Do no harm: reducing the potential for the misuse of life science research

Report of a Royal Society - Wellcome Trust meeting held at the Royal Society on 7 October 2004

Summary

The threat of advances in the life sciences being used for harmful purposes is a real one. The challenge that the scientific community faces is to identify what measures can be taken to manage or reduce this risk without jeopardising the enormous potential benefits from research advances. The aim of the joint Royal Society – Wellcome Trust meeting was to bring together practising life scientists with policy makers, funders and other interested parties to identify what the issues were and how they might be addressed. This report presents a summary of the key issues and challenges that emerged from the meeting and is not necessarily an expression of the views of the Royal Society or the Wellcome Trust.

The key points arising from the meeting and possible next steps were:

- Research institutions and funding agencies need to consider how to build on existing processes for reviewing research projects to ensure that risks of misuse are assessed in an appropriate and timely manner.

- Preventing publication of basic research would not prevent the misuse of advances in the life sciences.

- Self governance by the scientific community was favoured, rather than new legislation.

- Although some scepticism was expressed about the value of codes of conduct, it was suggested that the scientific community should take the lead in determining any codes of conduct or good practice, to pre-empt their introduction through legislation or other 'top down' approaches. National guidelines for good practice could provide the basis for individual organisations and employers generating their own codes. There was a call for the wider scientific community to be bought together to discuss the merits of producing guidelines for good practice, and then to start the process of drafting such guidelines if appropriate.

- Education and awareness-raising training are needed to ensure that scientists at all levels are aware of their legal and ethical responsibilities and consider the possible consequences of their research. University department heads, research institute directors, vice chancellors and Universities UK would be ideally placed to take this forward for the academic community. However, these bodies would need to be co-ordinated. The Association of British Pharmaceutical Industries and the BioIndustry Association could take the lead for industrial training.

1 Introduction

Following the September 2001 Washington DC and New York terrorist attacks and the US anthrax letters of autumn 2001 there has been increased concern that life sciences research could be misused enhancing the

threat of bioterrorist attacks. The increased political attention to this issue was illustrated by the House of Commons Science and Technology Select Committee inquiry into the scientific response to terrorism (House of Commons 2003). The UK Government will be chairing the 2005 Annual Meeting of the Biological Weapons Convention, which will focus on how the Convention could be strengthened through the content, promulgation and adoption of codes of conduct for scientists.

The Royal Society has a long standing interest in reducing the threat from biological weapons and strengthening the Biological Weapons Convention, and has produced a number of reports and statements on these subjects (for example Royal Society 1994, 2000, 2002, 2004a & 2004b). The Wellcome Trust published their position statement on bioterrorism and biomedical research (Wellcome Trust 2003) stating that the Trust was keen to work with other scientific organisations to identify how the scientific community could best address concerns regarding the potential misuse of life science research. Consequently, the Royal Society and Wellcome Trust agreed to bring together practising life scientists with policy makers, funders and other interested parties to discuss these issues.

The meeting was attended by 66 people, including academic, Government and industry scientists, representatives of funding bodies and learned societies, scientific publishers, scientific journalists, Government policy makers and other interested individuals. A full list of attendees is given in appendix two. The meeting comprised three opening presentations, followed by a series of discussion sessions. A summary of the presentations is given in appendix one.

Our thanks go to the group who advised on the programme of the meeting and the contents of the report. This advisory group comprised of Professor Brian Eyre FRS (Royal Society), Professor Julia Higgins FRS (Imperial College), Professor David Read FRS (University of Sheffield) and Dr Mark Walport (Wellcome Trust).

2 What are the issues?

A range of opinions was expressed on the size of the threat from misuse of life science research. Some believed that natural outbreaks of emerging diseases (such as SARS) are much more likely to occur than bioterrorist attacks, with greater impact in terms of loss of life. However, others commented that there was a considerable risk of the deliberate misuse of life science research.

It was noted that bioterrorism incidents had generated considerable political interest, disproportionate to the size of the events. For example, it was suggested that the geopolitical impact from the US anthrax letters in autumn 2001, which resulted in 22 cases and five deaths (Cole 2003), was of a similar scale to the 2002-2003 SARS outbreak, which caused an estimated 8098 cases and 774 deaths (Weiss & McLean 2004). Public perception of the risk posed by bioterrorism is vital, as this feeds into the geopolitical response to incidents. This echoes the Royal Society's report on biological weapons (Royal Society 2000) which stated that the main negative impact of a biological weapons attack may be panic, with consequent disruption of civilian services.

