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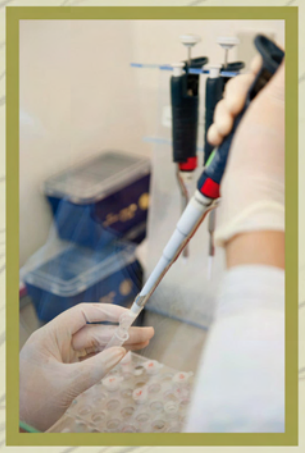

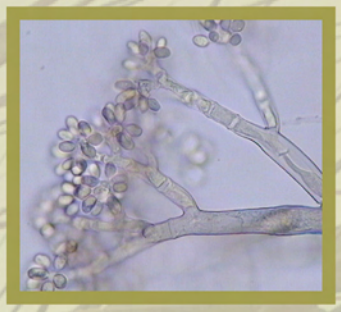

The Scientific Institute of Public Health, Belgian focal point for Biosafety

1990-2010: 20 years of risk assessment of GMOs and pathogens

Mission

Science at the service of Public Health, Food chain safety and Environment.

The Belgian Scientific Institute of Public Health (known as WIV-ISP) provides support for public health policy through scientific research, expert opinions and divisional tasks. On the basis of scientific research, WIV-ISP formulates recommendations and solutions in respect of priorities for a proactive health policy at the Belgian, European and international levels. WIV-ISP assesses the status of health and health indicators on the basis of scientific methods which it approves, develops and analyses within a certified quality framework. WIV-ISP develops advanced solutions for the diagnosis, prevention and treatment of current and emerging diseases, as well as the identification and prevention of health risks, including those resulting from the environment.

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FOREWORD

Twenty years after the implementation of the first European Directives on genetically modified organisms (GMOs), the Biosafety and Biotechnology Unit (SBB) of the Scientific Institute of Public Health (WIV-ISP) and the Biosafety Council have taken centre stage in Belgium. In close cooperation with the European Commission and based on a cooperation agreement, they offer scientific support at a federal, community and regional level as well as an international one. This unique combination proves that by cooperating with experts, testing common viewpoints and showing mutual respect, a central organisation can offer customised advice at all policy levels involved whilst ensuring that each level's own priorities are met.

The SBB was established by Dr. William Moens and developed from a one-person organisation in 1990 to a flourishing department with 11 scientists providing biosafety and GMO advice to members of the Biosafety Council and the environment administrations of the communities and regions. Over 20 years, the Biosafety Council, whose members include the most distinguished Belgian experts in a wide range of disciplines, has provided a wealth of scientific advice. This advice is used as the foundation for Belgium's biosafety policy and SBB training sessions and can be permanently consulted on the Biosafety Council and SBB websites.

In addition to providing expert advice, training and the secretariat for the Biosafety Council, the SBB, through its GMO Lab, also develops innovations in order to quickly identify GMOs. These new methods were recently implemented in Belgian routine laboratories and are now also being tested as a possible standard method by the community reference lab of the Institute for Health and Consumer Protection (JRC) of the European Union. This newly developed expertise also resulted in a new initiative: the establishment of a "Biotechnology and Molecular Biology" platform that will work with the Direction "Communicable Diseases" of the WIV-ISP to further develop, validate and implement molecular methods to quickly detect new risks with regard to either GMOs or new pathogenic agents threatening public health and food safety.

This book offers a number of ideas on how we can prepare ourselves to quickly and proactively identify and approach existing and new risks in this fast-evolving field by cooperating at a national and international level.
I would therefore like to thank all employees - those who have been with us since the very beginning and those who have dedicated themselves to this specific subject - for their achievements and their efforts to approach these problems even more efficiently and more innovatively in the future.

Dr Johan E. Peeters
General Director

INTRODUCTION

1990	2010
The European Union publishes the first legislation dedicated specifically to the use of genetically modified organisms (GMOs) and to the protection of workers from risks related to exposure to pathogenic organisms.	The European Commission presents the results of a general assessment of the European regulatory framework on GMOs; the international community is intensifying its actions in response to the emergence of new pathogens and the possible use of pathogenic organisms, whether genetically modified or not, for the purposes of bioterrorism.

1990 - 2010

Between these two dates, 20 years of development of the European regulatory framework, 20 years of adapting personal and collective protective measures for handling GMOs or pathogenic organisms, 20 years of research and development in the field of modern biotechnology, 20 years of GMO marketing and continued growth of areas where transgenic plants are cultivated across the world, 20 years of controversy on the potential health and environmental risks of certain GMOs, 20 years of questions about the social, economic and ethical consequences of certain applications of genetic engineering, 20 years of major changes in the field of biotechnological innovations and their acceptability.

1990 - 2010

20 years of biosafety in Belgium, that is to say, the assessment of risks to human health and the environment linked to the use of genetically modified organisms or pathogenic organisms.

On this twentieth anniversary, the Scientific Institute of Public Health (WIV-ISP) wanted to mark the occasion by publishing this book, a review of the major events of the past twenty years of biosafety in Belgium. It would be impossible to make this book an exhaustive work tackling the multiple facets of biosafety. The WIV-ISP has therefore chosen to look at these twenty years in a particular light, that of its Biosafety and Biotechnology Unit (SBB). It is therefore a oriented perspective but an expert perspective nonetheless. As we will see throughout this book, for twenty years, the SBB has played a key role in the Belgian contribution to the implementation of biosafety.

To begin this book, it appeared useful to describe, through some key events, the different historical stages that have led biosafety to become an entirely distinct discipline. In Chapter 1, we will take you up to the time of Louis Pasteur and the first specific actions in response to the potential risk posed by the exposure to pathogenic micro-organisms. We will see how the notion of biological risk has been defined and classified. In parallel, we will explain how the use of recombinant DNA techniques and the rapid explosion of their applications has also led to an awareness of potential risks associated with this technology. From the Asilomar Conference to the OECD Blue Book, going through the American guidelines, we will see how internationally accepted methodology and principles were adopted in relation to the assessment of biological risks. This journey through time will end in 1990 with a detailed description of the origin and contents of the first European legislation in the field of biosafety.

These legislations form the basis of the implementation of biosafety in Belgium. We will see in Chapter 2 how, in a complex institutional context, Belgium has chosen to set up a biosafety regulatory framework harmonised between the Federal State and the three Regions and consistent on the scientific viewpoint, in which all living organisms (pathogenic and/or genetically modified) which pose a risk to human health and the environment are taken into account. This framework relies on a biological risk assessment system common to the Federal State and to the Regions and is composed of two bodies: The Biosafety Advisory Council (BAC) and the Biosafety and Biotechnology Unit (SBB) of the WIV-ISP.

It is through its ongoing role as centre of expertise that, since the beginning of the 1990s, the SBB has been associated with risk assessment of GMO and pathogens. In Chapters 3 and 4, we will describe the different facets of this expertise work, through detailed facts and figures, firstly in relation to the use of GMOs and pathogens in a confined environment, and secondly, in relation to the dissemination into the environment and the marketing of GMOs.

While the SBB occupies a privileged place in the Belgian biosafety landscape, we will also see that it has become, over the years, a significant and recognised partner on the European and international stage. Chapter 5 will take us on a round-the-world tour which will illustrate the key role played by the SBB in the scientific representation of Belgium at a European and international level in the field of biosafety.

Informing and interacting with various target publics form an integral part of the role of a public service institution such as the WIV-ISP. In Chapter 6, we will therefore review the main communication and information activities to which the SBB has contributed in order to meet the needs of the public and various stakeholders.

We have also chosen to call in this book on different witnesses who have been involved, or who are still involved, in various ways in the field of biosafety in Belgium. We wanted to give these individuals the opportunity to contribute, both in order to illustrate in an anecdotal or descriptive way specific moments in the history of biosafety in our country, and also to show how the expertise within the SBB has grown thanks to the permanent interaction and collaboration with partners from various fields, whether biosafety professionals, notifiers, representatives from academia, representatives from the authorities or members of various associations.

This book therefore primarily aims to provide an account thorough evidence and recollections. It retraces the story of 20 years of biosafety in Belgium in its evolutionary context, showing how the implementation of a centralised system for the risk assessment of GMO and pathogens has enabled Belgium to develop highly valued, internationally recognised, scientific expertise in this area.
For us, as scientists at the SBB, this multidisciplinary expertise, organised so as to allow confrontation of opinions, based on solid data, open to other scientific disciplines, and as transparent as possible, should form the basis of political and public debate on the use of GMOs and pathogens.
However, this expertise process also sits within a continuously evolving environment. In addition, we wanted therefore to conclude this book with some prospective thoughts about what could be the future methodology and substance of the scientific assessment of biological risks.

We hope that you will enjoy flicking through this book and that you will make a date in 2030, for the next 20 years of history of biosafety in Belgium.

SBB team in 2010.
From left to right: Caroline Van Droogenbroeck, Amaya Leunda, Katia Pauwels, Marie Sciacqua, Adinda De Schrijver, Bart Brosius, Didier Breyer, Bernadette Van Vaerenbergh, Céline Verheust, Chuong Dai Do Thi, Philippe Herman et Martine Goossens.

CHAPTER 1
FROM LOUIS PASTEUR TO GMO REGULATIONS

"Biosafety": this is a term to which it is difficult, if not impossible, to assign a generic or internationally accepted definition. Indeed, it has several accepted versions depending on the discipline using it (veterinary, food, medical or environmental), its linguistic origin or even the country in which it is being used.
However, since biosafety is the focus of this book, we will start by giving the definition adopted in Belgium. Biosafety is defined there as "s*afety for human health and the environment, including the protection of biodiversity, during the use of genetically modified organisms or micro-organisms, and during the contained use of pathogenic organisms for humans*"[1].Biosafety therefore makes reference to safety for human health and the environment, genetically modified organisms (or micro-organisms) and pathogenic organisms[2]. These are the many clues that will allow us to explore the origins and first developments in this discipline, through this first chapter.

The exact moment of origin of biosafety cannot be clearly identified. This discipline has taken shape through different periods in recent history and through different fields (microbiology, molecular biology, veterinary science, guidelines relating to safety, etc). Based, on the one hand, on the history of life sciences and, on the other hand, on the Belgian definition of biosafety mentioned above, the first steps to this discipline were at the time of Pasteur and Koch (around 1890). It was indeed at that time that it appeared necessary to put in place some safety measures in response to the potential risk linked to the exposure to pathogenic micro-organisms. The first infectious diseases acquired in a laboratory were reported at that time. It was another few decades before the notion of a human health risk linked to the handling of pathogenic micro-organisms was clearly defined. Pioneers in the subject such as Sulkin and Pike[3] or Collins[4] actively contributed to the implementation of protective measures against biological risks following meticulous investigations carried out in microbiology laboratories.

The first safety measures in laboratories where pathogenic micro-organisms were handled were firstly implemented in North America and the United Kingdom at the beginning of the 1970s. They included working practices, personnel protection measures and physical containment measures aimed at limiting the spread of biological agents. Safety measures later applied in laboratories handling genetically modified organisms and micro-organisms (GMMs and GMOs) were largely inspired by these guidelines established in microbiology.

[1] Source: The cooperation agreement of 25 April 1997 between the Federal State and the Regions relating to administrative and scientific coordination in terms of biosafety.
[2] A pathogenic organism is a biological agent that can cause disease in immunocompetent humans and poses a risk for individuals directly exposed to it. The risk associated with a pathogenic organism is dependent on the significance of the disease or severity of the infection that it may cause, its infective potential, its host specificity, its biological stability, the availability and efficacy of prophylactic or therapeutic treatment or even its potential to survive and disseminate into the community or environment.
[3] Sulkin SE, Pike RM. Viral Infections Contracted in the Laboratory. New Engl J Med 1949;241(5):205-213 et Sulkin SE, Pike RM. Survey of laboratory-acquired infections. Am J Public Health 1951;41(7):769-781.
[4] Collins CH, Grange JM. The Microbiological Hazards of Occupations. Leeds: Science Reviews. 1990.

We note that in the beginning, biosafety was considered as a sub-discipline of personnel safety (linked to legislation aimed at protecting workers against different types of risks such as chemical or radioactive). However, biological hazard is distinct from other sources of hazard (chemical, radioactive) by the fact that micro-organisms can multiply *in vivo* (in a host organism) as well as *in vitro* (in liquid or solid medium).

'Biosafety is based on scientific roots but it is not a science in itself'

In Belgium, it was not until the 1980s that biosafety became an entirely separate discipline. The major event behind this development was the adoption at a European level of two Directives regulating the use of GMMs and GMOs. We will see throughout this book how experts at the Scientific Institute of Public Health (WIV-ISP, Brussels), brought together within the Biosafety and Biotechnology Unit (SBB), participated in the setting up and then implementation of biological risk assessment methodology and the first biosafety measures.

Before tackling the background to the Directives mentioned above, we should look back at two parallel developments. Firstly, the implementation of an internationally recognised biological risk classification system and secondly, consequences from the Gordon conference and two Asilomar conferences.

BIOLOGICAL RISK CLASSIFICATION

Originally, analysis of diseases acquired in the laboratory showed that certain pathogens were responsible for infectious diseases that were more severe than others. These observations led to a classification system for pathogenic micro-organisms. From 1969, the Public Health Service in the United States worked on the definition of four risk groups for pathogenic micro-organisms for humans. The work lasted for five years and the classification criteria were adopted in 1974[5].
At the same time as the American classification proposal, in 1979 the World Health Organisation (WHO) set up a working group on good microbiological practices. The work of this group led to the publication of a manual suggesting measures aimed at the protection of workers, the population, animal breeding and the environment[6].
As in the United States, the WHO adopted a classification system for pathogenic micro-organisms consisting of four risk groups. The work of the WHO would afterwards serve as a basis for a large number of national reference documents.
Thus, in Great Britain four "Hazard Groups" were also adopted in 1984[7], after a tentative trial of three categories (A, B and C) between 1975 and 1978 which was not finally implemented.

[5] CDC (Centers for Disease Control). 1974. Classification of Etiologic Agents on the Basis of Hazard, 4th Ed. U.S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control, Office of Biosafety, Atlanta, GA.
[6] World Health Organisation. Biological Safety Manual, 1st edition, Geneva, Switzerland: WHO, 1984.
[7] ACDP: Advisory Committee on Dangerous Pathogens. 1984. Categorization of biological agents on the basis of hazard and categories of containment. Health and Safety Executive.

Definition of risk groups for pathogenic (micro-)organisms for humans

- Risk group 1: (micro-)organisms recognised as non-pathogenic to humans or presenting a negligible risk to humans on a laboratory scale. Besides organisms whose harmlessness has been proven, this group therefore includes strains potentially causing allergies and opportunistic pathogens.
- Risk group 2: (micro-)organisms that can cause disease in humans and can pose a danger for individuals directly exposed to them; they are unlikely to spread to the community. There is usually effective prophylaxis or treatment available.
- Risk group 3: (micro-)organisms that can cause serious disease in humans and present a danger to individuals directly exposed to them. They may present a risk of spreading to the community. There is usually effective prophylaxis or treatment available.
- Risk group 4: (micro-)organisms that can cause serious diseases in humans and constitute a serious danger to individuals directly exposed to them. They may present a high risk of spreading to the community. There is usually no effective prophylaxis or treatment available.

(Source: Regional Orders on the contained use of GMOs and/or pathogens; these definitions are largely based on definitions adopted at an international level, particularly by the WHO)

In Europe, Directive 90/679/EEC[8] on the protection of workers against biological risk was adopted in 1990. It contains a non-exhaustive list pathogenic micro-organisms for humans, also distributed into four risk groups.
Belgium drew on all of this work in order to adopt three lists assigning risk categories to several hundreds of micro-organisms pathogenic to humans, animals and plants (bacteria, fungi, parasites, viruses, including prion proteins linked to transmissible spongiform encephalopathies) in 1993. We will return to the implementation and updating of these lists in Chapters 2 and 3, which still today constitute an internationally recognised reference source.

The setting up of risk categories (or risk groups) of pathogenic organisms led, at the same time, to the implementation of good practices and containment measures aimed at ensuring individual and collective safety. As was done for organisms, four levels of containment were thus also defined to which increasingly strict safety measures were associated. These four levels were adopted on an international level, though not necessarily with unanimous classification and containment criteria.

The different constitutive elements of what would be later known by the term "biosafety" were in place: risk classification of organisms on the one side and containment levels on the other. Between them, a key element would develop over time: the assessment of biological risks, which we will come back to later in this chapter.

[8] Council Directive 90/679/EEC of 26 November 1990, on the protection of workers from risks related to exposure to biological agents at work. OJ L 374 of 31.12.1990, p.1. This Directive was repealed in 2000 and replaced by Directive 2000/54/EC.

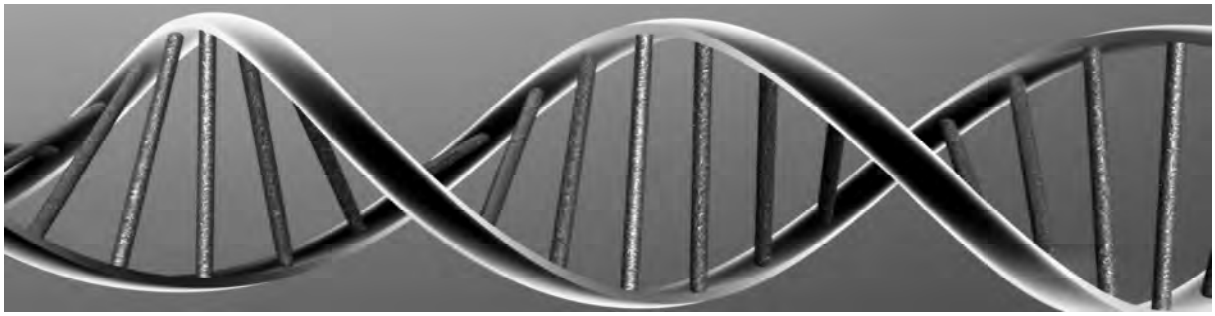

Working under
a Biosafety
cabinet,
it's easy to say!

RECOMBINANT DNA TECHNIQUES: A NEW FORM OF HIGH-RISK ACTIVITY

In parallel to the use of pathogenic micro-organisms in the laboratory, in 1970 we witnessed the emergence of a discipline which today has become inescapable: molecular biology. This discipline arose following a series of remarkable discoveries in fundamental research, beginning just before the middle of the last century when Avery established that deoxyribonucleic acid (or DNA) is the universal support of hereditary properties and contains the genetic information of living beings. This discovery was followed by the publication in 1953 of the work of Crick, Watson, Wilkins and Franklin identifying the double helix molecular structure of DNA[9], then in 1965 by the first description of restriction enzymes (by Linn and Arber), proteins capable of cutting DNA at specific sites.

The first laboratory applications of molecular biology were then able to begin. The techniques (also referred to by the term "genetic engineering") allow the insertion of a portion of DNA (containing one or more genes) into another DNA progressively refining it with the aim of precisely and efficiently modifying the genome and the hereditary characteristics of living organisms. The aim of researchers was sometimes fundamental (better understanding of the functioning of the genome) but numerous teams of scientists also aimed to generate organisms with new properties through the manipulation of DNA. This is how the first genetically modified organisms (GMOs) came into being, as well as the birth of so-called "modern" biotechnologies.

Rather rapidly, we witnessed an awareness of the potential risks associated with the use (still in its infancy) of these molecular biology techniques and products derived from them. The very first debates on genetic engineering took shape towards the end of the 1960s within the scientific community, particularly in North America. Is there not a risk that the combination of DNA sequences from different species, even unrelated (commonly known as "recombinant DNA"), will generate new types of pathogenic organisms? This questioning culminated in 1972 with the work of the team of Paul Berg. The American biochemist, one of the pioneers of



[9] Watson JD, Crick FHC. A structure for Deoxyribose Nucleic Acid. Nature 1953;171:737-738; Wilkins MHF, Stokes AR, Wilson HR. Molecular Structure of Deoxypentose Nucleic Acids. Nature 1953;171:738-740; Franklin R, Gosling RG. Molecular Configuration in Sodium Thymonucleate. Nature 1953;171:740-741.

recombinant DNA, successfully carried out the cloning of a fragment of the oncogenic SV40 virus in bacterial plasmid. However, his work led him, as well as some of his colleagues, to ask themselves about the risks with which researchers handling this type of DNA were being confronted (they were particularly concerned about possible health consequences of the deliberate or accidental transfer of SV40 tumoral genes into *Escherichia coli*, a bacteria commonly used in the laboratory but also naturally present in the human digestive system). These fears were reinforced by the use of these techniques by a growing number of researchers and by the fact that the scientists working at that time on recombinant DNA were largely biochemists, less respectful of or less accustomed to the application of safety measures than microbiologists.

'The Gordon Conference and the two Asilomar conferences: on key events for an initial collective awareness of hazards that could be presented by the use of recombinant DNA for researchers, the population and the environment.'

On Berg's initiative, North American scientists met in 1973, firstly at Asilomar then during the "Gordon Conference on Nucleic Acids". The scientific community committed itself to considering the potential risks linked to recombinant DNA techniques. Already at that time, the implementation of specific containment and personal protective measures was being considered. They were primarily to guarantee the safety of those exposed, essentially the scientists themselves, and to avoid any release into the environment. They were the first steps towards the concepts of "biosafety" and the assessment of risks associated here with activities involving recombinant DNA in the laboratory.

However, the major fallout of these first conferences was the appeal launched by Berg and some other scientists (including Watson) to the scientific community to impose a voluntary moratorium on experiments involving recombinant DNA until the holding of an international conference aimed at assessing the potential risks of this type of research[10]. Despite the protests of certain scientists (who wished to continue this type of experiment without restrictions), this appeal was upheld, at first only by North American researchers but then by some European and Japanese researchers.

The second Asilomar conference ("Asilomar Conference on Recombinant DNA Molecules"), organised by Berg, was held in February 1975. It brought together 150 scientists, but also some legal experts and journalists. The participants decided (non-unanimously) to lift the moratorium imposed one year earlier. They concluded, in particular, the necessity of managing research work involving recombinant DNA with strict guidelines[11] (see text box next page).

[10] Berg P, Baltimore D, Boyer HW, Cohen SN, Davis RW, Hogness DS, Nathans D, Roblin R, Watson JD, Weissman S, Zinder ND. Potential Biohazards of Recombinant DNA Molecules. Science 1974;185(4148):303.
[11] Berg P, Baltimore D, Brenner S, Roblin RO, Singer MF. Summary statement of the Asilomar Conference on recombinant DNA molecules. Proc Natl Acad Sci U S A. 1975;72(6):1981–1984.

Recombinant DNA: Key elements from the Gordon and Asilomar conferences

January 1973 – 1st Asilomar Conference: discussions on the potential hazard that the use of viruses in genetic engineering poses.
June 1973 – "Gordon Conference on Nucleic acids": discussion on the risks associated with recombinant DNA.
1974 - Setting up of the Committee on Recombinant DNA Molecules.
February 1975 – 2nd Asilomar Conference: the safety conditions of research involving recombinant DNA were discussed. Two basic principles were adopted:

- The containment to be adopted was to be integral to the design of the experiment;
- The containment should be adapted to the risk presented by the experiment.

Scientists established a classification of experiments involving recombinant DNA in order of increasing risk to human health and the environment. Four risk levels were identified: minimal, low, moderate and high risk. A series of increasingly drastic measures corresponded to these risk levels, designed to limit as far as possible the release of recombinant DNA organisms into the environment. Good laboratory practices as well as the training of workers comprised the basic measures for any handling of recombinant DNA. Physical containment measures to be put in place were described.
For any experiment, regardless of the level of risk, it was recommended to use biological containment barriers by choosing for example host cells and vectors that could not survive in normal environmental conditions. Certain experiments were simply forbidden: cloning of highly pathogenic micro-organism DNA or coding for toxins, large-scale experiments using recombinant DNA potentially harmful to humans, animals or plants.

In 1976, in reaction to the debates relating to recombinant DNA, Vittorio Sgaramella, head of the WHO microbiology safety measures programme, launched an appeal to the scientific community for this topic to be the subject of global action[12]. The underlying idea was to use safety measures successfully developed in microbiology for the containment of pathogenic organisms for recombinant DNA. A request to this effect was made by the WHO to the National Institutes of Health (NIH) in the United States.

In response to this request and particularly to the recommendations from the second Asilomar conference, in 1976 the NIH published the first guidelines specifically aimed at research activities involving recombinant DNA and the handling of GMMs in the laboratory[13]. These recommendations were revised in 1979 (with a relaxing of the safety conditions) following experience gained in the field and a better understanding of the actual risks.
The NIH guidelines represented the reference on which the majority of regulations regarding safety relating to the use of genetically modified organisms in the laboratory were subsequently developed.

[12] Sgaramella, Vittorio, World Health Organisation, letter addressed to Maxine Singer of the NIH (27/12/1976).
[13] National Institutes of Health, Donald S. Fredrickson: Guidelines for Research Involving Recombinant DNA Molecules. June 1976.

GMOs, FROM THE LABORATORY TO THE FIELD

With the development of recombinant DNA techniques and their adoption by a growing number of researchers across the world, potential applications of this technology also expanded. It rapidly became apparent that GMOs offered considerable possibilities in different applied fields such as medicine or the agro-food industry. The term "modern biotechnology" was used to distinguish applications arising from recombinant DNA techniques from those known as "traditional" that have been used within our societies, sometimes for centuries (see text box next page).

In the agro-food applications of modern biotechnology, Belgium played a pioneering role in terms of research and development. Indeed, at the end of the 1970s, the work by the team of Professors Marc Van Montagu and Jozef Schell at the University of Ghent made a significant contribution to the development of genetically modified plants. By exploiting the DNA transfer capacity of the bacterium *Agrobacterium tumefaciens* into certain plants, these researchers showed that it is possible to express "foreign" genes into a plant and its offspring[14,15]. This discovery paved the way for commercial exploitation of transgenic plants and the birth of numerous biotechnology companies (notably "Plant Genetic Systems" in Belgium).

This development also resulted in scientific products leaving the laboratory and coming into direct contact with the environment. As long as the genetic engineering developments were taking place in the laboratory, the assessment of potential risks focused on the impact to human health, essentially that of the laboratory staff. The deliberate release into the environment of genetically modified organisms (firstly for experimental purposes and then commercial) rapidly led to new questions about the way in which to assess and manage potential risks linked specifically to this type of application.

[14] Van Larebeke N, Genetello C, Schell J, Schilperoort RA, Hermans AK, Hernalsteens JP, Van Montagu M. Acquisition of tumor-inducing ability by non-oncogneic agrobacteria as a result of plasmid transfer. Nature 1975;255:742-743.
[15] De Block M, Herrera-Estrella L, Van Montagu M, Schell J, Zambryski P. Expression of foreign genes in regenerated plants and in their progeny. EMBO Journal 1984;3(8):1681-1689.

It was within this context that the Organisation for Economic Cooperation and Development (OECD) developed a series of scientific principles and recommendations specifically aimed at the assessment and management of risks linked to applications of recombinant DNA techniques in the environment.

Biotechnology

Biotechnology is defined by the Organisation for Economic Cooperation and Development (OECD) as "the application of scientific and engineering principles to alter materials by biological agents for the production of goods and services"[16]. This definition includes plants, animals and micro-organisms. Biotechnologies or "bioconversion technologies" are therefore the result of a combination of life sciences and new techniques from other disciplines such as biochemistry, biophysics, molecular biology or computer science. Classical or traditional biotechnologies are those used in the production of, for example, beer, wine or cheese. The more recent biotechnologies (also known as "modern biotechnology") are essentially based on genetic engineering.
Different categories of biotechnologies have been defined according to their objective and use. In Europe, these different categories have been assigned colour codes: green, red, white, yellow and blue. Throughout the rest of the world, the labels remain more explicit: "healthcare biotech, agrifood biotech, industrial biotech" etc.
Green biotechnology applies to the agro-food sector. For example, its aim is to develop plants with specific agronomical properties, plants or plant-derived products for food use, or plants producing biomaterials or energy.
Red biotechnology applies to the health sector. It generally exploits the synthetic abilities of micro-organisms or animal or vegetable cells for the large-scale production of medicinal products for human use (growth factors, interleukins, hormones, vaccines, etc.).
White biotechnology corresponds to industrial applications. Biological systems are used as alternatives to classical chemical processes, for example in the synthesis of polymers, fuels, solvents and textile products.
Yellow biotechnology includes technologies connected with the protection of the environment and the treatment or elimination of pollutants.
Finally, blue biotechnology is aimed at developing products connected with marine biodiversity, parapharmacy or even aquaculture.
It is useful to highlight that biotechnology is not static: developers exploit new knowledge at the molecular level or in the field of actual technologies (for example, nanotechnologies). As we will see later, the constant development of these applied techniques of modern biotechnology poses a very real problem for adapting biosafety legislation; the legislation generally evolves more slowly than the technology.

[16] Source: Organisation for Economic Co-operation and Development. A Framework for Biotechnology Statistics, OECD, Paris; 2005.

OECD ACTIVITIES

From 1982, the OECD published a first report dedicated to biotechnology[17]. It was the first intergovernmental document on the topic that took into account the environmental safety of GMOs and placed emphasis on the necessity of developing safety measures relating to new biotechnologies. Following recommendations from this report, in 1986 the OECD published a new report entitled: "Recombinant DNA Safety Considerations", later known as the "Blue Book"[18] (see text box). This work was carried out by an *ad hoc* group of governmental experts on biotechnology safety and regulations. Among the representatives of the Belgian delegation in this *ad hoc* group was an expert from the Scientific Institute of Public Health (known at the time as the "Institute of Hygiene and Epidemiology").

The OECD "Blue Book"

The recommendations from the OECD were mainly aimed at securing the commercial development of recombinant DNA technologies while ensuring the safety of the environment and human health. They pushed for the harmonisation of guidelines adopted by the Member Countries of the OECD by encouraging sharing of information on risk analysis and management linked to GMOs (the exact term used in the "Blue Book" was "recombinant DNA organisms"). The aim of the OECD was that the national regulations did not hinder technical progress in the field of recombinant DNA and ensured the protection of intellectual property and industrial secrecy. The importance of clearly informing the general public about the different aspects of biotechnology was also highlighted.
Recommendations from the "Blue Book" were firstly about large-scale industrial applications of recombinant DNA techniques and secondly about agricultural and environmental applications. More particularly in this domain, the OECD considered setting up general guidelines at an international level was premature. Nevertheless, the "Blue Book" insisted on the necessity of carrying out an assessment of potential risks prior to using GMOs in the environment. It also introduced two ideas that still cannot be ignored today within the methodology of GMO risk assessment: firstly, the fact that risk assessment should be done on a case by case basis; secondly, that the development of GMOs and their assessment should be done in stages, going from the laboratory to the greenhouse then to isolated trials and finally to large-scale trials.

The "Blue Book" contained new recommendations relating to the application of recombinant DNA technology and the use of organisms arising from this technology in industry, agriculture and the environment. The emphasis was placed on the assessment of biological risks. The content of this "Blue Book" was partly based on experience acquired in certain Member Countries of the OECD in terms of the use of GMOs. At the time when the "Blue Book" was published, real applications such as genetically modified bacteria producing insulin (for the treatment of diabetes) or the human growth hormone were, in fact, already approved for marketing. At the same time, genetically modified plants and the debate on their potential effects on the environment entered into the political arena. It is worth remembering that the first field trial was carried out in Belgium in 1986. The first marketing authorisation for a GMO agro-food was granted in 1992 in the United States (for the transgenic tomato *Flvr Svr*).

[17] Bull AT, Holt G, Lilly MD. Biotechnology: International trends and perspectives. Organisation for Economic Co-operation and Development (OECD), Development Centre, Paris, France; 1982. ISBN 92-64-22362-2.
[18] Recombinant DNA Safety Considerations: Safety considerations relating to the use of organisms obtained through DNA recombination techniques in industry, agriculture and the environment. Organisation for Economic Co-operation and Development (OECD); 1986. ISBN 92-64-22857-8.

Like the guidelines from the NIH on the use of GMOs in the laboratory, the recommendations from the OECD "Blue Book" serve as a reference, at an international level, for the risk assessment of GMOs released into the environment.
This work was supplemented in the years that followed by other reports aimed at taking into account new developments in the use of GMOs in industry, in the environment and in food[19,20,21].

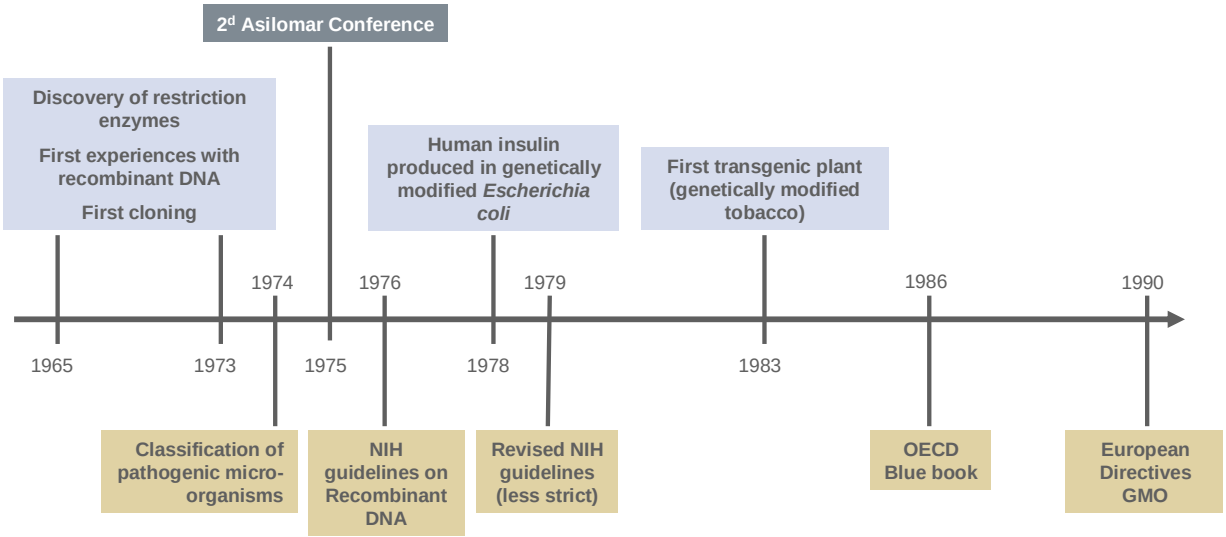


Figure 1.1 | *Significant historical elements of the development of regulations relating to GMOs*

At the time, in industrialised countries, the safety of modern biotechnology products was covered by a vast array of general legislative provisions in the fields of health, safety or even environmental protection. In addition to these various legal provisions, certain countries also had guidelines or recommendations treating, more specifically, the applications of recombinant DNA. The general tendency in developed countries was clearly to favour self-assessment and not to implement strict regulatory measures that could hinder technological development in this area. In its "Blue Book", the OECD recognised that "*there is no scientific basis for specific legislation to regulate the use of recombinant DNA organisms"*.

[19] Safety Considerations for Biotechnology. Organisation for Economic Co-operation and Development (OECD); 1992. ISBN 92-64-23641-7.
[20] Safety considerations relating to biotechnology: Scale-up of crop plants. Organisation for Economic Co-operation and Development (OECD); 1993. ISBN 92-64-24044-6.
[21] Safety Evaluation of Foods Derived by Modern Biotechnology: Concepts and principles. Organisation for Economic Co-operation and Development (OECD); 1993. ISBN 92-64-23859-6.

It was therefore going against this general trend that the Member States of the European Union began a negotiation process at the end of the 1980s, which ended with the adoption of directives specifically regulating the use of genetically modified organisms in 1990.

EUROPEAN DIRECTIVES RELATING TO GMOS

From the mid-1970s, as guidelines were being adopted by the NIH in the United States, several European countries (France, Germany, United Kingdom, Denmark) had already adopted measures aimed at ensuring the safety of laboratory activities involving recombinant DNA. These measures were the subject of an initial harmonisation at a European level in 1982[22], then in 1984[23] through texts inviting Member States to notify and register activities involving recombinant DNA in order to enable the potential enforcement of protective measures.

The necessity of implementing at a European level a specific legally binding regulatory framework for GMOs was essential in 1985 due to the aim of the European Union being to achieve a single market (an objective that was reached in 1993)[24]. The lack of harmonisation of national regulations on the use of GMOs, or even the absence of regulations in certain Member States, was detrimental to the achievement of the internal market. The European Commission therefore had to push for a coherent regulatory approach within the Union with two major objectives: protecting health and the environment, while guaranteeing the free circulation within the European Union of products originating from genetic engineering. In 1986, the Commission announced, in a European Council communication, its intention to prepare proposals for biotechnology regulations[25].

The Commission thus endeavoured to establish Directives[26] that would meet the challenges brought about by the development of recombinant DNA technologies:

- reconcile scientific and technical progress and safety;
- give fundamental and applied research the means for development and give industry the means to market useful products arising from this research, without hindering their efforts with paralysing bureaucratic controls.

[22] Council Recommendation 82/472/EEC of 30 June 1982 concerning the registration of work involving recombinant deoxyribonucleic acid (DNA). OJ L 213 of 21.07.1982, p. 15.
[23] Council of Europe Recommendation R(84)16 concerning notification of work involving recombinant deoxyribonucleic acid.
[24] We recall that at that time, between 01/01/1986 and 31/12/1994, the European Union (which was then called the European Economic Community) comprised twelve Member States: Germany, Belgium, Denmark, Spain, France, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal and the United Kingdom.
[25] European Commission. *Communication from the Commission to the Council, A Community Framework for the Regulation of Biotechnology* Com 86(573) final. Brussels: CEC, 4 November 1986.
[26] The European Directive is a juridical act that defines the objectives to be met by the Member States, to which it delegates the choice of methods. Once the Directive is adopted at a European level, it must be transposed into national law of each Member State, within fixed timeframes. The Directive is used to harmonise national legislations, particularly for a single market.

After two years of internal work supervised by the European Commission Directorate General XI (Environment, Nuclear Safety and Civil Protection), a first proposal of the text was submitted to the Member States[27]. After long discussions, the European Union finally set up two "GMO Directives" on 23 April 1990, *Directive 90/219/EEC* on the contained use of genetically modified micro-organisms[28] and *Directive 90/220/EEC* on the deliberate release of genetically modified organisms into the environment[29].

Straight away, we see that the European Commission and the Member States chose to maintain the distinction that had emerged over time between the use of GMOs in a contained environment on the one hand (laboratories, greenhouses, animal houses, large-scale production installations) and, on the other hand, their deliberate release into the environment (for the purposes of research or commercialisation). This distinction was based particularly on the differences existing between these two major categories of applications in terms of the nature of the risks and the protective measures to be implemented. It also reflected the stepwise approach of the development of GMOs. It was finally justified by the selection of a different legal approach for the two Directives.

Indeed, Directive 90/219/EEC was adopted on the basis of Article 130 S of the European Maastricht Treaty, i.e. with reference to the legal basis governing the European environmental policy. One of the features of this legal basis is that it enabled Member States who so wished to apply enhanced protective measures (as long as they were compatible with those set out in the Treaty), in accordance with Article 130 T of this same Treaty [30]. In the case of contained use, minimal harmonisation was therefore set at a Community level and Member States were able to apply stricter health and environmental protection regulations if they so wished.

Directive 90/220/EEC was adopted on the basis of Article 100 A of the Maastricht Treaty. This legal basis is specifically aimed at harmonising legislative, regulatory and administrative measures of the Member States (among which are product standards). On this basis, the European regulatory provisions strictly apply and

[27] Proposal for a Council Directive on the contained use of genetically modified microorganisms. Proposal for a Council Directive on the deliberate release to the environment of genetically modified organisms. COM (88) 160 final - SYN 131, 4 May 1988.
[28] OJ L 117 of 08.05.1990, p. 1.
[29] OJ L 117 of 08.05.1990, p.15.
[30] Maastricht Treaty, Article 130T: "The protective measures adopted pursuant to Article 130s shall not prevent any Member State from maintaining or introducing more stringent protective measures. Such measures must be compatible with this Treaty. They shall be notified to the Commission."

national governments cannot amend the contents of these provisions. Legislation in terms of the release of GMOs into the environment therefore has the primary objective of avoiding differences between the various national measures potentially generating competition. Harmonisation measures were aimed at establishing and ensuring successful running of the internal market, while ensuring a high level of environmental protection.

Another major feature distinguishes the two Directives: their fields of application. Whereas Directive 90/220/EEC applies to all GMOs (micro-organisms, plants and animals), Directive 90/219/EEC only covers genetically modified micro-organisms (i.e. bacteria, fungi, parasites and viruses). This limitation of the field of application of the "contained use" Directive (which did not appear in the initial proposal from the Commission) was contested by several Member States (including Belgium) during negotiations. It was nevertheless finally decided by the Commission to allow the adoption of the Directive, knowing that the Member States who so wished could, taking account of the flexible legal basis mentioned above, extend the field of the application to GMOs within the framework of the transposition into national law (which is what the majority chose to do). It was also expected that the Commission would make an additional legislative proposal covering the contained use of GMOs but this proposal never came.

The two Directives provided a notification and authorisation system for operations involving GMMs or GMOs. They were procedure Directives. Their main objective was the preventive management of risks (aimed at the protection of human health and the environment). The Directives were based on the general principle that risks from any contained use or deliberate release of GMOs should be assessed on a case by case basis before an activity could be authorised. Furthermore, considering that European environmental regulation is based on the precautionary principle and in the case of scientific doubt, there was reason to adopt preventive measures against damage by taking into account the worst case scenario and therefore the highest risk. We note that the Directives were qualitative in scope. Indeed, no limit value or quantitative threshold is mentioned.
The Directives also foresee the designation of specially competent authorities by the Member States to implement their provisions and to communicate with the public. It is also worth mentioning that these Directives did not apply to the transport of GMMs or GMOs.

The definition of a GMM/GMO in European legislation

One of the key provisions of the Directives was the definition of a "genetically modified organism", which was defined as follows: "*An organism, with the exception of humans, of which the genetic material has been altered in a way that does not occur naturally by reproduction and/or natural recombination"* (Article 2 of Directive 90/220/EEC). Directive 90/219/EEC gives a similar definition for the term "genetically modified micro-organism". The manner in which the genetic material is modified to result in a GMM/GMO is specified in an Annex to the Directives via three lists of techniques (see text box next page).

Genetic modification techniques

Directives 90/219/EEC and 90/220/EEC distinguished 3 categories of techniques in relation to the GMM/GMO definition.

1) Genetic modification techniques giving GMMs/GMOs covered by the Directives (non-exhaustive list):

- Recombinant deoxyribonucleic acid (DNA) techniques using vector systems (*this wording was specified during the revision of the Directives at the end of the 1990s, nucleic acid recombination techniques being defined as involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, in any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation);*
- techniques involving direct introduction into a micro-organism of heritable material prepared outside the micro-organism including micro-injection, macro-injection and micro-encapsulation;
- cell fusion (including protoplast fusion) or hybridisation techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally.

2) Techniques that are not considered as leading to genetic modification, on condition that they do not involve the use of recombinant-DNA molecules or genetically modified organisms:

- *In vitro* fertilisation;
- conjugation, transduction, transformation or any other natural process;
- polyploidy induction.

3) Genetic modification techniques to be excluded from the scope of the Directive, on condition that they do not involve the use of recombinant-DNA molecules or genetically modified organisms:

- mutagenesis;
- the construction and use of somatic animal hybridoma cells (e.g. for the production of monoclonal antibodies);
- cell fusion (including protoplast fusion) of cells from plants which can be produced by traditional breeding methods;
- self-cloning of non-pathogenic naturally occurring micro-organisms which fulfil the criteria of Group I for recipient micro-organisms (*this exclusion is only valid for Directive 90/219/EEC; the term "self-cloning" was defined during the revision of the Directive 90/219/EEC in 1998, as consisting in the removal of nucleic acid sequences from a cell of an organism which may or may not be followed by reinsertion of all or part of that nucleic acid (or a synthetic equivalent) with or without prior enzymic or mechanical steps, into cells of the same species or into cells of phylogenetically closely related species which can exchange genetic material by natural physiological processes where the resulting micro-organism is unlikely to cause disease to humans, animals or plants).*

Through this approach, the European Union therefore chose to regulate specifically the use of certain genetic modification techniques. Recombinant DNA is listed, as well as other techniques (injection, encapsulation, cellular fusion) which at the time were considered to lead to a non-natural modification of the genetic material of the host cell.

In contrast, the European Union chose not to regulate the use of other techniques. These latter techniques fell into two categories:

- firstly, techniques considered as not giving rise to genetic modification in the sense of the Directives (the resulting organisms are therefore not considered to be GMMs/GMOs). Natural transfer processes of genetic material such as conjugation, transduction, or transformation are identified;
- secondly, techniques giving rise to GMMs/GMOs but which are excluded from the application of the Directive. This covers genetic modification techniques that have been traditionally used for various

applications and of which it was considered at the time that there was a sufficient history of use in order to consider that the resulting organisms were of no known risk to public health or the environment. For example, GMMs and GMOs obtained by mutagenesis following exposure to ionising radiation or to mutagenic chemical agents were not covered by the Directives and therefore not subject to a risk assessment.

As can be seen, the definition of GMM/GMO in the European Directives (and therefore in the scope of these Directives) is based on the process of obtaining the organisms, addressing the methods used (genetic modification techniques) to obtain the GMM/GMO rather than the final product itself. At the same time, other countries such as Canada and the United States opted for different approaches, the characteristics of the organism (the product) or its use being the determining factor in justifying a risk assessment, rather than the technique used to develop the organism.

The GMM/GMO definition set in 1990 at a European level is still used today, 20 years later. However, we will see later in this book that this definition, and the list of techniques associated with it, remains the focus of intense discussions on a European level.

The Directive relating to the contained use of GMMs

Contained use is defined in Directive 90/219/EEC as "*any operation in which micro-organisms are genetically modified or in which such genetically modified micro-organisms are cultured, stored, used, transported, destroyed or disposed of and for which physical barriers, or a combination of physical barriers together with chemical and/or biological barriers, are used to limit their contact with the general population and the environment".* This Directive therefore applies to activities involving GMMs in installations such as laboratories, animal houses, greenhouses, hospitals or even industrial production areas.
The key provision of this Directive, described in Article 6, specifies that firstly, Member States should ensure that all appropriate measures are taken to avoid adverse effects on human health and the environment which might arise from the contained use of GMMs, and secondly, that the user should carry out an assessment prior to the contained use activities as regards the potential risks to human health and the environment. The criteria to be followed for this assessment are defined in an annex. This provision is therefore based on the notions of risk prevention and assessment.
Once assessed, in order to be implemented, the contained use of GMMs must receive authorisation from the competent authority of the Member State concerned. To grant this authorisation, a notification dossier had to be supplied by the user to the authority. In accordance with the Directive, Member States ensure that the competent authority arrange inspections or other control measures with a view to ensuring that the provisions of the Directive are met. Member States must also ensure that an emergency plan is set up in order to react effectively in case of accident and that individuals likely to be affected by an accident are informed about all aspects relating to their safety.

