

Life science research: opportunities and risks for public health

Mapping the issues

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Communicable Disease Surveillance and Response
Ethics, Trade, Human Rights and Health Law
Research Policy & Cooperation
Special Programme for Research and Training in Tropical Diseases



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1. Introduction

Outstanding advances have been made in the past few decades in the life sciences and in biotechnology, including genetic engineering, genomics, proteomics and bioinformatics. Knowledge obtained in the field of life sciences and the techniques developed hold the potential for improving human health, welfare and economic development in Member States of the World Health Organization (WHO). Although biotechnology has created many opportunities and applications for public health, medicine, agriculture and the food industry, this progress has important ethical, legal and social implications. The discipline of bioethics and concerns about a ‘genomic divide’ (1) in global health between the developing and developed world illustrate some of these implications.¹

This working paper addresses another public health implication of advances in life science research and development (R&D): its potential deliberate misuse to cause harm. Research, techniques and knowledge in the life sciences can be used for both legitimate and illegitimate purposes. Therefore, this raises the problem of how best to manage the risks associated with such research, techniques and knowledge without hindering its beneficial application to public health and welfare.

Managing the risks of science and technology is not a new issue, as nuclear research and technologies are already being managed and monitored. The challenges are, however, different, as the scale and access to nuclear technologies differ greatly from those of biological research and technologies. Fissionable materials are, for instance, easier to control than pathogens and toxins, and biological techniques are less expensive and sophisticated than their nuclear counterparts. Moreover, the wide, rapid diffusion and availability of life science R&D and expertise mean that its control must not affect its legitimate civilian and public health applications.

This working paper addresses an issue that is important to public health for at least four reasons.

Life science R&D for strengthening public health responses to natural, accidental or deliberate epidemics can have both benefits and risks for national and international public health.

The control mechanisms suggested by industry, government and nongovernmental sectors for managing the risks associated with potential misuse of life science R&D could hinder the development of a science that has much to offer for the benefit of public health.

¹ Bioethics, ‘the ethics of medical and biological research’, has been broadened to cover ethical issues in the life sciences, health and health care. *Bioethics and ethics in health systems WHO/EURO involvement: a position paper from the SCRC*. Report of the Standing Committee and Regional Committee Subgroup (SCRC) on Bioethics. (http://www.who.int/ethics/regions/en/euro_scrc_bioethics2002.pdf, accessed June 1, 2005)

Strong public confidence must be maintained in science, and scientific advice for policy-making must be supported. Coping with uncertainty and risks in the life sciences will require improved communication and openness on these issues.

The levels of information and experience on these issues vary among WHO Member States. Knowledge, understanding and awareness must be improved by informing governments, public health authorities and workers and the life science community and also the private sector, nongovernmental organizations and organizations involved in arms control and security about the potential misuse of the life sciences.

This working paper aims to identify the main issues associated with potential misuse of life science R&D in a general way, to promote informed discussion. The issues are reviewed from a public health perspective, as any mechanism designed to manage the risk of deliberate misuse would also affect public health. The aim of this paper is in line with the terms of Article 2(r) of the WHO Constitution, whereby WHO is 'to assist in developing an informed public opinion among all peoples on matters of health'. Guidelines or evaluative frameworks might be formulated in a second phase, in which WHO will be required to engage through a formal mechanism, e.g. by the establishment of a study group or expert committee.

The working paper is organized into six sections, following a risk assessment framework.² The present section provides an overview of the working paper. Section 2 gives some working definitions used in the paper and describes the role and activities of WHO in this field. Section 3 reviews some life science R&D that might be misused, while section 4 analyses the opportunities and risks associated with life science R&D. Section 5 underlines the importance of assessing the risks that life science R&D will be deliberately misused and reviews measures that have been proposed to manage and monitor the risks. The same section also draws attention to the drawbacks of those measures and their possible implications for public health. Building on the previous sections, section 6 presents the conclusions that can be drawn and their implications for public health.

² Risk is considered as 'the combination of two factors: the probability that a potentially harmful event will occur; and the potential damage such an occurrence would cause.' Organisation for Economic Co-operation and Development. *Emerging risks in the 21st century. An agenda for action*. OECD, 2003:30. See also Slovic P. The risk game. *Reliability engineering and system safety*, 1998, 59:73–77 for the social science perspective of risk. Although the framework of risk assessment was used to structure this working paper, risk assessment is not advocated or considered as the only or the most appropriate framework for dealing with the potential misuse of life science R&D.

2. Definitions and WHO involvement

2.1 Some working definitions

Public health is understood as ‘the science and art of promoting health,³ preventing disease, and prolonging life through the organized efforts of society’ (2). It ‘refers to all organized measures (whether public or private) to prevent disease, promote health, and prolong life of the population as a whole. Its activities aim to provide conditions in which people can be healthy and focuses on entire populations, not on individual patients or diseases. Thus, public health is concerned with the total system and not just the eradication of a particular disease. The three main public health functions are:

- The assessment and monitoring of the health of communities and populations at risk to identify health problems and priorities.
- The formulation of public policies designed to solve identified local and national health problems and priorities.
- To assure that all populations have access to appropriate and cost-effective care, including health promotion and disease prevention services.’ (3).

Life sciences comprise all sciences that deal with living organisms, including human beings, animals and plants. It is a broad field that encompasses biology, biotechnology, genomics, proteomics, bioinformatics, pharmaceutical and biomedical research and techniques.

Technology is understood as comprising products or artefacts (tangible products) as well as skills or tacit knowledge, the know-how (intangible factors) (4). Tacit knowledge, which includes scientific and technical knowledge, management techniques and principles embodied in people, constitutes an integral constituent of technology and is crucial in the ability to recognize technical problems, to develop solutions and to exploit those solutions in an effective manner (5,6).