Currently, the threat is most likely to be from known biological agents and easily accessible 'low tech' approaches. These involve knowledge, expertise and processes that are already in the public domain. However, in the future technological advances might make novel or non-conventional agents (and the means of delivering them) more attractive to terrorists and other individuals wishing to use them.

The challenge is to think beyond the obvious and identify those avenues of research and technologies that present risks of being misused for harmful purposes that are quite distinct from the original aims of the work. This needs imaginative thinking as the vast majority of work falls into the grey area of having some potential for misuse.

It was argued that the 'life sciences' should not be considered in isolation from other scientific disciplines, as the development and weaponisation of biological agents can involve techniques from fields such as mathematics, engineering, physics and computer science.

There was a perception that the UK Government was not 'joined up' on this issue: there is no clear lead Department or Agency and no obvious route into Government for the scientific community to seek guidance.

3 How can these issues be addressed?

3.1 Research funding

There was discussion about weighing up the risks of misuse of research proposals against the potential benefits. Some felt this 'risk-benefit' approach had the advantage of building on existing procedures, such as those for dangerous pathogens, genetically modified organisms and animal experiments, and that it was an appropriate tool for assessing whether research proposals should be undertaken. However, some participants commented that the difficulties in quantifying the potential risks undermined the 'risk-benefit' approach. It was noted that Nobel laureate Joshua Lederberg commented in 1975 (Lederberg 1975) regarding the then-fledgling technology of DNA splicing that it gave uncertain peril and certain benefit. It was suggested that this was equally applicable in assessing the potential for misuse of work in relation to the development of biological weapons. To address these concerns a framework for assessing risk would need to be developed. It was noted that there are currently no criteria for such assessing risks, so existing processes rely on the wisdom of those assessing research proposals.

The key roles to be played by funding bodies and research institutions were stressed, with both needing to consider how to build on existing processes for reviewing research projects to ensure that risks of misuse are assessed in an appropriate and timely manner. It was felt that funding bodies already have strong existing processes in place to assess the scientific merit and ethical implications of research proposals. These processes could be built upon to ensure that risks of misuse are considered during the review of applications; for example through including a specific question on application forms and introducing explicit guidance for referees and funding committees. It was suggested that institutions need to take responsibility for assessing and monitoring risks of misuse associated with ongoing research programmes. The processes for conducting risk assessments on genetically-modified organisms introduced by the previous UK Health and Safety Executive Genetics Modification Advisory Group (GMAG) were suggested as a potential model upon which to base such institutional systems.

Communication between funding bodies and research institutions is vital for any workable research funding based solution. For the majority of funding schemes the money is given to the institution rather than the individual. This means that university and institute department heads must engage in discussion about what systems and procedures might work in practice.

3.2 Communicating research results

The very strongly and widely held belief was expressed that preventing publication of basic research would not prevent its misuse. The reasons for this include:

- Information is likely to be published elsewhere such as in other journals, websites or conference proceedings, or communicated informally via e-mail, telephone or face-to-face discussion.
- Similar research will often be undertaken by others within two years.
- Publishing work allows developments to be used in work on countermeasures to biological agents, such as vaccines, and for use in strengthening public health measures. Suppressing publication would stop this happening, with the potential to hinder work with beneficial applications.

- Publishing makes others aware of unintended results. For example, the publication of the paper on the insertion of the interleukin-4 gene into mousepox (Jackson et al 2001) made a large number of researchers aware of the surprising discovery that the insertion of this gene enabled the virus to overcome both genetic resistance and immunisation to the disease.
- Publication is a vital method of communicating results amongst the international scientific community.
- Full methodological and experimental details must be published to allow peer reviewers and readers to evaluate the research.

In very rare cases consideration could be given to delaying publication of highly sensitive information, or releasing only some of the information into the public domain. However, in these cases there would need to be a very clear benefit in delaying publication.

3.3 Existing and possible future controls and oversight

It was agreed that existing regulatory processes did not assess whether experiments should be undertaken. Many of the current systems, such as those for dangerous pathogens, genetically modified organisms and animal experiments, address whether an experiment can be conducted safely, rather than whether the experiment should be conducted at all based on a consideration of the potential misuse of the research. For example, an experiment to reconstruct the 1918 influenza virus would be permitted providing it was conducted in a category 4 laboratory to ensure the required level of containment. However, there would not be any discussion of whether it would be wise to undertake the experiment.

