KONINKLIJKE NEDERLANDSE
AKADEMIE VAN WETENSCHAPPEN

IMPROVING BIOSECURITY

Dual-Use Considerations in the Research Chain, from Grant Application to Publication

Journalist's report on the symposium Improving Biosecurity, 5 October 2016, Amsterdam, hosted by the Royal Netherlands Academy of Arts and Sciences (KNAW) and the Biosecurity Office of the National Institute for Public Health and Environment (RIVM)

by Arno van 't Hoog

Fifteen years of debate and discussion about biosecurity have produced broad consensus: researchers should do everything they can to keep people with malicious intentions away from dangerous pests and technology. Nevertheless, countries such as Denmark and the Netherlands have different philosophies on, and different practical approaches to, regulating dual-use research. The symposium *Improving Biosecurity* underscored the diversity of approaches that are being taken.

This symposium was a follow-up to a policy paper on dual-use research, *Improving Biosecurity* (*Bouwen aan Biosecurity*), published by the Royal Netherlands Academy of Arts and Sciences (KNAW) in November 2013. 'Dual-use research' is research that could be used to develop biological and other weapons that threaten public health, animal health or the environment.

Johan Mackenbach, Chair of the Department of Public Health at Erasmus University Medical Center, Rotterdam, chaired the symposium, which was co-organised by the Academy and the Biosecurity Office of the National Institute for Public Health and Environment (RIVM).

The symposium, he said, had three goals:
- to raise awareness of dual-use elements in research in medicine and the life sciences
- to share information on how to deal with dual-use research
- to identify possible improvements in policies and practices

Six speakers offered their perspectives on policy, current practice and the way forward for dual-use research, with a panel discussion rounding off the proceedings.

Jos van der Meer kicked off with a presentation on the Academy's aforementioned policy paper. Van der Meer is Professor of Internal Medicine at Radboud University Medical Center in Nijmegen and a member of the Academy. His first contribution to the discussion of dual-use research came in 2007, when the Academy presented a code of conduct for biosecurity. He was also a member of the feedback group that the Academy consulted about its paper.

Van der Meer noted that life sciences and biosecurity were long seen as occupying two separate worlds, but that that changed abruptly following several incidents involving envelopes filled with anthrax sent to public officials in the United States in the weeks after the 9-11 attacks. Of the 20 people who fell ill, five

died of anthrax poisoning. A long FBI investigation traced the strain of anthrax used in the attacks to a US research laboratory.

Van der Meer told the audience that this finding set off alarm bells in the scientific community and society at large. One of the responses was to issue codes of conduct designed to enhance biosecurity. The Academy was one of the first academies of science to do so, in 2007. Among other things, the code was meant to raise awareness and foster a culture of responsibility, accountability and oversight.

A new debate was ignited in 2011, when virologist Ron Fouchier wanted to publish a study on the transmissibility of the H5N1 flu virus. His research attracted an enormous amount of international attention and sparked public debate on the risk of this knowledge being used to produce biological weapons versus the free exchange of information and academic freedom. Van der Meer argued that the issue of dual-use research should not be handled as it was in the Fouchier case – and that this was in fact one of the lessons of that case. Another lesson, he said, was that raising awareness is not enough. The case also highlighted the conflicting views of scientists on the one hand and security specialists on the other about risks and benefits.

In 2012, the Dutch government asked the Academy to update its policy paper by answering two questions:
- How should dual-use research be assessed?
- Who should do the assessing?

In Van der Meer's recollection, the basic assumption in *Improving Biosecurity* was that there is no zero risk. Van der Meer believed that there should also be a distinction between low and high risk, and that, because dual-use research is a complex business, no single scientific discipline can cover all the issues involved. He argued that:
- risks must be weighed against potential benefits
- assessing potential misuse is always challenging
- it is impossible to prevent every type of imaginable misuse

Other principles, he noted, centre on self-regulation, such as an external review, public confidence that the scientific community does a responsible job judging security issues, and weighing risks and benefits.

The Academy's policy paper strongly recommended establishing a separate advisory committee on biosecurity, as part of the National Health Council, that would advise both at a systemic level with regard to trends and technologies and on individual proposals and publications.

To the disappointment of Van der Meer and others, the Dutch government decided in 2015 that a new biosecurity advisory committee was not the way forward. It decided instead that biosafety officials within each relevant institution should play a key role, supported by the new Biosecurity Office at the RIVM.