Knowledge is also produced through *research and experimental development*.⁴ R&D covers three activities: basic research, applied research and experimental development. Knowledge can also be produced through intangible investments, such as education and training. As mentioned above, knowledge can also be tacit (know-how) and codified (in patents, scientific papers and information networks).

³ The WHO Constitution defines health as ‘a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.’

⁴ This working paper follows the Frascati definition of research and experimental development (R&D) for which R&D ‘comprise creative work undertaken on a systematic basis in order to increase the stock of knowledge, including knowledge of man, culture and society, and the use of this stock of knowledge to devise new applications.’ Organisation for Economic Co-operation and Development. *Frascati Manual: Proposed standard practice for surveys on research and experimental development*. Paris, OECD Publications Service, 2002, 30.

Dual-use R&D and technology have been defined as those research methods, knowledge and techniques that have, or may have, potential civilian and military applications (7). According to this definition, dual-use R&D and technology are not inherently hazardous, and both civilian and military applications can be legitimate. While dual use can be understood from various perspectives, this working paper is specifically concerned with the abuse of dual-use technologies, i.e. the appropriation of research and technology with legitimate purposes for illegitimate intentions and applications.

2.2 WHO involvement

This working paper should be considered within the context of resolutions and actions taken by WHO on the misuse of biology. The World Health Assembly (WHA) in 1967 resolved that ‘scientific achievements, and particularly in the field of biology and medicine—that most humane science—should be used only for mankind’s benefit, but never to do it any harm’ (WHA20.54). More recently, concern was expressed in the report of the advisory committee on health research on genomics and world health (2002). The report noted that ‘The potential misuse of genomics for the purposes of biowarfare is of particular importance’. It also raises important questions regarding the role of the biomedical research community and recommends that it take ‘a much more proactive role in controlling the hazards associated with the misuse of genomics for biowarfare’ (8). That community should also examine ‘the risk–benefit ratios of some of its current genetic engineering procedures’ and the adequate containment and monitoring of its work.

On a more practical basis, WHO has been in charge of monitoring research on smallpox virus (variola virus). Since the declaration of the global eradication of smallpox in 1980 (WHA33.3), WHO has been overseeing research on orthopoxviruses (WHA33.4). While a 1996 resolution recommended that ‘...the remaining stocks of variola virus, including all white pox viruses, viral genomic DNA, clinical specimens and other material containing infectious variola virus...should be destroyed on 30 June 1999 after a decision has been taken by the Health Assembly...’ (WHA49.10), this action was postponed in 1999 and 2002 (respectively WHA52.10 and WHA55.15) to enable further international research on variola virus and ‘to ensure that all approved research would remain outcome-oriented and time-limited and periodically reviewed’. International research on live variola virus is conducted at two repositories,⁵ where all research is to be conducted in an open and transparent manner and only with agreement and control of WHO. A new date for destruction is to be set when research and outcomes allow such consensus.

WHO has also been concerned with the possibility that biological and chemical agents might deliberately be misused to harm populations. In 1969, the Twenty-second WHA, in resolution WHA22.58, requested the WHO Director-General to continue to cooperate with the United Nations Secretary-General on the issue of chemical and bacteriological

⁵ Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America and the State Research Centre of Virology and Biotechnology, Koltsovo, Novosibirsk Region, Russian Federation.

(biological) weapons and the consequences of their possible use.⁶ The 1970 WHO report on *Health aspects of chemical and biological weapons: report of a WHO group of consultants* was the result of that work and echoed the concerns of Member States about the misuse of biology (WHA20.54). This report has recently been revised and updated with the 2004 publication of *Public health response to biological and chemical weapons—WHO Guidance (9)*.

This working paper also contributes to implementation of paragraph 2.4 of resolution WHA55.16 of 18 May 2002 wherein WHO Member States requested the Director-General ‘to examine the possible development of new tools, within the mandate of WHO, including modelling of possible scenarios of natural occurrence, accidental release or deliberate use of biological, chemical agents and radionuclear material that affect health, and collective mechanisms concerning the global public health response to contain or mitigate the effects of natural occurrence, accidental release or deliberate use of biological, chemical agents and radionuclear material that affect health.’ This project forms part of the programme of work of Preparedness for Deliberate Epidemics and is linked with the work of other WHO departments, including Research Policy and Cooperation, Research and Training in Tropical Diseases, and Ethics, Trade, Human Rights and Health Law.

3. Review of selected life science research and development, related techniques and their associated risks

In this section,⁷ we review some life science R&D and techniques and illustrate their potential misuse (10–23). The section is not exhaustive and is not intended to draw attention to certain techniques or knowledge. Given the rapid expansion of R&D in this field, new scientific breakthroughs might replace current techniques by more efficient ones. Likewise, fundamental research outputs might have future applications that cannot be foreseen.

Life science R&D that could pose a risk to public health includes standard techniques of molecular biology, microbiology and non-engineered microorganisms and toxins, and also new techniques, processes and knowledge. Recent advances in life science R&D and the period in which they are being developed differ from standard R&D and techniques in at least two ways. First, new techniques are rapidly expanding understanding of genes and their functions, of infectious disease mechanisms (pathogenesis), of the immune defence system and of biochemical pathways. This knowledge can lead to modification and manipulation of the genetic material of a potentially hazardous organism and its

⁶ In 1969, a WHO group of experts cooperated with United Nations experts in the following report: United Nations. *Chemical and bacteriological (biological) weapons and the effects of their possible use: report of the Secretary-General*. New York, United Nations, 1969.

⁷ This section has been written with the support of several research papers listed under section 7 (10–23).

products. Second, these new techniques and related knowledge can rapidly be made available throughout the world via the World Wide Web. Likewise, use of techniques such as high-throughput arrays,⁸ which, while not in themselves directly hazardous, could facilitate prohibited R&D.

3.1 Genetic engineering

Genetic engineering involves the transfer of genetic material into living organisms or modification of the genetic properties of organisms. From a public health perspective, the transfer or alteration of genetic material can lead to new therapeutics and treatments, such as gene therapy. The correction of defective genes by the introduction into cells of normal genes could stop the development of cancerous cells.