It was noted that funding bodies, such as Higher Education Funding Council for England (HEFCE), currently audit educational establishments and it was suggested that these processes could be expanded to cover the examination of procedures for assessing potential concerns of research misuse.

During the discussion about the role of regulation and oversight, the clear preference was expressed for self governance by the scientific community, rather than new legislation. For any system of self governance to work, it must have a high degree of transparency in order to ensure public trust.

3.4 Responsibilities of scientists and the utility of an ethical code of conduct for life scientists

There was no consensus on what the main justification would be for introducing an ethical code of conduct. The principal value of both ethical codes and codes of practice was seen to be in reinforcing norms and as educational and training tools. It is difficult to produce a code that is both specific enough to have a positive effect and sufficiently flexible to deal with changes in technology or wider applications. Consequently, there is the distinct possibility of a large number of codes being produced for very small, specific groups rather than a few broad codes.

Contracts of employment are currently used to enforce good practice. These could be expanded, and lessons learnt from industry for use in academia and Government research institutes. It was noted that there are many existing codes that could form the basis of future codes. For example, the criteria for chartered scientist or chartered engineer status could be expanded to cover the misapplication of their work. Consideration would need to be given to what would happen if there was a conflict between different codes that an individual had signed up to. For example, if a scientist's professional society's code did not agree with their contract of employment, which would take precedence?

A range of views was expressed on the merit of accreditation or registration of scientists. Some believed that it is inevitable that scientists will have to receive some form of accreditation. Others saw a fundamental problem that scientists do not have a clearly identified 'customer', unlike currently registered professions such as doctors or lawyers, and hence have no clear duties of care that could be codified.

Despite some scepticism being expressed about the value of codes of conduct, there was broad support for the proposal that the scientific community should take the lead in determining any codes, to pre-empt their introduction through legislation or other 'top down' approaches. National guidelines for good practice could provide the basis for individual organisations and employers generating their own codes of practice. Producing national guidelines for good practice would need an organisation (with the Royal Society being suggested) to take the lead in bringing together key stakeholders, and coordinating the necessary wider consultation.

3.5 Training and education of life scientists

It was widely agreed that it was essential to inform students of their legal and ethical responsibilities and to ensure that they consider the possible consequences of their research; although it was thought that it was rare for such training to occur at the moment. Opinion varied about the utility of teaching this to undergraduates: it was suggested that it would be difficult to introduce such subjects that would not be directly assessed into already full syllabuses. This was countered by noting that educating undergraduates who do not stay in science was a vital part of increasing understanding amongst the wider public. It was strongly agreed that as part of their induction all researchers at postgraduate level should be told about the legal and ethical responsibilities relating to their work. This could be included in existing induction courses that deal with health, safety and other general laboratory training. This training would apply to all incoming students, both national and international. Outlining the implications for researchers of international treaties, such as the Biological Weapons Convention, would be an integral part of the training.

In addition to student training, education would be needed for established researchers, as many current workers have not received any training. This would also need to be undertaken if other measures were implemented, such as altering funding application processes, as staff would need a good understanding of the potential misapplications of their work, to be able to complete an additional box on application forms outlining any possible misuses of their research. University department heads, research institute directors, vice chancellors and Universities UK would be ideally placed to take this forward for the academic community. However, these bodies would need to be co-ordinated.

In the same way, training at the induction stage was also suggested for those joining industry or public research facilities, particularly those at graduate level. Rather than being prescriptive it should be left to employers to judge the likelihood of misuse and the relevance to individual workers. Recommendations of best practice should be issued to employers, possibly through organisations such as the Association of British Pharmaceutical Industries (ABPI) and the BioIndustry Association.

Whilst the need for training and education was stressed, it was suggested that awareness raising approaches could proceed in an incremental fashion: a suitably aware core of workers would be able to raise awareness and promote good practice amongst their colleagues and act as whistleblowers.

It was noted that training and education have associated costs that need to be factored into organisations' budgets and resource requirements and that even with considerable funding and resources awareness might not become as widespread as desired. For example the National Authority for the Implementation of the Chemical Weapons Act had undertaken an extensive outreach programme that had failed to reach all of their target audiences, but it had made considerable progress in raising awareness of the Chemical Weapons Act. However, it was felt that there were lessons to be learnt from their experience.

