Symposium
'Challenges in evidence-based-biosafety'

Challenges in Evidence-Based Biosafety

Symposium organized by COGEM and BVF Platform

19 January 2017, Amsterdam

How effective are the measures currently available for preventing accidents with pathogens and GMOs? And is it possible to base decisions on an evidence-based approach? These were two important questions posed during the symposium on Challenges in Evidence-Based Biosafety, which took place on 19 January. About a hundred experts on biosafety gathered in the NH Barbizon Palace Hotel in Amsterdam to come up with ideas for improving biosafety measures in laboratories.

The symposium was organized by the Netherlands Commission on genetic modification (COGEM) and the Dutch Association of Biosafety Officers (BVF Platform). 'On the surface it appears that the containment measures and working instructions are highly effective,' said the chairman of GOGEM, Sybe Schaap, in his welcome speech. 'One might even argue that the current safety policies are in fact overkill, and form an undue burden that hampers technological developments. However, the evidence for the effectiveness of the measures is not always obvious. And work with pathogens and GMOs has expanded. This raises the question whether today's biosafety approach is geared to future developments.'

'Do we have to change?' asked Tjeerd Kimman from Wageningen University & Research, who chaired the symposium. 'Perhaps we could make our work simpler and save costs. Or we could make our work safer and more efficient, and make ourselves more trustworthy for society.'

High costs of containment

An important issue is the high costs of the kinds of containment that provide the highest protection level (BSL-3 and BSL-4), as these involve the use of autoclaves, HEPA-filters, safety cabinets, negative air pressure, centrifuges and other gadgets. Such advanced laboratories are popular with biosafety managers, but they are not always needed. 'I know laboratories that spent five to ten times more money on containment than was needed,' said Felix Gmünder, consultant at Basler & Hofmann in Switzerland. He introduced the concept of 'safe enough' as an alternative to 'as safe as possible'. The problem is how to define safe enough.

Risk assessment of the effectiveness of containment measures in its classic meaning is not possible, Gmünder explained. Realistic models of containment failure are not available, nor do we have data on the failure of individual containment measures. Moreover, there are no acceptability criteria: it is unknown how safe 'safe enough' is. So Gmünder is proposing that decisions should be made on the

basis of rules, standards and guidelines, and on expert reviews. During the discussion more ideas came up. If a laboratory has to be rebuilt, managers could take more time to critically evaluate the necessity of expensive containment measures. A budget for such an evaluation should be part of the building budget.

Personal failure often the cause of incidents

Allan Bennett, project manager at the Health Protection Agency in England, presented the results of a study on the causes of accidents and infections in laboratories. Unsafe acts or personal failure were far more often the cause than equipment failure was, the figures being 61 % for the former and 15 % for the latter. Bennett: 'We are obsessed with expensive technological features which can be certified. However, laboratory infections are generally the result of ignoring codes of practices or insufficient risk assessment.' According to Bennett, several things need to happen. Firstly, biosafety measures and their compliance must be monitored and evaluated regularly. Secondly, laboratories must promote the education of laboratory personnel and compliance with the rules. And thirdly, laboratories should collect data about the effectivity of their measures and procedures to support the evidence base of the biosafety practice.'

During the discussion, one biosafety officer told the audience how her laboratory now collects test data about the maintenance of HEPA-filters. The laboratory used to check the HEPA-filters annually, but once every four or five years might be enough. So the employers are now studying what happens to the filters if they postpone the checks. And the test results will be shared with other biosafety officers. This is an example of how laboratories can systematically collect and share data about the effectivity of their measures.

Wide divergence of biosafety practices

In some cases there is a risk of an accident developing into an event of international consequence. Laboratory equipment can fail, and procedures can fail because scientists or analysts are unaware of them, careless or not motivated to follow the rules. So a contagious pathogen could spread beyond the laboratory and beyond borders, resulting in an outbreak that is difficult to control.