Genetic engineering can, however, be deliberately misused. For instance, the insertion of new characteristics into microorganisms could, inter alia:

- facilitate the production of toxins that were previously difficult to produce on a large scale;
- make a pathogen resistant to the immune system or to antibiotics, hence rendering defensive measures ineffective;
- modify the environmental stability of a pathogen;
- create bacteria and viruses of greater virulence or render previously harmless organisms pathogenic;
- change the host specificity of microorganisms; or
- render the identification and detection of engineered pathogens difficult (e.g. to bypass current detection techniques).

Gene vector techniques via viruses or immunotoxins could also be misused to create vectors that carry specific diseases or ‘stealth’ viruses.

The dual nature of research on genetic engineering can be illustrated by the experiment conducted on the ectromelia virus (mousepox) in Australia in 2001 (24). In an attempt to control mice as pests, Australian scientists unexpectedly increased the virulence of mousepox. By inserting a gene responsible for the production of interleukin-4 into the mousepox genome, the scientists created a pathogen that overcame the immune defence of mice and even killed mice that had been vaccinated. This unforeseen result and its publication raised the question of whether the same technique could be applied to other orthopox viruses, such as smallpox. Subsequent research at St Louis University (United States of America) resulted in a recombinant mousepox virus containing interleukin-4 which is more virulent than that in the Australian experiments. The aim of the research was to explore novel therapeutics and prophylactics.

⁸ A microarray is ‘A grid of nucleic acid molecules of known composition linked to a solid substrate, which can be probed with total messenger RNA from a cell or tissue to reveal changes in gene expression relative to a control sample. Microarray technology, which is also known as “DNA chip” technology, allows the expression of many thousands of genes to be assessed in a single experiment.’ World Health Organization. *Genomics and world health. Report of the Advisory Committee on Health Research*. Geneva, World Health Organization, 2002, 205.

3.2 Genomics, functional genomics and proteomics

Genomics is the study of the structure of the genome and its action, while functional genomics allows understanding of how the structure of the genome operates.⁹ With the advent of genomics, the human genome and many virus and bacteria genomes have been sequenced.

R&D and techniques in genomics improve understanding of pathogenesis and hence knowledge about the treatment of infectious diseases. The resulting applications include improved vaccines, antibiotics and antivirals. The advent of genomics has permitted the development of ‘reverse vaccinology’, which allows, for instance, the construction of new vaccines for tuberculosis and malaria. The conventional approaches to developing vaccines took years. This new technique, in which the design of a vaccine is based on a computer analysis of the entire genome sequence of microbial pathogens, is much faster and more effective.

R&D in genomics should also help in making new drugs by identifying target sites, in ion channels and on proteins. With its use of computational methods, human genome sequencing furthers understanding of the structure of cell receptors and their interactions with ligands. This new knowledge about receptors makes it possible to develop new drugs by ‘reverse molecular pharmacology’.

Proteomics,¹⁰ which complements genomics, is the study of proteins expressed by genes. Proteomics thus makes it possible to identify the proteins expressed during microbial infection and disease and how they interact. Moreover, protein microarrays are being studied that will allow the identification of new ligand–receptor combinations with therapeutic applications. Proteomics holds the promise of identifying new proteins and pathways that will help in the early detection and diagnosis of diseases and improve the design of vaccines and antimicrobial compounds.

New and enhanced vaccines, diagnostic techniques and therapeutic drugs will also be useful in improving measures against the misuse of biological agents. Rapid methods for the detection and identification of biological agents are being developed with molecular techniques such as the polymerase chain reaction and use of DNA arrays.

Because proteomics can also be used to identify potential toxic proteins, however, the same knowledge and techniques that allow the identification of new drugs and vaccines could also be misused to cause harm. The knowledge and applications associated with pathogenesis could, for instance, be misused to defeat vaccines or immune system

⁹ Genomics is ‘The study of the genome and its action’, while functional genomics is ‘The development and implementation of technologies to characterize the mechanisms through which genes and their products function and interact with each other and with the environment.’ World Health Organization. *Genomics and world health. Report of the Advisory Committee on Health Research*. Geneva, World Health Organization, 2002, 203–204.

¹⁰ Proteomics is understood as ‘the development and application of techniques to investigate the protein products of the genome and how they interact to determine biological functions.’ World Health Organization. *Genomics and world health. Report of the Advisory Committee on Health Research*. Geneva, World Health Organization, 2002, 207.

defences. For instance, knowledge about receptors and ligands can provide information about toxic substances. The derived process ‘reverse molecular pharmacology’ could also be misused to develop new molecules that imitate ligands or new bioregulators that harm the immune and nervous systems.

Increasing knowledge about bioregulators (including peptides, neurotransmitters and cytokines), which are substances produced naturally in very small quantities by metabolism, could also be misused. Bioregulators are essential for regulating physiological activities such as blood pressure, heart rate and immune response and, as such, could be used to treat diseases. Yet, this same knowledge could be misused. For instance, overproduction of these substances could disrupt the immune system or cause other systems to fail. Increasing understanding of the innate immune system could provide information on generic protection from broad classes of microbial agents but could also provide information about how to disrupt the immune system. Moreover, new techniques in genetic engineering might allow large-scale production of these substances.

Furthermore, increasing knowledge in neurobiology leads to the synthesis of new pharmaceutical compounds to treat mental illness and other nervous disorders; but this knowledge also shows how the nervous system can be manipulated.

Genomics could also lead to the creation of synthetic agents. As synthetic replica of existing viruses have already been reproduced chemically (25, 26), new synthetic viruses could also be produced. Such synthetic products might provide pest control, against weeds, insects and rodents, and the development of new pharmaceuticals, but they could also be misused if they are resistant to existing antiviral agents or bypass the immune system.