Directive 90/219/EEC classifies genetically modified micro-organisms into two distinct groups. The GMMs in group I, the most safe, are characterised by criteria defined depending on the recipient organism, the vector, the insert and the resulting genetically modified micro-organism. For this type of GMM, the application of good microbiological practices and basic occupational safety and hygiene principles are considered sufficient. Any micro-organism not satisfying the criteria of group I is automatically classified as group II. For activities involving GMMs, the Directive describes additional containment measures that must be applied depending on the risk assessment result.
This classification into two risk groups quickly became impractical and complicated to implement. Moreover, it was not consistent with the classification of biological agents into four risk groups according to their danger to humans, which was adopted at the same time in the Directive 90/679/EEC on the protection of workers from risks related to exposure to biological agents at work (genetically modified or not).
For these reasons, the classification of GMMs into two risk groups was abandoned in 1998 during the revision of the Directive (and the adoption of Directive 98/81/EC[31]) in favour of a classification into four classes of GMM contained use activities depending on their potential risk to health and the environment (the notification procedure and the containment measures to be implemented being proportional to the intensity of the risk).

With the adoption of Directive 98/81/EC, the provisions of Directive 90/219/EEC were significantly amended to take into account the development of scientific knowledge and technology as well as the experience acquired in the Member States since Directive 90/219/EEC came into force. Directive 98/81/EC saw the thorough classification of activities involving GMMs (see below) but also administrative procedures and corresponding notification requirements (which were simplified for low risk contained use activities). Some other aspects were also specified, such as risk assessment criteria and methodology, provisions relating to the setting up of emergency plans and even provisions on the transnational dimension of risks and accidents caused by GMMs (see Chapter 3).

Since May 2009, Directives 90/219/EEC and 98/81/EC have been abrogated by Directive 2009/41/EC[32]. This new Directive did not bring any substantial amendment to the previously established legal system but aimed to restore legibility of the legislation. The provisions from the two previous Directives were integrated into a single text together with a series of

[31] Council Directive 98/81/EC of 26 October 1998 amending Directive 90/219/EEC on the contained use of genetically modified micro-organisms. OJ L 330 of 05.12.1998, p. 13.
[32] Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (Recast). OJ L 125 of 21.05.2009, p. 75.

decisions adopted over time, in order to specify the contents of these Directives[33]. Directive 2009/41/EC also integrates new rules of comitology[34] relating to the amendment procedures in response to technological progress.

The Directive relating to the deliberate release of GMOs into the environment

Directive 90/220/EEC covers the deliberate release of genetically modified organisms into the environment. Deliberate release is defined as "*any intentional introduction into the environment of a GMO or a combination of GMOs without provisions for containment such as physical barriers or a combination of physical barriers together with chemical and/or biological barriers used to limit their contact with the general population and the environment*".
The Directive actually distinguishes two types of deliberate release:

- those carried out for the purposes of research and development (for example field trials of transgenic plants);
- those carried out for the purposes of placing on the market (and which therefore cover products consisting of GMOs or containing them), i.e. supplying third parties or making them available to third parties.

We recall that Directive 90/220/EEC applies to any type of GMO, that is micro-organisms, plants or animals.

The Directive is based on the following general principles:

- Any deliberate release of GMOs into the environment can only take place after prior consent of the competent authority; this consent is granted after the authority has satisfied itself that the release will be without risk to human health and the environment;
- In order to obtain this consent, the notifier must supply a notification dossier comprising, in particular, a full assessment of the risks that the GMO could pose to human health and the environment. The information to be supplied in the notification is detailed in an annex of the Directive;
- In the notification, the notifier includes information about the data or results relating to other releases of the same GMO (within or outside of the European Union);
- The preliminary environmental risk assessment should be carried out on a case by case basis;
- The introduction of a GMO into the environment must be done in a stepwise manner; this means that the containment of the GMO is reduced and the scale of its release increased progressively, in steps, but only if the assessment of previous stages in terms of the protection of human health and the environment show that it is acceptable to progress to the next step;
- Placing on the market of a GMO cannot be considered without it having been subjected to satisfactory field trials at the research and development stage in ecosystems that are likely to be affected by its use.

Finally, the Directive imposes that the Commission and Member States must set up a procedure for the exchange of information on notified deliberate releases of GMOs in application of the Directive. The practicalities of this

[33] Decision 91/448/EEC (OJ L 239 of 28.8.1991, p. 23); Directive 94/51/EC (OJ L 217 of 18.11.1994, p. 29); Decision 96/134/EC (OJ L 31 of 9.2.1996, p. 25); Decision 2000/608/EC (OJ L 258 of 12.10.2000, p. 43); Decision 2001/204/EC (OJ L073 of 15.03.2001, p. 32).
[34] The decisional process associated with the European regulations is carried out in certain cases (generally when it is about adapting and amending these regulations for technical aspects) after consultation of commissions or committees, comprising national civil servants designated by the Member States. "Comitology" is the definition of the rules defining the functioning of these commissions or committees, and the status of their opinions.

procedure were defined afterwards via the adoption of different decisions of the Commission[35] and the establishment of the SNIF (Summary Notification Information Format) document containing a summary of the information supplied in the notification dossier.

There are two distinct procedures for the two types of deliberate release (for experimental purposes or commercial purposes).

Deliberate release for the purposes of research and development (Part B of the Directive)

The approval procedure is managed by each Member State within whose territory the release must take place. The competent authority must examine whether the notification is consistent with the requirements of the Directive and, if necessary, carry out tests or inspections.
If the authorities consider it to be necessary, they can organize a public consultation.
One of the characteristics of part B of the Directive is that it gives Member States the possibility to apply simplified procedures for certain deliberate releases for experimental purposes. This type of procedure can only be applied to GMO releases for which sufficient experience has been obtained. The practicalities and the application criteria of these simplified procedures were defined in 1993 and 1994 but only for genetically modified plants[36].

Deliberate release for the purposes of placing on the market (Part C of the Directive)

A Community approval procedure is required. A product can, from the moment that it is approved, circulate within the entire European Union territory. In this procedure, the notification dossier is sent by the notifier to a Member State who carries out an initial risk assessment ("Rapporteur Member State"). They can either refuse the release project or issue a favourable opinion. In this second case, the other Member States will then have a period in which it is possible to draw up comments or objections on the notification. If no objection is raised by these Member States, the competent authority of the Rapporteur Member State authorises the placing on the market and informs the Member States and the Commission of the authorisation. If a competent authority formulates a justified objection, the Member States and the Commission look to obtain a consensus on a final decision. In the case of ongoing disagreement, the Commission makes a decision according to the procedure provided in Article 21 of the Directive.

[35] Decision 91/596/EEC (OJ L 322 of 23.11.1991, p. 1); Decision 92/146/EEC (OJ L 60 of 5.3.1992, p. 19); Decision 94/211/EC amending Decision 91/596/EEC (OJ L 105 of 26.4.1994, p. 26).
[36] Decision 93/584/EEC (OJ L 279 of 12.11.1993, p. 42); Decision 94/730/EC (OJ L 292 of 12.11.1994, p. 31).

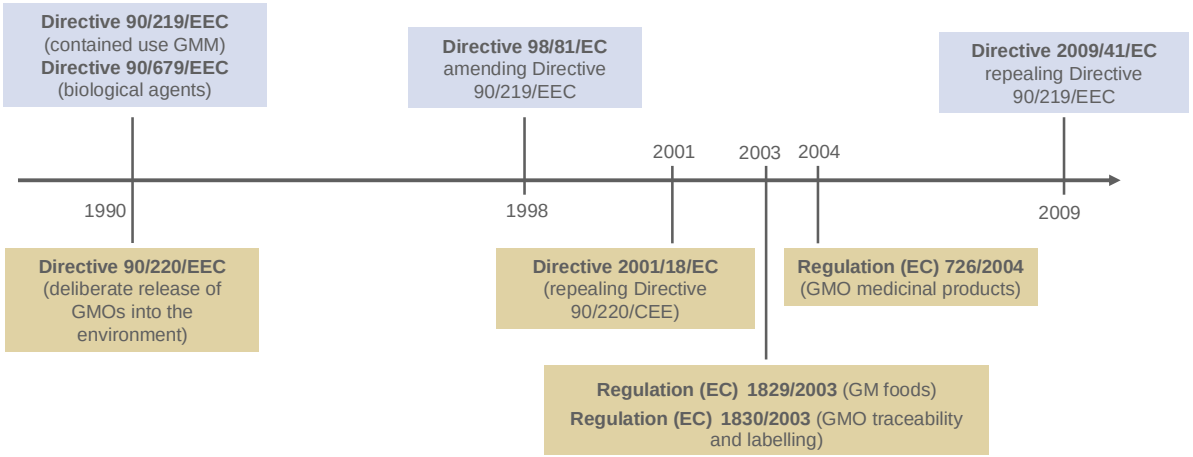


Figure 1.2 | *Historical overview of the European legislation relating to the contained use of GMMs and the deliberate release of GMOs into the environment*

When a product containing or consisting of GMOs is authorised for placing on the market, a Member State cannot prohibit, restrict or prevent the deliberate release of this product in its territory, if the conditions stated in the consent are met. However, when a Member State has justifiable reasons to consider that a product that has obtained consent poses a risk to human health or the environment, it may provisionally restrict or prohibit its use and/or sale on its territory ("safeguard clause"). The Directive then expects that a final decision will be taken between the Member States and the Commission on the validity of this measure within three months[37].

Directive 90/220/EEC was amended twice in 1994[38] and in 1997[39] (adaptations of the annexes regarding the information to be supplied in the notification). At the beginning of the 2000s, the European regulatory framework relating to the marketing of GMOs was overhauled. Directive 90/220/EEC was abrogated in 2001 by Directive 2001/18/EC[40]. Furthermore, GMOs destined for human or animal food, and medicinal GMOs for human or

[37] The safeguard clause has been invoked by the Member States on nine different occasions: three times by Austria, twice by France and once by Germany, Luxembourg, Greece and the United Kingdom. The implementation of these national measures never resulted in consensus at a European level (scientific evidence supplied by these Member States to justify the measures taken being contested) and is still under discussion today.
[38] Directive 94/15/EC (OJ L 103 of 22.04.1994, p. 20).
[39] Directive 97/35/EC (OJ L 169 of 27.06.1997, p. 72).
[40] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJ L 106 du 17.04.2001, p. 1).

veterinary use were the subject of specific regulations, namely Regulations (EC) 1829/2003[41] and (EC) 726/2004[42]. We will come back to the adoption and implementation of these Regulations in more detail in Chapter 4.

THE ASSESSMENT OF BIOLOGICAL RISKS

The assessment of biological risks is not based on theories developed by technocrats, but on an empirical basis following an awareness of the scientific community, firstly of the danger posed by the handling of pathogenic organisms (demonstrated through studies on infectious diseases acquired in the laboratory), and secondly of the dangers potentially associated with experiments involving recombinant DNA. These two aspects, as we have seen previously, are a matter for biosafety.

To this day, numerous risk assessments have been carried out across the world on the contained use of GMOs or pathogens as well as on the release of GMOs into the environment, their use as food for humans or animals, or as medicinal products. The basis for these risk assessments has evolved gradually taking into account the most recent scientific and technical data while proceeding via a proper scientific approach. We will see through the following chapters how, in Belgium, the Biosafety Advisory Council and the Biosafety and Biotechnology Unit were involved in this development, actively contributing to it through a multidisciplinary biosafety approach.

But before describing this Belgian contribution to biosafety, it would appear useful to describe in a few sentences the basic principles and methodology of biological risk assessment. As we have previously seen, this assessment constitutes the scientific basis that enables any activity involving GMOs and/or pathogens to be authorised or prohibited and, if necessary, possible measures to be imposed with the aim of limiting potential risks to human health and the environment.
Risk assessment is one of the three elements of risk analysis, the other two being the management of risks (which traditionally corresponds to the role of the decision-makers) and the communication of risks (with regards to the public, in particular). In theory, these three elements are separated and sequential but, in practice, the boundaries between these elements are sometimes quite hazy and permeable.
Biological risk assessment is a process that includes the identification, the probability of occurrence and the severity of a potential negative effect on human health or the environment associated with a specific use of a GMO or a pathogen. A known risk will lead to the implementation of appropriate prevention measures.

Without wanting to enter into the detail of these considerations (widely analysed by other authors), it is important to distinguish prevention (which is a response to a known risk) from precaution. According to the European

[41] Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed (OJ L 268 of 18.10.2003, p. 1).
[42] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136 of 30.04.2004, p. 1).

Commission[43], the precautionary principle can be invoked when the potentially dangerous effects of a phenomenon, product or process have been identified through scientific and objective evaluation, but this evaluation has not been able to determine the risk with sufficient certainty. Resorting to the precautionary principle therefore sits within the general framework of risk analysis but is a matter for risk management. Resorting to the precautionary principle is only justified when three preliminary conditions have been met; the identification of potentially negative effects, the assessment of available scientific data and the extent of scientific uncertainty.

Risk assessment does not take into account the notion of associated benefits, nor any other societal, economic or ethical aspect linked to the use of the assessed organism. These aspects will possibly be considered by risks managers at the time of decision-making. We note that in 2010, certainly at a European level, there are increasing calls for the potential socio-economic impacts of the use of GMOs to be specifically assessed. The question of knowing if such an assessment should be integrated into the current risk assessment process or treated in a separate way is still open.

Generally, risk assessment has the basic principles of being carried out on a case by case basis while being based on established science (known scientific facts, results published in recognised scientific journals).
As we have previously indicated, for organisms destined to be released into the environment, a step by step assessment is applied. The first assessment is carried out during contained use (clinical trials, *in vitro* development of the GMO, laboratory or greenhouse tests), the second assessment occurring, for example, during a field trial before moving on to a new assessment prior to the placing on the market. This last assessment relies mainly on the results obtained during the previous experiments. In certain cases, it will also be possible that the organism will be the subject of specific monitoring after it has been placed on the market.

Biological risk assessment methodology is based principally on the **5 stages** mentioned in *Figure 1.3:*

1. The characterisation of the GMO or pathogen. This stage takes account of the characteristics of the organism(s) used, the genetic material introduced in the case of genetic modification, the resulting GMO and the intended activity;
2. The identification of potential negative effects (such as, for example, diseases capable of affecting humans, including allergenic or toxic effects or even the transfer of inserted genetic material to other organisms). This step possibly enables a **hazard** to be revealed (notion often erroneously confused with that of risk);
3. The assessment of the exposure of the population and/or environment to the organism under consideration and the consequences of each negative effect if it occurs;
4. The assessment of the probability that each potential negative effect occurs;
5. The characterisation of the **risk**, which will possibly lead to the adoption of risk management measures.

[43] Communication from the Commission of 2 February 2000 on the use of the Precautionary Principle (COM(2000) 1 final).

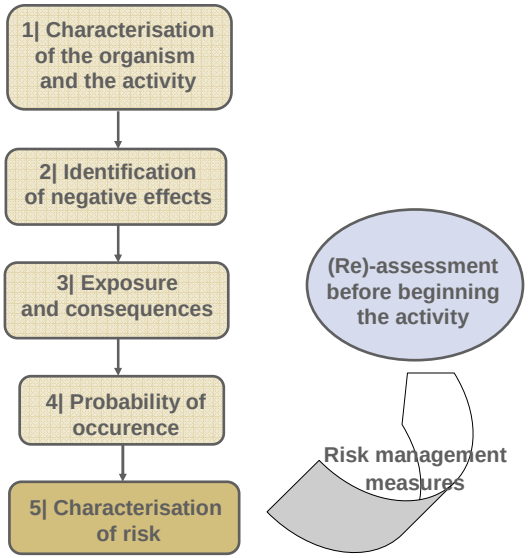


Figure 1.3 | *Biological risk assessment methodology applied to GMOs or pathogens*

In the case of a contained use activity, the procedure will end with the identification of the risk level associated with the GMO or pathogen used. On this basis, the containment measures and other protection measures (working practices, safety equipment, contaminated biological waste management) to be adopted are then determined. The analysis carried out leads to the classification of the contained use into one of the 4 existing risk categories (level of risk increasing from 1 to 4). The final stage consists of definitively classifying the contained use activity, which will be confirmed by a re-assessment of the whole procedure (*Figure 1.4).*

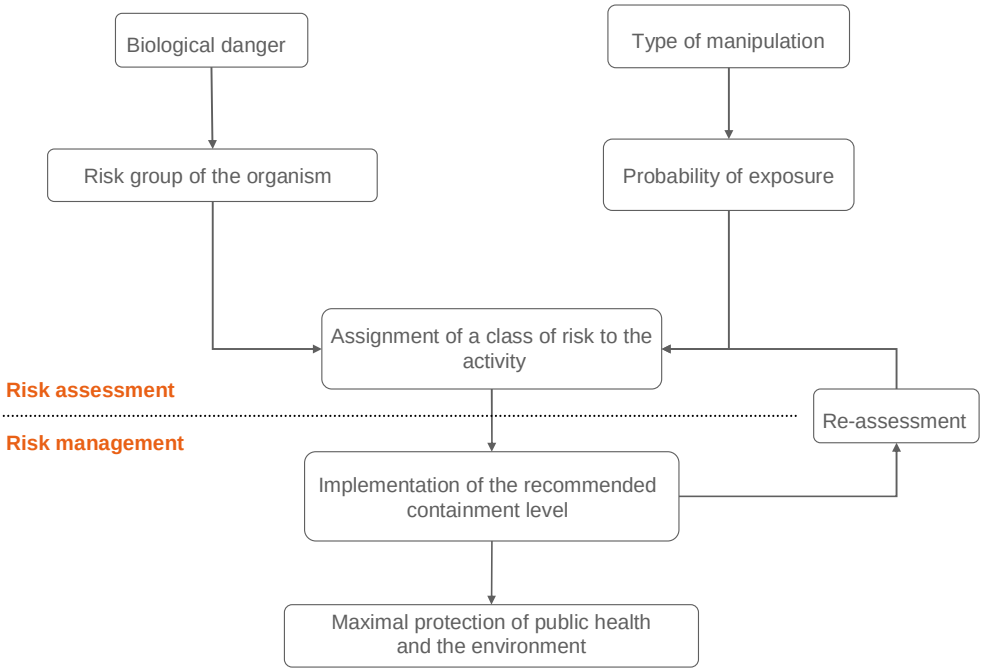


Figure 1.4 | *Application of risk assessment and adoption of risk management measures in the case of contained use of a GMO and/or pathogen*

In the case of deliberate release into the environment (experimental or commercial cultures) or a food use, the GMO must be fully characterised at a molecular level. The aspects linked to the potential consumption of the GMO (toxicity, allergenic potential, compositional analysis, nutritional value) and/or to its environmental impact (agronomic parameters, possibility of release or transfer of genes, impact on non-target species, etc.) are the subject of a detailed assessment.
The risk assessment consists of comparative analysis in order to identify possible differences between the GMO and its non-genetically modified equivalent, followed by an assessment of the nutritional, health or environmental impacts of these differences. This approach by comparison is based on two concepts: the concept of familiarity and the concept of substantial equivalence. The first states that the non-genetically modified organism used to develop a GMO is legitimately usable as an element of comparison in order to be able to identify the differences due to genetic modification. The second concept, that of substantial equivalence, specifies that it is the potential

risks linked to the composition differences between the GMO and its non-GM equivalent that must be studied. This second concept is applied in the case of food GMOs[44].
We note that the environmental risk assessment also applies to medicinal GMOs used during gene therapy trials or vaccination or being the subject of a marketing authorisation application.

The five stages of environmental risk assessment (*Figure 1.3*) will enable the potentially identified risks to be determined as being acceptable (considering the previously set protection objectives), in return for the implementation of appropriate risk management measures, if necessary.

'Biological risk assessments are carried out according to a methodology and principles recognised and adopted at an international level'

We have seen at the beginning of this chapter how the basic biological risk assessment principles have emerged from work carried out on an international level, in particular at the OECD. This trend was pursued and even strengthened over the years (see Chapter 5 for further details) as illustrated, for example, by the work carried out within the scope of the Codex Alimentarius in relation to food standards and within the scope of the Cartagena Protocol on biosafety[45]. In these instances, like in others, groups of experts are regularly brought in to refine, specify or illustrate the biological risk assessment methodology, for example in order to apply it to new types of organisms (insects, trees, fish, viruses, etc.) or to new characteristics (for example, drought-resistance or resistance to other extreme conditions). Although certain aspects of biological risk assessment are sometimes requestioned (for example the application of the concept of substantial equivalence in the assessment of food GMOs), the general principles (the five stages described earlier) remain unchanged to this day.

With time, the scientific representation of the experts involved in biological risk assessment has also evolved, especially in the field of GMOs. Whereas molecular biologists had been predominant in the early days of biosafety, this discipline has now been joined by environmental scientists, nutritionists, toxicologists and allergists. We will see in the next chapter how Belgium has been a forerunner in this diversification of scientific expertise.

The volume of useful scientific data and case studies supporting risk assessments has also grown considerably over time. This development has obviously contributed to improving risk assessment. However, it has also paradoxically led to an increase in questions. As Di Castri indicated in 1992, "Knowledge is like a sphere. By increasing its volume, the surface in contact with the unknown increases"[46].

The fact that risk assessment opens up new questions is nothing unusual, just like the absence of consensus between scientists on the interpretation of certain data. Indeed, this comes from a scientific approach that is not univocal but contradictory. These questions should lead to the implementation of new research and to the

[44] The notion of substantial equivalence was introduced by the OECD in 1993 in the debates on the safety assessment of foods derived from genetically modified organisms. It was largely used at an international level in health risk assessments of this type of GMO. The assessment of substantial equivalence involves the measurement of the presence and concentration of a series of significant constituents of the food (proteins, vitamins, carbohydrates, etc.). A transgenic product is considered to be equivalent to its conventional equivalent if these compositional analyses are identical. The establishment of substantial equivalence does not constitute a health risk assessment in itself, but an analytical element of the risk assessment, which can enable a decision to be made as to how to carry out this assessment (for example, by applying additional tests).
[45] Cartagena Protocol on Biosafety to the Convention on Biological Diversity. January 2000.
[46] Di Castri F. L'écologie en temps réel. In Theys J. et Kalaora B., (Dir.) La terre outragée. Les experts sont formels ! Ed. Autrement, Paris, 1992.

emergence of additional data. Unfortunately, financing problems, the destruction of field trials of transgenic plants, the lack of interest in this type of research or other factors also hinder the development of research in the field of biosafety.

Additionally, all too often, scientific controversy, rather than encouraging scientific debate, encourages polemic. This has been very apparent in recent years in the field of GMOs. Several factors have caused this state of affairs: the disclosure of preliminary scientific results to the general public, the abusive generalisation of scientific conclusions, the separation of certain experimental results from their context (biological risk assessment is an incremental and holistic process in which scientific data should be considered in their entirety), or even the confusion between "hazard" and "risk".

This work does not aim to deal with this controversial aspect of biosafety in any way. However, it would appear useful to mention it at the end of this historical and introductory chapter so as to put into as realistic context as possible the setting in which biosafety expertise exists and has been developed in Belgium over the last twenty years.

CHAPTER 2
THE IMPLEMENTATION OF BIOSAFETY IN BELGIUM

Although Europe adopted a specific GMO regulatory framework in 1990, it was not until several years later that the European Directives 90/219/EEC and 90/220/EEC were transposed into Belgian law[47]. At the beginning of the 1990s, Belgium was undergoing extensive institutional changes. This period was marked by the transfer of various competences from the State to the Regions, notably in the area of environmental protection. With the transposition of the two Directives mentioned above into national law, there was a crossover of numerous competences, which could sometimes be regarded as federal and sometimes as regional.
The Directives also address matters that are important for the scientific research sector or that have potential economic consequences linked to the development and marketing of GMO-based agricultural, food or pharmaceutical products. It was therefore important to avoid that disparities between federal and regional rules, relating in particular to the deliberate release of GMOs, would result in creating unequal conditions of competition or barriers to the development and marketing of products containing such organisms.

In 1987, Belgium's Interministerial Conference for Science Policy followed up the publication of the OECD "Blue Book" (see Chapter 1) by creating an *ad hoc* "*Biotechnology Regulations*" group. In 1989, this group proposed the creation of an "Interdepartmental Recombinant DNA Advisory Committee" (or "rDNA Committee") responsible for the evaluation of biosafety, in particular notifications introduced pursuant to the future Directive 90/220/EEC.

The early 1990s was marked by various uncoordinated initiatives in relation to the transposition of the GMO Directives. Firstly, the Flemish Region decided to transpose the two Directives in full into its environmental legislation (the VLAREM - "Vlaams Reglement betreffende de Milieuvergunning") for matters under its jurisdiction. Secondly, in October 1991 a Concertation Committee "National government - Regional executives" mandated the Regions and the Federal State to negotiate the transposition of Directive 90/220/EEC and the creation of an "rDNA Committee". At that time, it had already been suggested that this committee be supported by an "rDNA Secretariat" located within a department of the Scientific Institute of Public Health (WIV-ISP, known as the "Institute of Hygiene and Epidemiology - IHE" until 1996). At the same time, discussions were taking place between the three Regions with the aim of harmonising the transposition of Directive 90/219/EEC and creating an "rDNA unit" within the WIV-ISP, to provide scientific support to the Regions.

The WIV-ISP, in particular Dr William Moens, was directly involved in all of these discussions. In June 1992, the Institute organised a symposium bringing together the national and regional authorities, the industrial and academic sectors and other stakeholders. This symposium was an opportunity to review the progress of the transposition of Directives 90/219/EEC and 90/220/EEC in Belgium and highlight the importance of cooperation between the authorities concerned in this context.

Gradually, it became desirable for the authorities to settle once and for all, at the institutional level, the intervention of the Federal State and the Regions in matters covered by the above-mentioned Directives. To that end, a new legal tool was available, introduced previously by the Special Law on Institutional Reform of 8 August

[47] It is recalled that Directives 90/219/EEC and 90/220/EEC were supposed to be transposed into national law by 23 October 1991 at the latest !

1980[48]. Article 92 bis of this Law gives the State, the Communities and the Regions the possibility of concluding *Cooperation Agreements*, particularly on the joint creation and management of common services and institutions, the joint exercising of specific competences, and the development of joint initiatives.

In 1993, the negotiators agreed on the need to set up a single Cooperation Agreement covering all matters concerning biosafety, i.e. human health and environmental safety linked to the deliberate release of GMOs into the environment, but also to the contained use of genetically modified organisms and human pathogenic organisms. Thus they decided, through the adoption of this Cooperation Agreement, to cover the harmonised transposition and implementation between the different levels of competence of the two Directives 90/219/EEC and 90/220/EEC, also taking into account the provisions of Directive 90/679/EEC (see Chapter 1). They also chose to set up a biosafety scientific evaluation system common to the Federal State and the Regions, so as to guarantee objective and harmonious treatment of biosafety dossiers vis-à-vis the notifiers, the general public, the European Commission and the other Member States.

After another period of negotiations, a draft of the Cooperation Agreement concerning biosafety was approved by the various authorities concerned on 16 May 1995. The text of the agreement was modified in view of the opinions of the Council of State[49], particularly to clarify the respective roles of the bodies constituting the common scientific evaluation system for biosafety.
On 25 April 1997, the final text of the *Cooperation Agreement between the Federal State and the Regions on the administrative and scientific coordination concerning biosafety* was adopted by all parties[50].

The objects of the Cooperation Agreement concerning biosafety are:

- to transpose into national law and apply in a harmonised manner Directive 90/219/EEC regulating the contained use of genetically modified microorganisms, while extending this regulation to genetically modified organisms and pathogenic organisms. The Regions also committed to harmonising technical biosafety criteria and the classification of GMOs and pathogenic organisms;
- to transpose into national law and apply in a coordinated manner Part B of Directive 90/220/EEC on the deliberate release of GMOs into the environment for the purposes of research or development and any purposes other than placing on the market;

[48] Loi spéciale du 8 août 1980 de réformes institutionnelles / Bijzondere wet van 8 augustus 1980 tot hervorming der instellingen (*Moniteur belge/Belgisch Staatsblad* of 15.08.1980, p. 9434).
[49] Opinion L.24.527/9 of the Francophone Chamber of the Council of State of 3 October 1995; Opinion L.24.678/8 of the Flemish Chamber of the Council of State of 12 December 1995.
[50] The final version of the Cooperation Agreement was signed on 25 April 1997. It was formally approved at the Federal level by the Law of 3 March 1998 (*Moniteur belge/Belgisch Staatsblad* of 14.07.1998, p. 22773), in the Walloon Region by the Decree of 5 June 1997 (*Moniteur belge/Belgisch Staatsblad* of 14.07.1998, p. 22790), in the Flemish Region by the Decree of 17 December 1997 (*Moniteur belge/Belgisch Staatsblad* of 31.01.1998, p. 2890) and in the Brussels-Capital Region by the Decree of 20 May 1998 (*Moniteur belge/Belgisch Staatsblad* of 14.07.1998, p. 22850).

- to set up a biosafety scientific evaluation system common to the Federal State and Regions, comprising a "Biosafety Advisory Council" (the new name for the "rDNA committee" mentioned earlier) and the "Biosafety and Biotechnology Unit" located at the WIV-ISP;
- to coordinate regulatory provisions applicable to the management of waste from contained use activities, so that in case where such substances containing living GMOs were to be placed on the market, the provisions concerning deliberate release would be applicable.

The Cooperation Agreement concerning biosafety is the central legal text that regulates the implementation and management of biosafety in Belgium. Although it was not formally adopted until 1997, its objectives and general principles were defined in the initial stages of the negotiations. It was on this basis that the Regional and Federal authorities successfully led, in parallel to the negotiations on the Cooperation Agreement, discussions aimed at implementing Directives 90/219/EEC and 90/220/EEC into Belgian law.

IMPLEMENTATION OF DIRECTIVE 90/219/EEC

With regard to Directive 90/219/EEC, the decision to favour regional competences was swiftly made, thus confirming the choice already made at the European level to recognize the environmental scope of this Directive[51]. The objective of the transposition of this Directive into national law was not only to ensure its harmonised implementation between the three Regions, but also to improve certain legal and scientific weakness points existing in the European text. The legal basis on which Directive 90/219/EEC was adopted gave the Member States the option of adopting more stringent protection measures, should they so wish.

Firstly, unlike Directive 90/220/EEC, which applies to all genetically modified organisms, Directive 90/219/EEC only applies to genetically modified microorganisms (GMMs), i.e. bacteria, fungi, parasites and viruses. Organisms such as plants and animals were therefore not covered by this Directive. The regional authorities corrected this limitation of the scope of application (introduced by certain Member States during negotiations on the Directives - see Chapter 1) by also guaranteeing a risk assessment of genetically modified plants and animals used in laboratories, greenhouses or animal housing. This made it possible for appropriate containment measures to be adopted if necessary to protect human health and the environment during activities involving all types of GMOs.

Secondly, the scope of the Directive, even extended to GMOs, left out non-genetically modified organisms having pathogenic properties for humans, plants or animals. The authorities decided to include these organisms within the scope of the regional regulations, based on the following arguments:

- firstly, laboratories that use GMOs also occasionally handle non-genetically modified pathogenic strains;
- secondly, the safety of contained use activities involving GMOs is assessed taking into account the characteristics of the gene donor and acceptor organisms, particularly their pathogenicity for humans, plants or animals;

[51] Directive 90/219/EEC was indeed adopted on the basis of Article 130S of the Maastricht Treaty (see Chapter 1).

- finally, the authorities wanted to avoid differences between the containment levels established in Directive 90/219/EEC and those required by Directive 90/679/EEC (relating to the protection of workers from risks related to exposure to biological agents at work), which applies to human pathogens, including those that are genetically modified. The same kind of reasoning applies to phytopathogens and zoopathogens, in order to avoid differences between the "contained use" regulation and other plant- or animal-health legislation establishing containment criteria and levels for the use of quarantine pathogens[52].

Unlike the extension of the scope of application to GMOs, the extension to all non-genetically modified pathogenic microorganisms is specific to Belgium.

Thirdly, as mentioned in Chapter 1, the Directive provides for the classification of GMMs into two groups: group I (no risk to human health or the environment) and group II (all other organisms presenting a risk). This classification was not consistent with the internationally accepted system set up by the World Health Organization (WHO) for classifying biological risks into four risk categories, ranging from risk group 1 (no risk to human and animal health) to risk group 4 (the most pathogenic microorganisms). The regional authorities chose to adopt the WHO classification for the transposition of Directive 90/219/EEC.

Consequently, with a view to ensuring preventive management of risks to the environment and human health, the Regions adopted a very broad and coherent biosafety regulatory framework on the scientific level, that covers all living organisms that pose a risk to human health and the environment.
A scientific consequence of this decision was the drawing up by the Biosafety and Biotechnology Unit (SBB) of reference lists of microorganisms which, in their natural form, pose a risk to immunocompetent humans and animals or healthy plants. Several hundred microorganisms were thus listed and assigned to a class of risk based on existing international classifications, lists of microorganisms or pathogenic organisms recognised by other countries, and an in-depth analysis of the scientific literature[53]. These lists were appended to the regional legislation and form an internationally recognised reference source.

[52] The inclusion in the regional regulations of phytopathogenic organisms led, in 1995 and 1996, to bitter discussions between the regional and federal authorities and the SBB. Certain authorities were very reluctant to include this type of organisms in the "contained use" legislation in a generic way, either because they believed that their use in small quantities under laboratory conditions posed little or no environmental risk, or (for quarantine phytopathogens) because their use was already subject to the provisions of the Federal decrees relating to the control of organisms harmful to plants and plant products. These criticisms were taken into account in the preparation of the reference lists of phytopathogenic microorganisms and the containment criteria to be applied during their use.
[53] These lists have been updated several times by the SBB to take account of new scientific data concerning nomenclature, taxonomy and classes of risk. The lists can be consulted on the "Belgian Biosafety Server" (http://www.biosafety.be).

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The first GMO Directives: their implementation in Belgium, at the dawn of federalism

It was at the beginning of the 1990s that, as legal advisor at the Brussels Institute for Management of the Environment, I was involved with setting up a Decree transposing the Directive 90/219/EEC on the contained use of GMO, in close collaboration with the Biosafety and Biotechnology Unit at the Institute of Hygiene and Epidemiology (later renamed the "Scientific Institute of Public Health"), and with the Cabinet of the Brussels Minister for the Environment. The Decree, adopted on 9 December 1993, constituted the first transposition of the Directive in Belgium.

When it quite quickly became evident that the transposition and implementation, not so much of Directive 90/219/EEC, but particularly of Directive 90/220/EEC relating to the deliberate release of GMO, raised some competences and even more, some regional and federal concerns (while requiring high-level scientific knowledge), in line with the developments of this issue at European level, the work became like the composition of a real spider's web. Laws, royal and regional Decrees, cooperation agreements and legislative approval measures: the cocktail, which will later become relatively common, was ready.
How many discussions, article by article, mainly on Directive 90/220/EEC, in order to determine which authority, regional or federal, was responsible for such article, and in order to define the limits of a necessary "joint exercise of own competences". How many concerns, also, on guaranteeing absolute confidentiality and thorough examination of the dossiers, according to biosafety technical criteria which had to be harmonised within the Belgian economic union, while scientific knowledge on the subject was mainly present at the Institute of Hygiene and Epidemiology. Last but not least, how many discussions at political level in order to arrive at the final signing of the Cooperation Agreement on 25 April 1997.

At the working groups level, each member made significant contributions, both in the group in charge of preparing the Brussels Decree on contained use and in the group preparing the draft Cooperation Agreement (the latter having been specially set up within what became the CCPIE in 1995). The work was often dry, but it was shared and friendly. The circumstances led the participants – lawyers, environmental permits engineers, Ph.D. in biology, etc. – to make an effort to listen and understand the views of others and, conversely, to make themselves understood, sometimes in French, sometimes in Dutch.

The task was largely fascinating and constructive so that the texts drawn up and adopted have functioned for a long time, without having to be substantially amended.

[54] Until October 2009.

The transposition of Directive 90/219/EEC and certain amendments published in the interim by the European Commission led to the publication of three separate decrees, firstly in the Brussels-Capital Region in 1993[55], then in the Flemish Region in 1995[56] and finally in the Walloon Region in 1996[57]. The three transposition decrees were each integrated into the general framework of regional environmental legislation applicable to Classified Installations (see Chapter 3 for further information).

The harmonised transposition of Directive 90/219/EEC in Belgium was therefore completed before the adoption of the Cooperation Agreement. However, it was largely inspired by the general objectives and principles of that agreement.

IMPLEMENTATION OF DIRECTIVE 90/220/EEC

Fields trials of genetically modified plants began in Belgium in 1986. Belgium was the second continental European country, after France, to allow cultivation of GMO crops on its soil. In Belgium, as in other countries, the authorities viewed transgenic plants as potential new vegetable varieties. Transgenesis was perceived as one innovation among others which enabled new varieties to be selected more quickly. Trials of these plants in the environment were therefore treated in the same way as trials of non-transgenic varieties. Consequently, the Ministry of Agriculture first granted authorisation for field trials of genetically modified plants based on royal decrees relating to seeds.
Therefore, there was never a "legal vacuum" in Belgium with regard to field trials of transgenic plants. However, it was not until 1998 that a specific legal framework for this type of application was adopted in Belgium.

From 1990, Directive 90/220/EEC served as a frame of reference for the risk assessment of GMOs released into the environment. As this Directive had been adopted on the basis of Article 100 A of the Maastricht Treaty (see Chapter 1), its transposition into national law had to be carried out in strict compliance with the provisions of the Directive.

In 1991, the Law of 20 July *concerning social and miscellaneous provisions* set the general frame of reference for preparing the transposition of European legislation on the deliberate release of GMOs[58]. Article 132 thereof states that "*in order to ensure the fulfilment of obligations resulting from international agreements or treaties regarding the deliberate release of genetically modified organisms, the King, by means of a decree deliberated in the Council of Ministers, regulates the deliberate release of genetically modified organisms".* This law was later

[55] Arrêté du 9 décembre 1993 relatif aux installations effectuant des opérations mettant en oeuvre des micro-organismes ou des organismes, pathogènes ou génétiquement modifiés / Besluit van 9 december 1993 betreffende de inrichtingen die activiteiten verrichten waarbij pathogene of genetisch gemodificeerde micro-organismen of organismen worden aangewend. *Moniteur belge/Belgisch Staatsblad* of 25.01.1994, p. 1424.
[56] Besluit van de Vlaamse regering van 1 juni 1995 houdende algemene en sectorale bepalingen inzake milieuhygiëne (Hoofdstuk 5.51. van VLAREM Titel II - Biotechnologie). *Moniteur belge/Belgisch Staatsblad* of 31.07.1995, p. 20526.
[57] Arrêté du Gouvernement wallon du 13 juin 1996 modifiant le Règlement général pour la protection du travail en ce qui concerne l'utilisation d'organismes génétiquement modifiés et/ou pathogènes. *Moniteur belge/Belgisch Staatsblad* of 25/10/1996, p. 27405.
[58] Loi du 20 juillet 1991 portant des dispositions sociales et diverses / Wet van 20 juli 1991 houdende sociale en diverse bepalingen (*Moniteur belge/Belgisch Staatsblad* of 1.08.1991, p. 17002).

supplemented by the Law of February 22, 1998[59]. Article 222 of this Law provides for the charging of fees in aid of the Scientific Institute of Public Health and Article 226 confers special powers to officials responsible for overseeing compliance with the legal provisions regarding the deliberate release of GMOs.

As mentioned at the beginning of this Chapter, discussions aimed at drafting the decree for enforcement of the Law of 20 July 1991 (i.e. the decree transposing Directive 90/220/EEC) began in October 1991. However, finalisation of this decree took seven long years, leading to Belgium being convicted by the European Court of Justice for failure to transpose within the prescribed period[60]. The difficulty did not lie in the transposition of Part C of the Directive ("the placing on the market of GMOs"), as that was clearly an exclusively federal responsibility, but in the transposition of Part B ("research and development"). For this part, responsibilities were divided between different levels of power: agriculture and public health at the federal level and environmental protection at the regional level. Consequently, finalisation of the decree transposing Directive 90/220/EEC proved to be indissociable from the adoption of the Cooperation Agreement mentioned above. This agreement was a necessary step to specify the respective responsibilities of the various federal and regional authorities and the arrangements for the intervention of these authorities in the administrative and scientific coordination of biosafety, particularly via the setting up of the Biosafety Advisory Council and the Biosafety and Biotechnology Unit.

Once all the parties had signed the final version of the Cooperation Agreement in April 1997, the transposition of Directive 90/220/EEC was quickly completed. On 18 December 1998, the *Royal Decree regulating the deliberate release into the environment and the placing on the market of genetically modified organisms or products containing them* was adopted[61]. This Royal Decree transposed Directive 90/220/EEC as well as later additions and amendments thereto concerning the exchange of information, the "Summary Notification Information Formats" (Decision 91/596/EEC, replaced by Decision 94/211/EC and Decision 92/146/EEC), the possibility of applying simplified procedures (Decisions 93/584/EEC and 94/730/EC) and the amendment of the annex listing the information to be provided in the case of placing on the market (Directive 97/35/EC). It also included the provisions of the Cooperation Agreement concerning the deliberate release of GMOs into the environment (Article 3 of the agreement).
In accordance with the decree and the Cooperation Agreement, the federal authorities are responsible for issuing the authorisations required for the deliberate release of GMOs into the environment. However, in the case of experimental releases, a common authorisation procedure was established between the Federal State and the Regions. In this case, authorisations from the federal authorities are subject to the agreement of the competent regional Minister of the territory in which the trial is to take place.

[59] Loi du 22 février 1998 portant des dispositions sociales / Wet van 22 februari 1998 houdende sociale bepalingen (*Moniteur belge/Belgisch Staatsblad* of 3.03.1998, p. 5683).
[60] Judgment of 9 July 1998, case C-343/97.
[61] *Moniteur belge/Belgisch Staatsblad* of 31.12.1998, p. 42113.

AT THE BEGINNING OF THE 1990S, THE SBB WAS THE BELGIUM'S CENTRE OF SCIENTIFIC EXPERTISE IN BIOSAFETY

As mentioned in Chapter 1, the WIV-ISP became involved in the technical and scientific aspects of biosafety very early on, notably through its participation in discussions relating to the preparation of the OECD "Blue Book".

Between 1989 and 1993, in addition to its involvement in the discussions concerning the transposition of the "GMO" Directives, the WIV-ISP (namely Dr W. Moens) directly provided the scientific expertise in biosafety in support to the competent authorities. The vast majority of risk assessments concerned field trials of genetically modified plants. Two marketing authorisation applications for veterinary vaccines were also examined at that time (see Chapter 4).

Between 1993 and 1996, the transposition of Directive 90/219/EEC in the three Regions led to the signing of agreements between the Regions and the WIV-ISP[62]. In particular, those agreements tasked the Biosafety and Biotechnology Unit (SBB) of the WIV-ISP with carrying out, on behalf of the Regions, an expertise mission in order to advise the regional authorities on the implementation of Directive 90/219/EEC, particularly regarding the compliance of notifications with the technical annexes of the Directive. Thanks to the financing associated with those agreements, five additional experts were recruited to the SBB. The central role of the WIV-ISP and, in particular, the SBB as a permanent centre of expertise in the field of biosafety was thus consolidated.
Between 1993 and 2000, the SBB functioned mainly thanks to this financial support from the Regions. The financial contribution from the Federal State only became effective in 2000 (see text box at the end of this chapter). It made it possible to gradually build up the scientific staff at the SBB. At the end of 2010, it is made up of 11 scientists involved in expert appraisal tasks related to biosafety.

Therefore, biosafety scientific expertise was initially provided and organised by the SBB. For matters concerning the contained use of GMOs and pathogens, the SBB will keep over time this technical and scientific expertise role for the regional authorities. For deliberate release and GMO marketing applications, the risks to human health and the environment were assessed by the SBB until 1996, on the basis of the agreements passed between the WIV-ISP and the Regions and on mandate of the federal authorities.

Soon, however, the SBB complemented its own expertise with that available in Belgium's academic institutions. At the start of the 1990s, the tendency among European and international biosafety committees was to favour expertise centred around molecular biology. On the fringes of this trend, the SBB and the Belgian authorities chose to widen the expertise available to scientific disciplines covering environmental, agronomical and food/feed safety aspects. Thus, at the request of the regional and federal authorities, expert committees composed of scientists from different Belgian academic and scientific institutions were set up to complement the expertise of the SBB. A scientific committee "Transgenic plants" was created in December 1996 to contribute to the assessment of applications involving genetically modified plants. At the same time, a scientific committee "Recombinant viral vectors, virosomes, recombinant vaccines and gene therapy" was formed. In 1999, scientific committees "Genetically modified microorganisms - Bacteria and Fungi" (for applications involving

[62] The existence of these agreements was subsequently formalised in the Cooperation Agreement concerning biosafety (Article 18).

microorganisms other than viruses) and "GM Food and Feed" (for GMO applications for food or feed) were also established.

From 1996, applications for deliberate release of GMOs into the environment and applications for GMO marketing authorisation submitted via Belgium were systematically assessed within the framework of meetings of these scientific committees. Officials appointed by the competent ministers chaired the meetings: the representative of the Minister of Agriculture for transgenic plants, the representative of the Pharmaceutical Inspectorate for gene therapy trials or vaccines, the representative of the Foodstuffs Inspectorate for novel genetically modified foods. As can be seen, at that time, expert appraisal and decision-making tasks were quite merged.

Once the Cooperation Agreement had been adopted and the Biosafety Advisory Council (BAC) had been officially set up, the existence of the scientific committees was formalised in accordance with the provisions of Articles 9 and 11 of the agreement. Indeed, the Cooperation Agreement stipulates that the Council and the SBB should be supported by scientific experts. To this end, a common list of experts shared by the two bodies was established. This list was considered "common" as it could be used by both the Council and the SBB. The details of the experts included on the common list are entered into a regularly updated database. The list is published on the Biosafety Council website[63]. It is worth noting that the experts are consulted not only within the scope of assessing regulatory dossiers, but also within the scope of preparing other advices for the SBB or the Council (see Chapters 3 and 4).

The consultation of external experts is an important element of the Belgium's scientific biosafety evaluation system. Indeed, it enables the consultation on a case-by-case basis of experts specialising in specific matters. It also makes it possible to involve Belgium's academic community in biosafety matters. Furthermore, many scientists see an increase in the value of their research work due to their contributions to Council and SBB activities.

[63] See http://www.bio-council.be/

It is also expected that external experts (like advisory committees in general) will provide independent advice. This can be challenging in a context where scientists specialising in a particular domain are likely to have certain economic or personal interests that risk affecting their independence. The BAC and the SBB believe that this type of situation should not prevent the use of external experts. Nevertheless, certain measures have been introduced to deal with potential conflicts of interest. The members of the BAC are required to make annual declarations of interest (and before each meeting in relation to the matters on the agenda) and external experts are invited to do the same before the assessment of each application. As for the members of the SBB, they are contractually bound to comply with the professional code of deontology and confidentiality rules.

THE BIOSAFETY ADVISORY COUNCIL AND THE SBB: THE TWO PILLARS OF THE COMMON BIOSAFETY EVALUATION SYSTEM CURRENTLY IN PLACE IN BELGIUM

The implementation of the common biosafety evaluation system was formalised in April 1997, with the completion of the *Cooperation Agreement between the Federal State and the Regions on the administrative and scientific coordination concerning biosafety.* This agreement came into force the next year, following its approval by the different levels of power concerned.