Gigi Kwik Gronvall from the UPMC Center for Health Security in the USA studied global and national arrangements on biosafety, and interviewed experts about their vision on the prevention of such accidents. According to Gronvall, there is great divergence worldwide in the quality and quantity of biosafety norms, regulations and practices. Pathogens which could result in a laboratory accident are not adequately addressed by publicly available regulations. 'There is a great need for more data to inform biosafety policy,' she concluded.

Gronvall argued in favour of more investment in research on practices and equipment. This research could include procedural studies, for example to find out which protocols work best to inactivate anthrax spores, or which equipment works best for a given protocol. The research could also include behavioural studies. For example, how can employers be motivated to follow the rules? The results of these studies would help to promote a safety culture and to develop training materials.

Joint calamity control plan

Reinoud Wolter, from Public Health Rotterdam-Rijnmond, and Cathy Bakker, from Erasmus MC, explained how Rotterdam has prepared for a calamity, an accident outside the laboratory. If the environment is at risk of being exposed, not only institutional emergency forces, but also the external emergency forces – police, fire brigade, municipality, health care and the Harbour and Water Board – become involved. In Rotterdam, these forces drew up a joint calamity control plan, an 'Incidenten

Bestrijdings Plan', which describes the most important biohazard scenarios and gives the forces tools to effectively control the calamity. 'Communication is very important in this plan,' said Bakker. 'It is quite a big challenge to get the information across, between the institutional emergency forces and the external forces.'

The experts were trained last October. Erasmus MC had designed a scenario in which a desperate employee had wantonly spread a dangerous GM-norovirus via a plant sprayer. He wanted to end his life and take other people with him. The experts had to come into action during the training session that lasted a few hours. The team learnt how important it is to make clear the various tasks, goals and responsibilities, and to form and share a common picture of the situation.

One of the participants of the symposium feared that such training courses add to the feeling of unsafety among the broader public. But Bakker is not afraid of this happening. 'We didn't make the training course public. Besides, if we can explain that we are prepared in the case of a calamity, people will then trust us more than if we deny bad scenarios and do nothing.'

Improving worldwide practice

Anna Papa from Aristotle University of Thessaloniki showed that studies on the best protocols for handling a specific pathogen can really help to improve worldwide practice. An international group of experts conducted a study on the practices for working with Crimean-Congo haemorrhagic fever virus (*Journal of General Virology 2016*). In countries where CCHF is absent, CCHFV is classified as a hazard group 4 agent and handled in containment level (CL)-4. But is such expensive containment needed for all countries? Nowadays, most countries where CCHF is endemic perform diagnostic tests under BSL-2 conditions. In particular, Turkey and several of the Balkan countries have safely processed more than 100,000 samples over many years in BSL-2 laboratories. So what can other countries learn from their experiences?

The conclusion of the study was that the tests can be performed under enhanced BSL-2 conditions with equipment that complies with the standardized protocols in the countries affected. And the researchers had more recommendations. Technical advances arising in West Africa from the successful deployment of mobile BSL-3 laboratories for the Ebola outbreak could be applied in diagnostic laboratories in the CCHF endemic countries. Also, inactivation of sera would improve biosafety. According to Papa, the biosafety community can learn a lot from the nuclear industry. 'There safety is seen as an investment rather than as a short-term cost. Everyone within the organization constantly asks 'What can go wrong and how do we prevent it?''

Lack of information

It is unclear how often Laboratory-Acquired Infections (LAIs) occur in Europe. It is not always mandatory to report them, and many laboratories don't like reporting such incidents. Surveys could be a solution. Nicolas Willemarck from the Scientific Institute of Public Health in Belgium explained how his organization did several surveys among Belgian laboratories. In a first survey, of biosafety officers and occupational health practitioners, 213 institutions were invited to participate. In a second survey, of personnel, 26 institutions were invited. Approximately 53 % those contacted responded. The surveys provided a lot of information; they identified at least 73 LAIs, caused by 21 different organisms. The Scientific Institute of Public Health has built a platform that is intended to systematically gather information about laboratory incidents, their causes and the lessons learnt (www.biosafety.be).