Another new technique related to genomics is ‘biopharming’,¹¹ which involves genetic modification of plants for the production of pharmaceutical agents. Biopharming can be used to produce vaccines by plant biotechnology rather than from embryonated eggs or cultured cells. Biopharming could also be misused, e.g. by mass production of plant toxins.

The dual nature of research on genomics is illustrated by the investigation of differences in the virulence of variola and vaccinia viruses to understand the mechanism of the virulence of variola (27). Researchers compared the variola complement regulatory protein (SPICE, smallpox inhibitor of complement enzymes) with the corresponding protein in vaccinia virus (VCP, vaccinia virus complement control protein). Researchers demonstrated that SPICE is a more potent inhibitor of human complement than the corresponding protein in vaccinia virus. Disabling it could represent one method for the treatment of smallpox. In order to generate SPICE, the researchers mutated the amino acid sequence of the vaccinia complement regulatory protein VCP into that of the variola

¹¹ In biopharming, genes that hold the information of a desired pharmaceutical product are joined to DNA sequences in the host plant genome (e.g. corn or soya beans) by the same genetic engineering techniques used in the agricultural industry. The product of biopharming can be delivered through consumption or through a pharmaceutical preparation after extraction or purification.

protein. This experiment also showed that the recombinant vaccinia protein was much more efficient than its natural counterpart in overcoming human complement activation, suggesting that the pathogenicity of vaccinia virus could be enhanced by manipulating the inhibitor.

Another illustration is the successful cloning of the entire vaccinia virus genome as a bacterial artificial chromosome in *Escherichia coli* and its subsequent conversion into an infectious virus in mammalian cells (28). While the results of this research will facilitate study of the vaccinia virus genome, the results indicate that it is possible to manipulate not only vaccinia virus but also other orthopoxvirus genomes.

3.3 Bioinformatics

The development of bioinformatics,¹² the rapid sophistication of computing, information and instrumentation techniques have also favoured rapid advances in biology. Proteomics and genomics have generated large amounts of biological data on many genomes, which must be stored, classified and managed on databases.

Data from genetic engineering on viruses could, for instance, be instrumental in the development of new anticancer drugs. Bioinformatics could, however, also be misused, as biological information available on databases could be exploited, for instance, to increase the pathogenicity of organisms or to create new toxins.

Bioinformatics could also allow the identification of information on ethnic origin. The study of the human genome can provide information on genetic differences among various groups. Although the misuse of such information to cause harm might not prove technically feasible, plants and animals would be more vulnerable to such misuse because they tend to have little genetic variability.

The duality associated with bioinformatics and genomics is illustrated by the reconstruction of poliovirus from chemically synthesized oligonucleotides in the United States (25). Scientists at the State University of New York in Stony Brook reconstructed the poliovirus by chemical synthesis, using information on the genome available on the internet and by ordering custom-made DNA sequences. A similar experiment was conducted in 2003, with the assembly of the whole infectious genome of bacteriophage Φ X174 (5386 base pairs) in vitro from a single pool of commercially available, chemically synthesized oligonucleotides (26). Oligonucleotides are widely available and very useful for many researchers: oligonucleotides can be used for DNA sequencing, as primers for the polymerase chain reaction amplification, for mutagenesis and for single-nucleotide polymorphism analysis. For many scientists, however, synthesis of the poliovirus was ‘neither a novel discovery nor a potential threat’ (29) but rather, as it was shown with the assembly of bacteriophage Φ X174, it is the method of synthesis that is making progress. While synthetic genomics and the availability of oligonucleotides make

¹² Bioinformatics is understood as ‘the discipline encompassing the development and utilization of computational facilities to store, analyse and interpret biological data.’ World Health Organization. *Genomics and world health. Report of the Advisory Committee on Health Research*. Geneva, World Health Organization, 2002, 201.

new applications possible, there might be a risk of misusing bioinformatics and available oligonucleotides to synthesize all sorts of agents.

3.4 Related techniques

Techniques related to genomics, functional genomics and proteomics can also be misused. High-throughput screening techniques, rapid processing devices, combinatorial methods, microarrays and other devices are of great assistance in designing novel therapeutics and facilitate R&D on new vaccines, making their development much quicker than by traditional methods. Microarrays will offer enormous opportunities for preclinical diagnosis of disease, cancer therapy and the development of new classes of antimicrobial drugs, but could also be misused. Computer models for investigating the spread of diseases and sophisticated computer systems for identifying toxic compounds could also be deliberately misused.

Microencapsulation and aerosol techniques are being used to deliver drugs and are being studied for intranasal vaccine delivery. Such research might also be deliberately misused to design systems for airborne delivery of microorganisms and toxins.

4. Opportunities and risks for public health

Biotechnology, genomics and proteomics offer opportunities for improving human health through, for instance, the prevention, monitoring, detection, diagnosis and treatment of infectious diseases. The development of safer, more efficient antiviral agents, antibiotics and vaccines; novel therapies; and more precise and rapid laboratory diagnostic methods illustrate some of the promise of life science R&D for public health. Research into pathogenesis is essential for improving the treatment of infectious diseases, and research in the neurosciences will provide a better understanding of the nervous system that could lead to new treatment for depression and other nervous ailments. New techniques such as microarrays, bioinformatics, combinatorial chemistry and the polymerase chain reaction are essential for the advancement of life science R&D and for improving public health.

New life science research and technological applications will also affect the development of medical countermeasures. Investment in research on novel therapeutics and vaccines and on new detection and diagnostic methods will provide tools for countering both naturally emerging diseases and the deliberate release of biological agents. The preparedness and responses activities associated with such programmes might also include enhanced surveillance systems and the establishment of laboratory networks. Such research activities would in turn enhance national and international public health infrastructure, improve coordination and communication across sectors and give greater visibility to public health agencies.