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Appendix one: summary of presentations

1 Professor Robin Weiss FRS, Windeyer Institute of Medical Sciences, University College London
Making microbes more virulent

Professor Weiss emphasised that while making pathogens more virulent is not very difficult there are many ways in which enhanced pathogenicity may result from apparently innocuous activities. For instance, thoughtless use of antibiotics helps the spread of resistance genes, and xenotransplants may help a pathogen to cross species boundaries.

Talking about the risk of inadvertently finding a dangerous result in the course of normal basic research, Professor Weiss introduced the example of the genetically manipulated mouse pox virus. Researchers in Australia had introduced a gene related to the host's immune system into the virus, which only served as a tool in a project aimed at immunological approaches to contraception. They made the surprising discovery that the gene insertion enabled the virus to overcome both genetic resistance and immunisation to the disease. The researchers published this finding without further comment, but a popular science magazine picked it up and pointed out that the result might help malevolent scientists to create an invincible version of the human smallpox virus (although the predicted result might not be transferable).

Professor Weiss pondered the question of whether such research results which have the potential for misuse should be censored in any way, but he arrived at the conclusion that censorship would do more harm than good. He pointed out that, if genetic manipulation of pox viruses had been ruled out from the start, this would have deprived us of today's improved smallpox vaccines (the original vaccine was unsafe for a significant minority of patients), and of the eradication of rabies in Western Europe, which was brought about by the release of a manipulated pox virus. He also pointed out that mathematical modelling of epidemics and studies of host genetic factors in susceptibility to human infection could be just as open to misuse as research on the pathogen itself.

Summarising his presentation, Professor Weiss quoted from Lewis Wolpert's 2001 Faraday Lecture entitled '*Is science dangerous?*' saying '*censorship of scientific information is a slippery slope*.'

2 Dr Mark Walport, Director, Wellcome Trust
Safeguarding against the harmful misuse of research: a research funder's perspective

Dr Walport described the problem from the perspective of a funding agency. In November 2003 the Trust released a position statement on bioterrorism risk, concluding that an international system of self-regulation of scientists who work with pathogens and toxins would be the most efficient way of minimising the risk of this essential research. Summarising the Trust's position, he emphasised the strengths of the existing regulations and controls in the funding process, including peer review of grant applications, consultation of the Wellcome Trust Standing Advisory Group on Ethics (SAGE) in cases of ethical concern, and host institution responsibility.

Dr Walport presented three case studies of research that was funded in spite of the possible danger of double use. The cases were (1) the sequencing of the plague pathogen, *Yersinia pestis*; (2) research on botulinum toxin, which was originally investigated because of its role in food poisoning, but then delivered unexpected benefits in rare medical applications and more commonly in cosmetic ('botox') treatments, and (3) a study of short peptide mimetics of certain toxins, which were designed to carry payloads into neurons, thus opening possibilities both for the treatment of neurological disease and for misuse. In the last example, concerns of misuse were raised by referees, but following funding committee discussion and SAGE consultation, the Trust eventually funded the research. Asked whether the Trust has ever rejected a funding proposal on the grounds of possible misuse, he stated that he was not aware of any such case.

Dr Walport also presented results from a consultation the Trust held jointly with the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC). Members and chairs of review panels were asked about possible measures to tackle potential misuse. Preliminary results suggest that the scientists unanimously take the problem seriously, and that a majority would support a formal inclusion of misuse aspects eg in the application forms, and/or in guidelines to applicants or referees.

Summarising his talk, he stated that *'enhancing the [existing] mechanisms are sufficient for dealing with problems in this difficult area.'*

3 Dr Robin Coupland, International Committee of the Red Cross (ICRC)
Biotechnology, weapons and humanity

Dr Coupland explained that a standard model of regulation of weapons and their effects includes five main areas, namely the vulnerability of the potential victim, the use of the weapon, as well as its transfer, production, and development. Any measure of prevention would have to address at least one of these areas. For many widely used conventional weapons the most efficient protection would aim at the victim's vulnerability or the use of the weapon. In contrast, measures to block the misuse of biotechnology could operate efficiently in the earlier stages.