There is also little information on how often GMO-incidents happen in Europe. Directive 2009/41/EC requires EU member states to report on the contained use of GMOs and on accidents. However, the member states differ in how they interpret the rules. Margot Spreuwenberg, from the Human Environment and Transport Inspectorate in the Netherlands, gathered information about GMO-accidents in Europe. Only four member states reported accidents during the reporting period 2006-2009 – most of the incidents had no (potential) health and environment consequences. The Netherlands reported 13 accidents that had no health and environmental consequences in the period 2009-2014. The incidents varied from a laboratory fire (during which no GMOs escaped) to inefficient inactivation and the escape of a GM-Thale cress from a greenhouse facility.

Spreuwenberg believes an open mindset is important. Inspectors cannot force employers to be honest about incidents; they are dependent on their collaboration. 'So when we visit laboratories, we encourage an open culture. If people are afraid, they will not learn from what happened.' The Dutch inspectors (there are three in the whole country) share the lessons learnt in one laboratory with similar laboratories. Spreuwenberg: 'It would be good to do this on a European scale, but that's not easy. Everyone is already pretty busy in their own country.'

Preventing biological attacks

Andrew Weber, former Deputy Coordinator for Ebola Response at the U.S Department of State, stressed in his speech that, at the moment, a biological attack is more likely than a nuclear one. It is not difficult to build a facility. For instance, Kazakhstan built a large-scale fermentation unit in the 1990s, capable of producing an estimated 300 metric tons of weaponized anthrax in eight months. This facility has been dismantled thanks to negotiations, but there are enough threats remaining. Al-Qaeda had an anthrax facility in Kandahar, Afghanistan. They had good scientists, but, fortunately, no good starter culture. Isis is developing biological weapons.

Weber visited a Ugandan laboratory that had freezers full of anthrax samples, but had never thought about the threat of bioterrorism. 'So we made them aware of the necessity of taking security measures,' Weber explained. 'Such training courses are very important.' According to Weber, the international community must strengthen its defences against biological attacks. A first action must be the development of a bio-surveillance system that provides real-time awareness of the terrorist networks and biological weapons in the world. A second action must be the development of medical countermeasures such as vaccines against Ebola. And a third action must be the move away from culture-dependent diagnostic methods to modern, molecular diagnostic methods. This would diminish the need for culturing pathogens.

Revision of WHO biosafety manual

Kazunobu Kojima of the World Health Organization (WHO) invited the audience to come up with suggestions for improvements to the revised WHO Laboratory Biosafety Manual. This manual has served the global biomedical science community for more than three decades and has been translated into more than 10 languages. But as the manual is a living document, regular revision is indispensable in order to keep its content current and relevant.

The revised manual is flexible, ensures a practical, risk-based approach and removes the requirement for unnecessarily complex and expensive facilities. It moves away from focusing on four pathogen risk groups that need specific, group-dependent, levels of containment. Instead, the micro-organisms are categorized according to their pathogenicity *and* other factors such as route of transmission, epidemiology and stability. Besides, these factors differ between countries. Another difference in the new manual is that the procedures (high risk or low risk) will become part of the decision on which

safety measures are needed. Kojima: ‘So we place emphasis on risk assessment and risk mitigation processes rather than on risk groups. Training and refresher courses to maintain good working practices are also important.’

Improving the safety culture

‘Biosafety must become an issue for all stakeholders, from the top manager to the cleaner,’ said Felix Gmünder during the general discussion that was led by Gijsbert van Willigen, president of the European Biosafety Association (EBSA). Participants came up with more ideas to improve the safety culture in laboratories. ‘Scientists are sceptical. You have to explain the rationale of the rules to them,’ added Allan Bennett.

Summing up, Mieke Jansen, chair of the BVF-platform, drew a few conclusions at the end of the day. ‘We build different forms of containment and organize equipment, but the human factor appears to be a very important issue,’ she said. And secondly: the higher the protection level, the higher the cost. ‘So doing risk-assessments in the way the WHO is now suggesting is important. Besides, laboratories could collaborate more often and share facilities, both of which could save a lot of money.’