The Cooperation Agreement sets the definition of "biosafety", for legal purposes, in Belgium (Article 1). Biosafety is defined as "*the safety for human health and the environment, including the protection of biodiversity, related to the use of genetically modified organisms or microorganisms, and to the contained use of organisms pathogen for humans."*

This definition reflects the Cooperation Agreement[64]. It implies that all biological risks are managed within a single scientific and regulatory process. In this model, biological risks linked to well-known nuisances resulting from the pathological, toxicological or allergenic effects of pathogenic organisms are managed as such, but also serve as historical, medical, environmental and scientific references for the assessment and management of risks and uncertainties linked to genetically modified organisms. Biosafety applies to all types and uses of GMOs.

By providing, in this definition, for the protection of biodiversity during the use of GMOs, Belgium also established a legal link between biosafety and the concept of sustainable development, which was taken up a few years later as one of the basic principles of the Cartagena Protocol on Biosafety, an international treaty regulating the exchange of GMOs between countries (see Chapter 5).

Under this Cooperation Agreement, biosafety-related expertise is shared between two bodies in Belgium: the *Biosafety Advisory Council (BAC)* and the *Biosafety and Biotechnology Unit (SBB).*

[64] See definition of biosafety by William Moens (former head of the SBB) in "Nouvelle encyclopédie de bioéthique". Gilbert Hottois and Jean-Noël Missa. 2001. Eds De Boeck Université, 1st edition. ISBN 2-8041-3712-0.

The Biosafety Council is made up of representatives from the Federal Ministries responsible for agriculture and public health, as well as representatives appointed by the regional Ministers; the Minister of Employment and Labour and the Minister for Science Policy are also represented (Article 7(1) and (2) of the Cooperation Agreement)[65]. The BAC has 12 effective members and the same number of substitute members. Members are appointed by the King on the proposal of the Federal Minister of Public Health, for a term of four years which can be renewed.

The members of the BAC were not officially appointed until 2003[66]. Between adoption of the Cooperation Agreement in 1997 and the first official meeting of the members on 12 May 2003, the SBB temporarily performed the duties of the Council, in accordance with Article 19 of the Cooperation Agreement. During this period, all partners of the cooperation were already regularly invited to meetings, in particular during the finalisation of advices concerning applications for deliberate releases into the environment or marketing of GMOs submitted via Belgium.

The duties, structure and functioning of the BAC are described in Articles 5 to 11 of the Cooperation Agreement. The BAC advises the competent authorities regarding the biosafety of activities involving GMOs and pathogenic organisms. It can be consulted by the Regions or by the SBB for contained use activities. It must provide an advice to the competent authorities for applications relating to the placing on the market of products consisting of or containing GMOs, for applications for field trials of transgenic plants, and for applications relating to clinical trials in which a release of GMO into the environment is possible.

The BAC can also give an advice on its own initiative or at the request of a Minister. For certain matters or certain types of dossiers, the BAC can delegate some of its competences to the SBB.
In December 2003, Rules of Procedure were approved setting out administrative, management and communication working methods[67].

The Cooperation Agreement grants autonomy to the activities of the Biosafety and Biotechnology Unit in the field of biosafety and confirms them in a legal text (in particular via the provisions of Articles 12 and 18). The SBB advises the competent regional authorities in relation to the assessment of the biosafety of contained use activities involving GMO or pathogens. It provides ongoing scientific support to expert appraisal activities carried out by the BAC and runs its secretariat. The SBB also maintains its role as a permanent centre of expertise in the field of biosafety, in support of the federal and regional authorities.

In accordance with Article 12(3) of the Cooperation Agreement concerning biosafety, the SBB is also responsible for the administrative follow-up and archiving of biosafety dossiers, as well as the preservation and protection of confidential data. All dossiers introduced since 1986 are kept in the archives of the WIV-ISP and, if necessary, updated with the insertion of additional information.

[65] This composition, as defined in the Cooperation Agreement of 1997, is no longer in keeping with the institutional situation of Belgium in 2010, particularly due to the transfer of agricultural competences from the Federal State to the Regions. This is one of the arguments in favour of a revision of this agreement (see last Chapter).
[66] Royal Decree of 4 April 2003 appointing the members of the Biosafety Advisory Council (*Moniteur belge/Belgisch Staatsblad* of 6.05.2003, p. 24581), repealed by the Royal Decree of 2 September 2005 (*Moniteur belge/Belgisch Staatsblad* of 6.10.2005, p. 43156) and then by the Royal Decree of 7 October 2009 (*Moniteur belge/Belgisch Staatsblad* of 20.10.2009, p. 22774).
[67] The Rules of Procedure are available on the Council's website (http://www.bio-council.be).

Finally, the SBB ensures compliance with obligations imposed by European regulations with regard to the exchange and transmission of information and reports (Article 12(4) of the Cooperation Agreement). The Cooperation Agreement (Article 12) also gives the SBB the task of running the secretariat of the Belgian delegation within the framework of international missions (see Chapter 5).

Financing the biosafety evaluation system

The Cooperation Agreement of 25 April 1997 stipulates that the biosafety scientific evaluation system is to be financed by both the Federal State and the Regions.
The Regions fulfilled their contractual and financial obligations set out in Article 18 of the Cooperation Agreement well before it was officially adopted. Indeed, agreements were set up between the WIV-ISP and the Regions in 1993 for the Brussels Region, 1994 for the Flemish Region and 1995 for the Walloon Region, in relation to the implementation of Directive 90/219/EEC.
As for the Federal State, Article 15 of the Cooperation Agreement stipulates that it is responsible for the personnel, running and investment costs of the SBB, the running costs of the Council Secretariat and of the Belgian delegation at the international level, as well as Council meeting costs. Article 16 of the Cooperation Agreement also stipulates that the Federal State will cover travel expenses and expenses of experts on the common list for their participation in meetings .
This financing from the Federal State did not become effective until July 2000. Prior to that date, all the SBB costs mentioned in Article 15 of the Cooperation Agreement were met by the Scientific Institute of Public Health. Furthermore, given the lack of specific budget, experts and members of the *ad interim* Biosafety Council called upon within the scope of Council activities were not remunerated during that period.
Moreover, during the first years of its existence, the BAC did not even have a specific budget to cover expert appraisal costs directly linked to the assessment of biosafety dossiers (the Cooperation Agreement only stipulated the payment of travel and meeting expenses). Following repeated requests from the Biosafety Council, in 2007 the Federal State finally granted a structural budget to cover those costs.

G. Saelemaekers | Former Assistant Director at AMINAL

The transposition of the "contained use" Directives in the Flemish Region - My experiences with SBB

In 1993, I worked at the Environmental Technology Department of the General Environmental Policy Administration at AMINAL. My 'biotechnology' story started in a rather unusual and unexpected way in June that year. Because the director I was working for was absent at the time, I was given the task to participate in a EU meeting on GMOs in Heidelberg. I wasn't familiar with GMOs at all at the time. The only thing I knew about them was that a company in the Ghent region or the University of Ghent had done something spectacular with the genetic material of plants in 1985.

It was also not clear to me what my task in Heidelberg would be. I was only told that they would be discussing legislation on genetically modified organisms and that there was no problem for the Flemish Region as it had already implemented the directives in the Vlarem regulations. So my only reason for going to Heidelberg was to listen. I accepted the assignment and started to prepare.

There was nobody in our section who could tell me more about this subject, until someone advised me to contact Mr Moens of the IHE at the time. Our first conversation was fruitful. I received a wealth of information. The organisation (i.e. Mr Moens) was very pleased that the Flemish region was showing an interest in the GMO issue. After a few coordination meetings, I left for Heidelberg together with representatives from the other regions and the federal government. It became clear to me there that the European Directives (90/219/EEC on the contained use of genetically modified micro-organisms and 90/220/EEC on the deliberate release into the environment of genetically modified organisms) had not been adequately converted into the existing Flemish regulations. For example, the procedure of the two directives could not be directly integrated in the environmental permit system. So there was a lot more for me to do than just listen.

After the summer, the office of the Flemish Minister for the Environment was contacted to adjust the existing text for the implementation of Directive 90/219/EEC and to withdraw the implementation of Directive 90/220/EEC on field trials from the Vlarem regulations because it was deemed to be the responsibility of the federal government. From then on, the cooperation with IHE – and later WIV-ISP – and more specifically SBB would become a very important part of my activities. It would even define them. In order to adjust the conversion of Directive 90/219/EEC, I received help from IHE legist Mrs S. Wallijn. SBB provided the text for the Brussels Region to be used as a foundation for our implementation text. The Brussels Region had already completed the implementation.

SBB also insisted that the application area be extended to genetically modified organisms and pathogenic organisms for the implementation of Directive 90/219/EEC. The implementation was finally completed in 1995.

In the meantime, it also became clear that it was necessary to draft a cooperation agreement between the three regions and the federal government on the GMO issue. In the beginning of 1994, work got underway for the cooperation agreement between the regions and the federal government. SBB's cooperation was also indispensible here. What's more, it was mainly SBB that took the initiative for the cooperation agreement. That same year, more than 40 meetings were held with SBB or with the Flemish Region being supported by SBB!

Directive 98/81/EC was published in 1998 as an amendement for 90/219/EEC. An extensive committee was established in Flanders to adjust the Vlarem regulations. The committee consisted of people from industry, the Flemish Region and of course SBB. The implementation wasn't easy, one of the reasons being that a new Environment Minister had arrived: Vera Dua from the Flemish Green Party. Nevertheless, some important

changes were made to the Vlarem regulations, but it wouldn't be until 2004 that the new legislation came into force. SBB would continue to play an important role in the procedure as the body assessing and providing advice on technical dossiers. It also provided training courses for the inspectors. SBB was ready to help with anything related to GMOs in any way.

I would hereby like to offer my heartfelt thanks to all the people at SBB I worked with for their efforts, their help, their patience and their constructive cooperation. To me, it was more than a purely professional relationship. I made friends there.

The Belgian delegation in Heidelberg (from left to right: William Moens, Guy Saelemaekers, Eric Liégeois, Laurence Nick, Jean-Marc Collard)

CHAPTER 3
CONTAINED USE OF GMOS AND PATHOGENS

REGULATIONS AND THEIR CURRENT EVOLUTION

The Belgian legislation defines 'contained use' as follows:
"*Any activity in which organisms are genetically modified or in which genetically modified and/or pathogenic organisms are cultured, stored, transported, destroyed, disposed of or used in any other way, and for which specific containment measures are used to limit their contact with the general population and the environment and to guarantee a high safety level for the population and the environment*".
"Contained use" refers therefore to activities using genetically modified and/or pathogenic micro-organisms, transgenic plants or animals in a 'closed environment' such as laboratories, animal units, greenhouses and production units. They mainly include diagnostics, research and development and large-scale activities. Using GMOs in clinical trials as part of gene therapy is also considered 'contained use'.

Administrative and scientific harmonisation

As mentioned in chapter 2, Directive 90/219/EEC already specifically regulated activities of contained use at European level from 1990.
In Belgium, this Directive was transposed at regional level. This means that three decrees were to be drafted for the transposition: one for each Belgian Region. In order to ensure that the transposition of this Directive and of the Directive on the deliberate release of GMOs ran smoothly both at administrative and scientific levels, a cooperation agreement was concluded between the Federal State and the Regions.

The Regions incorporated the contained use regulations in their environment legislation. This means that contained use was linked to environmental permits for installations categorised as high-risk. When the European Directive was transposed into regional legislation, the scope was also extended to GMOs (the Directive only dealt with genetically modified micro-organisms – GMMs) and pathogens. This gave biosafety a broader meaning in Belgium referring to the management of the biological risks when working with genetically modified micro-organisms, transgenic plants and animals and pathogenic micro-organisms.

Directive 90/219/EEC was transposed in the Brussels Capital Region in 1993, in the Flemish Region in 1995 and in the Walloon Region in 1996. This was before the cooperation agreement was officially published, although its provisions had already been implemented.

In 1998, the Directive was amended by Directive 98/81/EC. The transposition of this new Directive became the responsibility of an *ad hoc* biosafety group established by the CCIEP (Coordination Committee for International Environmental Policy) in 2000[68]. This *ad hoc* group consisted of representatives from the Regions and their legal

[68] CCIEP acts as an interface between the Belgian federal and regional authorities and international environmental organisations. Its main task is to organise consultations between the federal and regional authorities to ensure that the national implementation of recommendations and decisions taken at an international level is well coordinated.

professionals. The Biosafety and Biotechnology Unit (SBB) was mandated to act as the group's secretariat and to provide expertise on the technical and regulatory GMO aspects[69]. The *ad hoc* group's main responsibility was to define the harmonisation points to transpose Directive 98/81/EC.

The *ad hoc* group's activities relating to the transposition of the Directive started on the basis of a draft decree of the Flemish Region. This draft has been developed in 1997 by the LNE administration ("*Leefmilieu-, Natuur en Energie*", which was previously called AMINAL, "*Administratie Milieu-, Natuur-, Land- en Waterbeheer*"), as part of a working group "Subcommittee on Hazardous Substances" in consultation with academics, industry and the SBB.

The various parties aimed to do more than simply review the regional decrees on the contained use of GMOs and pathogens based on the provisions of the new Directive. Other aspects were also taken into consideration, such as:

- the adjustment of the regulations to make them correspond better to what is happening in the field and to current experience, and hereby keeping protection of public health and the environment at the highest level as possible;
- suggestions from academics and industry, the competent authorities and the public;
- the necessity to integrate the jurisprudence;
- the publication by CEN (European Committee for Standardisation) of biotechnology norms which were considered a very useful technical complement to the implementation of the regulations;
- the necessity to emphasise inspection even more, including the role of the regional inspection services (according article 17 of the Directive), because the current regional regulations mainly focused on permit policy and regularisation of installations[70];
- the increasing need (including the legal obligations) for information and public participation;
- the precautionary principle, particularly in the context of the European Commission's communication on the subject (that was finally published in 2000[71]).

For the transposition of Directive 98/81/EC, it was decided to keep the extended scope including GMOs and pathogens. The environment legislation applying to installations categorised as high-risk continued also to be the general framework for this implementation. Specific regulations from each Region were also taken into account.

With regard to the draft decrees for the three Regions, the working group agreed on about twenty harmonisation points that were all included in the working group's conclusions. These were related to procedures, but also decisions on issues such as:

- the allocation of responsibilities and the management of biosafety in the installations (who are considered "users" as defined in the Directive, the appointment of a Biosafety Officer (or Coordinator) and in some cases of a Biosafety Committee);
- the management of waste resulting from activities of class of risk 1, for which Directive 98/81/EC does not impose inactivation (see text box next page);

[69] CCIEP – meeting no. 153 of February 8, 2000.
[70] This need was also in line with the establishment of the "European Enforcement Project of EU Directive 90/219/EEC" in 1998. See chapter 5 for more information on EEP.
[71] Commission communication on the precautionary principle. COM (2000) February 1, 2, 2000.

- the control by biological sampling with regard to the traceability of GMOs and pathogens.

Waste resulting from activities of class of risk 1

At the request of the competent authorities, the scientific Committee on "Genetically Modified Micro-Organisms – Bacteria and Fungi" (GMM Committee) of the Biosafety Council *ad interim* held a meeting on May 25, 2000 to assess the risks associated with biological waste management. In addition to the competent authorities, the SBB and experts of the GMM Committee, representatives from industry and NGOs were also invited. As a result of this meeting, it was decided to make the inactivation of waste resulting from class 1 activities of contained use compulsory according to a validated method. If such inactivation was not possible for technical reasons, the authorities should take the appropriate actions to guarantee the safety of human health and the environment without prejudice to the provisions of article 13 of the cooperation agreement on biosafety with regard to residual substances.

The ten months in which the *ad hoc* group on biosafety of the CCIEP worked together offered the opportunity to achieve the harmonisation referred to in the cooperation agreement on biosafety. This provided the three Regions with a foundation they could use to work further on the transposition texts.

Directive 98/81/EC was transposed for the Brussels Capital Region on November 8, 2001, for the Flemish Region on February 6, 2004 and for the Walloon Region on July 4, 2002 (this last decree being amended later by the decree of June 5, 2008 regarding procedures and various measures for the environmental permit decree of March 11,1999).

Directives 90/219/EEC and 98/81/EC have since been replaced by Directive 2009/41/EC, which consolidated Directive 90/219/EEC and subsequent amendments 94/51/EC, 98/81/EC and Council Decision 2001/204/EC.

Technical annexes to the regional decrees

As regards the transposition of the annexes of Directive 98/81/EC, it was decided to include *in extenso* the text as published in the ministerial decree of the Brussels Capital Region of September 22, 1998[72].

The annexes are technical and scientific. They are intended to help the user to assess and manage the biological risks. Taking into account their technical nature, it was of crucial importance that the annexes could be regularly updated based on the acquired experience, events in the field, scientific and technical progress and the evolution of European legislation. Every regional decree therefore provides a review procedure for the annexes.

[72] Ministerieel besluit van het Brussels Hoofdstedelijk Gewest op 22 september 1998 betreffende de herziening van de bijlagen van het besluit van de Regering van het Brussels Hoofdstedelijk Gewest van 9 december 1993 met betrekking tot de inrichtingen waarbij micro-organismen, pathogene organismen of genetisch gewijzigde organismen worden aangewend / Arrêté ministériel du 22 septembre 1998 portant révision des annexes de l'arrêté du Gouvernement de la Région de Bruxelles-Capitale du 9 décembre 1993 relatif aux installations effectuant des opérations mettant en oeuvre des micro-organismes ou des organismes pathogènes ou génétiquement modifiés (Belgisch Staatsblad/Moniteur belge, 20.11.1998, p. 37426).

Two examples of the SBB's activities resulting in the development of guidelines concerning biological risk assessment

The SBB has organised various events that are directly related to the implementation of the technical appendices of the regional legislations.
Thus, in 1995, the SBB invited Dr J. Richmond (CDC, US) to attend a conference on the rules of biosafety implemented in the United States in research and diagnostic laboratories handling *Mycobacterium tuberculosis* or bacteria that are multi-resistant to antibiotics. This conference resulted the following year in the SBB's publication of guidelines concerning laboratories handling *Mycobacterium tuberculosis* or samples contaminated with the Koch bacillus.

In May 2005, at the request of a number of biosafety professionals, the SBB organised a meeting aimed at gathering these users' requirements in order to improve the level of information provided on biological risk assessment.
The meeting was attended by 37 participants (universities, private sector and representatives from the regional competent authorities), all involved at various levels in the contained use of GMOs and/or pathogens. By the end of this meeting, the following needs had been identified:

- the need for standardisation in the field of biosafety;
- the need for detailed guidelines on biological risk assessment;
- a (standard) form containing the minimum requirements for risk assessment and containment measures;
- the need to exchange biosafety experiences and training (for biosafety managers).

In sum, the need to develop guidelines backed by examples to carry out biological risk assessment was clearly identified. The SBB was responsible for coordinating the drafting of this type of document by calling, where appropriate, on ad hoc groups of experts.

Besides the transposition of the Directive's annexes, the SBB also developed other annexes regarding the risks of vectors and inserts, cell cultures and reference lists of human pathogens, animal pathogens and plant pathogens[73] (see below).

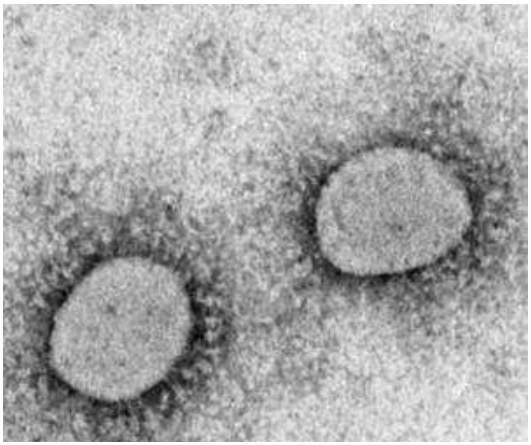
According to the cooperation agreement on biosafety, the SBB is the technical expert responsible for specifying the content of the annexes and distributing the content using all possible means. SBB specifically published articles and reports on risk evaluation of cell cultures, lentiviral vectors, manipulation of *M. tuberculosis* and practical examples of risk assessment (see text box and chapter 6). All these documents are available on the "Belgian Biosafety Server" (http://www.biosafety.be).

[73] When the Directive was transposed in the Flemish Region, certain parts of the abovementioned annexes were not included in the decree, i.e. the criteria for categorising transgenic plants and animals of risk class 1 and the criteria to classify viral vectors, inserts and cell cultures. The decree only states that these criteria are defined by the technical expert and are published on the SBB website.

Classification of human, animal and plant pathogens

The use of pathogenic (micro-)organisms can have harmful effects on public health and the environment. In order to prevent these, any biological risk linked to the contained use of these organisms should be assessed. As a first step in this assessment process, the intrinsic and potential harmful characteristics of the micro-organisms should be identified.
The harmful characteristics of natural pathogenic micro-organisms are identified based on scientific (literature) data. Based on this information, pathogenic micro-organisms can be categorised in several classes of risk (from class of risk 2 to class of risk 4, as class of risk 1 refers to micro-organisms that are not pathogenic).

The regional decrees describe the definitions of the classes of risk and the classification criteria. Three different classes of risk were described for micro-organisms that in their natural form may cause disease in immunocompetent humans and animals (classes of risk 2, 3 and 4). Micro-organisms that can cause disease in healthy plants are categorised in two different classes of risk (classes of risk 2 and 3).
In addition to describing the classes of risk, the annex to the regional decrees also includes reference lists of pathogenic micro-organisms. These reference lists were originally created in 1993 by the SBB during the transposition of Directive 90/219/EEC. They are non-exhaustive lists of bacteria and related organisms, fungi, parasites and viruses (and non-conventional agents such as prions) with an indication of the allocated classes of risk.
Due to factors such as additional scientific knowledge that has been gained since 1993, the reference lists have been reviewed several times (most recently in 2008) with regard to nomenclature, taxonomy and allocated classes of risk.



SARS coronavirus - A negative contrast transmission electron microscopy image of SARS coronavirus. (Credit: Charles D. Humphrey, Centers for Disease Control and Prevention, USA)

This review also aimed to create lists that would be sufficiently representative for the range of micro-organisms present in Belgium or (possibly) involved in contained use activities. The option was offered to include additional organisms in the list, such as those at the origin of newly emerging diseases (see text box next page).

Proposed classification of SARS Coronavirus

Severe Acute Respiratory Syndrome (SARS) is a respiratory disease that originated in the Guangdong Province in China. The first case was identified in mid-November 2002. The syndrome then spread to Asia, North America, Africa and Europe. A total of 8,422 suspected and probable cases of SARS, including 912 deaths, had been reported to the World Health Organisation (WHO) by late summer 2003. In response to this epidemic, the WHO coordinated an international collaboration which included clinical, epidemiological and laboratory investigations. The WHO initiated the efforts required to monitor the spread of SARS.
Based on data gathered during the epidemic, the etiological agent of SARS was identified as a new coronavirus.
Following cases of laboratory acquired disease in Singapore and Taiwan, biosafety issues relating to the required containment and work practices were raised.
In Belgium, at a time when no SARS cases had been reported, three laboratories requested authorisation to be able to handle this emerging virus for research purposes or to get the development of a vaccine off the ground. It was therefore necessary to carry out a quick analysis of the files relating to these requests, determine with certainty the class of biological risk and formulate biosafety recommendations adapted to this pathogenic organism which was still not widely known. To meet this need, the SBB set up an ad hoc working group in May 2003. This group comprised virologists from the country's different universities and experts from the Institute of Tropical Medicine in Antwerp, the Institute of Public Health (WIV-ISP) and the Veterinary and Agrochemical Research Centre (CERVA-CODA, Brussels). Based on the data available at the time and after an in-depth assessment of the biological risks, the ad hoc group proposed the risk group 3 for the SARS Coronavirus. Based on this conclusion, detailed biosafety recommendations for handling the virus were drawn up by the SBB. In June 2004, the findings of the ad hoc working group were published in the journal of the American Biological Safety Association[74].

The most recent review in 2008 occurred in various steps. The first step was a review of the taxonomy coordinated by BCCM (Belgian Coordinated Collections of Micro-Organisms) and the Divisions of Mycology and of Biosafety and Biotechnology of the Scientific Institute of Public Health (WIV-ISP). In order to review the classes of risk, the new lists with revised taxonomy and nomenclature were then presented to various *ad hoc* working groups gathering together experts from the SBB and experts in bacteriology, virology, parasitology and mycology with regard to human, animal and plant pathology. These working groups established whether new scientific literature information met the set definitions of the classes of risk and verified whether a change in class of risk could be justified for certain micro-organisms. Various classification lists (from the UK, Germany, Switzerland, The Netherlands and the European level) were taken into consideration. Consultation meetings were held to ensure that the definitions were unambiguously interpreted and that an agreement was reached with regard to the allocation of the classes of risk.

The reviewed lists were made available in 2009 on the web pages of the Belgian Biosafety Server[75], the final objective being to include them in the regional decrees.

[74] Herman P, Verlinden Y, Breyer D, Van Cleemput E, Brochier B, Sneyers M, Snacken P, Hermans P, Kerkhofs P, Liesnard C, Rombaut B, Van Ranst M, Van der Groen G, Goubau P, Moens W. Biosafety Risk Assessment of the Severe Acute Respiratory Syndrome (SARS) Coronavirus and Containment Measures for the Diagnostic and Research Laboratories. Applied Biosafety, 2004; 9(3):128-142.
[75] http://www.biosafety.be

THE PERMIT SYSTEM AND PROCEDURES

The three regional decrees describe various permit procedures, depending on the situation or installation where contained use activities take place and whether or not an environmental or operational permit has been obtained for the contained use of GMOs or pathogens (*Figure 3.1*).

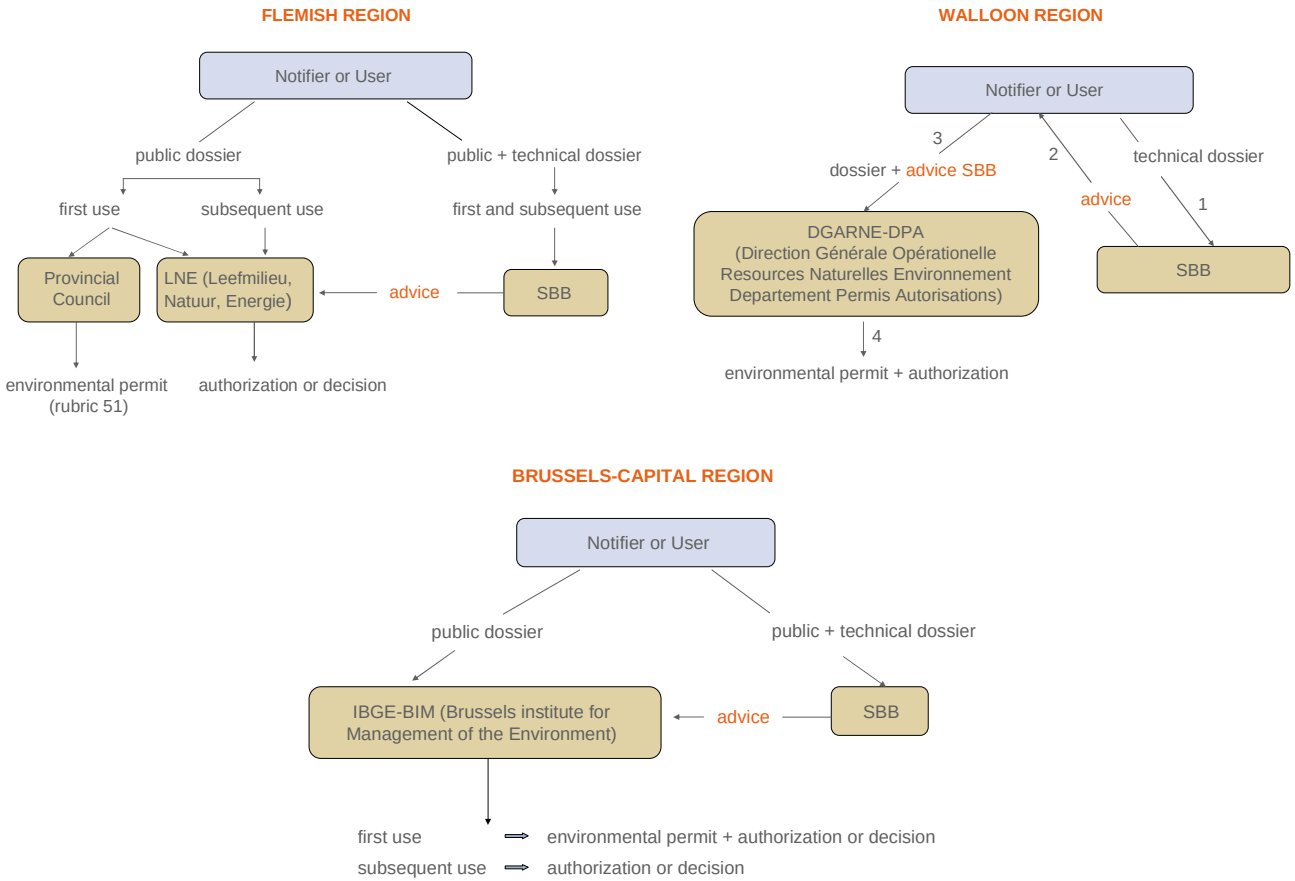


Figure 3.1 | *Regional decrees on contained use of GMOs and pathogens Procedures in the Flemish, Brussels and Walloon Region*

However, permit procedures themselves can also differ between Regions. The Walloon Region does not make a distinction between "first" and "subsequent use", but the Flemish Region and Brussels-Capital Region do (see below).

When an activity of contained use is reported for the first time to the competent authorities, the "first use" procedure applies. In this case, the operator has to apply for an environmental or operational permit or an extension of his existing permit for the contained use of GMOs and/or pathogens. This procedure also applies to the regularisation of installations already active in this respect when the regional decrees came into force.

However, if the installation already has the required environmental permit and has completed the "first use" procedure, the "subsequent use" procedure is followed. This involves either a new activity, a change in activity or a continuation of an activity for which the permit term has elapsed.

With regard to the notification procedure, the notifier submits a technical dossier and a public dossier containing the required information related to the biosafety assessment of the activities performed in an installation. The notifier can consult the SBB to obtain the necessary explanations to draft the dossier. In order to make the notifier's task easier, but also to ensure that all the required information is provided in the dossier, the SBB developed template forms in cooperation with the competent authorities.

The technical dossier contains a detailed description and risk evaluation of the scientific activities (including possibly confidential data), the infrastructure, work practices, waste management and all information enabling the technical expert (SBB) to assess the suitability of the containment measures for the activities.
The unique copy of the technical dossier is sent to the SBB. Apart from the SBB experts and the authorised regional officials, access to the technical dossier (excluding non-confidential data) is limited and only possible via a very strict procedure[76].

The public dossier is a vulgarised, non-confidential summary of the technical dossier. It is sent together with the technical dossier to the SBB (which will verify on behalf of the local authority whether the information in the technical and public dossiers is consistent) and also to the regional competent authority.

If a new environmental/operational permit or its extension is required, the regional procedures foresee a mandatory public consultation phase in which the public dossier can be viewed by every citizen at the local administration.

The SBB plays a central role in scientific expertise tasks related to the application of the regional decrees. It acts as a technical expert for the regional competent authorities and provides motivated advice on the risk assessment of contained use activities.
The evaluation of the biological risks is performed by the notifier according to internationally accepted methodology and principles described in chapter 1. The objective of a risk assessment is to evaluate the probability and seriousness of a potential negative effect on public health and the environment with respect to the

[76] As stated in Directive 2003/4/EC of the European Parliament and the Council of January 28, 2003 on public access to environmental information and repealing Council Directive 90/313/EEC.

relevant activity based on the available scientific information. The risk assessment is performed on a case-by-case basis for each new organism, each new technique and each change with regard to the activity's scale. The conclusions of such an assessment are in the motivated advice written by the SBB. Based on SBB's advice, the competent authorities define in the permits they provide conditions that the notifiers must observe for every used GMO or pathogenic organism.

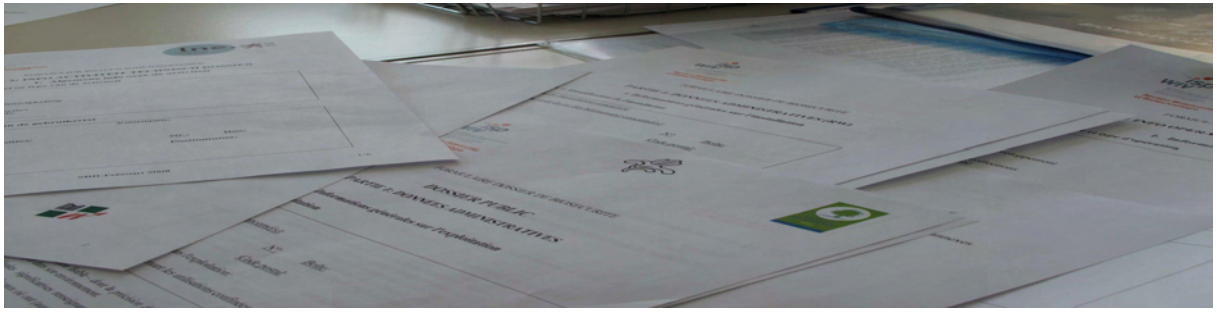
When the SBB has acknowledged receipt of a dossier to the notifier, its task is:

- to verify the file's conformity with the legal requirements;
- to establish whether the data of the public and technical dossiers are consistent and verify the confidential character of data indicated as such;
- to send a certificate of conformity to the competent authority, confirming that the contents of the public and technical dossiers correspond;
- to assess the suitability of the premises and containment measures for the proposed activities;
- to establish whether the provided information is complete, whether the risk assessment and suggested containment measures are correct, whether the waste management is appropriate, whether the prevention measures correspond to the activity's objective and used biological material;
- to send motivated advice to the competent authorities within a fixed period;
- to ensure that the dossiers are archived.

In the Walloon Region, the biosafety dossier – which only contains a technical part – is only sent to the SBB. The SBB sends its advice directly to the notifier, who adds it to the environmental permit application.

Depending on the activity's procedure and class of risk, the regional competent authority will or will not deliver a permit, of which the term must not exceed the end date of the environmental or operational permit.

Certain GMMs belonging to class of risk 1 can be exempt from the application of the contained use legislation if they are developed according to certain techniques as stated in annex II, part A of Directive 2009/41/EC.
The regional decrees of the nineties transposing Directive 90/219/EEC stated that exemptions could only be granted based on positive advice from the SBB. This legislation also made it possible for the SBB to write an authentication certificate for GMMs of class of risk 1 that meet the criteria of annex II to the abovementioned Directive, giving them a GILSP (Good Industrial Large Scale Practice) status. This still applies to the current



regional decrees, but in the Flemish Region GMMs are now automatically exempt if they meet the criteria of annex II, part A of the current legislation. In the other two Regions, this is only possible based on positive advice from the SBB.

The specific case of gene therapy involving clinical trials with a GMM is also governed by the regional legislation on contained use. Federal legislation on deliberate release of GMOs into the environment also applies to certain cases such as clinical trials with GMMs that may be excreted, clinical trials for ambulatory medicine and multi-centre clinical trials. In such cases, advice on the clinical trial's environmental risk assessment is provided by the Biosafety Advisory Council (see chapter 4).

We should remember that the cooperation agreement on biosafety states that the Regions can consult the Biosafety Advisory Council on any provisions regarding the contained use of GMMs and/or pathogens (article 6). Until now, this option has only ever been used once in the year 2000 for generic advice on managing waste resulting from activities of class of risk 1 (see above).

APPLICATION OF REGIONAL LEGISLATION

As already set out in the previous chapter, one of the SBB's key missions is to provide ongoing scientific support to the federal and regional authorities on the risk assessment of genetically modified and pathogenic organisms.

Any activity using GMOs or pathogens in the laboratory, animal house, greenhouse, hospital room or large-scale production installation is subject to authorisation by the regional authorities. The establishments concerned are mainly universities, government scientific institutes, pharmaceutical companies and clinical diagnosis laboratories. A few companies carrying out microbiological tests as part of product quality control or environmental monitoring are also concerned.

Between 1994 – the first year that legislation concerning the contained use of GMOs or pathogens was applied – and the end of 2009, no fewer than 3,000 motivated advices on operations relating to 1,125 files were issued in total by the SBB to the regional authorities (*Figure 3.2*).
Of these, only two were appealed. The notifiers objected to the imposed containment measures which, in their opinion, were too severe in relation to the risk and requested that the conditions imposed in the permit be adapted. The adaptation of the conditions for use was accepted in one of the cases.

Contained use activities can be divided into two main groups: those involving only GMOs and GMMs (44% of activities) and those involving only non-GM pathogenic organisms (37% of cases). Mixed activities in which pathogenic organisms and GMOs/GMMs are handled account for 16% of cases. We should point out that, following assessment by the SBB, 3% of notified activities prove to be outside the scope of the Decrees relating to contained use. In this case, authorisation relating to contained use is not required. The first regional Decrees made provision for exemption and application certification procedures for risk group 1 GMMs and GMOs (see the section "Authorisation system and procedures"). On this basis, the SBB had dealt with 16 requests for GMM exemption and 22 requests for risk group 1 GMM certification until 2002. At the time of writing, there have been no further requests for exemption or certification.

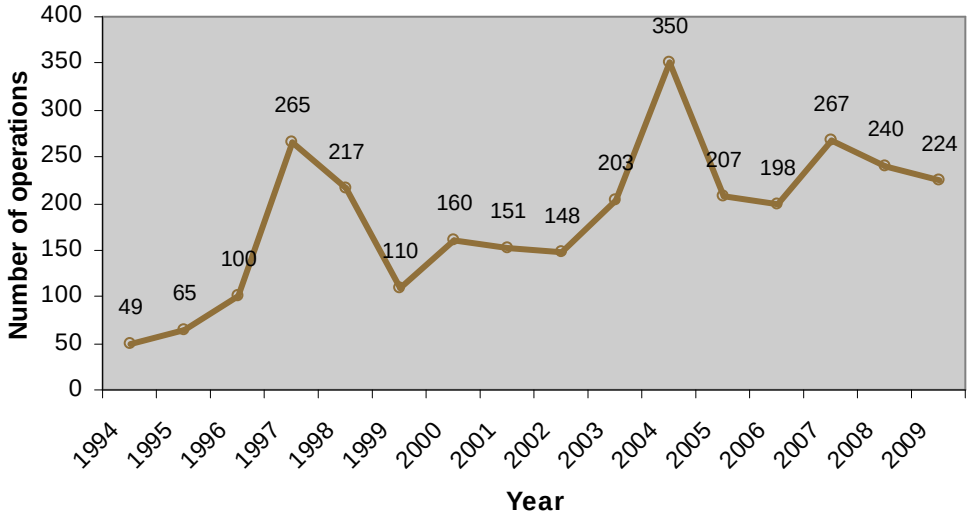


Figure 3.2 **|** *Contained use of GMOs and pathogens – Change in the number of notified operations in the three Regions (period 1994–2009)*

Besides the technical and scientific support provided to the authorities, the SBB is also at the disposal of users to help them prepare their applications, for example by guiding them in the biological risk assessment and organisation of their activities based on this assessment. To do this, users can consult the SBB before submitting applications. Since 1994, the SBB has carried out more than 550 consultations, peaking significantly in 1997 when the first Decrees were implemented in which prior consultation was compulsory. The obligation to consult the SBB is no longer required under current legislation, which explains the significant reduction in the number of consultations since the early 2000s, although these are still possible.

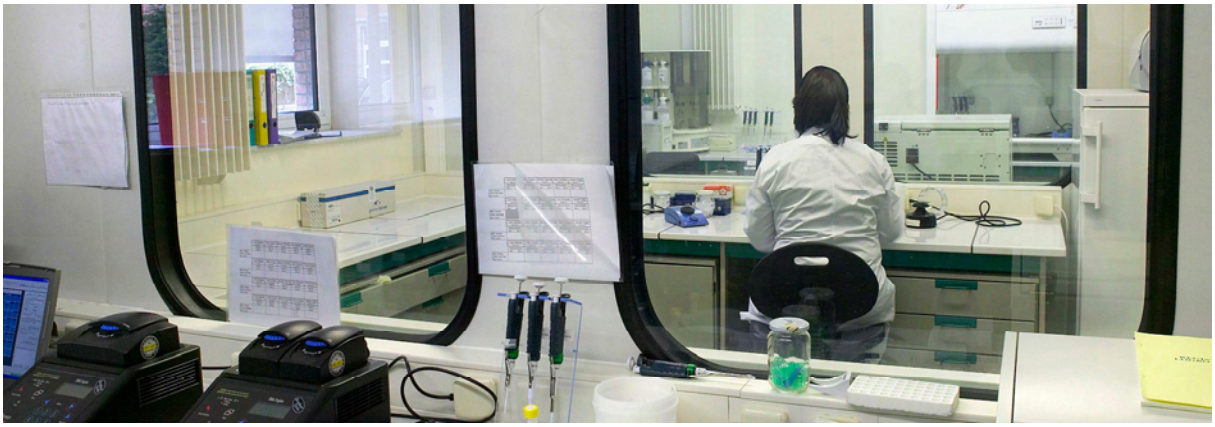
High-level containment laboratories

The contained use of GMOs and/or pathogens is categorised from 1 to 4 according to an increasing scale of risk (see Chapter 1). Level 3 and 4 facilities are regarded as high-level containment facilities.
In Belgium, the number of notified level 3 containment facilities currently stands at 79 since the implementation of the regulation on contained use (*Figure 3.3*). This figure includes laboratories (L3), large-scale production facilities (LS3) and animal houses (A3). There are no level 4 facilities recorded in Belgium.

These high-level containment laboratories are home to activities such as the handling of GMMs of class of risk 3 (for example: the Hantavirus or the GM *Brucella melitensis* bacterium), the large-scale production of certain recombinant viral vectors and the specific handling of highly pathogenic non-GMMs for man or animal (e.g. *Mycobacterium tuberculosis, foot-and-mouth disease virus*).

These facilities can be located in universities and Federal scientific institutes (24%), companies and private laboratories (40%) and, finally, hospitals and clinics (15%). It can be considered that all Belgium's high-level containment facilities have currently been notified.

We should emphasise that, among the clinical microbiology activities, the diagnosis of tuberculosis requires special attention from the point of view of biosafety as the disease is caused by *Mycobacterium tuberculosis*, an airborne risk group 3 bacterium. Based on the updating of scientific know-how, the technical progress observed and the information obtained from experts in the field, the SBB adapted the containment measures relating to the handling of *Mycobacterium tuberculosis* in 2006. The conditions imposed on clinical laboratories until then were very strict: for example, cultures could never be opened during or after the growth of mycobacteria, even to take samples through a septum using a needle. Opening the tubes was only permitted in a high-level containment laboratory (L3). As it happens, with the current culture methods, a significant proportion of false positives was observed, unnecessarily overburdening the L3 laboratories. In response to the difficulties encountered, the specific conditions adapted to the primo-identification of mycobacteria have been updated[77].



[77] Herman P, Fauville-Dufaux M, Breyer D, Van Vaerenbergh B, Pauwels K, Do Thi CD, Sneyers M, Wanlin M, Snacken R, Moens W. Biosafety Recommendations for the Contained Use of *Mycobacterium tuberculosis* Complex Isolates in Industrialized Countries. 2006. Réf. D/2006/2505/22. Available on the "Belgian Biosafety Server".

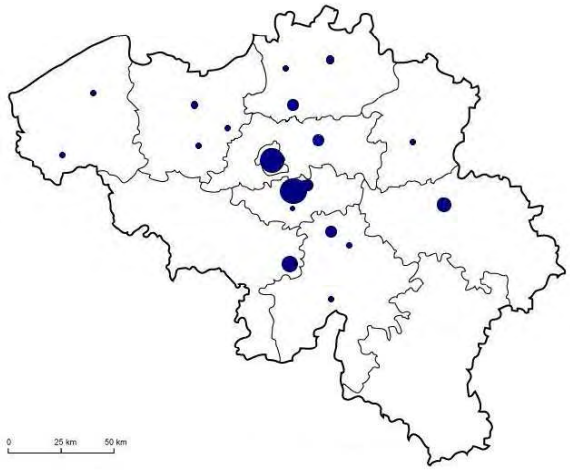


Figure 3.3 *| Location of high-level containment laboratories in Belgium. The blue dots indicate where the level 3 containment facilities are located. The size of the dots is proportional to the number of facilities in the commune or town*

In addition to the 79 facilities previously mentioned, there are 25 high-level containment laboratories that screen for cases of bovine spongiform encephalopathy using rapid tests (L3-BSE) (see below). These laboratories represent a special category as they are not required to meet all the technical characteristics of a standard L3 laboratory, but rather comply with the work practices and very strict waste management, given that the prions are particularly resistant to the conventional inactivation methods.

Evolution of notifications over time

Regional legislation came into force on different dates, namely 1994 for the Brussels Region, 1995 for the Flemish Region and 1996 for the Walloon Region. Thus, differences were observed from one region to the other in the number and distribution of notifications of contained activities over time.

The policy for implementing Decrees also varied from one region to the next.
In the Brussels Region, the implementation of legislation was accompanied by the sending of an informative letter to the operators of all types of potentially targeted facilities, inviting them to take the necessary steps to regularise their facilities. This letter was followed by a request for regularisation from most of these facilities in the first few years after the legislation was adopted.

The Walloon Region chose to send an informative letter to the potential operators of sites conducting clinical diagnosis activities. Shortly afterwards, the SBB organised group briefing sessions specifically for clinical diagnosis laboratories. These actions resulted in a significant number of requests for authorisation from medical and paramedical facilities such as hospitals, non-teaching clinics and analysis laboratories. The notification of other types of facility (universities, pharmaceutical companies) was more staggered.

In the Flemish Region, no letter was sent to potential notifiers. The requests for regularisation were therefore submitted gradually over the years. Another specific component of the Flemish Region lies in the fact that the European Directive was transposed into the Flemish decree VLAREM II under the title "Biotechnology". Due to a misinterpretation of this title, clinical diagnosis laboratories have long believed they were not affected by the legislation. Notifications relating to this type of facility have only been made since 2002, driven by a series of actions undertaken by the SBB such as working group meetings, conferences and joint consultations for laboratory managers, as well as the development of web pages on the "Belgian Biosafety Server"[78].

We should point out that, with regard to clinical diagnosis laboratories, it has proved necessary to clearly indicate that only microbiology laboratories conducting research and the deliberate multiplication of pathogens were affected by the regional regulations on contained use.

Besides clinical diagnosis laboratories, we have noted a major difference in the implementation of legislation between companies working in the field of biotechnology on the one hand and university research laboratories on the other.
Companies experienced few problems in applying the contained use legislation as they frequently boast long-standing experience in the application of international quality standards; their development and production activities are largely homogeneous and relatively stable over time; they have access to the financial and human resources necessary to implement this type of legislation.
Conversely, universities had to make a greater effort to apply the legislation in a coordinated manner. This is because their facilities are often located over several sites covered by different environmental permits or operating licences; a broad panoply of assorted activities are carried out there which vary considerably over time; significant rotation of the staff working there can be observed; their management is complex and poorly centralised; by their very nature, few university laboratories apply international quality assurance standards; any costs associated with compliance with biosafety standards are an obstacle for some university laboratories.