Given the benefits associated with biotechnology, genomics, proteomics research and related techniques, investing in life science R&D is worthwhile. Nevertheless, research into pathogenesis and genetic engineering techniques could be misused to enhance the pathogenicity or contagiousness of viruses and microorganisms, and neuroscience might be misused to manipulate human behaviour. Knowledge about agents and biological

pathways, such as the human immune system, could also be manipulated for misuse. The rapid spread of advanced life science R&D and the accessibility of information enhance research and life science techniques but could also be misused.

Another consideration regarding medical countermeasures is that investment in specific vaccines and therapeutics could divert capital and human resources from traditional public health priorities and infectious diseases. Furthermore, investment in preparedness and responses activities might not benefit public health surveillance in general and could have long-term consequences for national and international public health surveillance procedures and structures; for instance, it might distort the usual chain of reporting diseases and symptoms to authorities. There is also the risk that the enhanced visibility of public health agencies and their working relations with other communities could endanger their independence and scientific integrity and hence cause conflicts of interest.

5. Risks of misuse of life science research and development

Although assessing the risk of deliberately misusing life science R&D is an essential stage within a risk assessment framework, such an analysis would go beyond the scope of this working paper, which is limited to mapping the issues. Before devising methods to manage and monitor the risks associated with life science R&D and techniques, the risks that the new science will in fact be misused must be evaluated, as must the extent to which the risk is new. Assessing this risk might prove to be a difficult task. One element that might be taken into consideration is that, as history indicates, ‘Every major technology—metallurgy, explosives, internal combustion, aviation, electronics, nuclear energy—has been intensively exploited, not only for peaceful purposes but also for hostile ones.’ (30). It might be also useful to identify the different sources of life science R&D, as the risks might vary according to whether it derives from the scientific community; private companies working on pharmaceuticals and biotechnology and biodefence activities (although, for national security or for the protection of proprietary information, it might be necessary to classify some research results).

Risk assessment might be conceptualized as ‘the probability of occurrence of a hazard multiplied by the value of the consequences’ (31). Thus, ‘although the probability of a large-scale high-technology biological/chemical attack may be low, if it nevertheless happened with, improbably, all the many imponderables and uncertainties favouring the attacker, the consequences of the event could be great.’ (32).

Finally, it might be necessary to compare this risk with other types of risk to help policy-makers, who usually have a set of finite resources to establish priorities (33). Such an assessment and the resulting priorities might differ from country to country and might be set in cooperation with the sectors that generate the risks.

The various measures devised to manage and monitor these risks, while allowing the beneficial aspect of R&D to be exploited, are outlined below.

The deliberate misuse of biology and life science R&D is prohibited by the 1972 Biological and Toxin Weapons Convention and the 1993 Chemical Weapons Convention.¹³ The scope of both conventions is defined by a general purpose criterion. The Biological and Toxin Weapons Convention bans biological and toxin weapons, not in terms of particular biological agents, toxins or techniques but in terms of purpose. ‘Such an approach was adopted so as not to obstruct the many biomedical and other non-hostile applications of microbial or other biological agents and toxins, while at the same time enabling the Convention to cover any as-yet-unknown products of biotechnology and of scientific research that might find use as weapons.’ (34). While the prohibition is widely accepted by the 153 States Parties (35), the Convention has no effective verification procedure, a situation directly related to the duality of biological technology and knowledge.

Other existing arrangements address the public health and environmental risks posed by biological agents. For instance, the Cartagena Protocol on Biosafety to the Convention on Biological Diversity, which entered into force on 11 September 2003, requires the Party of export to notify the Party of import about the transboundary movement of a living modified organism that falls within the scope of the Protocol (Article 8). Likewise, research activities involving genetically modified organisms are subject to European Union directives (36, 37), which require Member States to establish a national authority that will ensure that risk assessments are done before the release of such organisms into the environment. These authorities will also receive notification of facilities that are newly involved in the contained use of genetically modified organisms and of research activities involving genetically modified organisms and pathogens. Likewise, the United States National Institutes of Health has established a tiered system for overseeing and reviewing research on recombinant DNA that they fund. These measures nevertheless focus on specific recombinant or genetic research and do not address the risk of misuse of life science R&D.

¹³ There are different views on this matter. Some argue that since the Biological and Toxin Weapons Convention does not mention the word ‘research’, it does not ban research for the production of agents and equipment for biological warfare. This view is challenged by persons who argue that misusing biology and life science R&D is prohibited by the Biological and Toxin Weapons Convention for the following reasons. First, doing research for biological warfare would go against the preamble of the Convention. Second, reinforcing previous declarations of review conferences, the fourth review conference declared that ‘The Conference, conscious of apprehensions arising from relevant scientific and technological developments, inter alia, in the fields of microbiology, biotechnology, molecular biology, genetic engineering, and any applications resulting from genome studies, and the possibilities of their use for purposes inconsistent with the objectives and the provisions of the Conventions, reaffirms that the undertaking given by the States Parties in Article I applies to all such developments’. Finally, since 1986, the States Parties to the Convention have been exchanging information in the form of confidence-building measures on areas of relevance to the Convention. One of the first measures to be taken was to exchange data on research centres and laboratories.

The Chemical Weapons Convention also prohibits the deliberate misuse of life science R&D. Toxins, whatever their origin or method of production, are covered by both conventions. In contrast to the Biological and Toxin Weapons Convention, the Chemical Weapons Convention mentions the word ‘research’ and states that ‘Industrial, agricultural, research, medical, pharmaceutical or other peaceful purposes’ are not prohibited (Article II.9(a)). Research is also mentioned in Articles V.14, X.2, XI.2(a) and (c) and in annexes. Technological advances are blurring the distinction between biological and chemical .

