed by DVZ-Daten-Service GmbH, Halle/Saale, Germany