The second speaker was Robin Fears of the European Academies Science Advisory Council (EASAC), who offered some background details on the gain-of-function report issued by the EASAC in October 2015. In gain-of-function studies, genes are experimentally modified to study determinants of biological function. Back in 2013, gain-of-function research, for example on H5N1, led to conflicting opinions and confusion, even within the European Commission (EC). The president of the EC invited the EASAC, which represents 28 national academies, to offer its unanimous advice on these issues.

The EASAC working group that was set up to meet this request focused on principles and strategies for regulating gain-of-function research, recalled Fears. Policy implementation was left to the national systems in each European Union (EU) Member State. A key message in the report is the importance of self-regulation, which refers to internal checks and balances in the scientific community, and not to freedom for scientists to do as they please.

Risk-benefit assessment is one of the vexing topics in the EASAC report. It cannot be a one-off calculation – it must be a continual process. It can be quite difficult to perform a quantitative assessment of a risk-benefit balance, because the metrics for risks and benefits differ. The public-health benefit is also hard to define and measure; it can be based on successes in such areas as the prevention of future disease, the production of vaccines, and the advancement of scientific knowledge generally.

The EASAC report makes a number of recommendations. For instance, it suggests that there is a role for the EC in collecting and collating available information on procedures and management activities in the EU Member States. There is a need to bring such information together at the European level. Moreover, national institutions need to understand current European regulations. Fears argued that there is no need for an EU biosecurity body, assuming that all Member States have clear advisory mechanisms in place.

Fears was followed by John-Erik Stig Hansen, who offered the Danish perspective on biosecurity. Hansen is Director of the Centre for Biosecurity and Biopreparedness, the Danish national authority.
Hansen said that Denmark has had a biopreparedness system in place for seven years now. Key to national legislation, he remarked, is UN Security Council Resolution 1540, because it requires national compliance. The Danish parliament passed legislation in 2008, and the following year the Centre for Biosecurity and Biopreparedness was tasked with acting as the Danish national authority.

The Danish system, Hansen said, has two main pillars. On the one hand, there are physical elements, such as security arrangements, locks and keys. On the other, there are the intangible elements, such as stimulating a security culture in institutions, including controls on the availability and distribution of key technologies.

In Denmark, scientists are required to have a licence to work with controlled substances and technologies. In addition, there is a system of inspections, both announced and unannounced. Sanctions for non-compliance include fines and imprisonment. Fines have been imposed on more than one occasion. No one has gone to prison yet, but the threat of imprisonment has certainly helped to ensure compliance.

Biosecurity often focuses on biological agents, i.e. viruses and bacteria, but delivery devices and production are also important. A production line for biological weapons needs seed stock, but also technological skills. Such skills cannot be acquired merely by reading up on them online. UN Security Council Resolution 1540 is also important in this respect, because it requires know-how and practical skills to be subject to controls.

Hansen argued that educating students about the dual-use aspects of research is key because it enables future scientists to screen their research for technologies of potential concern. In the majority of the cases, he said, a good institutional security culture is sufficient to address dual-use issues, but the Centre, he noted, is also available for consultation where this is required.

Hansen argued that the Danish biosecurity situation has improved considerably over the past several years. He said that, 12 years ago, inspections at 96 laboratories revealed that at about half of these at least one component of biological weapons research were accessible. That meant that Denmark was not in compliance with UNSC Resolution 1540.

Today, Hansen reported, Denmark is in full compliance. Institutions are subject to unannounced inspections that are truly revealing. Enforcement is therefore more or less unnecessary. In only one instance has the Centre had to ban a project. Biosecurity regulation does not hamper research, he argued. Despite strict guidelines and inspections, research still takes place freely, and Denmark still has biotech companies.

The Danish system is probably the strictest in Europe, said Hansen in answer to a question by Johan Mackenbach. Non-compliance is very serious, he said, especially if your country is a source of dual-use material that is then used in a weapons programme or terrorist attack.

Up next was Rik Bleijs, head of the Biosecurity Office at the RIVM, who focused on the biosecurity situation in the Netherlands. The Dutch Biosecurity Office was set up in 2013. With a staff of nine specialists, it serves as the national knowledge and information centre in this area, and as a bridge between government policymakers and the professional community.

Biosafety and biosecurity are closely related, he noted. When biosafety is well organised at an institution, about 80% of biosecurity will typically also be in place. Biosecurity consists of eight pillars, ranging from personal security to transport and awareness. In its advice to the Dutch government on biosecurity, the Biosecurity Office draws explicit connections between biosecurity and existing biosafety measures.