This explains why the notification of activities carried out in universities and research centres was made gradually. It must be emphasised, however, that the integration of decrees concerning the contained use of GMOs and pathogens within the general scope of environmental permits was definitely instrumental in prompting these notifications. This is because the notification of activities involving the contained use of GMOs and pathogens is automatically required by the regional authorities whenever making any application to build a laboratory or carry on activities that involve GMOs or pathogens.
Furthermore, in the case of research activities, the granting of subsidies by official bodies has for many years been linked to the obligation to be in possession of the requisite licences, notably for contained use.

[78] http://www.biosafety.be

All regions combined, the activities carried out in universities and government institutes represent the lion's share (43%) of all the notified activities (*Figure 3.4*). This is followed by clinical biology activities in hospitals and analysis laboratories (35%), then industrial and private laboratory activities (22%).

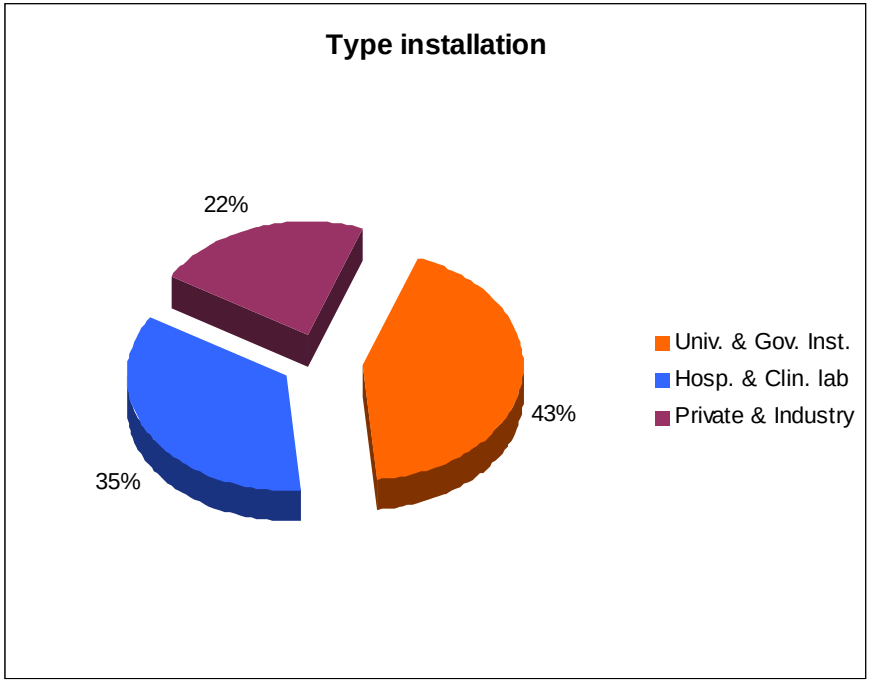


Figure 3.4 |*Distribution of the contained use of GMOs or pathogens by type of installation*

The implementation at regional level of the regulatory framework relating to the contained use of GMOs and/or pathogens has unquestionably heightened awareness of the biosafety aspects at user level. Even though safety measures were already adopted most of the time in the concerned facilities, the implementation of regional legislation helped to formalise and standardise the risk assessment of activities and the application of containment measures and work practices adapted to the identified biological risk. Such a tradition already existed in the industrial sector but was an innovation for many universities and public bodies. The implementation of biosafety measures in laboratories has also been greatly facilitated since 1994 by the setting up of local biosafety committees, staff training and monitoring, the drafting of manuals so that biological material can be used

in complete safety, the reorganisation, where appropriate, of the infrastructure and the creation of large databanks of biological material, etc.

It is also worthwhile pausing a while to discuss the role that has been played for a number of years by the biosafety officers appointed in each installation.
The appointment of a biosafety officer and the setting up of a biosafety committee became compulsory when Directive 98/81/EC was implemented in regional Decrees. Belgium was one of the few Member States that included this obligation in its legislation, thus drawing its inspiration from the UK where the tasks and duties of the "biosafety officer" had already been defined by the Health and Safety Executive (HSE).

In the first few years following the implementation of Directive 90/219/EEC, the competent authorities ensured, above all, that all the concerned facilities complied with the legislation. Once Directive 98/81/EC had been transposed, the main emphasis was placed on monitoring and inspection. Besides external checks carried out by the regional inspection services, the biosafety committee or the biosafety officer also monitors compliance with the biosafety measures adopted in the facility. The biosafety officer is therefore the ideal point of contact for the competent authorities and the SBB. On a proposal from the SBB, the biosafety officer's tasks have been listed in the regional Decrees. The tasks assigned to him are based on specific expertise and know-how. However, until now there has not been any structured training in Belgium.

A few initiatives aimed at organising such training have been undertaken but there is still no framework for issuing an attestation or official certificate that recognises the title of biosafety officer. However, since 2005, the SBB has expressed its interest in using its expertise and know-how to make such an initiative concrete. Contact was made with the competent authorities, then, in 2006, the SBB organised a meeting with the representatives of the operators concerned, namely universities, colleges and the Belgian Biosafety Professionals (BBP). This meeting helped to establish the guidelines for standardised training, enabling biosafety officers to gain the know-how and qualifications necessary for their position. The training would cover different topics such as "Regulation and Standards", "Risk Assessment", "Risk Management" and "Communication", where appropriate tackled at varying levels of complexity. Space would also be left for complementary training modules, for example to cover topics such as microbiology or molecular biology. Unfortunately, this initiative has until now not resulted in any concrete action. However, we would point out that actions in this sense have been implemented for a number of years by the European BioSafety Association (EBSA) (see Chapter 5).

In sum, the transposition of European directives and their implementation in Belgian legislation have enabled the SBB and the competent authorities to gain a general overview of all the possible contained use activities under way or planned in Belgium, whether at diagnostic, research or industrial biotechnology level.
Furthermore, it may be that certain research activities in a contained environment will develop towards applications that would then fall within the scope of the legislation concerning the deliberate release of GMOs. The monitoring of these activities may provide the competent authorities and the SBB with the opportunity to be prepared for the likely arrival of applications.

Let us quote as examples the in-laboratory construction of plants tolerant to a herbicide that will be subsequently used in field trials or for commercial purposes, and viral vectors that will be used in multicentre clinical studies as part of gene therapies.

Danielle Caucheteux | Head of Biosafety GlaxoSmithkline Biologicals

Reflections on the role and tasks of the Biosafety Officer

GSK Bio, formerly RIT, Smithkline RIT, and Smithkline Beecham, is an international company that since 1956 has used biological material (cells, tissues, bacteria, viruses, yeasts) in the production of vaccines for human use. It therefore had to deal with the risks linked to the use of pathogens and then GMO from very early days.

From the 1980s, the company created the position of "Biosafety Officer" in research and development. This position was under the management of the Scientific Director of the department. This role was challenging as its aims were to design the first biological safety laboratories (BL1, BL2, BL3), establish working practices and emergency procedures, provide the first courses in biosafety to company workers, audit on the ground practices and build the first contained production areas, in collaboration with a team of engineers and production personnel. At that time, the biosafety approach was mainly used in research, was unidisciplinary, largely based on the characteristics of the "biological agents" used and did not include their use. From then on, assigning the required containment levels for protecting exposed workers and the environment was based on the class of risk of the microorganisms used.

1996 was a critical year for safety including biological safety in Belgium. The Law on welfare at work as well as certain Decrees related to it (including one dealing with the protection of workers from risks related to exposure to biological agents at work) were published on 4 August 1996. Risk management should now be global and performed through a dynamic risk management system. In order to comply with this legislation and to ensure an overall understanding of risks, the Biosafety Officer and their assistant were transferred into the "SIPPT" (Internal Department of Prevention and Protection at Work) and worked under the direction of the Prevention Advisor in charge of the department. Other challenges also awaited the company and the Biosafety Officer's team, as since the promulgation of the Decree of the Wallonia Government (AGw) of 13 June 1996, it was bound to carry out an authorisation request for first use of GMO and pathogens that have already been used, sometimes for more than 25 to 30 years. These federal and regional legislations have contributed to change the role of the Biosafety Officer, promoted into "Biosafety Manager" at GSK Bio. Whereas previously, the role was essentially internal to the company and required thorough scientific knowledge as well as the ability to communicate with users (researchers, production personnel, engineers, etc.), the role took on a greater scope and, in addition to the skills already described, required general safety and environmental knowledge together with strategic qualities for drafting permit requests and negociating skills in order to collaborate effectively with the competent authorities.

The AGw of 4 July 2002 that regulated the role and tasks of the Biosafety Officer had little impact at GSK Bio as the company had already created such a position around 20 years earlier. Nevertheless, its Annexes as well as guidance from the SBB for drawing up biosafety dossiers are an invaluable aid in the assessment of risks and promote therefore a "risk-based approach" in order to define the appropriate prevention and protection measures.

The CWA 15793 "Laboratory Biorisk management standard" suggests a structured approach to the management of "biorisks". This approach is based on international standards such as OSHA standards 18001 and ISO 14000, which had already been in force at GSK Bio for several years and it highlights the significance of having an effective biosafety programme "in place and in use" (known and respected by all those involved). The approach is also very innovative in that it deals with not only the deliberate and non-deliberate use of biological agents but also the possibility of their malicious use. The consequences are therefore important for GSK Bio who currently employs more than 7,000 people in Belgium and the Biosafety Officer will, in time, have to collaborate with experts in safety and human resources in order to manage "biorisks" in a global and effective way.

In the pharmaceutical industry, the Biosafety Officer is increasingly confronted with the significant requirements of Good Manufacturing Practices (GMP). The aim of these standards is to ensure an effective "product" (vaccine) that is absolutely harmless for those to whom it will be administered. In the majority of cases, there is no clash between measures required by GMP and biosafety. Very rarely, there may be opposition. In this case, a thorough and multidisciplinary risk analysis is necessary in order to reach a consensus and set solutions acceptable to both parties. Thanks to organisations such as the European Biosafety Association (EBSA) and the Belgian Biosafety Professionals (BBP), it is relatively easy to find experts within this network of biosafety professionals, who have a forward-thinking and independent vision when these processes are carried out.

I would like to add that GSK Bio has always attached great importance to the relationships that it has with the SBB experts and readily contact them with any queries. It appreciates the openness of these experts, their ethics as well the quality of their delivered opinions.

In conclusion, in a pharmaceutical company such as GSK Bio, the job of Biosafety Officer has evolved in order to face the changes resulting from its growth but also in order to comply with current legislation and standards. The job, which was, at the beginning, an on-the-ground expert appraisal mission, has evolved into the role of manager. Biosafety Officer is a fascinating job. It provides an overall view of activities, working within a network of experts from different disciplines and therefore enabling the development of new skills.

Control and inspection

The regional decrees on contained use implement article 16 of the current Directive 2009/41/EC by providing inspection and control.
In Belgium, contained use was implemented as part of environmental legislation, so the environmental inspection services of each Region are responsible for inspections. When the inspection service was set up in the Flemish Region and the Regions had given their joint approval, this task was allocated firstly to "Toezicht Volksgezondheid" (Public Health Supervision) of the Flemish Community, as the environmental inspection services were facing a lack of staff at that time. It wasn't until 2005 that a team was set up in the Environmental Inspection Department ("Leefmilieu inspectie") to monitor installations where contained use activities take place. In Wallonia and Brussels, the inspections are carried out only by the environmental inspection services.

In addition to undertaking many other environmental legislation activities (controlling air, water and soil quality, noise pollution, etc.), these inspection services were now also responsible for inspecting the very complex matter of contained use of GMOs and pathogens. Training and technical support for these inspection services were therefore required. Under the agreements with the Regions regarding scientific and technical support to the competent authorities, this task was given to the SBB.

Since 2002, the SBB regularly organises training courses on risk assessment and risk management for the various inspection services in Belgium (three Regions and the Flemish Community). The first objective is to provide an introduction to risk assessment by providing a better understanding of the intrinsic biological hazards when using pathogenic and/or genetically modified organisms in laboratories, laboratory animal facilities or greenhouses.

The second objective focuses on the necessary and appropriate containment measures to restrict the risks for public health and the environment to a minimum. This includes in-depth explanation of adequate containment measures such as personal protection measures and the correct use of biosafety equipment. This means that an appropriate balance should always be struck between reflecting the required/recommended/optional containment measures for each containment level as unambiguously and as fully as possible on the one hand and approaching each contained use activity as an individual case on the other hand. At the request of the competent authorities and the inspection departments, the SBB therefore further specified certain containment criteria. This information is shared by organising (annual) training courses, updating web pages and providing *ad hoc* advice.
The SBB also introduced this type of inspection to other European inspection services by participating in the activities of EEP ("European Enforcement Project"), the European network of inspectors involved in contained use and deliberate release of GMOs (see chapter 5).

The three Regions employed different inspection strategies. The inspection services of the Flemish Region focus on activities that have been notified and the Walloon Region inspects all installations with contained use activities regardless of whether the competent authorities have been notified. The Brussels-Capital Region first inspects installations with the highest containment level.
If important violations are established during inspection, the supervising authorities set certain terms within which the inadequacies must be solved. In case of severe violations, the supervising authorities can stop the activities or close the installation.

Supervision generally contributes to better awareness of the concept of biosafety, resulting in many efforts to adjust and improve containment measures and so restrict the biological risks to human health and the environment to a minimum.
As more inspections were performed and inspectors were faced with practical problems in the field, a number of bottlenecks emerged. These problems mainly involved the scope of the legislation and difficulties with regard to the interpretation of some of the legislation's containment measures, which were too vague and needed to be made more specific. For example, it was never clear whether the legislation also applied to quality control laboratories only performing colony-forming unit counts without further identification of the pathogens or companies only storing and distributing GMMs without any manipulation.

Emergency planning

Still with the aim of minimising the potential harmful effects of the use of GMMs in a contained environment, Directive 2009/41/EC pays particular attention to accident prevention and management and imposes the requirement on Member States (Article 14) to establish emergency plans in order to react effectively in the event of an accident. To do this, any user concerned must send the necessary information to the competent authorities so that they can assess the risks and adopt suitable measures to provide rapid, coordinated assistance during an emergency. The Directive also provides for a notification procedure in the event of an accident (Article 15). The Commission and any Member State that might be affected by the accident must also be informed.

Chronologically, these articles were firstly transposed into the regional Decrees concerning the contained use of GMOs and/or pathogens. As seen in Chapter 2, the scope of Directive 90/219/EEC (restricted to GMMs) was extended to GMOs and pathogens in Belgium. The regional Decrees therefore stipulate that users submit the information required to establish an external emergency plan to the regional authorities which will consult the competent minister (FPS Interior) in order to draw up the emergency plan. An external emergency plan is required for risk group 2 contained use (large-scale production only) and for risk group 3 and 4 contained use.

In Belgium, the drawing up of external emergency planning is managed by the FPS Interior, and the associated exercises come under the responsibility of the Government Crisis Centre (see text box).

Emergency planning relating to GMMs

At its meeting of 19 December 2003, the Council of Ministers took the decision to invite the provincial and communal authorities to draft emergency plans for the contained use of GMMs. The current legal framework of this decision is the Ministerial Circular of the FPS Interior of 4 August 2005 (Belgian Official Gazette, 21/12/2005, p. 54623). A more general reference on the subject is the Royal Decree of 16 February 2006 relating to emergency plans (Belgian Official Gazette, 15/03/2006, p. 15407).

Since 25 January 2005, an agreement has been entered into between the Minister of the Interior (General Civil Security Division) and the SBB of the Scientific Institute of Public Health (WIV-ISP). This agreement stipulates that the SBB will give its opinions on the drafting and updating of emergency plans, draw up forms for assessing these plans and advise on the relevance thereof.

In the event of an accident, the SBB will provide scientific and technical expertise to the fire services and operational units of civil protection. This latter task implies that the SBB is able to respond via a telephone number

manned round the clock to the competent authorities in the event of an accident associated with the biological risk occurring in an installation located in Belgium.

The manager of an activity involving the contained use of GMMs must provide all the information necessary for drawing up an emergency plan, accompanied by an advice expressed by the SBB to the authority of the commune where the activity takes place, and send a copy to the provincial authority. To simplify the task of users, the SBB has drawn up a form and user guide for those responsible for activities, based on Appendix V, parts A, B and C of Directive 2009/41/EC.

Since the procedure was implemented, the SBB has issued 32 advices on emergency plans and organised several briefing sessions for the competent authorities. FAQs and web pages intended to inform the competent authorities and users have also been published. The SBB has also prepared a biosafety glossary for operators in the field. This glossary[79] includes the main biosafety terms found in emergency plan files. An annual activity report is sent to the competent authority.

Example of accidental spread in the UK

The accidental spread into the environment of the foot-and-mouth virus that occurred in Pirbright in the UK in 2007 demonstrated the paramount importance of drawing up an emergency plan, although in this case it was not a GMM but rather a pathogenic organism that was involved. The foot-and-mouth virus is a risk group 4 pathogenic organism affecting animals and is non-pathogenic in man. The disease is infectious and contagious and cannot be treated, although a vaccine does exist. The only effective way of containing it is to slaughter all potentially infected animals and take restrictive measures aimed at preventing the geographical spread of the virus. These measures have major economic consequences for both the farms and the country or countries affected. A case of foot-and-mouth disease was identified on 3 August 2007 at a farm in Surrey. A second farm, a few kilometres away from the first, was also affected a few days later. Consequently, all cattle transportation was banned in England, Scotland and Wales and 576 animals were slaughtered in the affected area.
The rapid implementation of a ban on cattle transportation, along with the demarcation of a 10 km surveillance perimeter around the affected farms and the decontamination of people and vehicles entering or leaving the perimeter helped to prevent a more wide scale spread of the disease.
An investigation into the origin of the virus revealed the involvement of the Pirbright site, at which two research centres were affected: one producing vaccines against foot-and-mouth disease on an industrial scale, the other being a government institute carrying out research into the virus. Based on the findings of the investigation, it was inferred that the viral contamination was probably linked to a containment breach resulting in an accidental spread of the virus into the environment.
It is worthwhile emphasising that following this accident and the Callaghan report, the British competent authorities embarked upon a complete overhaul of their legislation on the contained use of GM and non-GM pathogenic organisms. The aim is that future legislation will be based on the biological risk assessment and whose scope will be extended to zoopathogens.

[79] http://www.biosafety.be

APPLICATION OF THE LEGISLATION – SOME SPECIAL CASES

Advice to external clients

The SBB's expertise on contained use of GMOs and pathogens mainly involves tasks as technical expert performed for the Regions. However, the SBB has also provided its expertise at the request of other customers such as official authorities and private installations.
In two cases, the SBB was requested to give its advice on activities of contained use in other member states. The first member state, Luxembourg, asked SBB's advice on two activities, because Directive 90/219/EEC was not locally implemented in Luxembourg at that time.
The second request came from the Netherlands, to provide independent advice on a quarantine facility performing diagnostics and research on plant pathogens. This was because as the authority responsible, the requester did not wish to do so itself.
With regard to SBB's advice at the request of consultants, the main cases were:

- advice on the organisation of “Laboratoire National de Santé” in Luxembourg. This advice aimed at analysing the proposed containment measures and set-up of laboratories and laboratory animal facilities;
- the creation of an expert report on the infection risk to employees via the skin when exposed to infectious aerosols;
- a wide range of advice on decontamination, disinfection and biologically contaminated waste management in general (see below in the "infectious waste management" section).

BSE detection laboratories

In 2001, a network of laboratories had to be established for the quick diagnosis of BSE. The detection of BSE is part of the implementation of the regional decrees on contained use of pathogenic and/or genetically modified organisms. The SBB and the regional competent authorities were invited to meetings organised by the Institute for Veterinary Inspection responsible for approving these laboratories. The conclusion of these meetings was a list of biosafety measures drafted by the SBB on the design and technical characteristics of laboratories, working practices and waste management to be implemented with regard to the biological risks associated with the application of the PLATELIA BSE test for the quick detection of BSE[80]. The specific measures for BSE diagnostics were later included in the three regional decrees.

AIDS reference laboratories

At the start of 1996, the former Ministry of Public Health and the Environment asked the SBB to provide its advice on the draft royal decree *defining the criteria for recognising reference laboratories for acquired immunodeficiency syndrome*.
SBB's advice indicated that a number of biosafety measures were too strict for the risks associated with diagnostic activities performed in AIDS reference laboratories. The draft decree required a containment level 3 and some measures even had to meet containment level 4 criteria. The SBB pointed out that the risk assessment

[80] Leunda-Casi A, Pauwels K, Herman P, Verheust C, Zorzi W, Thellin O, Roels S, Van Vaerenbergh B. Risk assessment of laboratories involving the manipulation of unconventional agents causing TSE. 2009. Ref D/2009/2505/49. Available at http://www.biosafety.be

performed under the regional decrees takes into account the used micro-organism as well as the used volumes and techniques. Relevant containment measures are then defined based on this risk assessment. The SBB also stated that the Ministry of Public Health, Social Affairs and the Environment was responsible for the uniformity of the containment measures as a partner in the Cooperation Agreement between the Federal State and the Regions on the administrative and scientific co-ordination concerning biosafety.
Despite SBB's remarks, the royal decree of October 8, 1996 setting the criteria to recognise reference laboratories for acquired immunodeficiency syndrome was published[81] with containment measures much stricter than those of the regional decrees on contained use. The HIV reference laboratories had to meet the containment measures enforced by this royal decree.

Advice on the use of slurry coming from GMM fermentation in agriculture

The company Genencor NV contacted the SBB for advice on the derogation request to the former Ministry of Agriculture for using slurry, coming from the Genencor NV water treatment plant in Bruges, in agriculture.
This advice assessed the monitoring programme and sampling strategy to detection of GMMs in water treatment slurry. The strains used for the production had received a certificate stamp and/or self-cloning certificate and met therefore the criteria for micro-organisms of class of risk 1. They were also biologically contained by a drastic reduction in sporulation capacity. After analysing the inactivation method for downstream processing and the procedures used in the water treatment plant, it was proven that the quantity of GMMs in the water treatment slurry was far below the limit used in some other European countries such as Denmark (< 10^4 organisms/g).

BOTTLENECKS (LEGISLATION INTERPRETATION PROBLEMS)

In certain situations, the implementation of regional legislation resulted in problems with regard to procedures or the interpretation of the terminology. Here we describe a few cases of such problems with the implementation of contained use legislation.

The interpretation of the term 'storage' in the definition of contained use

In 2000, a notifier issued a request for a temporary exhibit of transgenic plants. The necessary measures were taken to eliminate any risk of spreading of the transgenic plants into the environment. After consulting the competent authority, it was decided that this type of activity fell under the definition of contained use (storage) and that the procedure for first use should be followed, which involved the application of an environmental permit and authorisation for the activity.

Based on this case, the *ad hoc* working group (see above) suggested later during the transposition of Directive 98/81/EC that in specific cases exemptions could be granted from the implementation of the legislation. This would apply to the use of GMOs of class of risk 1 in temporary exhibits, one-off demonstrations or storage for commercial objectives, provided that no manipulations occur and no waste is produced. In the end, these derogations were only included in the Brussels and Walloon decrees.

[81] Belgisch Staatsblad/Moniteur belge of 28.11.1996, p. 29910.

This meant that in the Flemish Region commercial companies or transport companies only temporarily storing products – including GMOs and/or pathogens – for subsequent distribution to customers still had to obey the legislation on contained use. An extreme case occurred when a company had to go through the full procedure, including the application of an environmental permit of the highest class, in order to store a GMM for gene therapy in a freezer.

The interpretation of "storage" was also discussed later with regard to waste treatment companies temporarily storing non-inactivated biologically contaminated waste coming from contained use installations before incineration. After internal consultation, the competent authority decided that in the Flemish Region these companies already had to meet very strict waste treatment legislation that guaranteed the safety of human health and the environment.

Contained use or deliberate release?

Another bottleneck in the interpretation of legislation was an experiment growing transgenic fruit trees in pots in a tunnel greenhouse on a field[82]. As the tunnel greenhouse was not a fixed structure as defined in the annexes to the regional decrees (greenhouse = a structure with walls, a roof and a floor designed and used principally for growing plants in a controlled and protected environment) both the regional and federal government had to be consulted to decide whether this activity had to be considered as deliberate release or not. In the end it was decided that the activity would be regarded as contained use and it was allowed under specific conditions: movement of the trees (in pollen-proof packaging) to a greenhouse (as defined by law) when flowering and destruction of all reproductive plant parts (pollen, seeds, tubers) in a validated way to ensure that the biological waste could not be a source of deliberate release into the environment.

Contained use of pathogens: inside or outside the scope?

Quality control laboratories

In the case of activities with pathogens, users and the competent authorities regularly ask questions about the scope. This has been the case for laboratories checking the quality of food, drinking water, samples of natural resources, production processes or finished products. In order to provide an answer that is as unambiguous as possible to users and the competent authorities, the SBB drafted a document at the request of the authorities explaining the criteria for including or not including certain activities with pathogens in the scope of legislation regarding contained use. The emphasis was on the deliberate character of the manipulation.

[82] The tunnel greenhouse consisted of aluminium pipes covered in plastic and/or insect screen (1 mm diameter) kept in place by ropes along the entire width. The tunnel greenhouses were provided with a sliding door at the front and back and the bottom was covered in landscape fabric.

For example, a colony-forming unit count[83] as such without cultivating reference strains as a positive standard under the European Pharmacopoeia or without any further enzymatic or microbial identification is not part of the implementation of contained use legislation.

Manipulation of animal cell cultures

The deliberate nature of activities is also considered when cell cultures are manipulated: only cell cultures infected deliberately as part of virus cultivation are in the scope of the contained use legislation. Primary cell cultures or cell lines naturally contaminated with pathogens due to their origin or by secondary contamination fall outside the scope.
This was also stated in the transposition of Directive 98/81/EC in the three regional decrees. The SBB also drafted guidelines on risk management for cell culture activities (see "Belgian Biosafety Server").

Autopsy

For the same reason, regional legislation on contained use does not apply to autopsies performed for medical diagnosis (anatomic pathology, legal medicine) or veterinary diagnosis of naturally infected animals. However, the legislation does apply to autopsies on deliberately infected laboratory animals (or laboratory animals inoculated with GMMs or transgenic mice).

SBB INTERVENTION IN OTHER MATTERS LINKED TO THE CONTAINED USE OF GMOS AND/OR PATHOGENS

Quarantine organisms

In February 2006, a consultation meeting took place between the Federal Agency for the Safety of the Food Chain (FASFC), the Directorate-General for Plant Protection and Plant Production Safety of the Federal Public Service (FPS), the representatives of the regional authorities and the SBB on the authorisation procedure for quarantine organisms harmful to plants and plant products. As a consequence of this meeting, it was decided that the FASFC would accept that permits supplied by regional authorities under the contained use legislation would be integrated into the FASFC's procedure for importing quarantine organisms.
There was bilateral cooperation. The regions gave the FASFC a list of authorised laboratories for contained use of quarantine organisms and the FASFC gave the regional authorities a list of laboratories from which it received applications.

[83] A colony forming unit calculation establishes the number of micro-organisms present in a sample or dilution through inoculation on a liquid or solid culture medium and incubation at the desired temperature. By using semi-selective culture media, a distinction can be made between the number of coliforms, enterobacteria, yeasts and fungi, etc. However, no distinction can be made between pathogenic and non-pathogenic organisms at that stage. After incubation, the colony forming units (CFUs) are counted. The pipes or Petri dishes remain unopened during this process. The CFUs may also contain pathogenic micro-organisms, but the deliberate propagation of pathogenic organisms is not the CFU count's main objective.

Import of GMOs and pathogens

Over the years, the SBB was contacted several times by notifiers who were unclear about which procedure was to be followed for the import or export of GMOs or pathogens. Some countries, including the United States, also request an import certificate of the country wishing to import the biological material.
At the specific request of the notifiers, the SBB drafted a number of certificates in the period from 1999 to 2005 confirming that the installation holds the required permits and meets the containment requirements for using certain GMOs or pathogens.
Since 2005, import authorisation has to be obtained from the Federal Agency for the Safety of the Food Chain (FASFC), at least for importing animal or plant pathogenic organisms. The requester has to have the required containment level and permits for contained use. The FASFC regularly contacts the SBB to make inquiries on the required containment level. The SBB always receives a copy of every import permit supplied by the FASFC. After many questions from notifiers and contacts with the FASFC, it has become clear that there is no import procedure for human pathogens.
With regard to importing GMOs, the Cartagena Protocol specifies that in case of contained use, the importing country's requirements must be followed. Belgium has never had an import certificate for GMOs.
The contained use legislation does not apply to the transport of GMOs and pathogens outside the installation. The notifier is referred to the international regulations regarding the transport of GMOs by road, rail, sea or air.

Protection of workers exposed to biological agents in the workplace

Regulation on the protection of workers exposed to biological agents

The regulation on worker protection applies to activities in which workers are exposed or are likely to be exposed to biological agents during their work. Before using group 2, 3 or 4 biological agents for the first time, employers must notify the Occupational Safety and Health Administration. The Administration verifies the content of the notifications and, if necessary, arranges for checks to be carried out in the companies by the Medical Inspectorate. The regulation in force in Belgium is the Royal Decree of 29 April 1999 (Belgian Official Gazette of 07/10/1999, p. 37917) amending the Royal Decree of 4 August 1996 on the protection of workers against the risks associated with exposure to biological agents at work. (Belgian Official Gazette of 01/10/1996, p. 25285) This regulation corresponds to the implementation of European Directives 90/679/EEC, 93/88/EEC, 95/30/EC, 97/59/EC and 97/65/EC. Directive 90/679/EEC was repealed by Directive 2000/54/EC in September 2000. The Belgian competent authority is FPS Employment, Labour and Social Consultation.

In August 2005, a collaboration protocol was drawn up between the Scientific Institute of Public Health (WIV-ISP) and the General Division for the Monitoring of Well-being at the Workplace ("Direction générale Contrôle du Bien-être au travail" - CBE in French) of the FPS Employment, Labour and Social Consultation. This protocol enables an exchange of information and an annual update regarding risk group 3 (and 4) contained use in Belgium.

Under this protocol, it is agreed that the SBB will extract from its global database the information on risk group 3 contained use which presents a risk to man and forward this information to the CBE. This is sent on an annual basis but data relating to the use of risk group 4 biological agents that represent a risk to man would require immediate notification. The CBE provides the SBB with data at its disposal on cases of laboratory acquired

diseases due to the exposure of workers during the contained use of GM or non-GM biological agents. These data are made anonymous before sending.

Management of infectious waste

The general objective of waste management is to protect human health and the environment against the damaging effect of waste products and to counter any waste of natural resources and energy. The SBB delivered his expertise on several occasions to assess the management of infectious waste.

Today a great deal of infectious waste is directly packed and transported for incineration as hazardous waste according to the valid ADR regulations. Although the packaging and eventual incineration as hazardous waste offers the necessary guarantees for human health and the environment, this waste flow results in high transport, energy and logistical costs. Hazardous waste should also be incinerated at very high temperatures that can only be achieved by rotary kiln incinerators.

Legal provisions with regard to waste management

Activities taking place in laboratories, companies or hospitals generate different kinds of waste, including infectious waste. Waste product management is a regional competence. In consequence, there are some differences in the definitions of infectious waste, but it is generally described as waste with a risk of microbiological or viral contamination, poisoning or injury during discharge and processing. Most infectious waste is covered by waste categories referred to as:

- High-Risk Medical Waste (Flemish Waste Prevention and Management Regulations);
- Special waste products (Brussels Capital Region: Implementing Decree of March 23, 1994, Belgian Official Journal of September 14, 1994);
- Class B2 waste products (Walloon Government Decree of June 30, 1994, Belgian Official Journal of September 3, 1994).

In addition to assessing disinfection methods for containers to be used in the transport of infectious medical waste products (Class B2) to incinerators (request of a company based in the Walloon region), the SBB was also occasionally contacted to verify the feasibility of alternative inactivation methods. For instance, processing methods inactivating infectious waste through saturated steam are being considered as an alternative to the immediate incineration of infectious waste. This method involves fewer requirements for further processing (incineration at lower temperatures, fewer transport requirements) and limits the waste volume and biological risk near the source.
At the end of the nineties, SBB helped to draft a waste processing plan for Class B2 waste products based on a waste decontamination system through saturated steam. It paid attention to the packaging and transport of the waste before and after decontamination, the good operation of the system, the validation and monitoring of the decontamination process and the training of staff.

At the request of the Public Waste Agency of Flanders ("Openbare Vlaamse afvalstoffenmaatschappij" - OVAM), SBB also recently helped to create a draft amendment to the Flemish Government decree regarding waste

prevention and management ("Vlarea") with a view to process high-risk medical waste to non-risk medical waste under certain conditions, creating a legal framework for a waste treatment method that involves grinding (volume reduction) and decontaminating (inactivating) infectious waste with saturated steam. As part of this draft legislation and on the basis of his expertise on validated inactivation methods for biologically contaminated waste, SBB could be indicated as a reference body to microbiologically monitor and validate the decontamination process.

The various regional authorities competent for the contained use of genetically modified and/or pathogenic organisms were informed of this initiative. If this alternative processing method has a broader scope (safety, economic and logistical considerations are to determine the feasibility of this alternative processing technique), it is advisable to have one and the same reference body responsible for consistent, microbiological validation of the chosen systems.

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Contained use from a biosafety perspective

Situation

Since the middle of the previous century, consistent efforts have been made to create rules for the safe use of biological agents, including genetically modified organisms (GMOs). These efforts were mainly initiated by bodies such as the World Health Organization (WHO), the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC) and the European Union (EU). The EU's policy has focused on limiting the risks of contained use of genetically modified microorganisms since 1990. This policy was reflected in Directive 90/219/EEC on contained use.

Since the transposition of the Directive in Belgium, biological safety has gained a broader meaning. It now refers to managing the biological risks of working with pathogenic microorganisms and genetically modified microorganisms, transgenic plants and animals. It regulates all activities with GMOs and pathogens in laboratories, laboratory animal housing, greenhouses and industrial installations.

Biological safety practices

Biological safety comprises a package of measures taken to guarantee safety during exposure to biological agents (including GMOs and pathogenic organisms). The use of GMOs has increased considerably in the past 25 years. Fast developments in DNA technology have led to an increased number of organism types that can be genetically modified. These developments offer new possibilities for biological or biomedical research. However, we also have to pay attention to their biological safety, because new techniques or new organisms may also involve new risks.

Ensuring biological safety

The current regulations and approach to biological safety are based on the following principles and methods for creating and implementing biological safety. They are based on a general prevention hierarchy:

• *Risk analysis and evaluation* are the cornerstones of the biosafety policy. They are the first, central step to identify any possible dangers for humans or the environment, to assess the chances of these dangers occurring, to evaluate their consequences and to create measures for controlling the risks. If the extent of the risk is uncertain, the precautionary principle is used.

• *Biological containment* means that risks to employees and the environment can be limited where possible by using biological agents, pathogens and GMOs that are less virulent, do not replicate (easily), cannot be transmitted (easily) or have properties that limit the transmission of their genetic material. The scientific foundation for these properties is generally good, although properties such as infectivity and transmission are often not quantitatively determined.

• *Concentration and embedding* is a principle that aims to enclose biological agents as much as possible, to limit working with infectious biological agents as much as possible (for example by using PCR amplification instead of cultivating microorganisms) and to restrict the number of areas where people work with biological agents.

• *Minimising exposure* is the next important step in limiting the risks ascribed to working with microorganisms. This includes actions known as safe microbiological practices (SMP): adequate and disciplined processes, wearing protective clothing and personal protective equipment (PPE), the prevention of aerosol formation, etc. In practice, this often involves the use of equipment that physically contains the microorganisms.

• *Physical containment* offers further protection to the lab worker and the environment and is obtained through physical barriers to prevent or reduce the spread of biological agents from the work area or laboratory. Physical restriction is obtained through a combination of equipment and structural facilities such as safety cabinets, isolators, filters, locks, etc.

• *Minimising dangers:* when the risks have been minimised by using the above methods, we can also limit the consequences of exposure to biological agents if exposure does take place. This includes measures such as safety signs, work regulations, incident and emergency procedures, preventive health checks and staff vaccinations.

The hierarchy of preventive measures described above is very similar to that of potentially dangerous work situations and should also be implemented by the prevention advisor.

Observations

The implementation of the rules for contained use is largely based on acquired experience, expert opinions and common sense. The legislation's objective is to protect humans and the environment. Although the rules are usually clear, the regulators have not always explicitly mentioned their objectives for each rule, which may make it difficult to evaluate them. It is important to know that the procedures for GMOs are derived from and largely identical to the procedures for non-GMOs. This is obviously because the risks of working with GMOs and non-GMOs and the measures to restrict these risks are very similar.

How effective are biosafety measures ?

Scientific literature's evaluation of the effectiveness of biosafety measures is fragmentary (Sedwell, 1995, Clin. Microbiol., Rev. 8:389–405). Also, few publications have evaluated these measures.

Are employees who are exposed to biological agents truly protected? Sometimes a laboratory infection has a clearly identifiable cause, for example non-compliance with the correct work regulations, needle stick injuries or high-risk activities with laboratory animals. However, in most cases it is impossible to find such a cause. It is possible that a clear cause goes unnoticed, but the containment measures can also be insufficiently effective, which may lead to infection via aerosols, for example (Dimmick et al, 1973, In A. Hellman, M.N. Oxman, and R, Pollack (ed.). Biohazards in biological research. Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., p. 264-266).

Monitoring laboratory infections is one of the most important methods of evaluating the effectiveness of containment measures. Laboratory infections can also indicate which measures should be taken to improve any inadequacies.

Because many laboratory infections are transmitted through aerosols, attention focuses mainly on evaluating biological safety cabinets. Biological safety cabinets can limit employees' exposure to biological agents, but they lose their effectiveness if they are not used correctly, positioned in the wrong place, not maintained well or not inspected and calibrated appropriately. Because the specific laboratory equipment, structural facilities and procedures complement each other, the effectiveness of all these biosafety measures must be evaluated as a whole. Sometimes we must ask the question whether the total laboratory environment effectively contains the handled biological agents.

The continuous improvement process of biosafety measures

Further underpinning of the scientific foundation for biological safety can promote the effectiveness of containment measures and compliance with them. However, considerable time and effort will be needed to make biologically safe practices fully evidence-based, insofar that is even feasible or necessary. From a scientific viewpoint, there are major challenges to support the effectiveness of separate measures and their mutual connection. Mathematical models, in which quantitative parameters of infectivity and transmission play a crucial part, can be helpful in this respect. Although biosafety practices are not supported by a very solid knowledge base, it does not seem advisable to drastically change current practice. Many measures can be effective and the number of bio-incidents and laboratory infections do not seem very sizeable, although the data available may be insufficient.

However, the integration of the biosafety policy into global business management would be a great long-term improvement. We must strive towards continuous improvement by making certain that biological safety becomes one of the links in the chain of the organisation's integrated care systems. CWA 15793:2008 Laboratory Biorisk Management Standard was published in 2008 (see ftp://ftp.cenorm.be/PUBLIC/CWAs/wokrshop31/CWA15793.pdf). It is an important, performance-based standard for the safe handling of substances that involve health risks. CWA 15793:2008 contains requirements to control the risks of handling, storing and destroying biological agents and toxins in laboratories. The goal of this standard is to provide the necessary measures to prevent the risks of processing, storing and discharging biological agents and toxic substances in laboratories as much as possible. The standard deals with biosafety, biological agents, bioterrorism, containment, bio-preparedness and bio-readiness. It can also lead to biological safety assurance in the future. This bio-risk management standard corresponds

to management systems and requirements ISO 9001:2008 (quality), ISO 14001:2004 (environment) and OHSAS 18001:2007 (safety) to ensure that this type of management system can be integrated in the organisation.

Biosafety Coordinator

In 2004, the Biosafety Coordinator (BSC) was included in the Flemish Region as a new position in VLAREM. VLAREM II stated that the BSC should have the skills necessary to perform his or her task and in particular previous experience with the contained use of genetically modified and/or pathogenic organisms.

The BSC's tasks include supervising the risk assessment of contained use by the users, coordinating notifications or permit applications, organising training, providing waste management, quality registration, supervising storage methods, internal transport, decontamination, etc. Perhaps the most important biosafety task is organising internal company inspections. The pace of technological change means that a 'readjustment policy' is an essential characteristic of an adequate, directive biosafety policy. This includes continuous or periodical evaluation, effective inspection and readjustment.

With increased attention to biosafety subjects and regulations in Belgium, many people in charge of biosafety (specifically Biosafety Coordinators and members of Biosafety Committees) are faced with operational challenges in their activities. As a result, Biosafety Coordinators established the *Belgian Biosafety Professionals Association* (BBP) in late 2005. BBP operates as a regional section of the European Biosafety Association (EBSA).

Only if we consider biological safety as one of the key points of the organisation's prevention policy and therefore also part of an integrated risk management policy, can this biosafety policy be continuously sustained and improved upon. Adequate biosafety management is inextricably connected to and supported by evidence-based biological safety. Biosafety is still evolving and legislation regarding certain aspects still leaves room for further clarification and interpretation. In addition to the daily implementation of biosafety, one of the other important tasks of the BSC is to monitor all developments and find out the best practices.

CHAPTER 4
DELIBERATE RELEASE AND PLACING ON THE MARKET OF GMOS

LEGISLATION AND RECENT LEGISLATIVE CHANGES

In Belgium, as elsewhere in the European Union, a GMO cannot be released into the environment for research and development purposes or placed on the market without first obtaining an authorisation from the competent authority. This authorisation is delivered depending on the outcome of a complex procedure involving case-by-case assessment of the risks to health and the environment of the use of the GMO.

As we saw in Chapter 1, the deliberate release of GMOs into the environment[84], including their placing on the market, was first specifically enshrined in law at European level in 1990 with the adoption of Directive 90/220/EEC. This legislation was then gradually supplemented and amended, with new texts being implemented.

Directive 90/220/EEC was repealed in 2001 by Directive 2001/18/EC. This new directive sought to enhance the efficiency and transparency of the decision-making process while ensuring a high level of protection for human health and the environment. It clarified a series of operational aspects of Directive 90/220/EEC. Its principal objectives were: to clarify the scope and definitions; to lay down common principles for case-by-case risk assessment; to enhance the risk evaluation and management processes (notably by taking due account of any direct or indirect, immediate or delayed, adverse effects, and of the requirement for the Commission to consult the competent scientific committees on any question which may affect human health and/or the environment); to improve the administrative procedures and authorisation system by introducing more stringent administrative deadlines; to improve the procedures for monitoring after placing on the market and to introduce a mandatory ten-year limit on the first authorisation; to increase the transparency of the decision-making process and allow for public consultation during the authorisation procedure; to establish registers for the purpose of recording information on genetic modifications in GMOs and on the location of GMOs; to introduce clear-cut requirements on the labelling and traceability of all GMOs placed on the market in accordance with the Directive.

In Belgium, Directive 2001/18/EC was transposed into national law under the Royal Decree of 21 February 2005[85]. This replaces the Royal Decree of 18 December 1998 transposing the previous directive, Directive 90/220/EEC, and still, in 2010, constitutes the reference legal text for the deliberate release of GMOs into the environment.

[84] Deliberate release is defined in European legislation as "any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment".
[85] *Moniteur Belge/Belgisch Staatsblad* of 24.02.2005, p. 7129.

Transposition into Belgian law of Directive 2001/18/EC

Directive 2001/18/EC of the European Parliament and of the Council came into force on 17 October 2002. This Directive was not, however, transposed into Belgian law until 2005 (resulting, notably, in Belgium being condemned by the European Court of Justice in September 2004 for delay in transposition).
This late transposition is explained, in part, by the complexity of implementing the Directive's provisions in the Belgian institutional context, a difficulty that had already been encountered in transposing Directive 90/220/EEC (see Chapter 2). But it was essentially due to the difficulty in obtaining political agreement on this highly polemic matter.
Work on transposition began, indeed, in September 2001, under the Ad Hoc Working Group on "Biosafety" of the Coordination Committee for International Environmental Policy (CCIEP – see Chapter 3), chaired by Dr William Moens (at that time Head of the SBB), and under the *aegis* of the Minister for Public Health. A draft Royal Decree for transposition was drawn up in October 2002, but rejected by the Council of Ministers. The political parties then in power (liberals, socialists and ecologists) could not agree on certain provisions of the draft Decree, and in particular measures relating to the precise details of the location of GMO field trials and, above all, the desire of the ecologists to ask for a socio-economic and ethical opinion (issued by a special expert committee of the Biosafety Advisory Council) on each project involving deliberate release or placing on the market, in addition to the scientific risk analysis (the European Directive allows for this possibility but does not make it mandatory).
After the change in federal coalition government in May 2003 (liberals and socialists, without the ecologists), debate of transposition restarted, but progress was slow. It was not until 21 February 2005 that the Decree transposing Directive 2001/18/EC was passed. In comparison with the previous Decree, the new regulatory provision simplified the administrative procedures for notification. It expanded and strengthened public information and participation, and established ex-post evaluation of the monitoring of the effects of field trials. The proposals for provisions concerning socio-economic and ethical evaluation were abandoned.

In parallel with the development of this horizontal directive (in the sense that it relates to all GMOs, irrespective of their fields of application), sectoral regulations have also been gradually established in the EU (see *Figure 4.1*). These regulations relate specifically to certain types of product, in particular those for use as food or feed, and medicinal products for human or veterinary use.

Products for use as food or feed

Until 1997, the placing on the market of GMOs or products derived from GMOs intended for use as food or feed was regulated by Directive 90/220/EEC. From 1997, food containing or consisting of GMOs was regulated by Regulation (EC) No. 258/97 on novel foods. It was against this background that certain GMOs (such as the Bt11 maize strain) were authorised for placing on the market, as well as several foods manufactured from GMOs (oils, flours, syrups, etc.). With regard to the latter, placing on the market was authorised under a simplified procedure (Article 5 of the Regulation) given that these novel foods were deemed to be substantially equivalent to existing foods or food ingredients as regards their composition, nutritional value, metabolism, intended use and the level of undesirable substances contained therein.