The risks associated with misuse of life science R&D could take various forms. Life science R&D involves a number of elements: some are tangible (i.e. bacteria, viruses, toxins, DNA sequences, publications, patents, blueprints), while others are intangible (the knowledge, techniques and expertise associated with publications and patents). Different measures and strategies may be required to deal with the tangible and intangible aspects of R&D. The first mechanisms for monitoring these risks were designed to monitor some of the tangible aspects, such as microorganisms and toxins, through legislation and regulations for the possession of and access to microorganisms and toxins. More recently, attention has been paid to measures that manage the less tangible aspects of the life sciences. While recognizing that some risks and benefits might be associated with the first set of measures, these are outside the scope of this working paper. In accordance with WHO resolutions and the research focus of this paper, we focus on the second set of measures.

Suggestions and initiatives for monitoring the risks posed by research activities that may be misused are organized below into two complementary areas of management: by research and its outputs (e.g. publications, patents, training) and by the responsibility of scientists carrying out life science R&D. These initiatives can be self-regulatory or be enforceable through legislation or regulation. The type of measures chosen can differ with the estimated risk posed by such R&D and their practicality.

5.1 Monitoring the risks by research

WHO has been active in this field since 1999, by overseeing research on variola virus. This system was not, however, originally created because of the potential misuse of variola virus research but rather as an outgrowth of WHO's involvement in eradicating smallpox. It is considered to be a temporary measure, pending destruction of the existing stocks of variola virus.¹⁴ Furthermore, variola is an example for which there may be few, if any, other analogous situations, and it is legally housed and handled in only two national facilities.

The WHO Advisory Committee on Variola Virus Research was established by the Fifty-Second WHA, which requested the Director-General, in resolution WHA52.10, 'to appoint a new group of experts which will establish what research, if any, must be carried out in order to reach global consensus on the timing for the destruction of existing variola virus stocks, and will:

- (a) advise WHO on all actions to be taken with respect to variola;
- (b) develop a research plan for priority work on the variola virus;
- (c) devise a mechanism for reporting research findings to the world health community;

¹⁴ While a new date for destruction date of smallpox virus stocks is to be set when research and outcomes allow, consensus on that issue might be difficult to reach. A consensus might be reached only after new, safe, effective vaccines and antiviral agents are developed and tested in suitable, adequate laboratory models. It has been argued that, as it might be possible technically to synthesize the smallpox viral genome from oligonucleotides, destruction of the existing strains might become irrelevant.

- (d) outline an inspection schedule to confirm the strict containment of existing stocks and to assure a safe and secure research environment for work on the variola virus, and make recommendations on these points;⁷

The Advisory Committee is composed of 18 members from all WHO regions and is advised by several academic scientific experts from such areas as public health,¹⁵ fundamental applied research and regulatory agencies (38, 39). It meets once a year in Geneva and publishes a yearly report on the meeting and on the research carried out in the two WHO collaborating centres that are allowed to retain variola virus.¹⁶ The Committee met for the first time in December 1999 and identified several priorities for research on variola virus, including the DNA sequence; diagnostic tests; antiviral drugs; hyperimmune globulin and neutralizing antibodies; vaccines; and animal models to facilitate evaluation of antiviral drugs, vaccines and diagnostic tests. They also discussed the monitoring of research. This international system has involved WHO in the monitoring of life science R&D and techniques related to smallpox.

The scientific community, research groups and the private sector have also made suggestions about the monitoring of research in the life sciences. These mirror some aspects of WHO's control of smallpox research.¹⁷ They propose a system to manage the risks of misusing life science R&D by identifying 'dangerous research and activities'¹⁸ or 'experiments of concern'¹⁹ which should be monitored. The monitoring would comprise a tiered peer-review system, whereby projects that are deemed dangerous would be peer-reviewed by scientists and public representatives. The Fink Committee of the United States National Academies of Sciences also recommended establishing a national science advisory board for biodefence, which would ensure continuing dialogue between the scientific and security communities and provide specific advice on research of concern and on the dissemination of life science research information (40). As a result, the United States Administration has decided to establish a national science advisory board for biosecurity, which will provide advice to United States federal departments and agencies

¹⁵ The Advisory Committee is different from the Ad Hoc Committee on orthopoxvirus infections, which is responsible for the post-eradication era vaccination policy and was established in accordance with WHA33.4 (14 May 1980). It is also in charge of smallpox vaccine stockpiles.

¹⁶ The latest report is WHO Advisory Committee on Variola Virus Research. *Report of the sixth meeting*. Geneva, World Health Organization, Department of Communicable Disease Surveillance and Response, 4–5 November 2004.

¹⁷ See for instance the Center for International and Security Studies at Maryland project on *Controlling dangerous pathogens* (http://www.cissm.umd.edu/documents/Pathogens%20project%20monograph_092203.pdf, accessed June 1, 2005); the International Institute for Strategic Studies – US (IISS-US) and The Chemical and Biological Arms Control Institute (CBACI) projected charter International Council for the life sciences industries; US National Academies, National Research Council, Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology. *Biotechnology research in an age of terrorism*. Washington, DC, The National Academies Press, 2004.

¹⁸ The Biological Research Security System (BRSS). See Steinbruner JD, Harris E. Controlling dangerous pathogens. *Issues in Science and Technology*, 2003, 19:48–54.

¹⁹ The Fink Committee identified seven classes of experiments deemed to be 'Experiments of Concern'. US National Academies, National Research Council, Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology. *Biotechnology research in an age of terrorism*. Washington, DC, The National Academies Press, 2004, 5–6.

that conduct or support life science research on ways to minimize the risks that legitimate knowledge and techniques will be misused to threaten public health and national security.²⁰ One of the difficulties associated with this type of mechanism is identifying what constitutes dangerous research. Other issues such as the appropriate level of reporting and the evaluation of experiments (i.e. at the individual level or in their wider context) might also arise.

The suggestions differ in the way in which the measures might be enforced. While some have suggested voluntary self-governance,²¹ others have proposed a regulatory-based approach.²² Nevertheless, both emphasize the need for some form of international monitoring system, both in order for national measures to be effective and to minimize the risk of unilateral measures that might hinder biomedical research in other countries.