Outreach is an important way to raise awareness on biosecurity and dual-use issues. The Biosecurity Office's website shares information, awareness products and toolkits on vulnerability, for instance. It also gives lectures and organises workshops.

Bleijs reported that discussions on dual use often start at the end of the research chain, when results are published. But the research process – involving the generation of ideas, funding applications, permits for genetic modification, and poster presentations – also demands attention. Bleijs argued that dual-use considerations should be a matter of ongoing discussion, involving funding agencies, colleagues and local biosafety officers.

Martje Fentener van Vlissingen, present in the audience, pointed out that researchers need to apply for many permits and licences and that all the information in these applications falls under the Dutch Freedom of Information Act. Combined, these documents provide a lot of information on ongoing dual-use research that could potentially be misused.

According to Kees Jan Steenhoek of the Dutch Ministry of Foreign Affairs, the Dutch Freedom of Information Act provides for exemptions: sensitive information need not be disclosed. This should allay concerns about biosecurity risks that an inflexible law would otherwise pose. Fentener van Vlissingen added that when information is not disclosed, people can start an appeal procedure, with a hearing at which further information may be made public.

A brief discussion took place at this point, prompted by a question raised by Johan Mackenbach: Why do Denmark and the Netherlands take such different approaches to biosecurity?

Bleijs answered first: by focusing on awareness among laboratory professionals and management, the Netherlands chose a bottom-up approach focused on self-regulation and geared towards offering advice on biosecurity policy, based in part on findings in the field.

Jos van der Meer was keen to know whether the impact of the Biosecurity Office's activities had been measured and, if so, how. Again Bleijs answered: in the beginning the level of awareness – for example, about the Academy's code of conduct – was quite low. He noted, however, that the number of people attending Biosecurity Office activities is rising and that discussions tend to be more detailed than before.

The fifth speaker was Ron Fouchier, Professor of Virology at Erasmus MC. He began by remarking that, thanks to scientific research, infectious diseases cause fewer deaths nowadays, even though pathogens are still responsible for one in four deaths worldwide. New infectious diseases are emerging, , he noted, such as SARS and MERS, while other pathogens still pose a risk, such as H5N1 bird flu, still present at poultry farms and markets in Asia. Thanks to intensive research, he said, new pandemic threats such as SARS can be stopped.

The questions virologists ask in order to understand and tackle these pathogens – questions about virulence, transmissibility, drug effectiveness, drug resistance, and vaccines – overlap with the list of seven Dual Use Research of Concern (DURC) experiments. The same goes for Gain of Function Research (GOFR), which has been a preferred virological research strategy for decades.

DURC and GOFR are everyday routine in virological research, he noted. That routine has been in place for a hundred years without incident, because biosafety has always been a key priority for researchers. He remarked that, in recent decades, attention has also shifted to biosecurity. Researchers have always kept dangerous bugs away from people and bad people away from dangerous bugs.

There are a host of international agreements and national and local regulations that apply to this type of research. Researchers obey every one of them, said Fouchier. On top of that, mechanisms within the scientific community and research process add extra checks and balances, from experimental design to funding and peer review.

Fouchier made a point of saying that, though he naturally complies with all rules and regulations, he disagrees strongly with the Dutch government's interpretation of EU regulation 428/2009. EU 428/2009 regulates exports of strategic goods such as military technology, but also pathogens. Fouchier does not believe that these rules should also apply to scientific manuscripts about pathogens, however, because the regulation explicitly excludes information already in the public domain, or information from basic scientific research. Fouchier also expressed the view that export controls are ineffective in a globally oriented research community, and that any delay in publication can hamper the battle against emerging pandemics.

The research performed by his lab on H5N1 met the exception criteria, said Fouchier, so why did he have to apply for an export permit? No other virologist in the Netherlands or the EU has ever applied for such a permit. Fouchier argued that the actual solution lies in communication and guidance, instead of repressive measures without impact.

Jos van der Meer asked what risks are associated with Fouchier's research. After all, that is what bureaucracy and permits are for. You have to put things into perspective, Fouchier responded. Zero risk does not exist. Researchers have accidentally become infected on rare occasions in the past. There have also been some biosecurity incidents, such as the aforementioned anthrax letters. But these did not result in a large number of deaths. Fouchier observed that more people can be killed with a machine gun bought on the black market in Amsterdam than by engaging in acts that violate biosecurity laws and regulations. He added that over the course of a hundred years of research, not a single man-made pandemic has occurred, even when biosafety and biosecurity measures were inadequate by present-day standards. All pandemics have come from nature, which should thus be considered the biggest bioterrorist. We should focus our attention on nature, not on scientists.