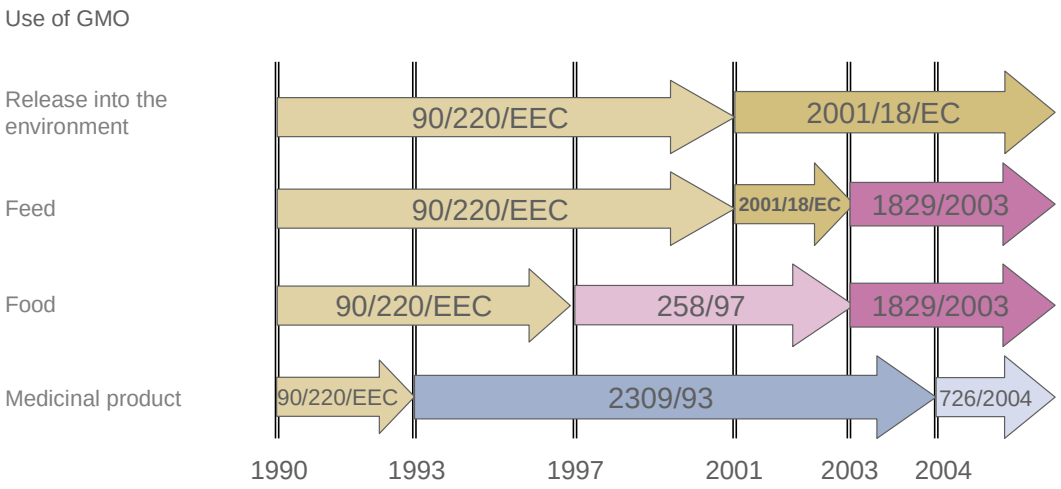

Figure 4.1 | *Changes in the European legislative framework for the deliberate release and placing on the market of GMOs*

These provisions on GM foods and derived products were replaced in September 2003 by Regulation (EC) No. 1829/2003 (also referred to as the "GM Food/Feed Regulation"). The scope of this Regulation extends not only to GMOs for use as food but also to those for use as feed (which had, up till then, been covered by Directive 90/220/EEC). Furthermore, in contrast to Directive 2001/18/EC which related solely to living GMOs, it also covers the placing on the market of food and feed derived from, but no longer containing GMOs.

This new Regulation establishes the principle of a single "one door – one key" authorisation based on two key factors:

- For GMOs for use as food or feed that are likely to be released into the environment, it imposes an environmental risk assessment to be undertaken in accordance with the principles laid down in Directive 2001/18/EC. It therefore creates a legal link between the "GM Food/Feed Regulation" and the GMO Framework Directive, so that a single procedure can be used for managing release into the environment and use as food or feed of a GMO;
- It establishes an authorisation procedure centralised at European level. When the European Food Safety System was revised, a new independent institution was in fact created to deal with risk assessment and communication: the European Food Safety Authority (EFSA). This Authority plays a central role in the risk assessment process and in contacts with the European institutions and notifiers. The Authority closely coordinates its activities with the Member States.

Medicinal products

In the field of medical applications, specific sectoral legislation for the placing on the market of pharmaceutical products was established in the EU in 1993 (Regulation (EEC) No. 2309/93). For medicinal products derived from biotechnology, the authorisation procedure is centralised and managed by the EMA (European Medicines Agency, formerly the EMEA, the European Medicines Evaluation Agency). This European agency was established in 1995 for the evaluation of medicines and is primarily responsible for coordinating scientific assessment of European applications for marketing authorisation of medicinal products. In 2004, the abovementioned Regulation was replaced by Regulation (EC) No. 726/2004, itself supplemented a few years later by Regulation (EC) No. 1394/2007. The latter established a Committee for Advanced Therapies, including gene therapies aimed at restoring, correcting or modifying physiological functions. In this case too, a central authorisation procedure was put in place under the *aegis* of the EMA.
In the same way as for food, there is a legal link between the sectoral legislation on "medicinal products" and Framework Directive 2001/18/EC. From 1993, a requirement to undertake an environmental risk assessment for medicinal products composed of or containing GMOs, as defined in the GMO Framework Directive, was imposed by law.

ORGANISATION AT BELGIAN LEVEL OF THE SCIENTIFIC ASSESSMENT OF THE DOSSIERS

Just as the legislative framework for the release of GMOs into the environment and their placing on the market has evolved over time, the same is true for the organisation at Belgian level of the scientific evaluation of the corresponding dossiers.

As indicated in Chapter 2, the scientific assessment of dossiers for granting authorisations for GMO environmental trials and for placing on the market of GMOs submitted through Belgium was undertaken until 1996 by the Scientific Institute of Public Health - WIV-ISP. The WIV-ISP worked at that time in direct support of the competent authorities (the Ministry of Agriculture for transgenic plants; the Pharmaceutical Inspectorate for gene therapy trials and vaccines; the Foodstuffs Inspectorate for genetically modified novel food).
From 1993, the financing granted under the agreements signed between the WIV-ISP and the three Regions enabled the Biosafety and Biotechnology Unit (SBB) of the WIV-ISP to expand and become a permanent centre for expertise in the field of biosafety, in support of the federal and regional authorities.

From 1996, the SBB and the authorities called for the scientific support of various Belgian university institutions for the assessment of the dossiers. Four scientific committees have been set up (see Chapter 2). New applications were therefore assessed systematically at meetings of these scientific committees, chaired by officials appointed by the competent ministers. Applications for deliberate release submitted under the simplified procedure were assessed directly by the Biosafety and Biotechnology Unit, under the *aegis* of the authorities[86].

[86] Directive 90/220/EEC established two types of procedure for experimental releases: a standard procedure (for a one-year authorisation) and a simplified procedure. The second procedure made it possible, subject to rigorous criteria based on "familiarity" with the plant species and given genetic characteristics, to submit a single dossier for the notification of an entire development programme, extending over a number of years or to a number of sites, for a given transgenic variety.

In April 1997, the cooperation agreement between the Federal State and the Regions on administrative and scientific coordination in the field of biosafety was finalised. It came into force the following year. The organisation of biosafety expertise at Belgian level was now shared between the Biosafety Advisory Council (BAC) and the Biosafety and Biotechnology Unit (SBB). Initially, in the absence of an officially constituted BAC (the members were not officially appointed until 2003), the SBB ensured transiently the competencies of the BAC and organized the assessment of the biosafety dossiers, always with the support of the scientific committees.

The *moratorium* on GMO authorisations

Authorisation decisions for the placing on the market of GMOs are taken at European level. From 1998, a *de facto moratorium* on new authorisations for the placing on the market of GMOs intended for cultivation or for consumption was put in place in Europe, at the request of several Member States. This *moratorium* was intended to respond to the concerns expressed by public opinion in those States and to serve as a means of exerting pressure for the establishment of a more comprehensive European legal framework, notably one which ensured the traceability and labelling of GMOs and products derived from GMOs.
This *moratorium* was gradually relaxed with the adoption of the new Directive 2001/18/EC, followed by the publication, in 2003, of Regulations No 1830/2003 (GMO traceability and labelling) and 1829/2003 (GMOs for use as food or feed).
The decision by the European Commission to issue an authorisation for the placing on the market of the Bt11 sweet maize on 19 May 2004 marked the end of the *de facto moratorium*.

In 1998, the Royal Decree transposing Directive 90/220/EEC into Belgian law was finally adopted. However, in the wake of a *de facto moratorium* on authorisation for the placing on the market of GMOs (see text box), the only applications relating to transgenic plants processed in Belgium from 1998 to 2003 were those relating to field trials. Most of the dossiers underwent the simplified procedure and were examined directly by the SBB.

In the early 2000s, the politicisation of the GMO issue made scientific assessment of related application dossiers increasingly difficult, and in particular those relating to the requests for authorisation of field trials with transgenic plants. There was, in fact, interference from political cabinet advisers in the scientific debate (certain advisers were even members of the *ad interim* Biosafety Advisory Council, and later full members), undermining the objectivity and independence of the risk assessment system put in place under the cooperation agreement.

The Biosafety Advisory Council was officially installed by the competent Minister on 6 May 2003. It was then able to take up formally his role of adviser to the federal and regional authorities in the framework of the ad hoc legislation and to assess biosafety issues at its own discretion. The SBB was also able to organise itself accordingly to fulfil its duties under the cooperation agreement, and in particular to ensure the scientific secretariat of the Biosafety Advisory Council, organise the practical expertise, hold archives and develop the scientific knowhow necessary for the Council to operate effectively. The BAC and SBB surround themselves with external experts. To this end, a list of experts common to both the Council and the SBB was drawn up (see Chapter 2).

Currently, the Council advises the competent authorities on all applications for the placing on the European market of transgenic plants submitted through Belgium under Directive 2001/18/EC – Part C, of GMOs submitted under the "GM Food/Feed Regulation", and of GMO medicinal products, together with all applications for field trials of transgenic plants or clinical trials. In addition, the Council has mandated the SBB to assess applications for the placing on the market of transgenic plants submitted through other Member States pursuant to Directive 2001/18/EC – Part C.

The SBB provides constant scientific support for the activities undertaken by the Council. It contributes directly to certain advices in the same way as the experts from the common list. The SBB also retains its role as permanent centre of expertise on biosafety, providing support to the federal and regional authorities.

METHODOLOGY FOR THE ASSESSMENT OF REGULATORY DOSSIERS

Until the Biosafety Advisory Council was officially put in place, regulatory dossiers were assessed by the SBB and members of the ad hoc scientific committees. For each dossier, a number of "expert rapporteurs" were appointed from among the members of the scientific committees, each of whom examined that part of the dossier corresponding to his specific field of expertise: molecular characterisation, agronomic characteristics, environmental risk assessment, toxicology, allergenicity, nutritional equivalence of food, and food safety. Draft advices were prepared by the SBB on the basis of expert reports, then discussed and finalised at meetings of the scientific committees, in the presence, initially, of representatives of the authorities and, from 1998, of members appointed unofficially by the partners to the cooperation agreement.

As soon as it came into operation, the BAC set to work on formalising the way in which it operated and in which it interacted with the SBB and external experts. In general, case-by-case assessment of biosafety dossiers by the Council is undertaken on the basis of the following procedure:

- The Council delegates oversight of the assessment of the dossier to a coordinator. The coordinator is a Council member with expertise in the matters involved in the dossier;
- Experts are selected from the common list on the basis of the expertise required and their availability. In order to prevent conflicts of interest, particular attention is paid to the independence of the experts concerned. The SBB may also be retained as an expert. The list of experts ultimately chosen to assess the dossier is validated by the coordinator and communicated to the Council members;
- The dossier is given to the experts, who are asked to provide an opinion on the information submitted by notifier and on the assessment of the risks to human health and the environment of the corresponding application. To assist them with this work, the experts generally respond to a list of questions drawn up by the Council and the SBB specifically for the dossier being examined;
- Consultation of the experts is undertaken in writing. If there are major differences of opinion between the experts, the coordinator may organise a meeting to which the Council members will be invited;
- The assessment reports serve as the basis for preparation by the coordinator, with the scientific support of the SBB, of a draft Council advice. The Council's advices are finalised at meetings of the members (or, more exceptionally, under a written procedure). The original reports of each expert are always appended (anonymously) to the final Council advices.

The time limits for submission by the experts and the Council of their advice depend on the type of dossier being assessed and the legislative procedure supporting the assessment. All Biosafety Advisory Council advices are published on its website[87].

As we illustrate in the pages which follow, the vast majority of the dossiers examined to date by the Council and the SBB have been regulatory dossiers relating to genetically modified plants. Dossiers relating to GMO medicinal products are regularly introduced but represent, on average, no more than two to three dossiers a year. To this one must add some specific advices issued at the request of a minister or competent authority and advices issued by the Council on its own initiative.

[87] http://www.bio-council.be

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The Biosafety Council

The biosafety of genetically modified organisms and organisms that are pathogenic to humans has been on the agenda of the Belgian authorities for about 14 years. On 20 March 1996, a group of experts gathered to exchange ideas on gene therapy. Since 25 April 1997, a cooperation agreement between the federal state and the regions has regulated the administrative and scientific coordination of biosafety. This cooperation agreement assigns biosafety assessment to the Biosafety Advisory Council (BAC), which cooperates closely with the Biosafety and Biotechnology Unit (SBB) of the Scientific Institute of Public Health (WIV-ISP). The interim BAC had its first meeting on 16 March 2001 and the BAC was officially established on 12 May 2003.

William Moens, who at the time was Head of the SBB at the Institute for Hygiene and Epidemiology (now called the Scientific Institute of Public Health) did much valuable work during this pioneering stage. His passion, perseverance, acuteness, scientific insight, experience and pragmatism resulted in a workable formula to assess biosafety in Belgium.

The assessment of genetically modified plants and microorganisms has been the BAC's main task right from the beginning. Its emphasis has always been on plants. Like elsewhere in Europe, transgenic organisms are the subject of much social debate in Belgium and at the BAC. Ever since its establishment, the BAC has adhered to the principle that the assessment of biosafety for humans, animals and the environment should rely on purely scientific, rational arguments arising from properly conceived and performed research and an expert interpretation of the research results.

The value of the BAC's work is directly proportional to the quality and the efforts of its members. The Belgian BAC consists of academics, researchers at scientific institutions and experts from various administrations. The members' fields of expertise cover various scientific disciplines. The members are not released from their normal duties to work for the BAC, which means that their BAC activities are additional to their regular work. The Biosafety and Biotechnology Unit of the WIV-ISP acts as the BAC's secretariat and could be described as its permanent core. In this capacity, the secretariat has developed highly valued expertise and experience over the years. The BAC always calls on external experts to study as many aspects of biosafety as possible.

Neutrality is almost non-existent for a subject such as the biosafety of genetically modified organisms. Scientific experts are also a product of their social background, their academic training, their field of work and their specific work environment. The ability to transcend one's own viewpoints in a dialogue with others is a necessary condition to constructively combine expertise and experience from various disciplines. The BAC pays considerable attention to this issue and frequently is confronted with divergent empathies.

There is a clear ongoing evolution in the study of biosafety. Whereas Europe has had a very strict view right from the start compared to e.g. the USA, we now see that the combination of healthy pragmatism and well-founded concern are resulting in less extreme positions. All techniques entail some risk and nobody can accurately assess future developments in advance. Simply and strictly following the precautionary principle without any subtlety immobilises everything. On the other hand, the BAC highly sympathises with the idea to proceed with caution.

In the EU, there is an interaction between national biosafety councils and the expert departments of EFSA (European Food Safety Authority). In an ideal world, there is a balanced symbiosis between partners. In reality, learning from each other seems not be obvious nor simple. Yet good communication is the key, as in any other parts of society. We continue to dream of a steady progress and we notice now and then a healthy evolution in suggestions being integrated in EFSA guidelines, and in directives prompting people to reconsider and to redirect some of their patterns of thought. In other words, biosafety assessment is a learning process and therefore a dynamic process.

The increasing number of similar or parallel dossiers is a constant challenge for biosafety councils. Many decades ago, William Faulkner wrote that familiarisation may be the perfect recipe to lose touch with the truth. If we apply this to the field of biosafety, it means that continuous vigilance and a persistent critical attitude are necessary in all evaluations. This is not easy in an overburdened world where many of us are facing increasing workloads.

The complexity of genetic transformations and the speed at which new modified organisms are emerging are a new source of concern in the biosafety field. The more transformations within a living being, the higher the probability of interaction between the native and the introduced or modified genes or gene products. In other words, the whole does not always equal the sum of its parts. Particularly in such cases proceeding with caution is of great importance. This attitude also results in a growing importance of reliable monitoring and follow-up systems connected with firm measures when and where necessary.

The methods used to genetically modify organisms are evolving fast. This evolution may not only lead to outdated legal definitions as laid down in texts such as Directive 2001/18/EC, but also makes things fuzzier with fading bounderies. In order not to lag behind, we need to think proactively and certainly consult with each other. Fortunately this is now happening in a European context.

To conclude: biosafety is becoming more and more complex. Hence biosafety assessment continues to require a lot of energy and imposes increasing responsibilities on evaluators at all levels. Only strong, competent, alert, correct and conscientious people are able to cope with this.

FIELD TRIALS WITH GENETICALLY MODIFIED PLANTS

Field trials with genetically modified plants are a logical step in the development of new varieties with modified characteristics. After having undertaken genetic modification, selection, a first screening and molecular analysis of the transgenic lines in a laboratory or greenhouse, small-scale trials are undertaken to monitor, in the natural environment, the stability and expression of the characteristic introduced, the agronomic properties of the plant, and safety for health and the environment. In the final stage, preselected elite lines are crossed with other varieties to transfer the transgenic characteristic to several varieties adapted to different climatic conditions, etc. Finally, as with traditional varieties, transgenic lines are tested before any registration in the catalogue of varieties[88].

A person or a company who wishes to introduce GMOs into the environment for experimental purposes must first obtain written authorisation from the national authority of the country within whose territory the experimental release is to take place. In Belgium, this authorisation is currently issued in accordance with the provisions of Part B of the Royal Decree of 21 February 2005.
The procedure for applying for authorisation is set out schematically in *Figure 4.2*. To summarise, the application (called "notification") is received by the competent federal authority (currently the Federal Public Service for Public Health, Food Chain Safety and Environment). The competent authority then asks for the Biosafety Advisory Council for its advice on the assessment of the risks that the GMO presents for the environment and human health. In parallel, a public consultation procedure is organised (and supervised by the competent authority). Comments by the public relevant to biosafety issues are taken into account by the Council in drawing up its advice.
Finally, the decision on the request for field trial is taken by the federal Minister(s) competent for public health and the environment based on the Council's advice and the outcome of the public consultation. The regional environment Minister for the Region in which the trial is to take place has a right of veto however.

[88] A variety may only be propagated or placed on the market in Belgium if it is on the national catalogue of plant varieties or that of the Community (which is a summary of the national catalogues of all the Member States listing all the agricultural or vegetable plant species that may be placed on the market or propagated within the European Union).

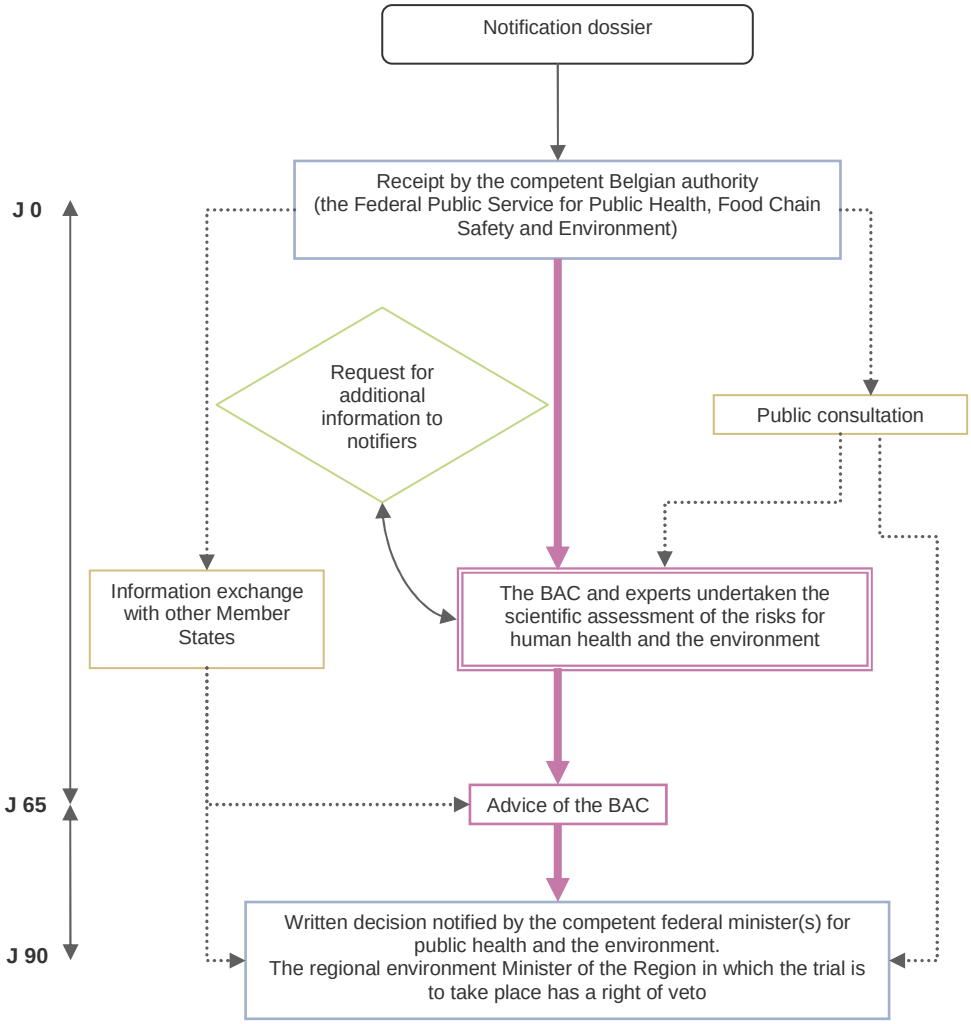

Figure 4.2 | *Application procedure for the authorisation of field trials of genetically modified plants*

Since 1986, the Belgian authorities have authorised 163 field trials involving genetically modified plants (*Figure 4.3*). The very first field trial notified in Belgium related to herbicide-tolerant transgenic tobacco. The last notification related to a poplar strain with a lignin content modified for the purposes of bioethanol production.

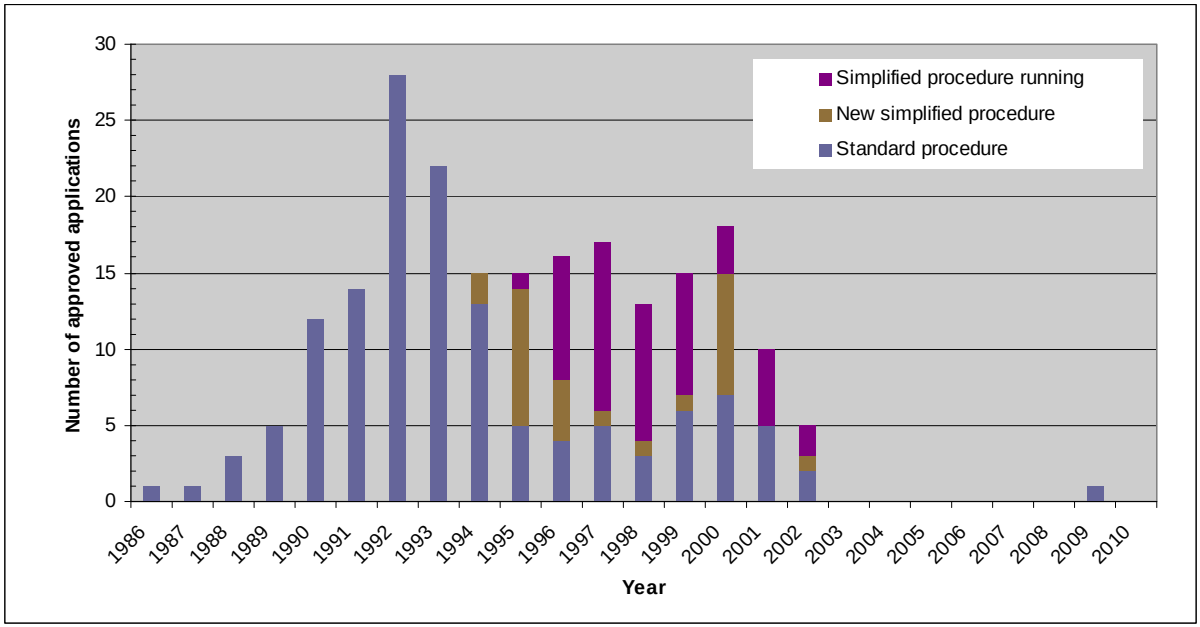

Figure 4.3 | *Field trials in Belgium involving genetically modified plants – Dossiers authorised from 1986 to 2009*

It is important to stress that each notification relates to a single GMO (case-by-case assessment) and that certain dossiers may be the subject of an authorisation valid for several sites and for several years[89].
The number of authorisations for the experimental release of transgenic plants increased between 1986 and 1992 (28 dossiers), then gradually declined until 2003. In terms of surface area, the top was reached in 2000, with a total of 18 field trials underway, covering a total surface area of 110.7 hectares (*Figure 4.4*). In 2003, the biotechnology private sector informed the Belgian Government that it would submit no new dossiers until the legislation on the experimental release of GMOs into the environment had been implemented clearly. The sector decided to halt the trials underway (see inset). The entry into force in 2005 of the new Decree transposing

[89] Directive 90/220/EEC, which was in force in Belgium until 2005, established two types of procedure for experimental release: a standard procedure (for a one-year authorisation) and a simplified procedure making it possible for authorisations extending over a number of years to be issued. In *Figure 4.3*, after the first year, these trials are listed under "simplified procedure running".

Directive 2001/18/EC has done little to change this situation. Just one dossier, from a scientific institution, has been submitted since then.

The *moratorium* by Belgian industries on field trials with transgenic plants

In 2002 and 2003, the Ministers for Public Health and the Environment decided to reject three field trials, despite positive advice from the *ad interim* Biosafety Advisory Council. These rejections related to a trial of a transgenic apple tree by Plant Research International in April 2002, a trial of transgenic oilseed rape by Aventis in April 2002 and a cultivation trial of transgenic apple trees by the Catholic University of Leuven (KUL) in April 2003.
These decisions were remarkable in more than one way. Firstly, they broke with the previously prevailing decision-taking procedures, which had followed the scientific advice submitted by the experts. Secondly, they were based, in certain cases, on considerations other than those relating to the potential risks to human health and the environment, i.e. the relevance of, or purpose served by, the trials proposed.
The Belgian biotechnology industry announced its voluntary halting of field trials in a press release issued at the end of 2002. In so doing, the industry sought to ring warning bells for the Government about the state of scientific research in Belgium in the field of agro-biotechnology (illustrated by the sharp fall in the number of field trials in 2001 and 2002, and coincidentally by the closure of several research centres of biotechnology companies). It called on the Government to draw up a clear, coherent and transparent policy in this field and asked that no requirements be laid down at Belgian level in addition to those imposed by the European Union.

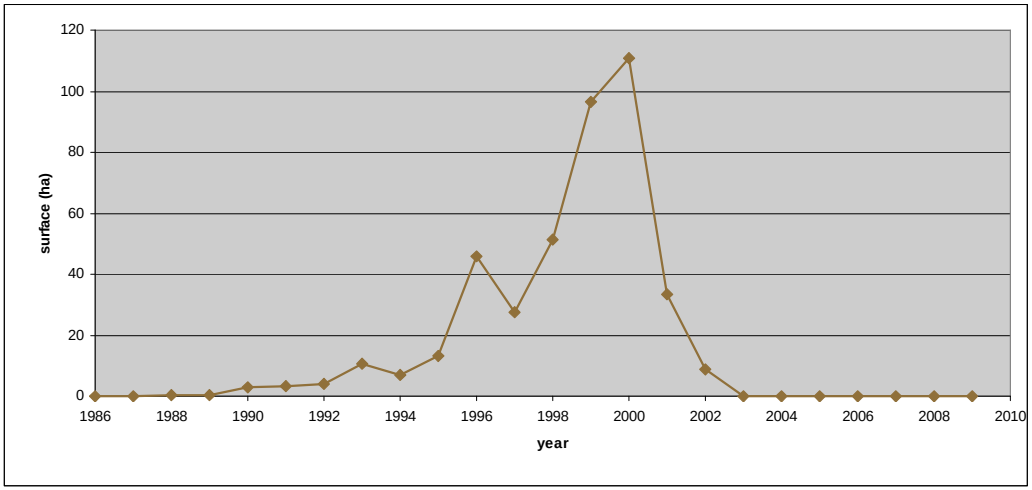

Figure 4.4 | *Total surface area under genetically modified plant trials in Belgium*

A detailed description of each of the field trials (description of the GMO, scientific advice, terms and conditions for authorisation) is available on the "Belgian Biosafety Server" (http://www.biosafety.be). Certain information is also available on the European Commission Joint Research Centre (JRC) database, which contains all the applications for deliberate release into the environment within the EU (http: //gmoinfo.jrc.ec.europa.eu/).

The GMO field trials authorised in Belgium generally relate to oilseed rape, maize, chicory and sugar beet (*Figure 4.5*). The characteristics most commonly tested are male sterility with a view to the development of hybrids and tolerance to glyphosate (Roundup®) or glufosinate (Liberty®) herbicides (*Figure 4.6*)

To summarise, to date, what has primarily been cultivated in Belgium, has been transgenic oilseed rape. This principally relates to field trials undertaken in the second half of the 1990s and which involved transgenic lines of the oilseed rape MS8xRF3 (SeedLink™ hybrid system). These lines were cultivated essentially for purposes of seed production for the development of new varieties, pending European authorisation for the placing on the market of the corresponding GMO (this authorisation was finally issued in 2007 – see the next section).

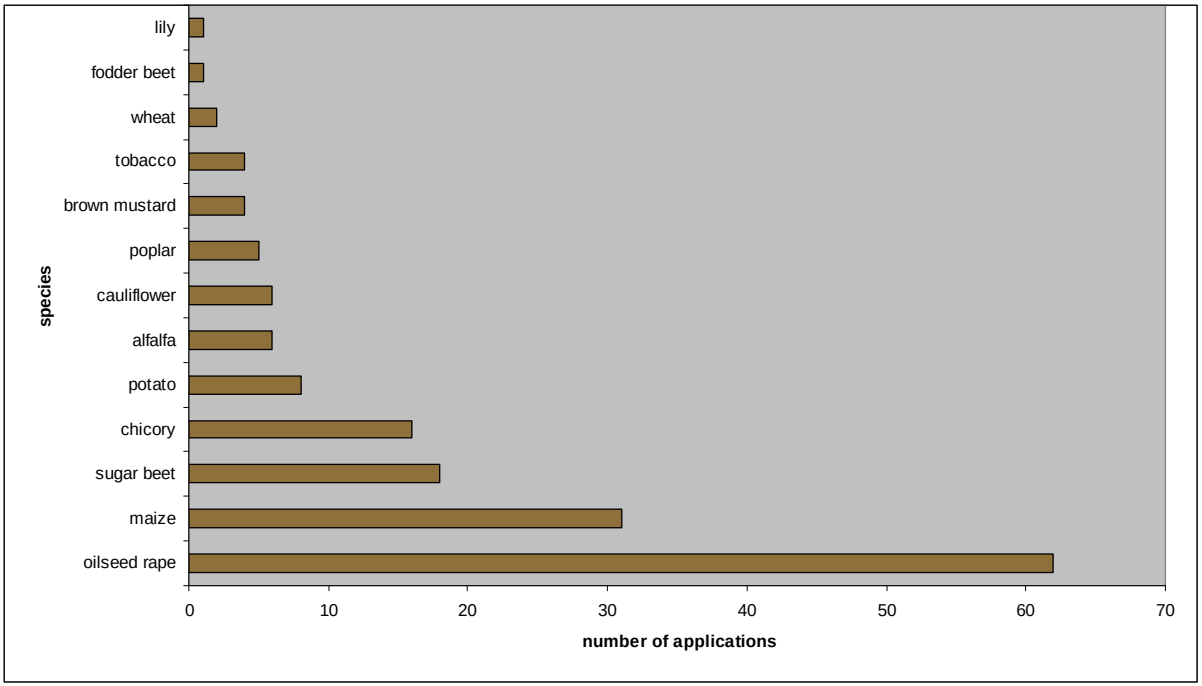

Figure 4.5 | *Field trials of genetically modified plants in Belgium – Breakdown by plant species (1986-2010)*

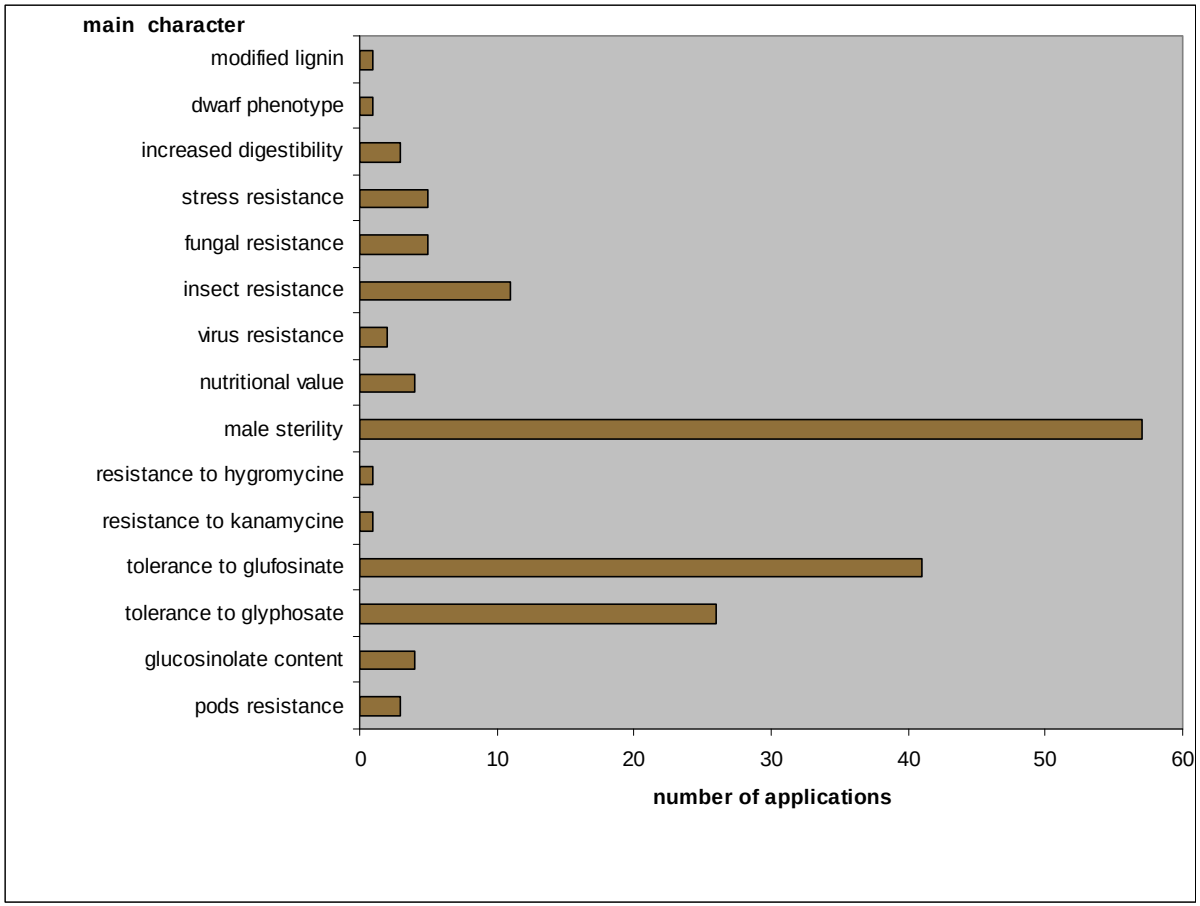

Figure 4.6 | *Field trials of genetically modified plants in Belgium – Breakdown by introduced trait (1986-2010)*

Patrick Rüdelsheim | General Partner Perseus

Where is it easy to work with a Genetically Modified Organism ?

Where is it easy to work with a Genetically Modified Organism ("GMO")? It is never really 'easy' and always requires an additional effort in comparison with non GM applications. Even so GMO activities are facilitated in countries with a clear legal framework, a science based risk assessment, a transparent decision making process and experienced people managing the evaluation.

During the early days of plant biotechnology, Belgium certainly was a prototype of such country. Even before the European GMO Directives were published, the Belgian authorities asked applicants to prepare the submissions for a field trial with GM plants in accordance with the draft Directives, helping both applicants and reviewers to gain experience in handling complex data requirements. Moreover, the requested information was of immediate relevance for risk assessment or risk management. *E.g.* data on pollen flow were instrumental in determining the usefulness of isolation distances or border zones surrounding a trial, when the risk assessment indicated that such additional measures were required. The decision making process was well established and could be monitored via communications and announcements on websites. Each application was accompanied by a description for the broad public, which also contained information on the process and on how stakeholders could exert their rights during the process.

Nonetheless a key component of an operational system remains the dedicated contribution of experienced people. Staff at the Federal Public Service and at the SBB were among the first -starting 1986- in the world to handle GMO trial applications. The number of field trials boomed quickly, placing Belgium at equal pace with France and the UK. Next to trials on research farms, almost all pioneering companies conducted field trials in Belgium due to the central geographic location, availability of qualified facilities and an operational regulatory system. These research and development activities were complemented by risk assessment projects, some establishing essential concepts that are now applied in risk assessment globally.

From an applicant's viewpoint the role of SBB has been highly significant. Always open for a preparatory meeting (the open invitation for a pre-submission consultation is a standard part of the SBB instructions) or an exchange on data requirements, SBB staff fostered the dialogue with stakeholders. While the data requirements are prescriptive, the case-by-case approach which is one of the central pillars of the GMO legislation necessitates scientifically justifiable choices. A frank discussion with the SBB experts has always been a good reference for elaborating a testing strategy. Furthermore, the Belgian Biosafety Council supported by SBB elaborated several guidance documents and opinions; and these complemented the succinct legal indications before the European Food Safety Authority assumed a more central role in GMO risk assessment and issued guidance documents. Evidently, SBB experts and applicants (as well as other stakeholders) not always shared the same opinion. Irrespective, difference in opinions were handled respectfully; the SBB insisting strongly on basing their views on scientific information.

It is impossible to reflect on the role of SBB, without giving tribute to Dr. William Moens. He drew the attention of different governmental services to biosafety and biotechnology, convincing them of the need for a centralised secretariat, composed of experts and operating as a service to the different authorities. In the complex Belgian situation this was surely not a sinecure. Dr. Moens succeeded in forming an expert team dealing with risk assessment as well as detection of GMOs. In addition, as Belgium opted early on to integrate activities with GMOs and handling of pathogens in a single legal framework, the team is now equipped to support a large variety of applications.

Part of the success of establishing SBB has to be attributed to the passionate contribution of Dr. Moens. He engaged people to be in violent agreement with or in constructive opposition of his views, and in any case triggering a lot of reflection. *E.g.* we debated the need for detection tools long before this became established as a legal requirement. It must be rewarding for him that this requirement is now well

accepted and that he can further develop his ideas being part of the Molecular Biology and Genomics Unit of the DG-Joint Research Centre at Ispra.

Over the years, the SBB expanded and the team continues to attract excellent people. Some have left and have been able to use the SBB formation as a solid basis for functions in other services (*e.g.* EFSA), academia and industry. The importance of this knowledge base should not be underestimated. With the EU GMO legislation spanning already two decades, a large diversity of deliberate release files being covered and several hundreds of contained use applications on a yearly basis in Belgium alone, the challenges for a neophyte are enormous. The SBB occupies a unique position, central to any biosafety aspect, relying on regional and international experts and operating as service to the authority mandated by the regional and national governments. Its staff is internationally recognized and contributes regularly to regulatory as well as scientific meetings.

Where is it difficult to work with a GMO? GMO activities are more difficult in countries with a legal framework that leaves uncertainty, a risk assessment that includes scientifically unfounded argumentation, an impenetrable decision making process and inexperienced people managing the evaluation.

As of 2000, it became very difficult to perform GMO field trials in Belgium. The involved Ministers already imposed in an *ad hoc* fashion some of the elements of the renewed GMO legislation (European Directive 2001/18/EC) but failed to implement the Directive until 2005. Notwithstanding a positive advice from the Biosafety Council, some applications were rejected without proper justification or possibility for redress. In consequence, at the end of 2003 all industrial applicants announced a voluntary suspension of any field trial activity until correct implementation of the renewed European Directive.

While developers looked for locations abroad to continue their development programmes, gradually all trial activities were dismantled. Also risk assessment or other accompanying research in Belgian fields was suspended. One day those that oppose field trials should be requested to justify why they have prevented our own researchers to obtain first hand information on their products and why our valuable risk assessment research had to be discontinued.

Although being in the centre of this turmoil, the SBB managed to keep a rare form of neutrality, focussing on science based risk assessment, discussing data requirements with some, reminding others of the legal implications of their positions, and gradually adapting to a reality in which Belgium was no longer on the forefront of biotechnology developments in the field.

In 2007, almost 20 years after the first field trial in Belgium an application was made for a small scale research field trial with GM poplars. While the FPS, the Biosafety Council and the SBB were exemplary in applying the ‘Part B’ procedure, complications at the political decision step illustrate that it will still take time before the process is fully predictable. Meanwhile, the area cultivated with GM crops continues to expand globally every year. Almost all of them incorporate technology ‘made in Belgium’, in one of our world-class research labs and biotech companies. The SBB has and I trust will continue to have an important role in ensuring that these projects are realized while securing optimal protection of human health and the environment.

PLACING ON THE MARKET OF GMOS FOR THE PURPOSES OF CULTIVATION OR FOR FOOD OR FEED USE

Placing on the market under Directive 2001/18/EC

Authorisation for the placing on the market of a GMO is issued at European Union level. Such authorisation involves the free movement of the authorised products throughout the territory of the European Union. Hence all Member States are concerned.
The authorisation procedure is based on interaction between the national authorities and the European Commission (*Figure 4.7*). The special feature of this procedure is the fact that it involves a national phase followed by a Community phase. The applicant submit a notification to the competent national authority of an EU Member State. This Member State becomes the "rapporteur" for this dossier and undertakes an initial assessment of the dossier. An assessment procedure is then undertaken at EU level, during which the other Member States may submit comments, objections or requests for information on the notification. If objections are raised and maintained, the Commission asks for the opinion of the European Food Safety Authority (EFSA). Finally, and only if the EFSA's opinion is favourable, a Commission draft decision is submitted for vote to the Member States.

A qualified majority is required to authorise the GMO. If a qualified majority cannot be achieved between the Member States, the decision is adopted by the Commission.

Since the GMO Directives were implemented in 1990, Belgium has only had three dossiers to process as a Member State rapporteur. For two of these dossiers (a transgenic soybean applied for by Bayer Cropscience in 1998, and a genetically modified sugar beet applied for by Monsanto in 1999), the scientific risk assessment was never completed, these dossiers first being declared incomplete before being withdrawn from the authorisation procedure by the companies in 2004.

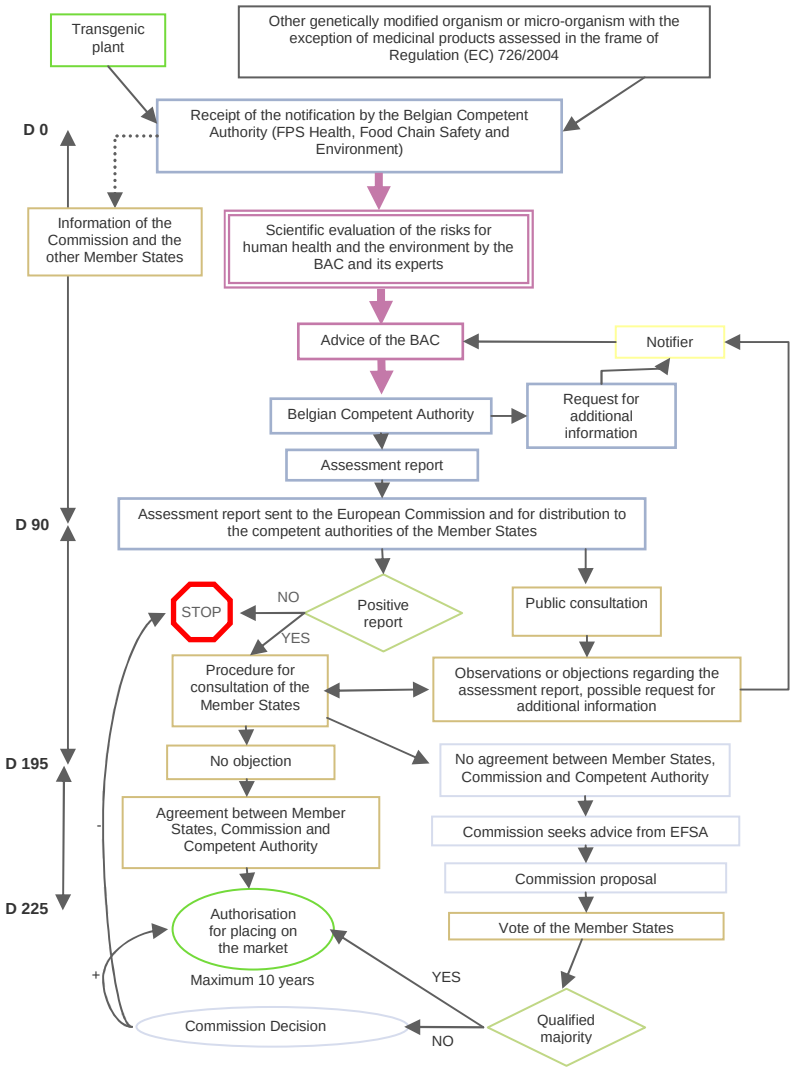

Figure 4.7 | *Application procedure for marketing authorisation of a GMO under Directive 2001/18/EC*

The third dossier (ref. C/BE/96/01) related to a genetically modified MS8xRF3 line of oilseed rape developed by Plant Genetic Systems. The management of this dossier is a perfect illustration of the complexity of the GMO authorisation procedure at European level and the length of time it takes. This was also the first dossier which the Biosafety Advisory Council had to deal with following its official installation (see text box).

Dossier C/BE/96/01: a (very) long story …

(A detailed history of the assessment and authorisation procedure for this dossier is available at: http://www.biosafety.be)
This dossier was submitted in December 1996. Since the Biosafety Advisory Council was not yet in place at that time, it was assessed by the "Transgenic Plants" and "Novel Food/Feed" Scientific Committees established by the SBB and the authorities. The safety of the transgenic plant and derived products destined for food or feed use was assessed (this being undertaken under Directive 90/220/EEC until the "Novel Foods" Regulation came into force in 1997).
Following the positive advice from the experts, the competent Belgian authority indicated in its assessment report at the end of 1996 that it was in favour of this GMO being placed on the market.
The Community authorisation procedure then took its course (comments from other Member States, additional information provided by the company) and a decision authorising the placing on the market was finally submitted for vote by the European Commission, on three occasions. The vote was postponed each time.
In 2001, following the adoption of the new Directive 2001/18/EC, the company submitted an updated notification. This dossier was finally assessed at the beginning of 2004 by the newly constituted Biosafety Advisory Council. Based on the Council's advice, the Belgian competent authority indicated that it was in favour of the import of this GMO and its use as feed, but was against its cultivation. This conclusion was communicated to the other Member States and the European Commission so that the Community authorisation procedure could continue.
In 2005, the EFSA, for its part, gave a favourable opinion on the import of this GMO and its placing on the market as feed. The decision-making procedure at European level could then be finalised. In the absence of a qualified majority (for or against) at Member States level, the Commission finally adopted the decision authorising the placing on the market of the GMO in 2007 (Decision 2007/232/EC). The authorisation covers the import into the European Union of this genetically modified oilseed rape for the same uses as any other oilseed rape, including uses as or in feed, but with the exception of cultivation or uses as or in food.

Most of the dossiers processed by Belgium under Directive 2001/18/EC (and previously under Directive 90/220/EEC) relate to dossiers submitted through other Member States. In this regard, Belgium can contribute to the authorisation procedure at two levels in relation with risk assessment:

(i) Once an assessment report has been forwarded by the Member State rapporteur, the other Member States have 60 days to submit any comments or objections;

(ii) If objections are made, additional information is requested from the notifier and the Member States have a further 45 days to maintain or remove their objections.

As is shown in *Figure 4.8*, this type of dossiers was, for the most part, assessed before 2000, the very first dossier processed, in 1993, relating to tobacco. During the first years, the advices were issued by the SBB, under the aegis of the competent authorities. Due to staff shortages and a lack of resources, the SBB's expertise then focussed on aspects relating to the detection and identification of GMOs (molecular characterisation), to the environmental risk assessment and to the monitoring plan. Between 2003 and 2008, the SBB continued to assess

this type of dossier and to issue advices to the competent federal authority under delegation by the Biosafety Advisory Council. Since 2008, the way in which this type of dossier is assessed is decided by the BAC on a case-by-case basis. Assessment of the few dossiers submitted in 2008 and 2009 (relating to genetically modified carnations) was again delegated to the SBB by the Biosafety Advisory Council.