The private sector, which is important in biotechnology and the life sciences, has also been active in this respect. It suggested for instance that a global organization, the International Council for the Life Sciences Industries, regrouping biotechnology firms, large pharmaceutical companies and other sectors be established.²³ This organization would first provide a mechanism for promoting contributions from the private sector to life science R&D and society in a responsible, sound, ethical manner. Second, it would provide a platform for the various sectors involved in life science R&D. A charter has been drafted to define the principles and mission of this council.

With regard to the products of life science R&D, such as publications and patent applications, the editors of several journals, including *Nature*, *New England Journal of Medicine* and *Science*, have agreed on a statement on scientific publication and security (41). The statement mentions that, while independent verification is important for biomedical research and biodefence systems, they recognize that bioterrorism raises concern for potential abuse of published information. It continues by stating that editors will deal 'responsibly and effectively' with papers that raise 'safety and security issues' and that 'on occasions an editor may conclude that the potential harm of publication outweighs the potential societal benefits. Under such circumstances, the paper should be modified, or not be published'. The American Society of Microbiology, the publisher of 11 peer-reviewed journals in the microbiological sciences, has adopted policies and procedures to address the potential risks associated with misuse of the results of research articles. Such policies concern manuscripts dealing with select agents.²⁴ They reported that 'In 2002, of the 13 929 manuscripts submitted to ASM [American Society of Microbiology] journals, 313 select agents manuscripts received special screening, and of these two manuscripts received additional screening by the full ... publication board. The

²⁰ For more information, see <http://www.biosecurityboard.gov>, accessed June 1, 2005.

²¹ See footnote 19.

²² See footnote 18.

²³ The Chemical and Biological Arms Control Institute (CBACI) and the International Institute for Strategic Studies-US (IISS-US) initiative for an International Council for the Life Sciences Industries (<http://www.iiss.org/newsite/showdocument.php?docID=561>, accessed June 1, 2005)

²⁴ See Department of Health and Human Services, 42 CFR Part 73, Office of Inspector General 42 CFR Part 1003, RIN 0920-AA08, Possession, Use, and Transfer of Select Agents and Toxins. *Federal Register*, Friday, 13 December 2002, 240.

statistics through July 2003 are 8557 manuscripts submitted, 262 select agent manuscripts screened, and none referred to the publication board for further review.’ (42).²⁵

This reaction is one of self-governance but also one of self-policing. Editors who censor scientific ideas and discoveries on the basis of their potential misuse might be seen as being responsible, but this might prove to be difficult. Censoring manuscripts is especially difficult in the absence of agreed guidelines for deciding what is dangerous to publish. In contrast, a recent report from the United States National Academies of Sciences, on the release of genome data in the public domain, ‘concludes that current policies that allow scientists and the public unrestricted access to genome data on microbial pathogens should not be changed.’ (43). It argues that ‘security against bioterrorism is better served by policies that facilitate, not limit, the free flow of this information.’ (44). While the Committee recognized that data on all organisms raise some concern, it recommended that ‘Rapid, unrestricted public access to primary genome sequence data, annotations of genome data, genome databases, and Internet-based tools for genome analysis should be encouraged.’ (45).

5.2 Monitoring the risks as a responsibility of individuals and scientists

Governing life science research clearly has an ethical dimension. One of the central ethical challenges lies in weighing the potential benefits of such research against the risk for abuse. This involves both technical issues (How likely are particular results to occur?) and moral issues (How should such results be evaluated, in terms of their benefit or harm to society?). As the results of such considerations depend on a society’s willingness to take certain risks under given circumstances, the decision should not be left to individual researchers but may be best addressed by a competent public body. Unlike physicians,²⁶ who have to make moral choices about the treatment of their patients and who are usefully guided in their decision-making and weighing of conflicting professional obligations by a code of ethics, life science researchers are not expected to make moral choices about what constitutes an acceptable risk to society but rather to adhere to standards defined on the basis of collective judgement, such as by a broadly based professional organization or an appropriate public body. Such standards are formulated in a code of conduct (guiding acceptable behaviour) rather than a code of ethics (guiding moral decision-making).

Most initiatives have taken the form of codes of ethics or of conduct and principles of practices. The documents in which they appear can convey different messages and can have different aims, according to their audience (46, 47). Some might raise awareness about the potential misuse of life science R&D within the life science community. Others might increase the individual and collective responsibility of life science scientists, educate the global scientific community by highlighting the social and ethical

²⁵ See also American Society of Microbiology. Life sciences publishers take steps to address potential misuse of information by bioterrorists, 15 February 2003. (<http://www.asm.org/Media/index.asp?bid=15031>, accessed June 1, 2005)

²⁶ Many physicians take the Hippocratic Oath when they enter medical practice or, sometimes, other professional oath and pledges.

implications of conducting biological research and raising awareness about international legal norms that ban misuse. The purposes and functions of these codes vary in accordance with the extent to which they are voluntary or subject to some form of legal enforcement. Unlike in other professions (e.g. law and medicine), however, such codes might be difficult to enforce, as there is often no central body to sanction defaulting members by preventing them from working.

Nevertheless, several international codes have been drawn up or suggested. For instance, the World Medical Association ‘urge all who participate in biomedical research to consider the implications and possible applications of their work and to weigh carefully in the balance the pursuit of scientific knowledge with their ethical responsibilities to society.’ (48). The International Committee of the Red Cross launched the Biotechnology, Weapons and Humanity initiative to reduce the risk that the life sciences would be used to the detriment of humanity. In addition to an appeal to governments, industry, science and medical communities, the Committee has been working with scientists in the life sciences to adopt ‘professional and industrial codes of conduct aimed at preventing the abuse of biological agents.’ (49).