In September 2002 ICRC published its '*Appeal on biotechnology, weapons and humanity'*, expressing concern over the growing risk of the hostile use of biotechnology, and asking military and political authorities and scientific communities to deal with the problem in responsible ways. Specifically, scientists were asked to:

- Scrutinise all research with potentially dangerous consequences and ensure it is submitted to rigorous and independent peer review,
- Adopt professional and industrial codes of conduct aimed at preventing the abuse of biological agents,
- Ensure effective regulation of research programs, facilities and biological agents which may lend themselves to misuse, and supervision of individuals with access to sensitive technologies, and
- Support enhanced national and international programs to prevent and respond to the spread of infectious disease.

Dr Coupland emphasised the need for synergy between measures covering different aspects of prevention, much like fire hazards are reduced by a range of measures from the choice of building materials through to the training of fire fighters. Among the different avenues, he stressed education as the most important and the area that still needs much improvement. He pointed out that, to his knowledge, in the UK there is only one university where science undergraduates take a mandatory session on weapons conventions.

Summarising his talk, he stated that *'we have to work in a web of prevention, and whilst we have a responsibility to minimise the risks in our own domain, we have to join up our thinking and action.'*

The overheads for all three presentations can be found on the Royal Society website (http://www.royalosc.ac.uk).

Appendix two: List of attendees

Name	*Organisation*
Dr Helen Almey	Office of Science & Technology
Dr Brian Balmer	University College London
Professor Martin Bobrow FRS	Cambridge Institute for Medical Research
Judy Britton	Office of Science & Technology
Dr Helene Browne	University of Cambridge
David Carr	Wellcome Trust
Dr David Coates	dstl Porton Down
Dr Katharine Cook	Wellcome Trust
Andy Coughlan	New Scientist
Dr Robin Coupland	International Committee of the Red Cross
Dr Jofey Craig	Parliamentary Office of Science and Technology
Professor Malcolm Dando	University of Bradford
Professor David Read FRS	Royal Society
Professor Ray Dixon FRS	John Innes Centre
Dr Simon Edwards	Royal Society
Dr Stacey Efstathiou	University of Cambridge
Professor Brian Eyre FRS	Royal Society
Professor John Finney	University College London
Dr Alf Game	Biotechnology and Biological Sciences Research Council
Claire Glen	Royal Society
Dr Nick Green	Royal Society
Dr Michael Gross	Birkbeck College
Professor Julia Higgins FRS	Royal Society
Professor William Hill	University of Edinburgh
Phillip Hurst	Royal Society
Dr Tom Inch	National Advisory Committee to the National Authority for the implementation of the Chemical Weapons Act
Dr Robin Irvine	University of Cambridge
Sir Alec Jeffreys FRS	University of Leicester
Ahmed Kassem	British Medical Journal
Dr John Keddie	gsk
Professor Bill Keevil	University of Southampton
Alan Kendall	University of Oxford
Dr Amit Khandelwal	Chemical Industries Association
Dr Jeff Kipling	gsk
Dr Paul Logan	Health and Safety Executive
Professor Mike Lord	University of Warwick
Dr Cait MacPhee	University of Cambridge
Professor Martin Maiden	University of Oxford
Professor Duncan Maskell	University of Cambridge
Dr Caitriona McLeish	SPRU, Sussex University
Dr Helen Munn	Academy of Medical Sciences
Dr Paul Nightingale	SPRU, University of Sussex
Kate O'Shea	Royal Society
Dr Petra Oyston	dstl Porton Down
Dr Tony Peatfield	Medical Research Council
Professor Charles Penn	Health Protection Agency

Professor Julian Perry Robinson	SPRU, University of Sussex
Dr Anthony Phillips	Health Protection Agency
Fiona Proffitt	Science
Dr Rachel Quinn	Royal Society
Dr Brian Rappert	University of Exeter
Professor Nick Rawlins	University of Oxford
Professor Michael Roberts	Central Science Laboratory DEFRA
Liz Sawyer	Health and Safety Executive
Sarah Senior	Health and Safety Executive
Martin Sexton	Wellcome Trust
Professor Adrian Smith FRS	Queen Mary College
Dr David Smith	CABI Bioscience UK Centre
Laurie Smith	Academy of Medical Sciences
Professor Brian Spratt FRS	Imperial College
Professor Rick Titball	Dstl Porton Down
Dr Emmanuelle Tuerings	World Health Organisation
Dr Mark Walport	Wellcome Trust
Professor Robin Weiss FRS	University College London
Dr Monica Winstanley	Biotechnology and Biological Sciences Research Council
Dr Angela Woodward	VERTIC