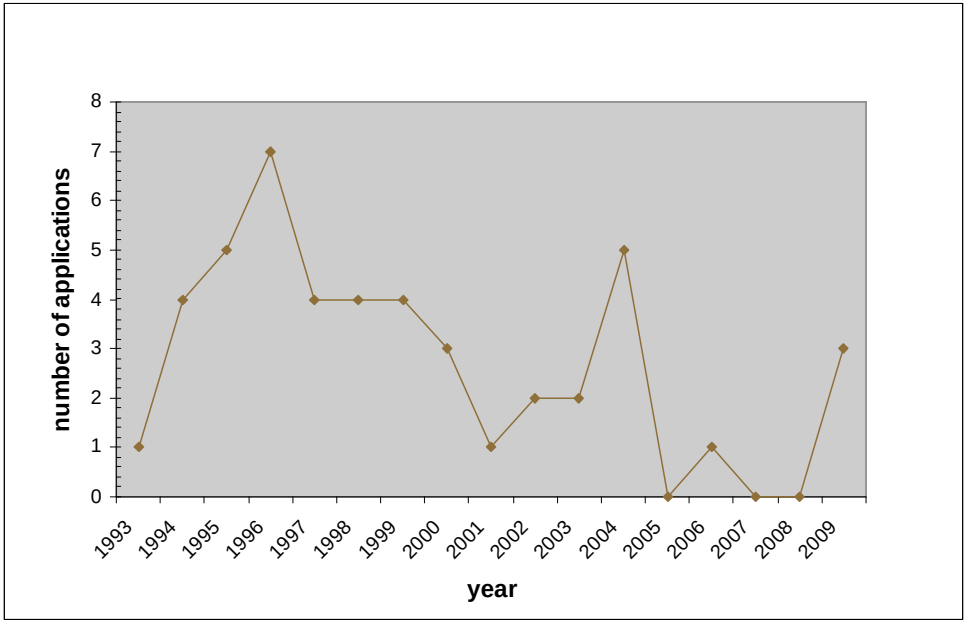

Figure 4.8 | *Placing on the market of genetically modified plants – Number of dossiers submitted through other Members States under Directive 2001/18/EC (Directive 90/220/EEC prior to 2001)*

As can be seen, there has been a significant fall since 2005 in the number of dossiers submitted under Directive 2001/18/EC. This coincides with entry into force of Regulation (EC) No. 1829/2003 (see below). Since that date, only a few dossiers relating to GMOs not intended for use as food and/or feed (for example, cut flowers, or a transgenic potato variety developed for the industrial production of amylopectin-enriched starch) have been processed under Directive 2001/18/EC. Almost all the applications for marketing authorisation of transgenic plants are now submitted under Regulation (EC) No. 1829/2003, despite the fact that the legislation gives notifiers the

possibility of splitting applications between the Regulation (for food/feed aspects) and the Directive (for cultivation aspects). Clearly, therefore, the notifiers prefer the single authorisation procedure ("one door – one key"), making it possible to submit a single application for authorisation for food and feed use, cultivation or deliberate release into the environment.

With respect to Directives 90/220/EC and 2001/18/EC, more than half of the dossiers submitted at European level relate to transgenic maize and oilseed rape which are herbicide-tolerant or insect-resistant or have male sterility (*Figure 4.9*). It should be noted that most GMOs that are the subject of an application for marketing authorisation in the EU have already been authorised to this end in other countries, such as the USA, Canada or Japan.

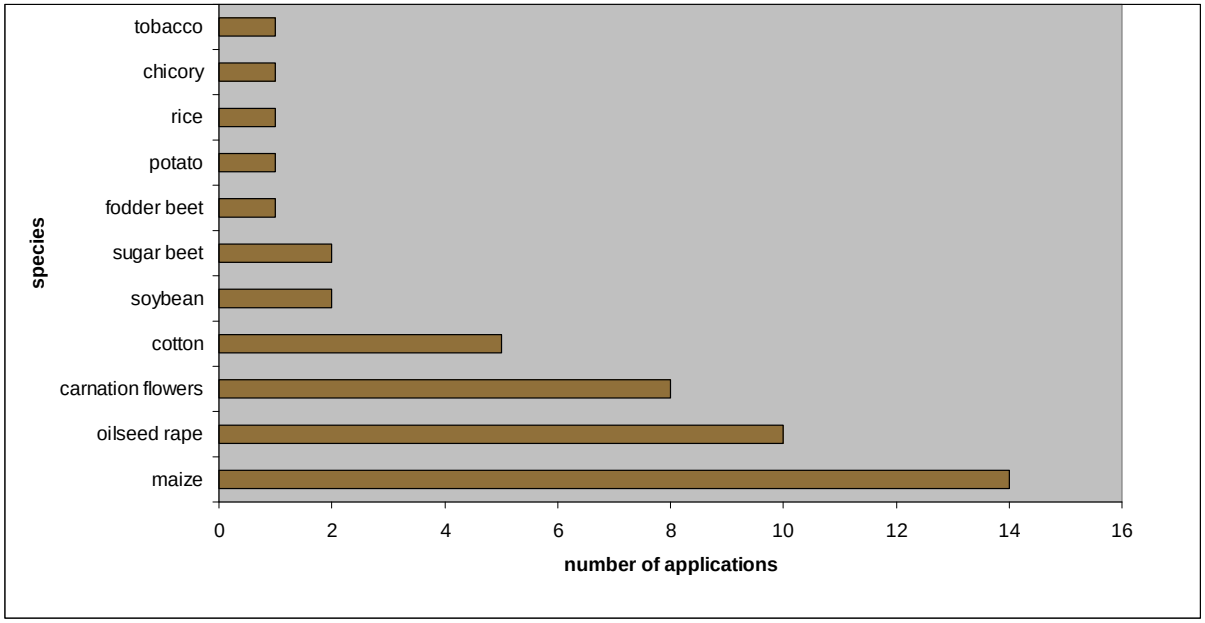

Figure 4.9 | *Placing on the market of genetically modified plants under Directives 90/220/EEC and 2001/18/EC – Breakdown of notifications by plant species*

The list of GMOs authorised for placing on the market under Directives 90/220/EEC or 2001/18/EC is available on the "Belgian Biosafety Server"[90]. Twenty two authorisations were issued between June 1994 and May 2010 for genetically modified plants (eight for maize, seven for oilseed rape, four for carnations and one each for soybean, chicory and potato). A genetically modified micro-organism was also authorised in July 1997.

Within the European Union, only the transgenic maize MON810 strain is actually cultivated. To recap, there has been no commercial cultivation of transgenic plants on Belgian territory to date.

Biosafety considerations linked to the placing on the market of herbicide-tolerant plants

In January 2004, the SBB organised a workshop on the "Safety considerations for herbicide-resistant plants to be placed on the European market". The objective of this workshop was to collect and share scientific information on the potential risks to human health and the environment associated with the imminent marketing in Europe of herbicide-tolerant transgenic plants. Representatives of the United Kingdom, France, the Netherlands, Denmark and Belgium set out their experiences in practice and their questions about the evaluation and management of the cultivation of this type of GMO.
This workshop pinpointed the need for a clear and harmonised procedure at European level for assessing this type of GMO, the importance of an exchange of information between authorities, risk assessors and notifiers, and the desirability of developing guidelines to assist with risk assessment and the preparation of notification dossiers.

[90] http://www.biosafety.be

Placing on the market under Regulation (EC) No. 1829/2003

As mentioned previously, the placing on the market of GMOs for use as food or feed has been governed for some years now by Regulation (EC) No. 1829/2003. The dossiers relate either to new GMOs or to applications for authorisation renewals submitted in accordance with Article 11 of the Regulation and relating to GMOs previously authorised under Directive 90/220/EEC or Regulation (EC) No. 258/97 but now expired.

The risk assessment procedure for the placing on the market of genetically modified food or feed is centralised. The application is first sent to a Member State, but the dossier is immediately forwarded to the European Food Safety Authority (EFSA), which undertakes the scientific assessment of the application and finally draws up an opinion, for submission to the European Commission, on each dossier examined. The EFSA assessments are undertaken by the GMO Panel, a group of independent scientific experts assisted by specialised working groups.

The "GM food/feed" Regulation nevertheless allows for a contribution by the Member States to the risk assessment process (Article 6.4). The Member States may submit their comments on the notification to EFSA during a 90-day consultation period (mandatory consultation procedure of the competent authorities established under Directive 2001/18/EC). When the EFSA then publishes its opinion, it must indicate in the annex to that opinion how the comments made by the Member States were taken into account in its corresponding opinion.

In this context, the Biosafety Advisory Council, with the scientific support of external experts and the SBB, takes part in this consultation procedure in respect of all dossiers submitted under the Regulation which relate to genetically modified organisms. Dossiers relating solely to derived products (flour, oils, sugars, etc.) are not examined by the Council.
Secondly, since the end of 2005, the competent Minister has asked the Council to provide him with an advice on all dossiers submitted under the "GM food/feed" Regulation, in addition to the final opinion published by EFSA. This advice covers all aspects of the notification (molecular characterisation, environmental impact, nutritional and compositional analysis, toxicity and allergenicity). The Belgian authorities determine their position on the European Commission draft decisions primarily on the basis of this advice and the EFSA's opinion. The draft decisions are submitted to the vote of the Member States under a comitology procedure identical to that applied in respect of Directive 2001/18/EC.

The role and involvement of the Biosafety Advisory Council in the authorisation procedure under Regulation (EC) No. 1829/2003 are summarised in *Figure 4.10*. As can be seen, several months, if not several years, may lapse between the submission of a dossier by the applicant and the publication by EFSA of its final opinion on this dossier. This very long time span complicates the work of the experts, the SBB and the BAC involved in assessing a dossier. The time spans are often due to requests by EFSA for the notifier to provide information or additional experimental data.

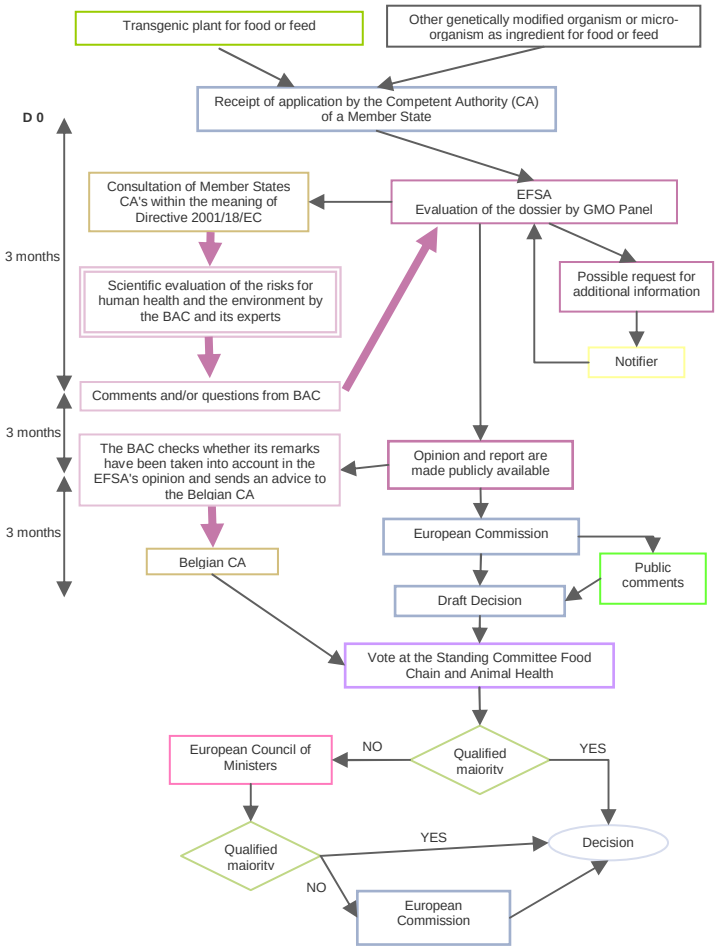

Figure 4.10 *| Application procedure for marketing authorisation of a GMO or a derived product under Regulation (EC) No. 1829/2003*

Belgium is one of the few Member States to contribute actively and systematically to the risk assessment process. It should be noted that the number of advices and other documents published by the Biosafety Advisory Council and relating to dossiers submitted under the "GM food/feed" Regulation has greatly increased in the past few years (*Figure 4.11*). Between the date on which it was officially installed until the end of 2009, the Council has processed no fewer than 75 dossiers (including eleven relating to renewal applications) and issued 26 advices to the competent Minister, five of these relating to renewal applications and a third to GMOs with more than one transformation event ("stacked events")[91].

Of these advices, twenty have been positive. These advices are, however, often accompanied by generic recommendations addressed to EFSA or the competent authority. Such recommendations relate, for example, to epidemiological monitoring of the incidences of allergies to plants which are not known to have an allergenic effect, or to the inclusion of dietary fibres in plant compositional analyses. With some dossiers, the Council has included in its positive advice comments relating to scientific weaknesses that have no impact on biosafety or suggestions for additional research.

On six of the dossiers, the Council has issued a negative advice or refused to give an advice. The grounds invoked are the absence of conclusive data, or the poor quality of the scientific data provided.

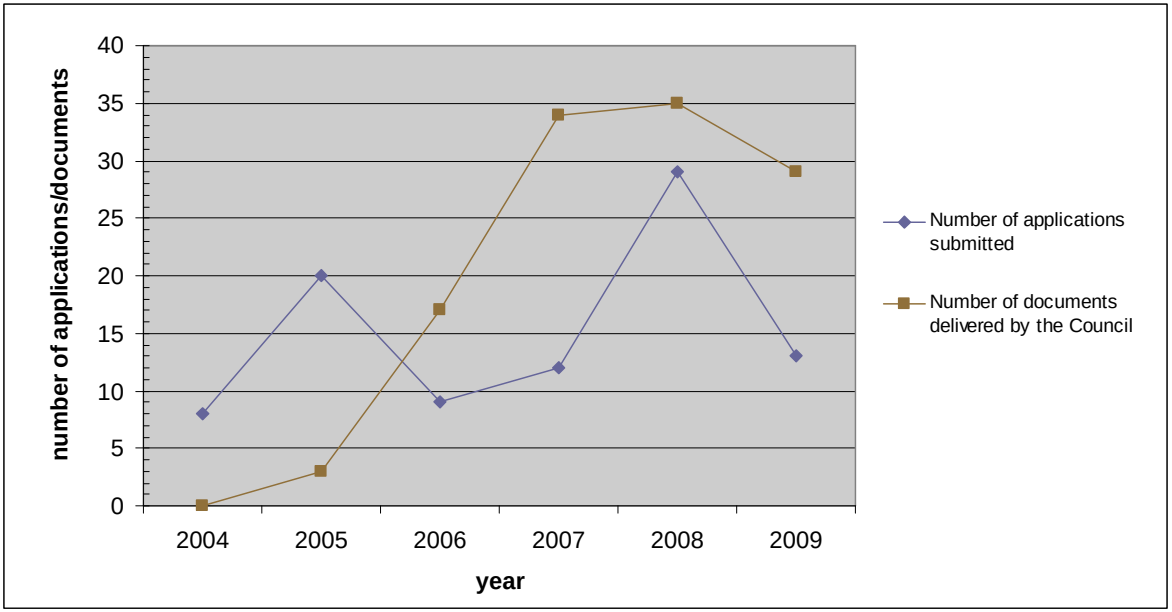

Figure 4.11 | *Evolution of the number of dossiers submitted under Regulation (EC) No. 1829/2003 and documents issued by the Biosafety Advisory Council in this regard*

[91] The advices issued by the Biosafety Advisory Council are available on its website, http://www.bio-council.be

The full list of GMOs authorised for placing on the market within the EU under Regulation (EC) No. 1829/2003 is available on the European Commission website[92]. The transgenic plants authorised to date (June 2010) are chicory, cotton, oilseed rape, tobacco, soybean, sugar beet and potatoes. These have primarily been plants that are herbicide-tolerant or insect-resistant. The fact that these GMOs have been authorised in the EU does not necessarily mean that they are actually present on the European market. Their use continues to be limited in 2010 and the GMOs authorised are essentially used as feed.
For the moment, only a limited number of GMOs and derived products can be sold for human consumption. These are products deriving from genetically modified soybean or maize, such as soya burgers, tofu, corn flour or popcorn. To these must be added seed oils derived from cotton, maize, soybean or oilseed rape, as well as maize starch, flour and glucose. Although these GMOs and derived products are authorised in Europe, most wholesalers refuse to put them on sale.

The participation of the BAC and the SBB in the regulatory risk assessment process has also contributed to enhancing the transparency of the EFSA's work. For example, following remarks by certain Member States, including Belgium, EFSA has been required, for some years, to provide a summary indicating how the comments and observations made by the Member States have been taken into account in each of its scientific opinions on regulatory dossiers.

Furthermore, the interaction between EFSA and Member State risk assessment committees has also increased over the years, notably following inputs by the BAC. This has, indeed, led to direct interaction with EFSA on generic issues linked to the assessment of dossiers relating to GMO food/feed. As a result of the systematic assessment of these dossiers, several scientific issues relating to nutritional, toxicological or allergenicity aspects were repeatedly raised by Belgian experts (for example, the inclusion of dietary fibres in compositional plant analyses, the scientific quality of toxicity testing on animals, the assessment of the allergenicity of the whole plant). These issues were submitted to the EFSA GMO Panel through various channels (consultation of Member States on dossiers, forum with national experts organised by EFSA, competent authority) and finally resulted in a bilateral meeting in December 2008. This direct meeting between EFSA and the Biosafety Advisory Council gave each of the parties a better understanding of the concerns of the other and led to consensus on certain issues.

Finally, the Biosafety Advisory Council also issues advices on environmental risk assessments relating to certain types of dossiers submitted under Regulation (EC) No. 1829/2003 and that include cultivation. Before it can be cultivated in the European Union, a genetically modified plant must be the subject of an in-depth environmental risk assessment (ERA) intended to identify all the adverse effects it may have on the environment. In accordance with Articles 6.3(c) and 18.3(c) of Regulation (EC) No. 1829/2003, the initial ERA must be undertaken by a Member State, selected by the EFSA from among voluntary candidates.
Belgium, acting through the BAC, is one of the few Member States to volunteer for this type of assessment. The Council and the SBB see this as an opportunity to build on and improve their experience in environmental risk assessment and to share their expertise in this field with EFSA experts as well as other Member States.
To date, the Council has dealt with three dossiers of this type: EFSA/GMO/UK/2006/30 (maize 59122x1507xNK603), EFSA/GMO/CZ/2008/54 (maize 88017) and EFSA/GMO/BE/2009/71 (maize MON89034 x MON88017). The evaluation procedures were still underway in mid-2010.

[92] http://ec.europa.eu/food/dyna/gm_register/index_en.cfm

GMO MEDICINAL PRODUCTS, GENE THERAPY AND VACCINES

Medicinal products for human use: Clinical trials and deliberate release for the purposes of research and development

In human medicine, clinical trials are a mandatory stage in the development of new medicines. The development of a new product is undertaken step-by-step and generally takes 10 to 15 years. After a preclinical phase of laboratory research on animals or cell cultures there are human clinical trials. Three successive clinical trial phases with convincing findings are required to prepare an application dossier for the placing on the market of a product. Phases II and III trials are, for the most part, multicentre (involving several hospitals) and international.

As for all human clinical trials in Belgium, gene therapy clinical trials using genetically modified organisms or involving medicinal products containing GMOs are governed by the Act of 7 May 2004 on human clinical trials[93] that transposed Directive 2001/20/EC. Under this Act, this type of trial must be approved by an accredited ethical committee and obtain prior written authorisation from the Minister responsible for public health. In addition to these generic provisions, clinical trials involving GMOs must also comply with the legislative provisions on biosafety.

In any event, activities taking place in contained facilities (for example, a hospital) must obtain an authorisation from the competent regional authority(-ies) in accordance with the legislation on contained use of GMOs and/or pathogens (see Chapter 3). The authorisation is issued for a given operation in a given facility and for a defined period of time. The term "operation" may cover a specific experimental protocol but also a full clinical trials programme if those trials can be deemed to be uniform from the point of view of biosafety (e.g. phases II and III protocols using the same recombinant vector in a given therapeutic unit). The initial authorisation may also cover later changes to the trial protocol which was initially submitted (e.g., new formulation or new specifications for a gene therapy product), provided these changes have no impact on biosafety.

At Belgian level, an additional authorisation may also be required in certain cases according to the provisions of Article 13(2) of the Royal Decree of 21 February 2005 governing the deliberate release of GMOs into the environment (transposing Directive 2001/18/EC). This relates, for example, to certain multicentre trials (i.e. carried out in several facilities), or trials where the physical and/or biological confinement cannot be guaranteed due to the way in which the clinical trial is conceived (trials involving outpatient medicine) or the type of recombinant vector used. The procedure followed is, in broad terms, identical to that followed for an application for the deliberate release of a GM plant and the competent authority must ask for the opinion of the Biosafety Advisory Council before authorising the trial (see above). Here too, the authorisation may cover a specific clinical trial undertaken at different sites or a full clinical trials programme.
This link between the two specific regulations in the field of biosafety (contained use and deliberate release into the environment) was opted for at Belgian level (in 1998) to guarantee optimum assessment of the risks to human health and the environment of the use of a GMO in a clinical trial. The decision on whether or not to assess a clinical trial under the Royal Decree of 21 February 2005 is taken on a case-by-case basis by the competent authority, based on preliminary information provided by the notifier and after consultation of the SBB.

[93] *Moniteur Belge/Belgisch Staatsblad*, 18.04.2004, p. 39516.

It should be pointed out that this *modus operandi* is not applied uniformly at European level. Not all the Member States have the same approach to distinguish between aspects relating to deliberate release and contained use in the specific case of clinical trials. The approaches adopted by our Dutch and British neighbours illustrate two extremes: For the first, only the "Deliberate Release" Directive is appropriate to adequately assess and manage the risks; for the second, the biological confinement of gene therapy vectors and their use in controlled hospital environments mean that they should first be assessed under the "Contained Use" Directive. The position adopted by these countries and other European countries is set out in detail in a report commissioned by the European Commission in 2007[94], but the European Commission has not yet ruled on this matter.

In Belgium, the first clinical trial of a medicinal product containing a GMO was notified in 1996. It related to a gene therapy trial involving a recombinant *Herpes simplex* virus developed for treating cancers. From 1996 to 2009, a total of 24 clinical trials were notified (*Figure 4.12*).

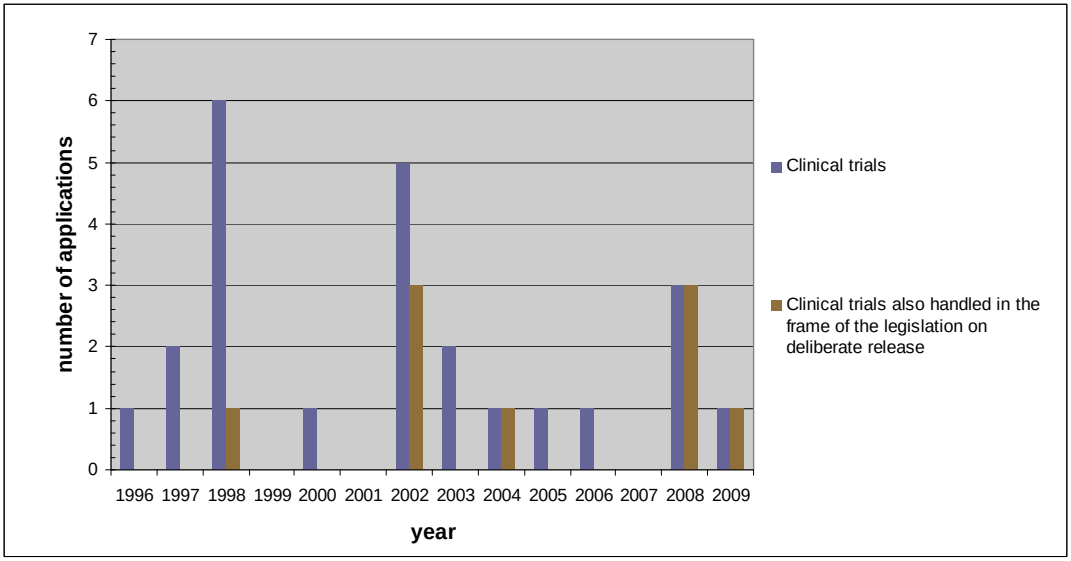

Figure 4.12 **|** *Evolution in the number of clinical trial dossiers involving GMO medicinal products for human use*

The vast majority of these trials relate to therapeutic vaccinations to treat cancer and primarily involve the adenovirus and vaccinia virus (*Figures 4.13* and *4.14*). A detailed description of each trial (protocol title, trial sponsor, recombinant vector type, authorisation procedure, hospital where the trial took place, investigator's name, etc.) is available on the "Belgian Biosafety Server"[95].

[94] Perseus BVBA. Analysis of the applicability of the contained use legislation for clinical trials. 2006.
[95] http://www.biosafety.be

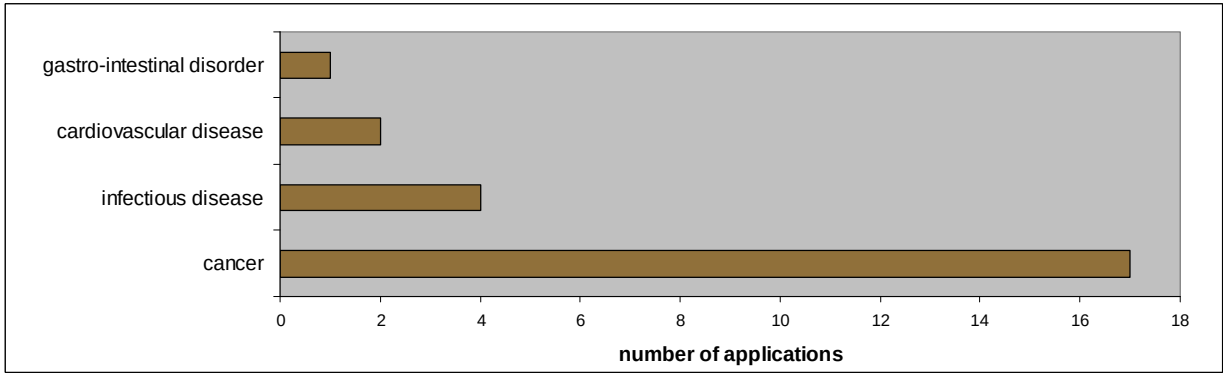

Figure 4.13 **|** *Clinical trials involving GMO medicinal products for human use*
Breakdown of the dossiers based on their therapeutic indication

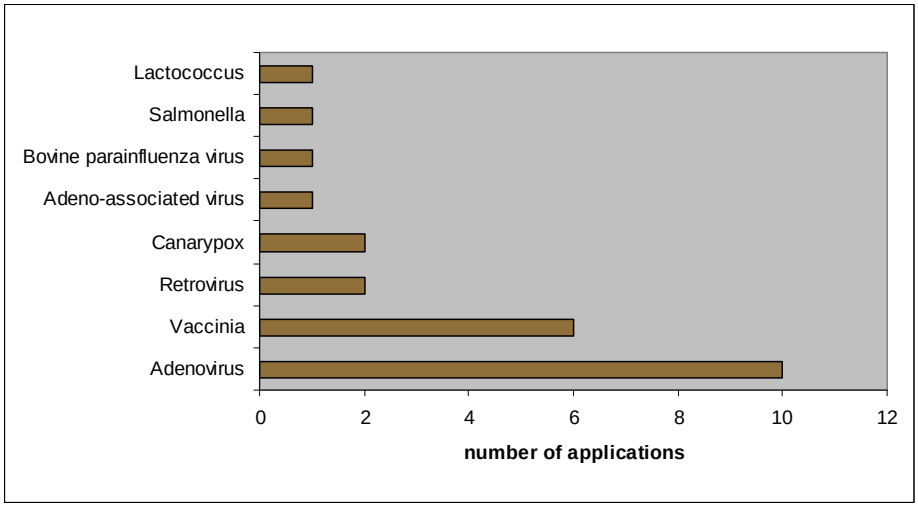

Figure 4.14 **|** *Clinical trials of GMO medicinal products for human use*
Breakdown of the dossiers by GMO type

The "Gelsinger case"

In December 1999, the first death in a gene therapy clinical trial was reported in the press. The patient (Jesse Gelsinger) had died in the United States of America after being injected with an adenovirus vector during a clinical trial at Pennsylvania University.
On this occasion, the SBB undertook an exhaustive analysis of the scientific literature and information publicly available on this case. The subsequent report was submitted to the *ad interim* Biosafety Advisory Council and to experts of the "Recombinant viral vectors, virosomes, recombinant vaccines, gene therapy" scientific committee. The objective was to assess, in the light of the "Gelsinger case", the regulatory procedure in place at that time in Belgium for gene therapy clinical trials, including the ways in which the various players involved interacted.
The *ad interim* Council, the SBB and the experts concluded that the "Gelsinger case" did not call into question gene therapy clinical trials and that there was no need to change the legislation to enhance patient safety but that it must be ensured that the existing rules were complied with.
The "Gelsinger case" is described in detail on the "Belgian Biosafety Server".

Medicinal products for human use: Placing on the market

To be placed on the market, all medicinal products derived from biotechnology (and therefore also medicinal products containing or consisting of GMOs) must obtain an authorisation issued by the European Commission upon advice of the European Medicines Agency (EMA). Access to the Community market for GMO medicinal products is subject to the centralised procedure laid down in Regulation (EEC) no. 2309/93, as amended by Regulation (EC) no. 726/2004. If authorisation is granted, it is automatically valid for all Member States of the European Union.

The applicant submits an application dossier for registration to the EMA and this will be assessed on the basis of scientific criteria concerning the quality, safety and efficacy of the medicinal product concerned. The assessment is undertaken by one of the EMA's scientific committees, i.e. the Committee for Medicinal Products for Human Use (CHMP). In the case of medicinal products for human use containing or consisting of GMOs, the application must be accompanied by information making it possible to undertake an environmental risk assessment in accordance with the provisions of Annex II of Directive 2001/18/EC[96]. This assessment is undertaken in consultation with the bodies established by the Community or the Member States, in accordance with Directive 2001/18/EC. In Belgium, this risk assessment is performed by the Biosafety Advisory Council.
Specifically, the EMA appoints an expert rapporteur for each dossier. He drafts a report on the environmental risk assessment associated with the use of the GMO medicinal product. This assessment relates to the risks to the biotic environment, as well as to the potential hazards of the GMO for those in the vicinity of the person treated or for care staff, and to the risks to public health. In his report, the rapporteur highlights any shortcomings in the dossier and, if necessary, proposes a list of questions to be sent to the notifier. The BAC and the Belgian external experts, who have beforehand been granted access to the "environmental assessment" part of the dossier, are

[96] This risk assessment applies to medicinal products containing or consisting of GMOs, but not to medicines produced from GMOs. The latter include, for example, insulin produced from recombinant bacteria or, a more recent development, human anticoagulant protein present in the milk of genetically modified goats.

asked to react (as are the experts in the other Member States) and to pinpoint issues which the EMA rapporteur may not have considered. The Council's advice indicates any additional information that should be obtained to supplement the environmental risk assessment.
The dialogue between the EMA and the Member States normally ends at this point. It is only on an exceptional basis that the Member States are consulted to provide their assessment of any responses provided by the company to the questions posed. The EMA does, however, keep them informed of progress with the dossier.
The role and involvement of the Biosafety Advisory Council in the authorisation procedure under Regulation (EC) No. 726/2004 are summarised in *Figure 4.15*.

The first application dossier for authorisation for the placing on the market of a medicinal product for human use consisting of a GMO was filed with the EMA in 2006. This dossier related to a recombinant adenovirus developed to treat cancers. Other dossiers have been submitted since and examined by the Biosafety Advisory Council as part of the Member State consultation procedure (*Table 4.1*).

Year filed	Treatment type	GMO type
2006	Anti-cancer treatment	Recombinant adenovirus
2008	Anti-cancer treatment	Recombinant adenovirus (2 dossiers)
2008	Anti-flue vaccine	Attenuated influenza virus
2009	Anti-cancer treatment	Recombinant adenovirus

Table 4.1 **|** *GMO medicinal products for human use*
Dossiers submitted at European level (situation at the end of 2009)

However, up to now, none of these dossiers for a GMO medicinal product for human use has been granted an authorisation for placing on the market within the European Union.
The EU is not the exception in this regard. Currently, only China has authorised the placing on the market of two gene therapy products, specifically two recombinant adenoviruses: Gendicine®, authorised in 2003 for treating various cancers, and Oncorine™, authorised in 2005 for treating cancer of the pharyngonasal cavity.

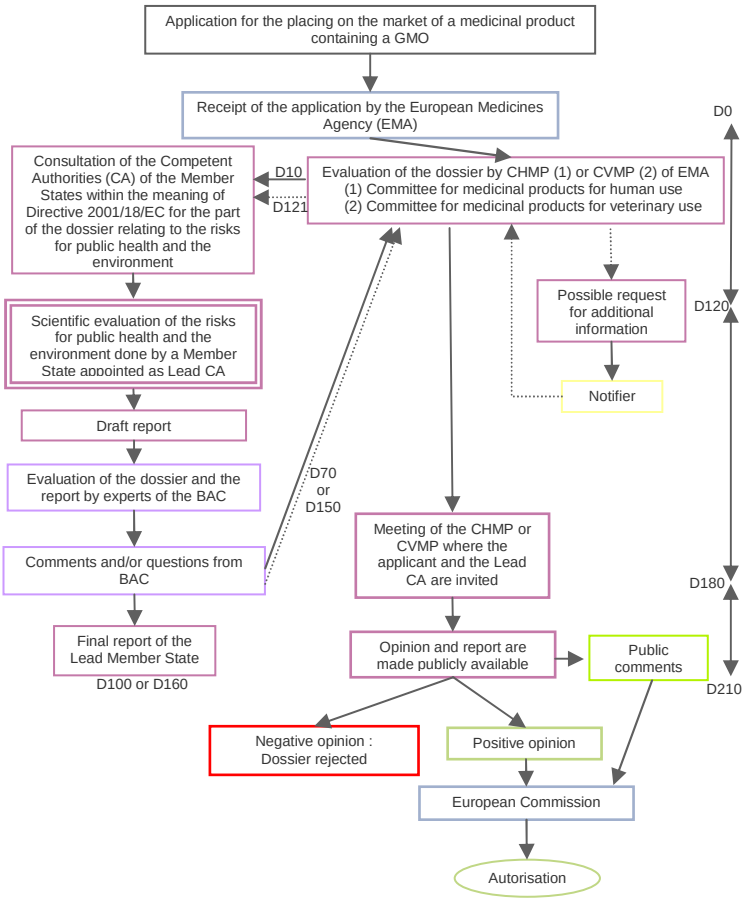

Figure 4.15 | *Application procedure for marketing authorisation of a medicinal product for human use containing or consisting of GMOs under Regulation (EC) No. 726/2004*

Medicinal products for veterinary use: Deliberate release for the purposes of research and development, or for placing on the market

As with medicinal products for human use, the development of new medicinal products for veterinary use is undertaken step-by-step. In a first time, the medicinal product is developed and tested in the laboratory. In terms of biosafety, if the new medicinal product contains or consists of a GMO, authorisation by the relevant competent regional authority(-ies) is required according to the legislation relating to the contained use of GMOs and/or pathogens for activities involving the use of this product and taking place in contained facilities (laboratory, animal housing facility).
As for medicinal products for human use, the authorisation may be issued for a given operation in a given facility and for a defined period of time. The term "operation" may cover a specific experimental protocol but also a full clinical trials programme if those trials can be deemed to be uniform from the point of view of biosafety (e.g. research activities using the same recombinant vector in a given facility). The initial authorisation may also cover later changes to the trial protocol which was initially submitted, provided these changes have no impact on biosafety.

In a second phase of the development of a medicinal product, it is generally necessary to undertake field trials, that is to say tests on animals which are not confined. For this type of activity, a prior authorisation must be obtained according to the provisions of Article 13(2) of the Royal Decree of 21 February 2005 governing the deliberate release of GMOs into the environment. The procedure followed is identical to that for an application for deliberate release relating to a medicinal product for human use and the competent authority must first ask for the advice of the Biosafety Advisory Council before authorising any trial (see above). Here too, the authorisation may cover a specific trial undertaken at different sites or a full trials programme.

Finally, before being placed on the market, all medicinal products derived from biotechnology (and therefore also medicinal products containing or consisting of GMOs) must obtain an authorisation for placing on the market issued by the European Commission upon advice of the European Medicines Agency (EMA). As with medicinal products for human use, access to the Community market for GMO medicinal products for veterinary use is subject to the centralised procedure laid down in Regulation (EEC) No. 2309/93, as amended by Regulation (EC) No. 726/2004. If authorisation is granted, it is valid for all Member States of the European Union.
In this case, assessment by the EMA is undertaken by the Committee for Medicinal Products for Veterinary Use (CVMP). For a medicinal product for veterinary use containing or consisting of GMOs, an environmental risk assessment must be undertaken in accordance with the provisions of Annex II of Directive 2001/18/EC. In Belgium, this risk assessment is performed by the Biosafety Advisory Council.
The role and involvement of the Biosafety Advisory Council in the authorisation procedure under Regulation (EC) 726/2004 are identical for medicinal products for both veterinary and human use (*Figure 4.15*).

Up to now, all of the dossiers relating to field trials or to the placing on the market of GMO medicinal products for veterinary use processed in Belgium have related to vaccines.

Prior to 1993 and implementation of the centralised procedure laid down in Regulation (EEC) No. 2309/93, two dossiers were processed by Belgian experts (at that time, the SBB, in close cooperation with the competent

federal authority). They related to applications for authorisation for placing on the market filed under Directive 90/220/EEC, i.e.:

- a vaccine against the porcine Aujeszky disease (genetically modified virus). This product was authorised in the EU in December 1992 (authorisation amended in July 1994 – Decision 94/505/EC – to cover a new form of administration);
- the Raboral recombinant vaccine for preventing rabies in foxes (see text box next page). This product was authorised in the EU in October 1993 (Decision 93/572/EEC).

Since 1993, 16 other dossiers relating to medicinal products for veterinary products containing or consisting of GMOs have been examined by Belgian experts and/or the Biosafety Advisory Council (see *Table 4.2*).

Year	Dossier type	Species targeted	Indications
1993	Placing on the market	Pigs	Vaccine against the porcine Aujeszky disease
1997	Field trial	Cats	Vaccine against leukaemia
1999	Field trial	Cats	Vaccine against leukaemia
1999	Placing on the market	Cats	Vaccine against leukaemia
2000	Field trial	Horses	Anti-flue vaccine
2000	Placing on the market	Cats	Vaccine against leukaemia
2000	Placing on the market	Hens	Vaccine against infectious bursal disease and Marek's disease
2001	Field trial	Cattle	Vaccine against Salmonella infections
2001	Placing on the market	Horses	Anti-flue vaccine
2001	Placing on the market	Rabbits	Vaccine against myxomatosis
2002	Placing on the market	Horses	Anti-flue vaccine
2003	Placing on the market	Cats	Vaccine against leukaemia
2004	Field trial	Cats	Vaccine against AIDS in cats
2007	Placing on the market	Horses	Anti-flue vaccine
2007	Placing on the market	Horses	Anti-flue vaccine
2009	Placing on the market	Cattle	Vaccine against infectious rhinotracheitis

Table 4.2 **|** *Veterinary GMO dossiers processed in Belgium.*
Breakdown based on species targeted and the indications (situation at the end of 2009)

A detailed description of the five field trial applications (including the BAC's advice and the authorisation of the competent authority) is available on the "Belgian Biosafety Server"[97].

Although Europe has not, to date, authorised the placing on the market of any GMO medicinal products for human use, nine GMO vaccines for veterinary use have, however, been authorised for placing on the market (out of the 13 applications examined by Belgian experts since 1992). A full list and brief description of these vaccines is also available on the "Belgian Biosafety Server".

Raboral

In the 1980s, the French company Rhône-Mérieux developed an anti-rabies recombinant vaccine: Raboral. It was an attenuated strain of the Vaccinia virus which, by adding a single gene, expressed the glycoprotein G of the rabies virus. The application dossier for marketing authorisation of this recombinant vaccine was filed in both Belgium (1992) and France (1993) under Directive 90/220/EEC. It was the second application dossier for the placing on the market of a GMO in Europe, after the vaccine against the porcine Aujeszky disease. Authorisation was granted by the European Commission on 19 October 1993. The decision states that the vaccine is intended to be distributed manually or by aerial drops in the form of bait to foxes containing the viral suspension, but only on the instructions of the national health authorities.
Major vaccination campaigns were undertaken in Belgium and this new vaccine, more stable than the vaccine containing the attenuated rabies virus, proved to be the vaccine of first choice. Since the end of the 1990s, Belgium has been officially recognised as being free of rabies in urban and forest areas.
Raboral V-RG® is currently distributed by Merial in Europe and around the world. In Canada and the USA, it is used to vaccinate not just foxes but also coyotes and raccoons.

[97] http://www.biosafety.be/DTB

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Development and marketing of a recombinant rabies vaccine

In 1984, M.-P. Kiény of the company Transgène in Strasbourg, published an article in the journal "Nature" describing the development of a recombinant vaccinia virus, which expresses the glycoprotein G (antibody inducer) from the rabies virus. A link between Jenner and Louis Pasteur was established. Seven years later, in 1991, the team of Professor P.-P. Pastoret (Faculty of Veterinary Medicine, University of Liège) published in the same journal, an article testifying the large-scale elimination of rabies in foxes by oral vaccination using this recombinant vaccinia-rabies virus (VR-G). The aim of using this live, genetically modified vaccine was specifically to improve the biosafety aspects in the frame of the fight against fox rabies by vaccination. Indeed, it was necessary to find an alternative to conventional vaccines that were formed from the live attenuated rabies virus and which presented residual pathogenicity to certain animal species.

A national programme of vulpine rabies elimination using VR-G was then carried out over the next decade. In total, 2,500,000 vaccine doses were distributed between 1989 and 2000 over an area of 10,000 km². In 2001, Belgium was declared free from rabies by the World Health Organization and the World Organisation for Animal Health.
Field trials of oral vaccination using VR-G were preceded by numerous tests in the laboratory and experimental stations in order to assess the efficacy, safety and stability of this new live vaccine produced using genetic engineering techniques.
In experimental stations, the lack of residual pathogenicity of VR-G was demonstrated in both the target species (adult and juvenile foxes) and non-target species. No clinical signs or lesions were observed in foxes up to 18 months following vaccination. The absence of pathogenicity in this species was proven, regardless of the dose or route of inoculation. The safety of the VR-G administered orally was also shown in 3 laboratory animal species, 5 domestic species and 14 wild species, which could possibly compete with foxes for the consumption of vaccine baits. No excretion with transmission of immunising titres of VRG could be detected in foxes, dogs, cats, cattle, wild boar, badgers or ferrets. The genetic stability of VR-G was verified by sequential *in vitro* (cell lines) and *in vivo* (fox, mouse) passage. Epidemiological risks linked to the appearance of asymptomatic carriers of the rabies virus were dismissed. An experimental study had indeed been able to show the existence of an early or delayed death phenomenon in foxes, consequences of an interaction between vaccination and natural infection.

Following these various tests, a first deliberate release of the VR-G into the environment took place on 24 October 1987 in the Marche-en-Famenne Military Camp, a site closed to the public. This trial was carried out after having obtained authorisation from the Belgium High Council for Health and that of the competent military authorities. Two hundred and fifty vaccine baits were manually distributed over an area of 600 ha. The VR-G was contained in an aluminium and plastic capsule and enclosed in a chicken head. This was a worldwide first. This first trial, as well as a second one carried out in 1988 over an area of 435 km² within the province of Luxembourg, confirmed the safety of VR-G in the target species as well as in wild and domestic non-target species. The fate of a significant selection of vaccine bait samples was meticulously monitored on field. This included monitoring the evolution of the viral titre and length of survival of the virus in diverse environmental conditions, together with the identification of potentially exposed animal species including invertebrates, etc. The long succession of safety tests carried out in the laboratory and in the field showed that, in terms of biosafety, this genetically modified vaccine was better than conventional vaccines currently used. From Zyklon B gas that was still used in the 1970s for destroying foxes, to the VRG vaccine distributed by helicopter and which enabled eradication of the disease in 1999, there is no doubt that spectacular progress had been made in terms of efficacy but also in terms of biosafety.

OTHER ADVICES OR DOCUMENTS ISSUED SPONTANEOUSLY BY THE BIOSAFETY ADVISORY COUNCIL OR THE SBB

Quite apart from advices relating to regulatory dossiers, the Biosafety Advisory Council and the SBB regularly issue specific or generic advices, either at the request of the authorities or on their own initiative. Both bodies have also published guidelines in various fields relating to risk assessment or the content of application dossiers for GMO authorisation.
A brief description is provided below of certain key advice notes and documents.

Field trial protocols for transgenic plants (1999)

In 1999, the SBB, in consultation with the competent authorities and with the support of experts of the "Transgenic Plants" scientific committee, coordinated the drawing up of protocols for field releases with transgenic plants. Protocols were drafted for sugar beet, oilseed rape and chicory[98]. These protocols set out the procedures to be followed for each sequence of operations (from sowing to harvesting) involved in the various trials for the production of GMOs (e.g. the holding of a log book) and monitoring of the parcels of land after harvesting, including waste management and treatment of any volunteers. They also include annual reporting to the competent authority.
The objective pursued by these protocols is to guarantee the containment of field trials to the parcels concerned and to prevent any admixture with food or feed.
These protocols laid down general risk management measures. Depending on the case-by-case risk assessment for each GMO, the Biosafety Advisory Council or the competent authority may, of course, impose additional terms and conditions on trials that are not set out in these protocols.
In the years following their drafting, these protocols have been regularly updated to take into account the development of scientific knowledge and any new legislative requirements. For example, in 2002, the oilseed rape

[98] The protocols are available on the "Belgian Biosafety Server".

protocol was substantially amended on the basis of the findings of a specific working group established by the SBB and composed of scientists and other experts in organic farming, conventional farming, natural reserves and even the beekeeping world.
It should be noted that, in the absence of any field trials with transgenic crops in Belgium since 2002, the protocols have not been updated since then.

Guidelines on molecular characterisation of transgenic plants (2000)

Molecular data (insert size, number of copies, location in the host genome, stability, etc.) are an integral part of the information required in notification dossiers related to the deliberate release into the environment or the placing on the market of transgenic plants.
In assessing the dossiers submitted under Directive 90/220/EEC, the SBB noted significant variations in the quantity and quality of the scientific data provided for the molecular characterisation of GMOs. To remedy this situation, the SBB took the initiative, in 2000, of drawing up guidelines for notifiers and setting out the level of detail and scientific rigour required for such molecular data. This initiative continued the work undertaken by a group of European experts put in place by the European Commission, work which was not completed due to a lack of consensus.
Using the last version of the document drawn up by the European working group as a starting point, the SBB drafted a Belgian version of these guidelines. The document was finalised with the help of experts in the scientific committees. Consultation with EuropaBio[99] was also organised so that the practical experience of companies drawing up notification dossiers could be taken into account.
Guidelines exists in two versions: one for dossiers for the placing on the market of transgenic plants (Part C of the Directive) and the second, simplified, for dossiers for field trials with transgenic plants (Part B of the Directive)[100].
Although they date back almost ten years, these guidelines are still relevant for notifiers. It should also be pointed out that this work has, for some years, been extended through the activities of an OECD expert group in which the SBB takes part (see Chapter 5). This group is working on the drawing up of a document aiming at informing risk assessors how to use molecular characterisation data and explaining the scientific foundations underlying the application of molecular characterisation to GMO environmental risk assessments.