The scientific community continues to discuss the idea of codes, in anticipation of the Biological and Toxins Weapons Convention ‘New Process’ meetings in 2005. The Royal Society in the United Kingdom has suggested that scientific responsibility and ethics in research could be attained by the incorporation of a universal set of standards for research into international treaties and by increasing the awareness of researchers of such treaties and implicit codes of ethical conduct (50). The United States National Academies of Sciences have underlined the ethical issues related to the conduct of biological science; one task of the newly established US national science advisory board for biosecurity will be to formulate codes of conduct for scientists. In addition, in June 2004, the American Medical Association’s Council on Ethical and Judicial Affairs approved guidelines to prevent malevolent use of biomedical research. These are now part of their code of medical ethics (51).

Other measures to enhance individual responsibility have been suggested, including the concept of international criminalization and making individuals responsible and accountable for their involvement in the hostile exploitation of life sciences and biotechnology (52). It might also be useful to emphasize collective responsibility, however, as devolving responsibility to individuals in situations of uncertainty and disagreement has certain limitations (53). Individual researchers might be unable to foresee the potential ramifications of a specific research project. For instance, separate research results might be harmless when taken by themselves but when combined with results from other fields could yield products that might be misused.

It has been suggested that the risks of the misuse of life science R&D should be managed by more stringent measures that are enforced through regulations and legislation (54). For instance, it has been suggested that facilities and scientists working with certain pathogens, genetic material and toxic products from microorganisms be registered and licensed, that facilities be inspected and that information on the genomic sequences of certain pathogens be restricted. On the basis of a system of approved credentials, access

to certain fields of research might be restricted to licensed scientists. Some of these regulations are already in place in several countries.²⁷

Some of the measures and strategies that might be selected to manage and monitor the risks associated with misuse of life science R&D might themselves pose a risk to public health. Measures that are too intrusive or restrictive could be disastrous for the advancement of science and for public health. The risk for the public health community is that poorly designed controls would slow down the production of knowledge that is beneficial for human health. Likewise, the ‘over-regulation’ of companies and anti-infective research in general could stifle research and the opportunities for the developing countermeasures. Some might therefore have substantial short- and long-term consequences for public health: they might be expensive to implement and reduce the attractiveness of certain areas of medicine. Moreover, tightening control on life science R&D in areas deemed sensitive and the related dissemination of results (such as vetting publications, classifying research results, a ‘tiered’ system or controlling patents in the life sciences) might all affect the conduct of life science research.

Scientific research is rightly considered to be an accumulation of knowledge that involves stages of refutation and replication. Scientists are responsible for disseminating their results via a system based on peer-review and appraisal. As publishing the methods and results of scientific research is essential and critical for the advancement of science, restricting publications or part of publications might distort the fundamental mechanisms of disseminating scientific knowledge and endanger both the quality and the amount of research being done on public health issues. In the long term, it might affect the development of new health products. Likewise, restricting the advance of life science R&D might affect the development of new medical countermeasures.

The issues are therefore whether the current measures are adequate to manage and monitor the risks or whether new measures need to be taken. There might be a need to also consider whether rules and regulations have any realistic chance of success in this regard and whether new suggestions for risk management suggestions can be designed so as not to impair the beneficial aspects of useful R&D. A fine balance must therefore be struck between furthering the public health benefits of life science R&D and limiting its potential risks—a balance that allows the flowering of new techniques and knowledge and gives researchers useful guidance on how to manage the associated risks.

²⁷ Implementation of the Directive (2000/54/EC) of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work and of the European Council directive (90/219/EEC) of 23 April 1990 on contained use of genetically modified microorganisms requires countries of the European Union to notify to the competent authority information that includes the name and address of the premises and a description of the work to be undertaken. See for instance: Federal Republic of Germany. *Legislation in the Federal Republic of Germany related to security and oversight of pathogenic microorganisms and toxins*. Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction. Geneva, 28 July 2003, (BWC/MSP.2003/MX/WP.13) and Sweden. *Possible Measures for Ensuring Security and Oversight of Work with Microorganisms*. Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction. Geneva, 5 August 2003, (BWC/MSP.2003/MX/WP.15).

6. Conclusions and further considerations

Risk management and monitoring will have to take into account the fact that science is intrinsically dynamic. New scientific breakthroughs might require new measures to be taken and require that the measures be flexible enough to allow scientific and technological change. This suggests that any future action will need to be ‘dynamic’, or part of a process, rather than ‘static’.

A wide array of control measures has been suggested, with various labels, including ‘oversight’ mechanisms, self-governance, self-policing, self-censorship, best practices, codes of conduct and of ethics, measures for international criminalization, legislation and regulations. The differences imply nuances in regard to their enforcement. The issue of consistency among this wide array of control measures might also be considered.

The appropriateness and efficiency of risk management and monitoring measures may also be considered. The risks associated with deliberate misuse of life science R&D may be defined and its sources identified. An assessment might be made of whether these risks can be successfully managed and monitored, and there may be a need to identify who might be responsible for such an assessment and for communicating the results to the scientific community, policy-makers and the general public. Poorly designed measures will have public health implications, and it is prudent for the public health community, including WHO, to be aware of such measures. Member States might consider the risks and opportunities for WHO if it addresses such issues, for instance, whether its neutrality would be affected.²⁸

To conclude, in the light WHO’s current activities, its contribution to national and international discussion is to emphasize the public health perspective of the issues. Whatever the measures taken, WHO will safeguard the public health benefits of life science R&D and maintain the policy established by its Member States, which emphasizes that strengthening public health infrastructure and research for naturally occurring diseases is one of the most effective methods for preparing against deliberate epidemics (WHA55.16). WHO and other entities might therefore understand the impact of such measures on global public health preparedness and response. WHO Member States might be kept informed about the issues and awareness of relevant ethical issues might be raised by setting up a scientific committee or study group. That initiative would build on existing WHO activities and expertise and consolidate the stance it has taken on the issue so far.

²⁸ For the risks to WHO, see for instance Kaplan M. The efforts of WHO and Pugwash to eliminate chemical and biological weapons—a memoir. *Bulletin of the World Health Organization*, 1999, 77:151–152.

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