The final speaker, Kees-Jan Steenhoek of the Dutch Ministry of Foreign Affairs, outlined how the Dutch government sees non-proliferation and export controls. He noted that he and Fouchier have disagreed on that topic for the past four years.

It is useful to bear in mind, Steenhoek insisted, that there are a number of bio-threats out there. He gave one example: ISIS websites have shown that organisation's interest in acquiring anthrax and the Zika virus. It wants to use bioweapons as well as chemical weapons. A Moroccan terrorist cell possessed materials to produce tetanus neurotoxins. So there is a threat and it is very real, said Steenhoek. We should therefore consider very carefully how to handle materials used in the life sciences and the findings of life science research, including new threshold-lowering technologies such as gene editing and synthetic biology.

Steenhoek said that Fouchier had made a compelling case for continuing to do research; after all, he said, infectious diseases remain a threat – so export controls should not impede legitimate research. And indeed, he insisted, proportionality and balance are woven into the international system of agreements and regulations, such as the guidelines of the Australia Group, the architecture of the Biological and Toxin Weapons Convention, and paragraph 3 of UNSC Resolution 1540, which makes export controls obligatory.

So in practice, we do not block publications, said Steenhoek. The Dutch Ministry of Foreign Affairs assesses risks and benefits carefully and decides whether a licence should be granted. Ron Fouchier needed a licence, and he got it only three days after actually filing his application.

It became clear that the difference of opinion between Fouchier and the Dutch Ministry centred on the definition of basic scientific research. The case went to court, but the legal dispute was not resolved. First, a lower court ruled in favour of the Ministry. However, the court of appeals ruled that there was no basis for further legal proceedings because Erasmus MC had already been granted an export licence for Fouchier's research paper. Both Fouchier and Steenhoek regretted this outcome because they had desperately wanted a ruling on whether basic scientific research counts as an exemption criterion for export controls on dual-use research.

The Dutch approach to biosecurity is bottom-up in nature and focuses on self-regulation, argued Steenhoek, and it is stimulated by dialogue and by guidance from the government. Apart from informal contacts, there are a number of procedures: early-classification requests, test requests (sondage), and finally requests for export licences.

Fouchier asked why the Ministry of Foreign Affairs does not take the H5N1 case to the European Court of Justice, to see whether the Dutch interpretation of international law is correct. Unfortunately, said Steenhoek, that appeal is not possible because the court in Amsterdam never touched on that fundamental question.

Robin Fears noted that a new EU proposal for export licences had recently been published. Steenhoek's view was that one should not expect a radically new approach because the EU combines several existing international regimes on biosecurity.

During the panel discussion that followed, attention returned to the Dutch government's decision not to set up an independent committee on biosecurity under the Health Council, as the Academy had recommended in 2013. Jos van der Meer said he thought this decision should be reconsidered, because the committee would have added value.

Jos Rokx of the Ministry of Education, Culture and Science, who coordinated the government response to the Academy's policy paper, said that current procedures had not been designed from scratch. He noted that there had been procedures in place at the Ministry of Foreign Affairs, and that the Biosecurity Office was developing very nicely. Before rushing to create new procedures and institutions, he argued, we should first see whether we can expand on existing practices.

Koos van der Bruggen, who acted as secretary for the Academy's advisory panel, said one of the main arguments for setting up a new committee was independence from government institutions. Another was that the committee would be able to focus on more than just export controls. Steenhoek replied that the recommendation favouring a new independent body was a departure from the idea that biosecurity required a bottom-up approach.

In winding up the panel discussion, Mackenbach asked whether, governance issues aside, scientists take their responsibility for effective self-regulation seriously. Fouchier insisted that he and his colleagues take biosafety and biosecurity very seriously.

How do you know whether the current system in the Netherlands is actually working as it should, asked John-Erik Stig Hansen. Of course everybody will say they are fully in compliance, he argued, but are they? The best way to find out, he argued, would be to inspect Dutch laboratories: if everyone believes that everything is in place, why not inspect them and see how difficult it is to acquire dual-use material? The inspection should be combined with police and intelligence reports on acquisition attempts over the past 10 to 15 years. These two pieces of information should be the basis for further decision-making on improving biosecurity, he said.

Preferred citation: Royal Netherlands Academy of Arts and Sciences (2016). *Improving Biosecurity. Dual-Use Considerations in the Research Chain. Symposium 5 October 2016 by the Academy and RIVM.* Amsterdam, KNAW.