Guidelines on the public dossier (2001-2003)

The Royal Decree of 18 December 1998 regulating the deliberate release into the environment and placing on the market of products consisting of or containing GMOs (and transposing Directive 90/220/EEC) imposed a requirement for all notification dossiers for deliberate release of a GMO into the environment for experimental purposes to contain a *proposal of information for the public*. The objective was to ensure that citizens were informed, in terms that could be clearly understood by the public at large of the activities undertaken by companies and research centres in the biotechnology sector. Such public information dossiers would also serve to initiate the public, so that it can learn, weigh the risks incurred against the benefits obtained, reach an opinion on these developments and products, etc.

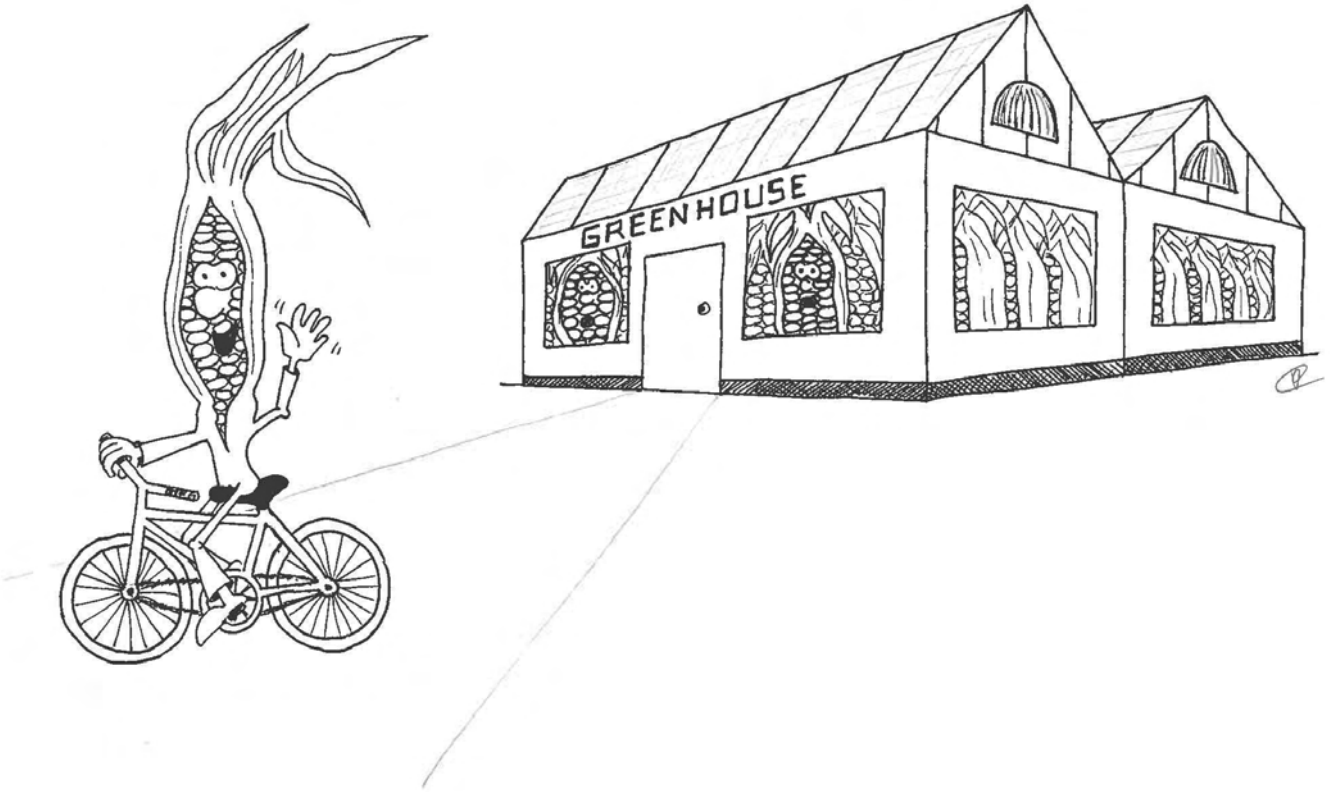
[99] EuropaBio, the European Association for Bioindustries, was created in 1996. Its objective is to promote and represent the biotechnology industry at EU level.
[100] The guidelines are available on the "Belgian Biosafety Server".

In the absence of precise indications in the legislation on the way the public information dossier should be drawn up, the SBB coordinated the drafting of guidelines. These were prepared by a working group specifically established for this purpose and gathering together experts specialising in the field of information and communication. To summarise, these guidelines required notifiers to use clear, user-friendly and simple language, to explain the scientific terms and concepts, and to avoid statements for which there is no scientific evidence and refrain from advertising messages. In addition to general or rather technical data relating to risk assessment, the notifiers were also asked to include in their public dossier information relating to the socio-economic aspects in order to meet the concerns of the public at large about the social impact of the use of GMOs.
The first guidelines for field trials with transgenic plant were issued in 2001. They were revised in 2002 and 2003 to take into account the recommendations and criticism expressed by the various players in this field. Similar guidelines for the deliberate release into the environment of genetically modified organisms were drawn up in 2003[101].
When Directive 2001/18/EC was transposed into Belgian law (Royal Decree of 21 February 2005), the public information provisions were set out in the legislation itself. Annex VIII A of the Decree[102] sets out in general terms the elements to be taken into consideration in information intended for the public in relation to the deliberate release of GMOs for experimental purposes or the placing on the market of GMOs. The objective continues to be to enable the public to be informed about this type of activity and therefore to be able to contribute, with a full knowledge of the facts, to the public consultation procedure.

Guidance notes for the safety assessment of genetically modified crops for food and feed use (2003)

In the early 2000s, risk assessment of GMO intended for food/feed use was undertaken in accordance with respectively Directive 2001/18/EC (feed) or Regulation (EC) No. 258/97 (food). Although these legislative texts set out the criteria to take into account in assessing the risks to human or animal health, these provisions were relatively general.
In consultation with the Belgian competent authorities, the SBB therefore put in place a working group, composed of scientists chosen from among the experts of the ad hoc scientific committees, to draw up guidance notes on the risk assessment of genetically modified plants for food or feed use. This work was completed in April 2003[103].
The objective of these guidance notes was to supplement the regulatory provisions on a case by case basis by providing notifiers and risk assessors with guidance in choosing the type and extent of studies that should be undertaken in support to risk assessment. The guidance notes dealt with aspects of molecular characterisation, toxicology, allergenicity and nutrition.
They were intended to be future proof and to constantly take into account the latest scientific data. However, they have not been updated since their publication due to the setting up of EFSA, the implementation of Regulation (EC) No. 1829/2003 and the adoption, at European level, of a guidance on the same subject in 2004.

[101] These documents are available on the "Belgian Biosafety Server".
[102] See http://www.biosafety.be
[103] Van Haver E, De Schrijver A, Devos Y, Lievens S, Renckens S, Moens W. Guidance notes for the safety assessment of genetically modified crops for food and feed use. 2003. Edited by ISP-SBB. *Bibliothèque royale de Belgique/Koninklijke Bibliotheek van België,* nr D/2003/2505/16. Available on the "Belgian Biosafety Server".



Advice of the BAC on the "Farm-scale evaluation of GMHT crops" (2004)

In January 2004, shortly after its official installation, the Biosafety Advisory Council was instructed by the Federal Minister for the Environment to provide an advice on the report "on the rationale and interpretation of Farm-Scale Evaluation (FSE) of genetically modified herbicide-tolerant (GMHT) crops", published a short time before[104]. This report was the result of a four-year research programme, commissioned by the British authorities, to examine the possible effects on biodiversity (insects, plants, weeds, invertebrates, etc.) of changes to agricultural management practices associated with the use of genetically modified crops (in this case, beet, maize and oilseed rape) when compared with weed control used with non-GM crops.

[104] For more information, see http://www.defra.gov.uk/environment/quality/gm/crops/fse.htm

The Council advice had three objectives: (i) to get the opinion of Belgian scientists on the FSE report itself; (ii) to assess the extent to which the FSE report provided elements that were new and relevant to the environmental risk assessment of transgenic plants; (iii) to assess the impact which this study would have on assessment of the regulatory dossier C/BE/96/01 (Bayer's transgenic MS8xRF3 oilseed rape), which was being processed by the Biosafety Advisory Council at that time (see above).
To draw up this advice, the Council asked for the opinion of a group of scientific experts, set in a very short deadline, and also provided NGOs familiar with the issue of transgenic plants (in this case, Friends of the Earth, GeneWatch, Greenpeace and *Collectif d'Action GénEthique*) with the opportunity to express their views on the British report.
The conclusions of the Biosafety Advisory Council, as well as all relevant documents on this matter, are available on the "Belgian Biosafety Server".

Advice of the BAC on the EFSA procedures (2006)

In February 2006, the Federal Minister for the Environment asked the Biosafety Advisory Council for an advice on the procedures followed by EFSA for the scientific evaluation and the risk assessment of GMO for food and feed use and on the European decision rules pertaining to the marketing authorisations given to these GMOs.
The Council's advice was finalised in May 2006 and was also communicated to EFSA. The constructive criticism given in this document and those submitted by other Member States (during a colloquium organised in May 2006 between the EFSA GMO Panel and the Member States) led EFSA to change the procedures to ensure greater transparency and ongoing dialogue with the advisory bodies of the Member States. Since then, all comments provided by a Member State on a GMO dossier during the assessment phase must be followed up by the EFSA GMO Panel in the form of a public document indicating clearly how the comments were taken into account by EFSA in reaching its opinion and setting out the scientific grounds for why certain comments were not taken into account.

Guidelines on GM stacked events (2007)

An increasing number of the GMOs notified under Regulation (EC) No. 1829/2003 are developed through traditional crossing of genetically modified lines, thereby creating GM stacked events. This type of GMO being deemed at European level to be a new GMO, it must undergo a risk assessment in its own right, this assessment taking into account, however, the results of the risk assessment undertaken for each of the genetically modified parent lines.
In 2007, the Biosafety Advisory Council published guidelines on the assessment of GM stacked events. The objective of this document was to assist notifiers in identifying the extent to which the results of the risk evaluations of the genetically modified parent lines could be taken into account, and should eventually be supplemented by new data generated in the frame of the risk assessment of the stacked events. These guidelines were based in particular on a scientific publication drawn up by the SBB, members of the Biosafety Advisory Council and external experts[105].

[105] De Schrijver A, Devos Y, Van den Bulcke M, Cadot P, De Loose M, Reheul D, Sneyers M. Risk assessment of GM stacked events obtained from crosses between GM events. Trends in Food Science and Technology 2007;18(2):101-109.

At the end of July 2007, EFSA published a guidance on the same subject[106]. This document did not conflict with the guidelines drawn up by the Biosafety Advisory Council although certain parts were set out in more detail in one document or the other. As a result of the publication of the EFSA guidance and to avoid unnecessary duplication of guidance documents for notifiers, the Council ultimately decided to align himself with the EFSA recommendations.

Advice of the BAC on a new genetic modification technique (2007)

In April 2007, the Federal Public Service for Public Health, Food Chain Safety and Environment asked the Biosafety Advisory Council to provide an advice note on the following question: "Should the "Targeted Gene Repair" technique be considered as a technique of genetic modification yielding genetically modified organisms in the meaning of Directive 2001/18/EC?". This question was addressed to the Council as part of more general discussions underway at Member States level on the legal status of certain new techniques of genetic modification. The Council concluded[107] that the "Targeted Gene Repair" technique was a technique of genetic modification within the meaning of the Directive. It noted, however, that this technique might be viewed as being a form of mutagenesis, a technique producing GMOs excluded from the scope of the Directive, and it concluded that there were scientific arguments for considering the "Targeted Gene Repair" technique to be comparable to mutagenesis from a regulatory viewpoint.
This advice is of particular note because the expert evaluation undertaken jointly by the Biosafety Advisory Council, SBB and external experts led to the publication of a scientific paper[108].

Advices of the BAC and the SBB on documents prepared by EFSA or the EMA

To conclude this non-exhaustive list of documents produced by the Biosafety Advisory Council and the SBB, it should be pointed out that both bodies have, on several occasions, submitted advices (on their own initiative or at the request of the authorities) on draft guidelines or other documents prepared by EFSA or the EMA. The advices of the Council and the SBB are provided either directly to the competent authority or submitted to the relevant European body as part of the public consultations on these documents.
This was the case, for example, with the following documents:

- "EFSA Draft guidance for renewal of authorizations of existing GMO products lawfully placed on the market" (2006);
- "EFSA Draft Report on the Safety and Nutritional assessment of GM Plant derived Foods/Feeds - The role of animal feeding trials" (2006);
- "EMEA Guideline on Scientific requirements for the Environmental risk assessment of gene therapy medicinal products" (2007);
- "EFSA general guidance on statistical considerations for the safety evaluation of GMOs" (2008);

[106] Guidance Document for the risk assessment of genetically modified plants containing stacked transformation events by the Scientific Panel on Genetically Modified Organisms (GMO). The EFSA Journal 2007;512:1-5 <http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178623591786.htm>
[107] The Council's advice is available on its website, http://www.bio-conseil.be
[108] Breyer D, Herman P, Brandenburger A, Gheysen G, Remaut E, Soumillion P, Van Doorsselaere J, Custers R, Pauwels K, Sneyers M, Reheul D. Genetic modification through oligonucleotide-mediated mutagenesis. A GMO regulatory challenge? Environ. Biosafety Res. 2007;8:57-64.

- "EFSA Guidance document for the risk assessment of genetically modified plants and derived Food and Feed" (2008 and 2009);
- The general principles of dealing with the problem of unintentional release (dissemination of body fluids of patients treated) of viruses or viral vectors (2009).

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20 years of biosafety in Belgium - A view from an outsider that became an insider

Contacts from the very beginning

My first contacts with the Belgian biosafety advisory structures date back to the beginning of the 1990s. At that time I worked for a period of four years at the Dutch GMO advisory committee (COGEM) and the Dutch GMO office, for which I attended a number of technical and regulatory meetings on GMOs organised by the European Commission and the OECD. The Biosafety and Biotechnology Unit (SBB) was always present at such meetings and I rapidly understood that the SBB played a central and crucial role in the area of biosafety in Belgium.

Pathogens in the contained use legislation

When I started to work in Belgium at the end of 1997, I only knew the Dutch and the European GMO regulatory framework. I still had to discover the Belgian one. The first thing I had to do was to try and understand the Belgian federate system, with its economic and cultural communities, its special status of Brussels, and see how biosafety was organised in that system. I started to concentrate on the contained use legislation. I was surprised to learn that the Belgian contained use legislation – I should correctly say the Flemish-, Brussels- and Walloon contained use legislations – not only included GMOs in their scope, but also pathogens. At the European level human pathogens are only part of the workers protection legislation, and the Dutch had followed that regulatory approach. I was very convinced of that approach and for a number of years I lobbied to have pathogens removed from the Flemish contained use legislation. This did not make me very popular at the SBB. Today I look differently at this situation. This is because from a practical point of view it makes sense to have pathogens and GMOs under the same regulatory umbrella. Both are living biological entities that, depending on their characteristics, may pose a hazard to the worker, public health, and/or the environment. They are often used in the same laboratories, and they all require the same thorough risk assessment and the application of the same type of precautionary measures.

From a mere regulatory point of view the overlap between the contained use legislations and the different legislations that cover pathogens, may lead to inefficiency. This overlap is not likely to disappear in the future as it concerns regional legislations at the one hand, and federal legislation at the other. In some areas there is a need for a better coordination between the different levels, for instance in the area of animal pathogens.

A crucial role in biosafety

The SBB has played a crucial role in the development of biosafety in Belgium. In the first years that role was different than it is now. At that time some government authorities were not very active yet in the area of biosafety, which made it possible for the SBB to put its mark more clearly on biosafety policy. This has changed over the years. In this, the co-operation agreement between the federate state and the regions concerning biosafety has been very important. With this agreement the Biosafety Advisory Council was established and the role and tasks of the SBB were more clearly defined. It led to a better distinction between policymaking on the one hand and administrative and advisory tasks on the other hand. Policymaking clearly was not the task of SBB. It also clearly

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defined the role of the SBB as the secretariat of the Biosafety Advisory Council. In practice the regional authorities have mandated the SBB to perform all the contained use advisory work. All deliberate release dossiers are assessed by the Biosafety Advisory Council.

The SBB as part of the Scientific Institute for Public Health

The SBB has been part of the Scientific Institute of Public Health from the very start. It has never been part of any goverment administration. This has the advantage that the SBB has always been away from bureaucracy and has stayed relatively close to science.

Professionalizing the biosafety profession in Belgium: the BBP

Biosafety and biosecurity have evolved quite significantly. Differenct actors have organized themselves and over the years they have become more experienced in the management of biosafety in the various types of laboratories and other settings. At a given point a number of people active in biosafety in Belgium started to get together for informal exchanges of information. Soon it was decided to start an association under the umbrella of the European BioSafety Association (EBSA). The Belgian organization got the name 'Belgian Biosafety Professionals' (BBP, see www.ebsaweb.eu/bbp). The BBP Steering Team ensures the practical management. In the fall of 2005 the first Steering Team elections took place. BBP held its launch seminar in March 2006.

The BBP's main objective was to promote awareness, knowledge and understanding of biosafety. The goal of BBP is to contribute to the exchange of information and experiences between biosafety professionals, follow up on relevant new regulatory or technical developments, and defend the interests of the biosafety professionals who are active in Belgium. The association gathers about 85 members stemming from universities, public research institutes, private companies and service providers. One of the areas in which BBP tries to be active is the sometimes gray field between legislative requirements and actual practice. What does a specific requirement exactly mean? How should it be interpreted in practice? For this BBP has developed a number of socalled 'biosafety practices'. These are not intended to be THE only and only correct or acceptable practice, but can be used as a useful guidance for the implementation of biosafety measures in the daily practice of biosafety professionals.

Over the years BBP has organized a growing list of trainings, workshops and seminars on different topics, such as emergency planning, risk assessment, biosafety cabinets, waste management, decontamination practices, design and construction of biocontainment laboratories. Its yearly one-day seminar is now known as 'The Belgian Biosafety Symposium'.

Although individuals working at SBB or for government authorities are not admissible as members of BBP, as one of BBP's tasks is to defend the 'end user interests', BBP has developed a good working relationship with both the technical expert body and the authorities. Depending on the subject, SBB was for instance invited to give presentations or to participate to activities and discusssions, organized for BBP members. SBB has also been consulted on a number of proposed draft practices.

The need for a new Co-operation Agreement on Biosafety

The importance of the Co-operation Agreement on Biosafety between the Belgian federal state and the regions was already described above. It has ensured that in contained use the same principles are applied in all three regions, and it makes the Biosafety Advisory Council function in practice. In its current state, however, the co-operation agreement is no longer up to date. One of the major reasons is that the division of competencies between the federal state and the regions has changed. Agriculture is no longer a federal competence and there are other changes that affect the agreement. That is why the co-operation agreement needs to get an update. To further improve the functioning of the biosafety system it is important that the roles of the different actors are further separated in a new agreement. I have always found it odd that persons directly involved in delivering permits for activities with GMOs are able to be a member of the council.

The functioning of the Belgian Biosafety Advisory Council

Where the biosafety system has been operational for 20 years now, the Biosafety Advisory Council has only been active since 2003. The members have been changing over the years, but also the advices have been evolving. With gaining more experience, the advices have become more coherent and more consistent. This has created room for taking up bigger challenges in the form of performing the environmental risk assessments for EFSA dossiers for the marketing of genetically modified crops, which are now being undertaken.

The council is much in debt with the people of the SBB because they form and excellent secretariat that is very constructive and supportive in their activities for the council.

GMOs are a politically sensitive issue

Genetically modified organisms – and their safety – have always been a politically sensitive issue. Not in the area of contained use, but in the area of deliberate release and even more so in the marketing of GMOs. The SBB and the Biosafety Advisory Council have always had to keep afloat in this arena. There have been challenges to the system where politics tried to intervene in the advisory processes, but the council has always been able to stick to the science. And that's the best the SBB and the council can do: keep to the scientific facts only and process them in the most objective manner, so no one can ignore them. Of course, there still is a political process that follows after having delivered a scientific advice, but that political process has to respect the procedures set out in the biosafety legislation.

The future of biosafety in Belgium

Contained use activities with GMOs and pathogens in Belgium have been growing over the years, and they are not likely to diminish. Also deliberate release activities in Belgium are likely to grow again. In the area of field trials with GM plants this may be hesitant, but in the biomedical areas more things are to come. At the European level the number of dossiers for the market approval of GMOs is also growing. This means that for the coming years the Belgian biosafety structures should remain supported, or even further expanded. The first 20 years of biosafety in Belgium have passed, but for sure at least another 20 years will follow.

The biggest challenge in the 20 years ahead lies in learning from experiences with GMOs and using that knowledge to loosen the biosafety regulations in areas where it is responsible to do so. In my years at the Dutch GMO office I saw many contained use dossiers that were more of the same. And three quarters of the activities in contained use fall into the categorie of 'no or negligable risk'. Also in deliberate release many traits are repeated in different dossiers, and over the years we have for instance already formed a good idea about the environmental impacts of traits such as glyphosate tolerance. There must be ways of making the biosafety assessments in these areas more efficient, and ways of reducing the administrative burden for applicants. Perhaps also in the coming years there may be room for a renewed discussion on whether to follow a process-based or a product-based biosafety approach.

Guarding fairness and proportionality

Looking back at 20 years of biosafety inside and outside Belgium learns us that it is an area that has been evolving. That evolution is likely to continue in the future. The fact that GMOs are widely debated keeps the pressure on the kettle. This forces everybody involved in biosafety to keep on improving the system, and to build further on the science as it unfolds. It is my goal to positively contribute to this future evolution and to guard that the GMO evaluation system remains deeply rooted in science and remains fair and proportionate.

DETECTION, IDENTIFICATION AND QUANTIFICATION OF GMOS IN THE ENVIRONMENT AND FOOD OR FEED: AN EXPERIMENTAL PROCESS COMPLEMENTARY TO THE EXPERT APPRAISAL ACTIVITIES OF THE SBB

Since its creation, the Biosafety and Biotechnology Unit (SBB) of the WIV-ISP has always carried out scientific research activities in the laboratory alongside its expert appraisal activities.

At the start of the 1990s, research was commenced (particularly within the scope of an EU project BRIDGE) into the application of PCR (Polymerase Chain Reaction[110]) as a detection and identification method for pathogenic fungi or fungi of biotechnological interest (*Streptomyces*, *Trichoderma*, *Aspergillus*, yeasts). This research marked the beginning of the SBB laboratory's specialisation in the development and application of gene detection and identification methods in food and environmental matrices. These methods are essentially based on the use of PCR.

In the years that followed, the SBB participated in various projects funded at Belgian level (WIV-ISP, Federal Science Policy, Ministry of Public Health, Ministry of Agriculture) or EU level (particularly via the 5th Framework Programme of the European Commission) related to various topics such as:

- the characterisation of environmental pools of antibiotic-resistance genes and gene flows between these pools linked to human activities;
- the effects of the use of antibiotics in livestock farming on the emergence of resistant bacterial strains;
- the detection of antibiotics and antibiotic-resistant germs in meat;
- the assessment of CEN standards relating to the detection and identification of genetically modified microorganisms released into the environment;
- the development of standardisation methods to support food chain safety in relation to the detection, identification and quantification of GMOs in foods containing GMOs.

More recently, the SBB laboratory has been involved in the EU's Co-Extra project (financed by the 6th Framework Programme of the European Commission) on the coexistence and the traceability of GMOs with a view to ensuring the coexistence of supply chains using GMO products, conventional products or products derived from organic farming. In particular, the SBB's research activities in this project have addressed improved performance levels and the reduction of costs in relation to GMO detection and quantification methods via the use of PCR.

These various projects have resulted in the establishment of recurrent collaborations with other Belgian and European laboratories involved in the detection and identification of GMOs, particularly the *Instituut voor Landbouw- en Visserijonderzoek* (ILVO, Flemish Institute for Agricultural and Fisheries Research) in Melle and the *Centre wallon de Recherches agronomiques* (CRA-W, Walloon Agricultural Research Centre) in Gembloux.

[110] The polymerase chain reaction, PCR, is a molecular biology technique invented by K Mullis in 1983 and patented in 1985. It enables the *in vitro* generation of several billion copies of a DNA fragment located between two known and selected sequence regions, using an extract of DNA and specific primers comprising short synthetic oligonucleotides. PCR is now widely used, for example, for diagnostic purposes to detect the presence of a specific DNA sequence in a given organism.

Furthermore, from 1997, following the approval of the cooperation agreement on biosafety, the existence of the SBB laboratory was ratified in this legal text. One of its main roles is to support the country's inspection services within the scope of monitoring the deliberate or accidental release of genetically modified organisms into the environment or the marketing of GMOs, particularly for food purposes.
This surveillance requirement stems from several provisions established by European Directives 2009/41/EC and 2001/18/EC and their transposition into Belgian law, and by European Regulations (EC) 1829/2003 and (EC) 1830/2003. This legislation introduces rules for the traceability and labelling of genetically modified organisms and products derived from GMOs throughout the food chain. The European regulations establish compulsory labelling of products intended for human or animal consumption if they contain more than 0.9% GMO per ingredient. The Member States must ensure that product inspection and control measures, including sampling checks and qualitative and quantitative analyses of foodstuffs, are applied.

However, it should be pointed out that the SBB did not wait for the implementation of the cooperation agreement or the aforementioned European regulatory texts in order to draw the attention of the Belgian and European authorities to the importance of developing and mastering the molecular genetic techniques required to detect and identify GMOs. That is because detection and identification constitute the key to enable the competent authorities to exercise their duties of regulating the market and overseeing the provisions in force regarding surveillance, traceability and labelling.
In December 1996, the Belgian authorities placed the SBB in charge of checking the import into Europe via Belgium of transgenic maize by the Swiss company Ciba-Geigy (now Syngenta), a transgenic maize that was not authorised in the EU at that time. Analysis of the genetic map was completed within two weeks (in collaboration with the Robert Koch Institute in Berlin) and confirmed the presence of unauthorised transgenic maize. Beyond the controversy surrounding this first importation of GMOs into Europe, this analysis demonstrated the possibility of quickly tracing specific GMOs with a sensitivity of at least 1 transgenic grain among 1,000 others.
Soon after the first analyses aimed at detecting and identifying GMOs, the idea of a European network of GMO laboratories was launched in 1999 in Ispra (Italy), at the Joint Research Centre (JRC) of the European Commission. This network was opened by the European Commissioner for Research, Philippe Busquin of Belgium, in December 2002. The WIV-ISP had the honour of delivering the inaugural speech in front of the directors of some 50 scientific institutions and the international press. The European Network of GMO Laboratories (ENGL) is currently made up of over 100 member laboratories appointed by the competent authorities of the 27 Member States, Norway and Switzerland. This initiative prompted the emergence of similar networks in Asia, the United States and the Maghreb countries. The principal missions of the ENGL are the development, harmonisation and standardisation of sampling, detection, identification and quantification methods for GMOs or GMO-derived products from a wide variety of matrices, covering seeds, cereals, foodstuffs, animal feed and environmental samples. In June 2008, the JRC and the ENGL arranged the first global conference on GMO analysis.

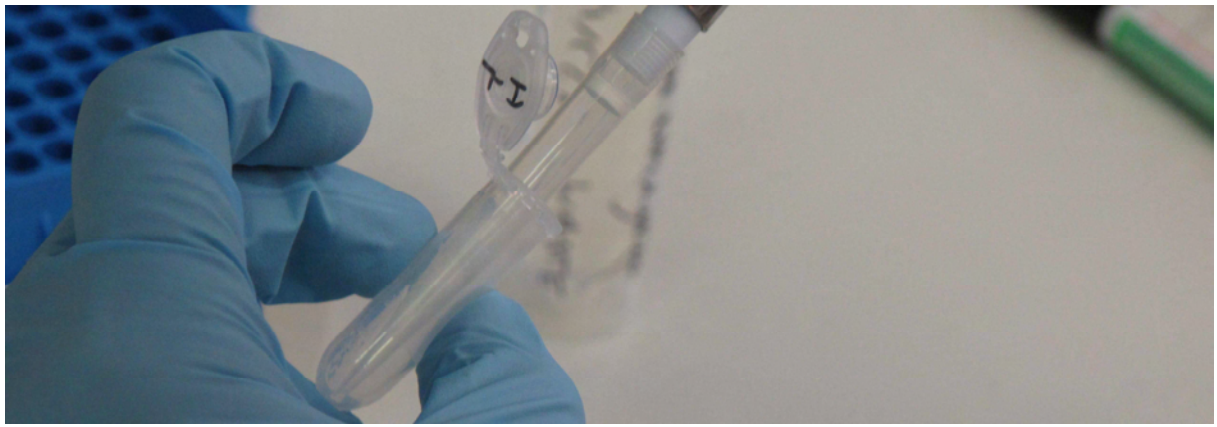
The Belgian component of the ENGL, namely the National Reference Laboratory for Genetically Modified Organisms (NRL-GMO), was officially set up in 2006. It is made up of the WIV-ISP (the federal laboratory for the GMO detection) and the ILVO and the CRA-W which house the regional GMO detection laboratories. The NRL-GMO is coordinated by the WIV-ISP. It works to support the Belgian Federal Agency for the Safety of the Food Chain (FASFC) within the context of implementing Regulation (EC) 1830/2003. In particular, it has the task of

promoting the application and development of new GMO detection, identification and quantification methods in food matrices.
It should be noted that the SBB has been ISO 17025 accredited for its GMO detection, identification and quantification activities since 2003. In 2009, it also obtained a flexible scope of accreditation within the framework of this same standard for all GMO analyses[111].

The European consortium ENGL, including the Belgian NRL-GMO, works to support the European Union Reference Laboratory for GM Food and Feed (EURL-GMFF, formerly the Community Reference Laboratory), which was established in accordance with the provisions of Regulation (EC) 1829/2003. The main task of the EURL-GMFF is the scientific assessment and validation of detection methods supplied by notifiers within the framework of marketing authorisation applications for GMO food or feed.

This pooling at the EU level of efforts to detect and identify GMOs is now all the more justified, due to the growing number and diversity of GMOs grown or marketed in the food industry worldwide. In 2009, no fewer than 144 different GMOs, corresponding to 24 plant varieties, were marketed in 30 countries.

The analysis activities of the SBB have recently led to the development and patenting of an original approach to GMO detection. This integrated approach, in use since 2005, makes it possible to simplify the identification and quantification stages. It consists of three sample analysis stages, all based on real-time PCR technology[112].
In the first stage, the possible presence of GMOs in the sample is investigated in a generic way. To this end, the SBB developed an original tool, COSYPS (Combinatory SYBR®Green PCR Screening), comprised of a PCR-based GMO detection platform, which uses a combination of various primers, coupled with a mathematical model



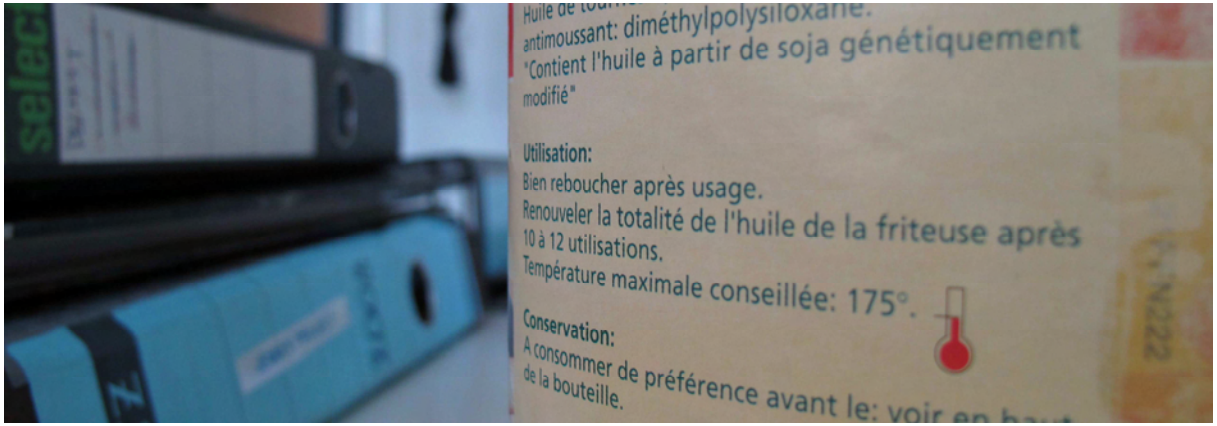
[111] When the scope of accreditation (i.e. all the accredited tests or tests that fall within the field of accreditation) of testing laboratories is too rigid, it can prevent swift adaptation to clients' needs. A flexible scope of accreditation enables a laboratory to self-assess, under certain conditions, new test methods and to add them to its scope of accreditation.
[112] Real-time PCR technology is based on the detection and quantification of a fluorescent reporter whose emission is directly proportional to the quantity of DNA fragments generated during the PCR reaction. The entire process is automated from start to finish.

enabling the identification of potential GMOs present in a sample by applying an original algorithm. This unique system has been patented[113] and its methodological principles published[114].

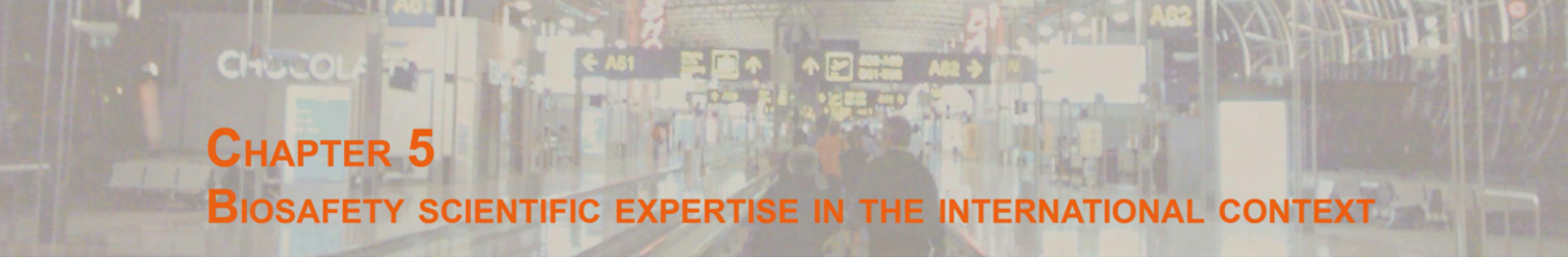
The second stage consists of specifically identifying the GMO(s) present in the analysed product. This is done using methods supplied by the notifiers within the framework of their marketing authorisation application. These methods were initially validated by the EURL-GMFF and were then validated separately by the SBB.
Finally, a third stage enables the GMO(s) present to be quantified in cases where it is necessary to check the application of provisions regarding labelling.

To date, all GMOs falling within the scope of Regulation (EC) 1829/2003 can be identified using the detection platform developed by the SBB. This represents 26 different GMOs corresponding to a wide variety of plants (maize, soybean, rapeseed, rice, cotton, sugar beet, potato).

Since June 2010 and the reorganisation of the WIV-ISP, GMO laboratory analysis and research activities have been integrated into a newly created "Biotechnology and Molecular Biology Platform". The GMO laboratory is therefore no longer part of the SBB. Despite this functional separation, it is clear that the laboratory activities and expert appraisal activities regarding GMOs will continue to actively interact in the future. Indeed, these two aspects are complementary and share the same objective of supporting the competent authorities in the field of biosafety.



[113] Van den Bulcke M, Lievens A, Leunda A, Mbongolo Mbella G, Barbau-Piednoir E, Sneyers M, Transgenic plant event detection - Patent Application WO2008EP51059, Application number 08708376.2 filed on 29/01/2008, Publication: 07.08.2008
[114] Van den Bulcke M, Lievens A, Barbau-Piednoir E, Mbongolo Mbella G, Roosens N, Sneyers M, Leunda Casi A. A theoretical introduction to "combinatory SYBRGreen qPCR screening", a matrix-based approach for the detection of materials derived from genetically modified plants. Anal Bioanal Chem 2010;396(6):2113 -2123.



CHAPTER 5
BIOSAFETY SCIENTIFIC EXPERTISE IN THE INTERNATIONAL CONTEXT

Since it emerged across the Atlantic in the 1970s, the topic of biosafety has become firmly established on the international scene. It is now on the agenda of numerous official organisations where it is addressed from various angles. This evolution has made the management of biosafety at the local level more complex and highly dependent on the results of international processes. It has also led to an increased need for coordination and networking.

As a permanent centre of biosafety expertise in Belgium, the Biosafety and Biotechnology Unit (SBB) has played a key role in the scientific representation of Belgium at the European and international level since the beginning of the 1990s. Moreover, this central role is recorded in the Cooperation Agreement concerning biosafety (Article 12). Although other Belgian experts contribute to certain international scientific activities in the field of biosafety, either individually or on behalf of their institutions, in this chapter we have chosen to focus on the contribution of the SBB.

The central role of scientific support played by the SBB is important for both the Belgian authorities and the SBB itself. At the level of the concerned authorities and administrations, it ensures the continuity of technical and scientific expertise and the scientific consistency of Belgium's position within the different bodies. A single point of contact also makes it possible to simplify the flow of information to authorities and government agencies. For the SBB, participation in working groups on a European or international level makes it possible to establish scientific contacts with foreign experts and integrate into expertise networks which are likely to generate projects or lead to scientific publications.

Scientific activities at the international level can be split into two broad categories: firstly, direct scientific support to the Belgian authorities within the scope of the official authorities' work or the implementation of the GMO regulatory framework. Secondly, participation in activities of various professional organisations working to support actors in the world of biosafety.

SCIENTIFIC SUPPORT TO THE COMPETENT AUTHORITIES

Implementation of the European regulatory framework

From the late 1980s and the negotiation of the first GMO Directives in Europe, the Belgian authorities have benefitted from the ongoing technical and scientific support of the SBB during discussions in the European institutions (Commission, Council). Currently, the scientific support provided by the SBB to the federal or regional authorities mainly translates into participation in meetings of the competent authorities and committees dealing with application of Directives 2009/41/EC and 2001/18/EC [115] and Regulation (EC) 1829/2003.

[115] Article 12 §5 of the Cooperation Agreement stipulates that the SBB provides the Secretariat of the Belgian delegation during international missions, particularly during meetings of the European Committees referred to in Article 21 of Directives 90/219/EEC and 90/220/EEC.

The SBB has also been involved in the different phases of the evolution of the European regulation, in the adaptation to the technical and scientific progress of annexes of directives and regulations, and even with the drafting of guidelines or explanatory notes to support the implementation of directives and regulations. The documents to which the SBB has contributed include:

- explanatory notes concerning risk assessment referred to in Annex III of Directive 90/219/EEC (2000);
- criteria for establishing the safety, for human health and the environment, of certain types of GMMs in accordance with Annex II, Part B of Directive 90/219/EEC (2001);
- guidance notes on the objective, elements, general principles and methodology of the environmental risk assessment referred to in Annex II of Directive 2001/18/EC (2002);
- guidance notes supplementing Annex VII of Directive 2001/18/EC concerning monitoring plans (2002).

More recently, the SBB has also actively contributed to the drafting of the European Food Safety Agency (EFSA) guidance project on the environmental risk assessment of genetically modified plants.

In addition to the aforementioned official meetings, the European Commission also organises technical meetings where general or specific questions about biosafety are addressed. This is generally done within the framework of working groups in which the SBB regularly participates at the request of the competent authorities. These discussions between experts are important as they often lead to the drafting of recommendations that are valuable tools to assist with the implementation of regulations for those involved on the ground.

The themes addressed in the expert groups include the general principles of risk assessment, the monitoring of insect-resistant plants, the use of antibiotic resistance markers, the molecular characterisation of GMOs and the development of a common register of molecular data.
A recent example is the working group on "new techniques", which was set up by the European Commission to assess whether the use of certain techniques leads to genetic modification within the meaning of the definition of GMO in Directives 2009/41/EC and 2001/18/EC (see text box next page).

Working group on new techniques

At the European level, an organism is only defined as being genetically modified if it has been developed via certain techniques. Thus, the GMO regulation specify, in Annexes, techniques whose use (i) does not lead to GMOs, (ii) leads to GMOs covered by the regulation or (iii) leads to GMOs excluded from the scope of the regulation. In recent years, however, new genetic modification techniques have appeared (including some likely to quickly lead to commercial applications), for which it is not always obvious whether they fall within the scope of the GMO regulation. In an attempt to put an end to this legal uncertainty, and following the request of several Member States, at the end of 2008, the European Commission set up a permanent group of experts ("New techniques working group") tasked with assessing a list of new techniques and supplying a scientific opinion to the competent authorities so that they can come to a decision as to whether or not those techniques are covered by Directives 2009/41/EC and 2001/18/EC. The SBB was appointed by the competent federal and regional authorities to represent Belgium in this group of experts.
In addition to the activities of this group, the Commission took two other initiatives: the creation of a Task Force responsible for assessing the challenges in terms of detection and monitoring of GMOs associated with the use of these new techniques; the implementation of a project with the aim of evaluating the potential socio-economic impacts of those techniques. The SBB is also involved in these two initiatives.

European Enforcement Project

The European Enforcement Project (EEP) was set up in 1997, following a Dutch initiative and thanks to start-up funding from the European Commission. At first, it consisted of a network of inspectors involved in the follow-up of Directive 90/219/EEC. In 1999, the German authorities set up a parallel network for inspectorate activities associated to Directive 90/220/EEC. The two networks were soon merged and now form a single group composed of representatives of the 27 Member States of the EU (plus Iceland, Norway and Switzerland) involved in inspectorate activities associated to GMOs.
The EEP is a platform for discussion and exchange of information between inspectors in relation to problems stemming from inspection, surveillance and compliance of the two Directives mentioned above (and their successive revisions). Information and expertise is exchanged through seminars and joint inspections.

From the outset, the SBB has participated in the activities of this network, to support the competent regional and federal authorities in Belgium. It has, for example, been responsible for setting up and maintaining the first website for European inspectors. Later, it participated in drafting various inspection procedures and checklists. In 2008, the SBB actively contributed to establishing the scientific programme of the annual meeting of the members of the network, organised in Belgium by the Flemish Community and the Federal Public Service for Health, Food Chain Safety and Environment.

Participation in the work of international bodies

The SBB is also first in line to provide scientific support to the competent authorities and to enable them to fulfil their legal obligations within the scope of the activities of international bodies or the implementation of international treaties in the field of biosafety, and also, more recently, biosecurity.

UN and Cartagena Protocol on biosafety

In the environmental field, since 1995, the preparation of international meetings at Belgian level have been performed within the framework of the Coordination Committee for International Environmental Policy (CCIEP). The CCIEP serves as an interface between the Belgium's federal and regional authorities and the international organisations in the environmental field. In particular, it has the task of arranging dialogue between the federal and regional levels with a view to the coordinated implementation at national level of recommendations and decisions taken at international level. These concerted positions require preliminary discussions at both - political, technical and scientific levels. In the case of GMOs, this relates to the United Nations Convention on Biological Diversity (CBD) and, more specifically, the Cartagena Protocol on biosafety, which is associated with it.

This multilateral treaty regulates the international exchange of genetically modified organisms (known as "living modified organisms" in this context - see text box) and was ratified by Belgium in April 2004. The negotiation and implementation of this treaty have mobilized the expertise of the SBB significantly for several years.

The Cartagena Protocol on Biosafety

On 29 January, after five years of difficult negotiations, ministers and official delegates of more than 130 countries meeting in Montreal adopted a multilateral environmental treaty, the "Cartagena Protocol on biosafety to the Convention on Biological Diversity". As its full name implies, the Cartagena Protocol follows on from the United Nations Convention on Biological Diversity and was drawn up to meet the requirements of Article 19 of the Convention. The Cartagena Protocol came into force on 11 September 2003, after 50 countries had ratified it.
This Protocol governs "transboundary movements, transit, handling and use of all living modified organism (LMO) that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health". Therefore, it regulates the transfer of LMOs between countries via a system of prior notification and consent. Its main objective is to give importing countries the opportunity and ability to scientifically assess the risks associated to products resulting from the use of modern biotechnology.
To this end, the Protocol provides a series of measures relating to notification procedures, methodology and criteria to be taken into account in the risk assessment of LMOs, to capacity-building in developing countries and to the establishment of a legal instrument covering liability and redress in case of damage.
Another notable element of the Protocol is the creation of a Biosafety Clearing-House (BCH). This is a website for the exchange of scientific, technical and legal information in the field of biosafety.

Belgium became involved in the negotiation process in 1996, when an international working group was set up with the mission of drawing up a biosafety protocol. The SBB not only provided its scientific expertise at the time, but also took on a coordination role in Belgium throughout the negotiation process. Initially comprised of just one expert from the SBB, the Belgian delegation gradually grew to include representatives of the various government agencies and offices involved, as political and commercial aspects emerged in the negotiations. After the adoption of the Protocol in January 2000, the central role of the SBB in the process culminated with the role of coordinator during the Belgian Presidency of the EU in 2001.

The implementation of the treaty in Belgium, which followed its ratification in 2004, led to the distribution of responsibilities between the different bodies concerned. The SBB has maintained its traditional role of technical and scientific support to the authorities for matters concerning risk assessments. The Biosafety Advisory Council is also consulted from time to time for some of these matters. For some years, discussions have been underway within the framework of the Protocol to identify and analyse the tools (guidance, criteria, methodology, etc.) currently used in the assessment of GMO risks and to determine whether those tools should be supplemented in relation to specific aspects of risk assessment, particularly the assessment of certain types of GMOs (fish, invertebrates, trees, pharmaceutical plants, etc.) or certain characteristics introduced (abiotic stress, etc.).

Moreover, the SBB has been entrusted with the role of national focal point for the Biosafety Clearing-House (BCH) due to its significant experience in the development and management of biosafety information exchange systems (see Chapter 6 for more information). Shortly after the adoption of the Protocol, the SBB also participated in the international panel of experts set up by the Secretariat of the CBD to provide technical assistance for the development of the BCH. As the focal point for the BCH, the SBB developed the Belgian component of the BCH, the "Belgian Biosafety Clearing-House"[116]. It also ensures that Belgium's obligations with regard to the exchange of information established by the Protocol are fulfilled.

Didier Breyer (SBB), spokesperson for the Belgian Presidency of the European Union in 2001, at an international meeting of the Cartagena Protocol

[116] Website accessible at the following address: http://www.biosafetyprotocol.be

WHO: Poliomyelitis laboratory containment and eradication plan

Poliomyelitis is an infectious and contagious disease caused by an RNA virus, the poliovirus (there are actually three types of virus). In 1988, the World Health Organization (WHO) adopted a resolution calling for global eradication of poliomyelitis. A global eradication plan of an infectious disease had previously been successfully carried out for smallpox (declared eradicated in 1979).
In June 2002, the "European Region" of the WHO[117] (of which Belgium is part) was certified as being free from the transmission of wild poliovirus, thus joining the WHO's "Americas" and "West Pacific" regions. In the same year, within the framework of the global eradication plan[118], the SBB was designated "National Coordinator" in order to prepare and keep up to date an inventory of laboratories holding wild poliovirus and/or any potentially infectious biological material. This task was carried out in collaboration with the Division Public Health and Supervision Operational of the WIV-ISP, which is responsible for preparing the report on the poliomyelitis eradication plan, sent each year to the WHO.

Within the scope of its role as national coordinator, between June and November 2002, the SBB performed a national survey of the laboratory containment of wild poliovirus. The survey covered 411 institutions and led to a report being sent to the WHO in 2003. This report documented the way in which the survey had been carried out (in accordance with the requirements of the WHO). It identified eight laboratories holding biological material containing wild poliovirus. In 2005, an additional report on the progress of the implementation of the eradication plan in Belgium was published[119]. The inventory of laboratories is updated annually. Since 2006, only four laboratories are still listed as holding biological material containing wild poliovirus. The laboratories that must be covered by the national inventory are medical analysis and/or research laboratories, as well as laboratories in other sectors that could hold biological material collected at a time when wild poliovirus was still circulating (in Belgium or abroad).

There is considerable delay in execution of the global poliomyelitis eradication plan. The world will be declared free of wild poliovirus transmission when the WHO Global Commission for the Certification of the Eradication of Poliomyelitis is in a position to conclude that all WHO Regions have documented the absence of wild poliovirus circulation for at least three consecutive years and that all material containing wild poliovirus is adequately contained under laboratory conditions. In 2010, at the global level, we are still at the pre-eradication phase.

The global eradication plan is actually subdivided into different phases (from the pre-eradication phase to the phase of post-vaccination with an oral form of the vaccine). For each phase, there are increasingly strict requirements in terms of laboratory containment and the working practices adopted. Indeed, the probability of a wild poliovirus infection associated to the virus being held in a laboratory is negligible, but the risk will increase with time. Once vaccination will be stopped, the possibility of poliovirus being reintroduced into the community from a laboratory could represent a global public health threat.

[117] This geographical area extends well beyond the borders of the European Union: http://www.who.int/about/regions/euro/en/index.html
[118] WHO global action plan for laboratory containment of wild polioviruses. WHO, 1999. WHO/V&B/99.32 (replaced in 2003 by a second edition, ref. WHO/V&B/03.11).
[119] Sneyers M, Herman P, Moens W. Polio eradication and laboratory containment program of wild polioviruses in Belgium: Laboratory survey and inventory phase. Archives of Public Health 2005;63:57-65.

It should be pointed out that once polio is eradicated, the polio vaccine will still need to be prepared (in an injectable form with an inactivated strain - IPV) for public health reasons, as was done for smallpox on the same scale. In the post-vaccination phase, it can be expected that a very high containment level will need to be applied to laboratories holding wild poliovirus or that produce the injectable form of the vaccine. Significant investment will therefore be necessary for the large-scale production units. Furthermore, the WHO has published guidelines on this subject[120] that the SBB helped draft.

The implementation of these particular containment measures in Belgium will probably require the implementation of a Royal Decree setting out provisions on the subject, particularly the containment levels required depending on the different phases of poliomyelitis eradication. The maintenance of vaccine production (inactivated injectable form) in Belgium will also require the establishment of a specific emergency response plan. The SBB is responsible for informing the laboratories concerned about the biosafety measures in place for handling listed biological material.

Biosecurity

The war in Iraq, the attacks of September 11 2001 and the attacks with *Bacillus anthracis* spores (also erroneously referred to as "anthrax"), which followed in the United States, have revived fears about the use of biological agents in bioterrorism activities. Furthermore, the increase in the number of laboratories handling biological agents is likely to increase the risk of laboratory accidents, the accidental release of agents responsible for infectious and/or contagious diseases and the use of this biological material for malicious purposes.

Finally, the publication of works such as the chemical synthesis of a poliovirus in 2002 (via synthetic biology)[121] or even the laboratory reconstitution of the influenza strain responsible for the "Spanish flu" in 1918[122], further strengthen the idea that the development of biological agents for criminal or terrorist purposes is not limited to science fiction. Those terrorist activities could be directed against humans, animals, the food chain or even crop plants[123].

Various initiatives have therefore been taken (particularly by the United Nations as well as at the European level) to reduce the potential risks linked to a terrorist attack or a deliberate or accidental release of biological material or pathogenic agents, whether genetically modified or not.

The biosecurity and biorisk aspects (greatly) exceed the field of competence of public health and are not currently covered by the duties formally entrusted to the SBB by the Cooperation Agreement concerning biosafety.

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[120] World Health Organization. Guidelines for the safe production and quality control of IPV manufactured from wild polioviruses. Geneva: World Health Organization; 2003.
[121] Cello J, Paul AV, Wimmer E. Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. Science 2002;297:1016-8.
[122] Tumpey TM, Basler CF, Aguilar PV, Zeng H, Solórzano A, Swayne DE, Cox NJ, Katz JM, Taubenberger JK, Palese P, García-Sastre A. Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus. Science 2005;310(5745):77-80.
[123] Historically, however, there are few examples of the use of biological weapons by terrorists. To date, no biological weapons of mass destruction projects have come to light. There is no evidence to show that biological weapons could form part of the standard arsenal of terrorist organizations. And even if the intention were there, the technological capacity, production and use of biological weapons still seem to be limiting factors.

Nevertheless, this subject obviously has several points in common with biosafety. The scientific and technical expertise of the SBB can therefore be used in the field of biosecurity, particularly in relation to the contained use of GMOs or pathogens (risk assessments, formulation of motivated advices, containment measures, laboratory inspections, updating risk groups of human, animal and plant pathogenic organisms). It is within this context that the SBB has already been asked several times to provide scientific support to the Belgian FPS for Foreign Affairs, Foreign Trade and Development Cooperation.

Thus, at the end of the 1990s, the SBB participated in the work of an *ad hoc* group set up to develop a Protocol to complement the Biological and Toxin Weapons Convention (BTWC, see text box). The SBB is involved in the follow-up of this Convention by participating in meetings of experts at the Belgian and European levels to support the activities of the FPS for Foreign Affairs. The SBB also performs ongoing work collecting and archiving documents relating to the BTWC.

The Biological and Toxin Weapons Convention

The Biological and Toxin Weapons Convention (BTWC), which was adopted in Geneva in 1972 and came into force in 1975, aims to prohibit the development, manufacture and storage of bacteriological (biological) or toxin weapons and to destroy them. Belgium ratified this Convention in 1975.
An original feature of the Convention is that it does not prohibit biological weapons as such, but rather the purpose for which they are developed and used. However, its effectiveness remains limited as it is undermined by institutional shortcomings and lacks a real verification mechanism.
In order to strengthen the control of implementation of this Convention, a special group of experts was set up between 1995 and 2001 in order to negotiate a Protocol to be attached to the Convention. The aim of this Protocol was to establish effective verification measures, essentially via a voluntary declaration by the States of installations and activities that might be of interest within the framework of the Convention, as well as the possibility of inspecting installations and carrying out inquiries at installations and on the ground. Due to a lack of consensus between the countries, this Protocol was never adopted.

The SBB is also represented within the Belgian coordination group responsible for monitoring the application of the BTWC and UN Security Council Resolution 1540[124]. This group, directed by the FPS Foreign Affairs, is also composed of representatives of the Belgian Ministry of Defence, the FPS Public Health, Food Chain Safety and Environment, the FPS Interior and the FPS Justice (State security).
For several years, the SBB has participated in the collection of data to complete the questionnaire on confidence measures required by the UN in collaboration with the FPS Foreign Affairs (coordination), the Ministry of Defence and the FPS Public Health.

Recently, the SBB has also been involved in the consultation process initiated at the European level by the Commission (following the publication by the Commission of a green paper on bio-preparedness[125]) on ways of reducing biological risks and improving preparation and response capabilities.

[124] Resolution 1540 on the non-proliferation of weapons of mass destruction.
[125] http://europa.eu/rapid/pressReleasesAction.do?reference=MEMO/07/289&format=HTML&aged=0&language=EN&guiLanguage=frr

Organisation for Economic Cooperation and Development (OECD)

As mentioned in Chapter 1, the OECD was one of the first international organisations to specifically look into biotechnology and biosafety in any depth. Since the beginning of the 1980s, modern biotechnology has formed an integral part of its work programme. In the continuation of the publication of the "Blue Book" on recombinant DNA safety considerations (1986), working groups made up of experts from member countries were set up. One of the main objectives of the work on biosafety carried out by the OECD is to facilitate harmonisation between member countries of procedures for notifying and assessing potential risks associated to activities involving GMOs. Indeed, reciprocal recognition of data and assessment methods can improve mutual understanding of risk assessments and increase the effectiveness of the evaluation process.
At the request of the CCIEP, the SBB was designated as the expert representing Belgium in the two OECD working groups that deal with matters directly related to biosafety. The SBB participates in meetings of the groups and intersessional activities (workshops, etc.), and directly contributes to the drafting of numerous documents. In some cases, experts from the common list of the Biosafety Council and the SBB are consulted to provide a more specific scientific contribution to the preparation of certain documents.

Working group for Harmonisation of Regulatory Oversight in Biotechnology

The main activities of this working group, which has existed since 1995, consist of developing and publishing scientific reports (known as "consensus documents") that can be used as a source of information in the preparation of applications for deliberate release of GMOs into the environment or within the framework of risk assessments of those GMOs. The aim of these documents is to compile and organise the relevant scientific information for assessing the risks of a certain number of transgenic organisms, focusing on two areas: the biology of vegetable, animal or microbial species, and specific traits introduced into GMOs (insect resistance, herbicide tolerance, etc.)[126].
Since a few years, the group has also been working on the development of other types of documents concerning particular aspects of the risk assessment process (molecular characterisation, environmental risk assessment, etc.).

The Working group has also developed the "BioTrack" website, to which the SBB contributed extensively in the first few years, thanks to its expertise in biosafety website development. This website contains documents produced by the group as well as a "products" database of GMOs approved for marketing in OECD countries[127].
In order to avoid unnecessary repetition, the BioTrack website has been largely coordinated with the Biosafety Clearing-House of the Cartagena Protocol for several years.
It was within the framework of using the BioTrack site that the OECD developed a unique identification system for transgenic plants in 2002. This system initially had a purely technical function aimed at facilitating access to information contained in the "products" database, but was soon adopted at the European and then international level within the framework of the traceability and control of GMOs (see text box next page).

[126] The full list of documents published by this working group is available on the OECD website at http://www.oecd.org/document/55/0,3343,en_2649_34385_2500215_1_1_1_1,00.html
[127] See http://www.oecd.org/topic/0,3373,en_2649_34385_1_1_1_1_37437,00.html

OECD - Development of a unique identification system for transgenic plants

At first, the names used by companies for GMOs (e.g. MON810 or Bt11) were developed in a non-standardised way. With the increase in the number of GMOs being marketed, it became more difficult to search for information about those GMOs or exchange information between national authorities. To overcome this problem, in 2002, the OECD developed a unique identifier system for transgenic plants. Each new genetically modified plant authorised for marketing is now assigned a unique code by its developer comprising nine alphanumeric characters; this becomes its global reference code (e.g. MON ØØ810-6, or SYN-BTØ11-1).
This system is a good example of the application at the regulatory level of work started at a technical level. Indeed, the unique identifier system soon grew beyond the OECD group of experts when it was incorporated into the European regulatory framework on GMOs. It is now the unique identification mechanism for transgenic plants used within the framework of the Cartagena Protocol.
The identification system for genetically modified plants was revised in 2006 by the OECD, which is currently working on the development of a similar system for genetically modified microorganisms and animals.

Task Force for the Safety of Novel Foods and Feeds

This expert group has been active since September 1999. Its activities complement those of the Working group on Harmonisation of Regulatory Oversight in Biotechnology and are also followed up within the framework of the "BioTrack" website. The Task Force works on consensus documents dealing with aspects of biosafety posed by certain plants grown and used for food or feed[128].

One of the first activities of the Task Force was to collaborate with the Working group on Harmonisation of Regulatory Oversight in Biotechnology on a study of the implications of biotechnology and other aspects of food safety, following a request made to the OECD at the end of 1999 by the G8 Heads of State and Government. The work of the two groups has led to the publication of reports on the effects on environmental safety and health safety of using products resulting from modern biotechnology[129, 130.] Within the framework of this request from the G8 leaders, the OECD also set up an *ad hoc* group made up of senior officials and national experts with public responsibilities in the field of food safety. The work of this group led to the publication in 2000 of a compendium of international organisations with food safety activities[131], as well as a general overview of national food safety systems and activities [132]. The SBB provided the secretariat of the Belgian delegation participating in this *ad hoc* group.

[128] The full list of documents published by the Task Force is available on the OECD website at the address http://www.oecd.org/document/9/0,3343,en_2649_34391_1812041_1_1_1_1,00.html
[129] OECD, doc C(2000)86/ADD2, 13 June 2000.
[130] OECD, doc C(2000)86/ADD1, 31 May 2000.
[131] OECD, doc SG/ADHOC/FS(2000)4/FINAL, 16 May 2000.
[132] OECD, SG/ADHOC/FS(2000)5/FINAL, 9 May 2000.

European Committee for Standardisation (CEN)

The development of European standards in the field of modern biotechnology was started in December 1992 by the European Commission, to complement the implementation of Directives 90/219/EEC, 90/220/EEC and 90/679/EEC. The Commission tasked the CEN, namely its technical committee TC233, with developing 54 standards covering several fields of application of these Directives.
The standards are applied on a voluntary basis and do not constitute binding legal instruments. However, they prove very useful for defining, in real terms, the technical specifications, codes and methods of analysis that constitute the technical tools required to implement the regulations.
The CEN has worked in close collaboration with the Member State authorities responsible for implementing the above-mentioned Directives, as well as with the committees of experts set up to adapt those Directives to technical progress.

It is within this context that the SBB contributed to the drawing up and use of standards, at several levels:

- advisory role to the General Inspectorate of Methodology (Ministry of Economy) during discussions with the European Commission about the mandate given to the CEN;
- participation in several meetings of the TC233 committee;
- formulation of advices and recommendations on standards under development, via the Belgian Institute of Standardisation (IBN), Belgium's official representative body to the CEN;
- implementation of a research programme (financed by the scientific support plan for standardisation of the Belgian Science Policy) with the aim of preparing a guide to implementing standards related to the identification, detection and monitoring of GMOs intended to be introduced into the environment.

The standards prepared by TC233 were one of the technical instruments used in the revision of the regional regulations on the contained use of GMOs at the end of the 1990s. The work of the TC233 Committee ended in the early 2000s[133].

[133] In the 1990s, the SBB also participated in the work of the CEN TC275 Committee. This committee of experts developed a series of standards in the field of sampling and detection of food ingredients containing GMOs or produced from GMOs. The work of the TC275 Committee was suspended for several years and the standards were taken up by the ISO (International Organization for Standardization). Within this context, a new committee, ISO TC 34/SC 16, has recently been set up. It will soon begin a revision of all standards relating to analysis methods for the sampling and detection of GMOs and derived food products; in particular, a possible extension of the scope of these standards will be considered to include the analysis of biomolecular markers in general.

OTHER INTERNATIONAL ACTIVITIES AND NETWORKING

In addition to its activities of scientific support for Belgian authorities and representation in official organisations, the SBB has, since its creation, participated in the activities of various professional organisations at the European and international levels that directly or indirectly address the issue of biosafety.

European Federation of Biotechnology (EFB)

The EFB was founded by European researchers in Switzerland in 1978. Its aim is to promote interdisciplinary cooperation between scientific institutions and companies in Europe in the field of biotechnology. Initially only accessible to institutions, it was opened up to individual participants in 2001.
The SBB mainly participated in the activities of the EFB towards the end of the 1990s. At that time, a working group (Working Party on Safety in Biotechnology) was in place to deal with aspects of biosafety associated with the use of biotechnology. Through that participation, the SBB notably contributed to the publication of three scientific articles on the transport of infectious and biological material, assessment of the risk of releasing microorganisms into the environment, and the DNA content of biotechnological process waste (see Chapter 6 for the full references for these articles).

American Biological Safety Association (ABSA)

ABSA was founded in 1984 to promote biosafety as a scientific discipline and to meet the growing needs of biosafety professionals. ABSA represents the interests and needs of biosafety professionals and provides a forum for the ongoing exchange of information in this area.
The cooperation between the SBB and ABSA dates back to 1996, when the Belgian Biosafety Server website was being developed by the SBB (ABSA already had a website at that time). Since then, the SBB has regularly participated in the annual conference organised by ABSA in the United States. This conference provides an opportunity for numerous exchanges of information with foreign experts (representing advisory bodies, academia and business). This participation enables the SBB to update its information and maintain contacts in the field of risk analysis and management, mainly in relation to the handling of GMOs or pathogenic organisms in a contained environment.

The SBB also contributes to the content of the ABSA journal through the publication of scientific articles. In 2010, the SBB has been awarded by the American Biological Safety Association Council and Awards Committee for its publication entitled “Contained Use of Bacteriophages: Risk Assessment and Biosafety Recommendations”. The Richard C. Knudsen award is given to the authors of an article published in *Applied Biosafety* that describes significant contributions in areas of scientific investigations and/or health and safety. Following an invitation of ABSA, an expert from the SBB attended the 53rd Annual Biosafety Conference in Denver (Colorado) and gave a lecture on the awarded article content.

European BioSafety Association (EBSA)

EBSA was created in 1996. Like ABSA in the United States (with which it maintains very close connections), EBSA is a centre of interest in Europe and a place to exchange information relating to all matters connected with biosafety.
The SBB made a contribution from the first stages of the founding of EBSA in 1996, particularly by contributing to the implementation of the first scientific activities and the development of the association's website. Since 1996, the SBB has regularly participated in meetings and other activities organised by EBSA. Here too, the aim is to meet and exchange information with other European scientists involved in biosafety.

In particular, the SBB has been part of the EBSA Biosafety Professional (BSP) Competence Task Group since 2006. The activities of this group aim to better define the tasks and responsibilities of biosafety professionals, i.e. people hired by an employer to coordinate and provide advice or set up procedures for biosafety-related matters. Some initiatives within this field have already been undertaken by ABSA for several years, particularly with the introduction of two certification programmes for biosafety professionals ("Registered Biosafety Professional" and "Certified Biosafety Professional"). In Europe, these tasks and responsibilities are not specified in Directives 2009/41/EC and 2001/18/EC and only a few countries (such as Germany, the United Kingdom and Switzerland) have defined certain requirements on the subject. In Belgium, the Regional Decrees concerning the contained use of genetically modified organisms and/or pathogens explicitly provide for the appointment of a biosafety coordinator, defining the corresponding duties in a generic manner.
The EBSA Task Group initially worked on defining tasks and training requirements for biosafety professionals and then prepared an inventory of the training available in different European countries, thus showing, by comparison, the gaps existing in this area. In 2008, EBSA then decided to continue its work in this area with the ultimate aim of adopting a CEN Workshop Agreement (CWA), a document similar to a standard based on the consensus of the workshop participants (which is open to all biosafety professionals)[134]. The work is currently ongoing in association with the CEN and the NEN, the Dutch Standardisation Committee. The final document should define different aspects of biosafety professionals, in particular their role and tasks, basic training, necessary experience and skills, as well as a framework for the training and certification programmes.

Lastly, it should be mentioned that, since 2008, the SBB has also been working on developing the Laboratory Biorisk Management Standard Guidance CWA 1579[135]. The aim of this document is to establish the necessary requirements for controlling risks associated to activities in microbiological containment laboratories, that is, laboratories where pathogenic organisms and toxins are handled. This document concerns both biosafety and biosecurity, and also meets the WHO objectives regarding biological safety in the laboratory. This process was started jointly by EBSA and the Canadian Science for Human and Animal Health, and is financially supported by the EU among others. Once completed, this document will be adopted on a voluntary basis (application of an ISO standard) by the laboratories concerned.

[134] See http://www.ebsaweb.eu/EBSA+Activities/Biosafety+Professional+Competence.html for further information.
[135] See http://www.ebsaweb.eu/EBSA+Activities/Laboratory+Biorisk+Management+Standard-p-187.html for further information.

European Advisory Committees on Biosafety (EACB)

In 2006, on the initiative of the Dutch (COGEM) and Swiss (SECB) biosafety committees, a network of European biosafety committees active in the field of the deliberate release of GMOs (Directive 2001/18/EC) was set up. These committees deliver advice and opinions on which the competent authorities base their final decisions. The sharing of knowledge and experience between the members of these committees is particularly useful in order to improve risk assessments in a field as sensitive as that of GMOs.
One year later, on Germany's initiative, a similar but distinct network was set up between the European biosafety committees active in the field of the contained use of genetically modified microorganisms (Directive 2009/41/EC). As advisory bodies for the Belgian authorities, the Biosafety Council and the SBB became involved in these two networks from the outset and have participated in the annual meetings. In 2009, the Council and the SBB organised the annual meeting, which was held in Brussels on 29 and 30 October. On that occasion, the two networks of Committees (contained use and deliberate release) met jointly for the first time, making it possible to address matters linked to both Directive 2009/41/EC and Directive 2001/18/EC. The scientific programme focused on several emerging issues in the field of biosafety: transgenic trees, the use of genetically modified plants for the production of products for therapeutic use, gene therapy and new genetic modification techniques.

Belgian Biosafety Professionals (BBP)

The Belgian Biosafety Professionals association provides a forum for those responsible for biosafety in Belgium, which has the objective of sharing experience in biosafety practices and regulation. It is also a local section of the EBSA. Since the creation of this association in March 2006, the SBB and the BBP have collaborated with the common aim of helping biosafety professionals to implement biosafety measures within the installations concerned. Within this framework, symposia and workshops have been organised by the BBP, to which members of the SBB have contributed several times, particularly with talks.

RECENT DEVELOPMENTS

As can be seen from the preceding paragraphs, the SBB is present as a centre of expertise for biosafety in numerous European and international bodies. The SBB is also included in the database of experts used by the European Commission within the framework of TAIEX (the Technical Assistance and Information Exchange Instrument). TAIEX is an instrument to support a series of beneficiary countries, which aims to provide expertise regarding the application and enforcement of EU legislation through the organisation of activities such as seminars, workshops, expert missions or study visits[136].

In addition to this "institutional" representation, several requests have been addressed to individual experts over recent years. Indeed, some European and international bodies have put together databases of experts for their own specific needs. The scientists of the SBB, members of the Biosafety Council and some experts from the common list drawn up by the Council and the SBB are therefore included in various capacities in those databases and may be called upon to provide expertise on a case-by-case basis.

[136] Further information on http://ec.europa.eu/enlargement/taiex/

The bodies concerned include the European Food Safety Authority (EFSA), the European Medicines Agency (EMA) and the European Commission, which put together databases of experts to assist their scientific committees, scientific groups or other working groups in the frame of their risk assessment activities.
We shall also mention the roster of experts of the Cartagena Protocol. It contains biosafety experts designated by governments, who can be consulted on request to give advice and other forms of support to developing countries to assess risks, develop human resources and promote institution building, in matters related to implementation of the Protocol.

This increased involvement of Belgian scientists in international contexts is beneficial for all parties: the bodies concerned can of course benefit from the fact that some Belgian scientists from academia have been involved in GMO risk assessment for many years; the scientists themselves can strengthen their expertise through their participation in international activities; finally, the quality of the network of experts available to the Biosafety Council and the SBB becomes even better.

CHAPTER 6
COMMUNICATION AND INFORMATION

Informing and interacting with various target audiences is an integral part of the work of a public service institution such as the WIV-ISP. As a centre of biosafety expertise and archiving, the Biosafety and Biotechnology Unit (SBB) holds a large amount of scientific and legal information that is likely to be of interest to different groups. In the heated context that surrounds the public debate on GMOs, official and independent bodies such as the Biosafety Council and the SBB have a role to play in the distribution of objective, transparent, reliable and referenced scientific information. Furthermore, informing the public about biosafety is also increasingly becoming a legal obligation (as in other environmental areas). Directive 2001/18/EC, the Cartagena Protocol and the Aarhus Convention[137], for example, include specific provisions relating to public information.

Since the creation of the SBB, its experts have therefore strived to meet the needs of the general public and stakeholders via different forms of communication and information (websites, publications, reports, participation in debates and conferences, training, educational activities, etc.). Over the years, other authorities and bodies involved in the field of biosafety have also contributed to similar initiatives. In this chapter, we will provide a non-exhaustive description of the main communication activities organised by the SBB or to which it has made a significant contribution.

WEBSITES

On 1 March 1996, the SBB launched the "Belgian Biosafety Server" (BBS, accessible at http://www.biosafety.be). This website aims to be an interactive information tool on biosafety issues for authorities, users and the general public. Although it was not as obvious in 1996 as it is now, it was not by chance that the internet was chosen by the SBB as a channel for distributing information. Indeed, the SBB very quickly sensed the possibilities that it could offer in terms of the ability to handle enquiries, daily information management, speed of access, universality and cost.
The initial aim was to facilitate the administrative and scientific life of individuals and institutions that are subject to biosafety regulations in Belgium. The second aim was to explain the general, legal and scientific context of those regulations. However, the site soon proved to be useful to many other people, including outside Belgium: competent authorities of other Member States, businesses, environmental groups, consumer associations, private individuals.

[137] Aarhus Convention on access to information, public participation in decision-making and access to justice in environmental matters (1998).

The BBS provides precise, detailed information on legal elements, the evaluation system and administrative aspects linked to the implementation of biosafety in Belgium. In addition to the full text of all the regulations concerned, an online guide is available for scientists working in contained installations, who are involved in field trials or clinical trials, and those involved in the marketing of GMOs in the European market. Descriptions of deliberate releases of GMOs authorised in Belgium (field trials of transgenic plants and clinical trials with medicinal GMOs) are also published on the site in the form of a database.
The BBS is one of the few websites entirely dedicated to the field of biosafety; indeed, it has become an international reference[138]. It has also given exposure to the Scientific Institute of Public Health and Belgian partner institutions.
Moreover, this site served as the basis for the development of the Belgian node of the information sharing mechanism established under the Cartagena Protocol on Biosafety, the Belgian Biosafety Clearing-house (BBCH - http://www.biosafetyprotocol.be). As the national focal point for the Biosafety Clearing-House, the SBB is responsible for maintenance of the BBCH and its interaction with the central portal of the BCH (see Chapter 5).
Finally, the Biosafety Advisory Council also has a website (http://www.bio-council.be). This site is developed and managed by the SBB. In particular, it contains the full text of the advices issued by the Council.

TRAINING AND EDUCATION

The experience acquired in assessing biosafety applications and analysing the corresponding scientific literature has been harnessed by the SBB to design teaching and training modules for users and the authorities. Currently, these modules are primarily aimed at those involved in the contained use of GMOs or pathogenic organisms. These modules are adapted to the needs of the users each time. However, the basics remain the same: awareness of risks associated with the handling of GMOs and pathogenic organisms, introduction to risk assessment methodology, description of applicable risk management measures. The modules combine theoretical descriptions, examples of the activities concerned and practical exercises.
Training sessions are regularly delivered to staff of the inspection departments of Belgium's Regions and Communities. Since 2009, the SBB also introduced certified training for State scientific personnel, which focuses on laboratory biosafety.

Furthermore, since 1996, biosafety teaching and awareness modules covering all aspects of the discipline have also been taught at Belgium's universities and *Hautes Écoles*. These modules are taught by SBB experts as part of general courses or specific training in biosafety.

Finally, between 2003 and 2006, the SBB contributed to the organisation and implementation of a project in partnership with developing countries to train delegates from those countries in the use of the Biosafety Clearing-House of the Cartagena Protocol. This training was conducted in collaboration with the Royal Belgian Institute of Natural Sciences, the national focal point of the Convention on Biological Diversity[139].

[138] See for example Francisco M. Biosafety and regulation. Nature Biotechnology 1999;17:89
[139] This training was possible thanks to financing by the Belgian Federal Public Service for Foreign Affairs, Foreign Trade and Development Cooperation. Delegates from the following countries participated: Cameroon, Djibouti, Madagascar, Burkina Faso, Central African Republic, Niger, Republic of the Congo, Mauritania, Togo, Burundi, Mali, Senegal, Comoros, Guinea and Côte d'Ivoire.

SBB and participatory forums

The use of modern biotechnology and its implications in terms of biosafety has been the subject of debate in society for several years. In this respect, several initiatives have been undertaken by the Belgian authorities with a view to establishing links between the different players in the worlds of science, the economy and civil society. As a centre of biosafety expertise, the SBB has participated in several of these initiatives, for example:

- Citizens' panels organised in 2003 by the Foundation for Future Generations in the Belgian towns of Beernem and Gembloux. These panels discussed the criteria to be taken into account with a view to authorising the experimental and/or commercial cultivation of genetically modified plants (see http://www.fgf.be/UserFiles/File/fgf_panel_ogm.pdf).
- A citizens' panel in Flanders, organised in 2003 by the viWTA (*Vlaams Instituut voor Wetenschappelijk en Technologisch Aspectenonderzoek*), a Flemish para-parliamentary institute. This panel issued an opinion to the Flemish Parliament on the question of GM food
  (see http://www.biosafety.be/PubFora/Documents/FinalAdviceviWTA.pdf)
- The political process entitled "*Printemps de l'Environnement/Lente van het Leefmilieu",* which aimed to establish firm agreements to secure the commitment of different levels of power in environmental matters. It was organised in 2008 on the initiative of the Prime Minister, Regional Ministers and the Federal Minister of Climate and Energy. Some 200 people representing civil society, business, trade unions, NGOs and experts were split into working groups to produce opinions on different topics. The SBB participated in the "GMO" workshop, where it performed the role of rapporteur. Further information on the results of this initiative can be found in the last chapter
  (see also http://www.printempsdelenvironnement.be/).

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The SBB and public information on modern biotechnologies

In the early 1990s, European countries did set up specific regulations concerning the contained use and the marketing of genetically modified organisms. Having been invented, discussed and developed in scientific laboratories, modern biotechnologies were surfacing on the political agenda of the European states which therefore had to tackle new issues for which they did not necessarily had the adapted scientific tools in their own administrations.

At that time, as a young doctoral student in political science at the University of Liège, the issues raised by the surge of biotechnologies in our societies were a godsend for political science research and, more specifically, for *Science and Technology Studies* and risk analysis. Set up in 1995 within the Scientific Institute of Public Health, the Biosafety and Biotechnology Unit (SBB) was the ideal place to closely study the decision-making process as regards authorisation for contained use or placing on the market of GMOs.

Between September 1998 and September 1999, I therefore paid a weekly visit to the SBB members who were astonished to see a "soft scientist" so interested in "hard sciences". Still warmly welcomed by the members of the division, my period of hands-on observation was very precious for gathering data for my doctoral thesis. Exchanges with SBB members helped me to gain a better understanding of the role played by the public administration in the handling of biotechnology files.

The SBB's operation was underpinned by a structure that was sometimes difficult to implement between science, public administration and political power. During this period it seemed to me that the SBB was the dumping ground for extreme tensions both at European and Belgian levels about the issue concerning the opportunity for developing the marketing of GMOs. Then under the stewardship of William Moens, the SBB very quickly established itself as a unique place to produce scientific expertise at the service of the public administration.

Besides the scientific handling of the requests sent to it, the SBB was also a pioneering place in the field of public information, notably through the creation of its website which still today cannot be ignored by anyone wishing to obtain information on the subject. This task of providing public information in the field of GMOs was naturally an additional benefit for successfully completing my studies on the issue of public information on modern biotechnologies[140]. The main aim of this work was to give a socio-political support to the implementation of a public information system. It also resulted in a few concrete ideas or areas for consideration in terms of the problems associated with organising a system for informing the public on biotechnologies by the authorities and, more precisely, by the Biosafety and Biotechnology Unit.

[140] Sébastien Brunet and Catherine Zwetkoff (2000). Etude sur la question de l'information du public en matière de biotechnologies modernes. 88 pages. University of Liège. http: //hdl.handle.net/2268/13009

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marcel poppe & Katrin Bilmeyer | Vita Vitalis

A difficult task at the interface between the economy and social responsibility

Long before there was any mention of GMOs, I met one of the most enthusiastic discoverers of this development, Jeff Schell (1935-2003). Together with his friend and colleague, Marc Van Montagu, he found the '*Agrobacterium tumefaciens'* and discovered that it was possible to use this bacterium to transfer DNA to plants and hence cross the species barrier. At the time, he expected to develop plants that would no longer need artificial fertiliser and would obtain the nutrients they need from the air.

As a professor at the university of Ghent, he was offered a position as a scientific director at Monsanto with an annual budget of $ 600 million. After duly considering this attractive offer, he made his decision: *"If I accept, I will no longer be a scientist. I will be in the commercial circuit."* In 1978, he became director at the German prestigious *Max Planck Institute for Plant Breeding Research* in Cologne, where he stayed until he retired.

Judging from the still ongoing discussions on the application of GMOs, this was clearly the right choice. It is the only way to work on development free from value judgements, to do fundamental research and to hold discussions in a scientifically responsible way. After all, science requires the permanent scepticism of the scientist. Unfortunately, we see that more and more scientists come up with unrealistic solutions for various reasons, out of commercial interest or in an effort to obtain a grant. Some say they can fight poverty and blindness with GMOs or that GMO's are the solution to global hunger. A blinkered view, short-sighted and scientifically irresponsible. They don't see *'the big picture'.* The opponents' grievances are to do with biodiversity, contamination, ecological and possible health problems.

These contradictions and the problems which may arise from them make social discussion inevitable. However, this 'discussion has not reached any conclusions in the past 20 years.

When these discussions started in 1986, Katrin Bilmeyer and I established a non-profit organisation, Vita Vitalis, in order to participate in discussions on GMOs responsibly. We started by gaining information that we felt was necessary from various scientists involved in the development and applications in Belgium and the Netherlands (Ghent, Leuven, Gembloux, Wageningen).

After thoroughly investigating the field, we contacted groups who were likely to be opposed (Greenpeace, Friends of the Earth, Wervel). We also spoke to the socialist, Christian Democratic and green parties. A political debate was necessary, as the Ministry of Agriculture had to provide the permits for the required experimental fields and applications. This was because the Ministry had the legal authority to regulate experiments with new varieties.
When assessing the dossiers, the administration of this Ministry always involved the Institute for Hygiene and Epidemiology, which is now referred to as the Biosafety and Biotechnology Unit (SBB) of the Scientific Institute of Public Health.

On 23 April 1990, the European Directive 90/220/EEC on the deliberate release into the environment of genetically modified organisms (GMOs) came into force. The directive provided items such as the precautionary principle due to the risks to the environment and public health and compulsory communication to the public. EU directives aim to harmonise the common market and member states must transpose the directives into domestic law.

In Belgium this immediately resulted in a tug of war between the federal and regional ministries about who was competent for what. The Flemish government saw the directive as an environment directive, which is its responsibility. The Federal government emphasised the economic aspect and saw it as its responsibility. The fact that the Ministry of Agriculture and the Institute for Hygiene and Epidemiology (IHE/SBB) was processing the requests in practice at the time was important.

It is worth pointing out here that both the Ministry and the IHE had helped to develop the directive at the European level. Both had gained the required expertise in various ways, including training courses organised by Europe, coordinated investigation in the *Biotechnology Research for Innovation Development and Growth in Europe* programme (BRIDGE), international workshops and by developing a network of experts.

Despite all this, the distribution of authority between the Federal Government and the Regions is still relevant, even to this day. In 2009, the Federal Government prohibited a field test with GM poplars in Flanders. The Minister of Agriculture in Wallonia, Benoit Lutgen, wants to keep his region GMO-free. In other EU countries such as France, Austria, Germany and the Netherlands the debate on what purpose GMOs serve and whether they should be permitted is still ongoing, and experimental fields with GMOs have been destroyed.

There are also supporters and opponents on the international scene. There are discussions on GMO authorizations between the US and Europe, the US always aiming to support its industrial urge for expansion and Europe playing the waiting game on allowing GMOs in its food and on its fields.

That was a brief history of the political situation in the past 20 years.

In 1987, we wrote an article entitled "*Biotechnologie, schaap met vijf poten of zevenkoppige draak?" (Biotechnology, five-legged sheep or seven-headed dragon?)*. The article was meant to draw attention to the new possibilities and possible dangers of GMOs. It was published in former monthly '*Socialistische Standpunten'* (1987 issue 4). The scientific agency of the socialist party was organising a work group led by Prof. Etienne Vermeersch in order to determine its political standpoint on the technique. All this came to an end after the socialist party's election defeat.

We were also in contact with Flemish Member of Parliament Ms. Trees Merckx-Van Goey of the Christian Democratic Party. On 9 February 2000 she introduced a motion in which she wrote the following: *"Nobody is bursting with impatience to start using GMOs. Consumers are reluctant and farmers may fall victim to monopolies formed by a limited number of large multinationals. From an economic point of view, Flanders is one of the top areas for biotechnology research and development, with companies such as Innogenetics and Plant Genetic Systems. The creation of GMOs is therefore very much our concern. Various existing advisory bodies of the Flemish government are in an ideal position - each with its own point of view - to make a useful contribution to a well-founded, broad social debate in preparation for a parliamentary debate."*

Millions of Belgian Francs and Euros went to many projects and studies investigating how to involve citizens into this debate, all without any result to date.

A brief overview:

- 1986: Flanders Technology Foundation (STV) report *'Maatschappelijke aspecten van de biotechnologie in Vlaanderen' (Social aspects of biotechnology in Flanders).* This report was the result of the investigation of the same name performed on behalf of STV at the Genetics Laboratory in Ghent. Two investigators (Dani De Waele and Patrick De Smet) worked on this report from November 1985 to 1986.
- The report was published in 1987 in a popularised form under the title *'Biotechnologie, een waaier van toepassingen' (Biotechnology, a wide range of applications)*. It was put together by Dani De Waele.
- In February 1990 the the Flemish Minister for the Economy, Mr. De Batselier (1988/1992), set up the Flemish Biotechnology Action Programme with a budget of 910 million Belgian Francs (€ 22,558,310.75) divided between the Flemish government and industry.
- 1990: Information Seminar for NGOs 'Regulation of genetically modified organisms in the European Community' (DGXI of the European Commission in Brussels).
- On 28/29 June of the same year, the Flemish Biotechnology Action Programme organised a hearing on the possibilities and possible threats of biotechnology.
- 1991: Workshop 'Public education on biotechnology' Jezus-Eik, Belgium (Flemish Biotechnology Action Programme)

- 1992: Symposium on the Belgian Implementation of the European Biosafety Regulations on Biotechnology organised by William Moens (IHE). This is where we were introduced to William Moens and the IHE. We noticed that Mr. Moens kept his distance from us. When we told him about our vision of the application of GMOs and the communication of information to the public in a telephone conversation that lasted about one and a half hours, we eventually managed to break the ice.
- Information Seminar 'Implementation of EC Directives 90/219/EEC and 90/220/EEC on the contained use and deliberate release of genetically modified organisms' (DG XI of the EC in Brussels).
- 1994: Mina Council ad hoc work group on genetically modified organisms by the Flanders Environment and Nature Council. This resulted in the advice *'regarding social and environmental aspects linked to activities with GMOs*' to the Flemish policy.
- 1996/1997: Ministry of Economic Affairs - ad hoc committee of the Industrial Property Division. The objective was to gain insight into the various viewpoints of social organisations, industry and science with regard to the European Directive on patenting biotechnological inventions. Three meetings were held, on 14 October 1996, 10 December 1996 and 1 October 1997.
- 2000: The Flemish Parliament recognised a need for a broad social debate. The motion from Ms. Trees Merckx-Van Goey was approved (see above). Several advisory councils were asked to give their opinion. The Flemish Institute for the Investigation of Scientific and Technological Aspects (viWTA) associated with the Flemish Parliament started a pilot project (2002-2003) called *'New impulses for the debate on Genetically Modified Food*'. This project included a public forum (2003). Prof. Marc Van Montagu was in the expert panel.
- 2001: Seminar on *'Sustainable Agriculture in the Third World: Defining a role for Transgenic Crops and Research'* organised by the Federal Council for Sustainable Development in cooperation with the Flemish Inter-University Councils of the Flemish and French-speaking communities of Belgium and the Royal Academy for Science Overseas.
- 2001: The Flemish Institute of Biotechnology (VIB) organised an exhibition called *'Eet es genetisch' (Taste some genes)* in Ghent.
- Debate series: *'Biotechnology in agriculture and food*' in Ghent organised by VIB.
- 2002: Following the discussions in Lisbon, the European Commission developed a consultation document calling on citizens to provide their thoughts and comments on the introduction of GMOs and the application of biotechnology.
- Conference: '*The role of biotechnology in industrial sustainability'* organised by VITO.
- 2003: Stakeholders' forum: '*New impulses for the debate on genetically modified food'*. 15 September 2003 organised by viWTA.
- 2004: On 30 November Minister of the Environment Bruno Tobback organised another workshop on the applications of GMOs saying: *'This gives us the opportunity to certainly realise one of the objectives of this workshop on GMOs: to provide a central platform for discussions on GMOs and to urge the various stakeholders to move towards further reflection together.'*
- The Royal Flemish Academy of Belgium for Science and Art also wanted to make a contribution to come to a well-founded dialogue and organised a work group led by Prof. Van Montagu also attended by industry and NGOs. The aim was to create a document that would clarify the possibilities and scientific knowledge in this field to be used as a foundation for further social debate. Unfortunately it was a complete failure.

In this jumble of conferences and workgroups, political pressure, EU discussions and regulations, IHE/SBB had to play its part.

We contacted Mr. William Moens, Head of Division of IHE/SBB, again on the occasion of a research project (*GMO releases: managing uncertainties about biosafety)* on behalf of The Open University Faculty of Technology led by Prof. Les Levidow, Dr. Susan Carr and Dr. David Wield. The implementation of directive 90/220/EEC in EU countries (1994/1995) was investigated. Katrin Bilmeyer (Vita Vitalis) was asked to investigate this in Belgium. After about a year of questions, investigations and meetings with

EU partners, a first version of the document was ready. We presented it to Mr. Moens and asked him to verify whether this was a correct representation of the Belgian situation at the time (May 1995).

His response was to invite us to discuss the new law on 'biosafety'. He also asked us what type of relationship Vita Vitalis wanted to have with the IHE experts and what formal arrangement we would like. According to him, this was only possible with mutual respect. To us it was obvious and essential to gain the correct insights.

Our experiences with other government bodies were of a different nature: little openness and difficult contact. We noticed that the IHE was taking its task seriously under Mr. Moens' leadership when we received its corrections, which had taken the institute a total of 54 hours to make.

Directive 90/220/EEC clearly states that the information on experimental fields had to be public. This meant that this type of information must be communicated to the public. It was the gateway to a public debate. However, the Directive itself didn't mention a public debate. It was therefore not SBB's responsibility to organise or stimulate such a debate. Nevertheless, the SBB made compulsory communication of information a tool that could have been the foundation for a public debate. Public forms were developed in a work group that we participated in. These forms had to be completed by applicants for field tests with GMOs (companies and scientific institutions). They had to provide technical and scientific data, including the measures to be taken in case of accident.

At our insistence, socio-economic aspects were also included. This created the possibility of responding to the applicants and engaging in a debate. We pointed this out to all NGOs focusing on this issue. We indicated the possibility of engaging in this sought-after discussion in order to come to a more open atmosphere. Unfortunately, our cries were in vain.

A well-founded dialogue cannot gain momentum without the political will to deal with this on a structural level. We suspect that this will not be happening any time soon.

The efforts to find a suitable place for biotechnological applications in society are often disrupted by legislation. The Directive on deliberate release of GMOs into the environment is intrinsically ambiguous. It is an environmental directive, but simultaneously aims to harmonise the European market. Economic and environmental interests were poured into a single piece of legislation. This ambiguity is strengthened by the Lisbon treaty, which put the emphasis on the knowledge economy. *(European Commissioner Philippe Busquin presented nano- and biotechnology as top priorities in an effort to stem the brain drain to the US).*

Economic interests are usually difficult to align with environmental requirements and health aspects. The SBB regularly found (finds?) it difficult to obtain the right scientific data. Companies are hiding behind commercial confidentiality. Biosafety assessment will therefore often be torn in two by economic and political interests on the one hand and social responsibility on the other.

The surface area occupied by GM crops in North and South America, China and South Africa is increasing (*a total of 134 million ha*), whereas in Europe it is decreasing (*it fell by 11% in 2009 compared to 2008)*. This is probably because several EU countries are using the European safeguard clause.

For more information, visit: www.vitavitalis.be / www.forum-jeff-schell.eu

BIOSAFETY AFTER 2010
CHALLENGES AND PERSPECTIVES

Twenty years ago, the Belgian authorities chose to adopt a biosafety evaluation system common to the Federal State and the Regions, organised around two bodies: the Biosafety Advisory Council (BAC) and the Biosafety and Biotechnology Unit (SBB). The criteria for the harmonious implementation of provisions relating to biosafety, scientific reasoning, transparency and independence which governed the setting up of this system twenty years ago, remain relevant today.

The composition of these two bodies and the subject itself have evolved over the years, both qualitatively and quantitatively. The gradual increase in the human resources of the SBB has made it possible to form a multidisciplinary team that can effectively support the work of the BAC. This has also contributed to diversifying and consolidating the permanent expertise available to support the federal and regional authorities, both in the field of environmental and health risk assessments of GMOs as well as in the evaluation of the contained use of GMOs or pathogens.

The BAC and, even more, the SBB are in permanent contact with numerous biosafety experts from other countries and with scientists from Belgian and foreign universities. These contacts provide the opportunity to develop very useful interdisciplinary collaborations to address scientific issues relating to the use of GMOs or pathogens. These long-standing collaborations have enabled various tools such as websites, recommendations and peer-reviewed publications to be established, which can assist with biological risk assessments. In addition to the work of the BAC and the SBB, the incorporation of the scientific community into the work of these two bodies certainly constitutes a guarantee of scientific reliability.

However, biosafety, like any other discipline, is constantly evolving. The development of new applications of modern biotechnology (implementing new genetic modification techniques or second-generation GMOs), the emergence or re-emergence of certain infectious diseases, or even the interaction with other topical issues such as biosecurity or nanotechnology, are new challenges that the BAC and the SBB must adapt to over the coming years.

Furthermore, although the field of biosafety expertise is open to the scientific world in general, the sensitive task of assessing biological risks on a case-by-case basis must now be adapted to the growing interest of the general public, NGOs and professional associations. Paradoxically, expertise is an increasingly sought-after resource for public action and social choices, but is also increasingly challenged. The monopoly of the "traditional" sciences in the expertise work is being partially questioned by some political decision-makers and sectors of civil society. Consideration about the ethical, ecological, economic or social implications of applications of modern biotechnology have now joined the concerns about the public health and environmental protection impacts that were predominant in the early years. In this context, it seems inevitable, and even desirable, that traditional scientific expertise should interact with other types of expertise, to make a more valuable contribution to the public debate.

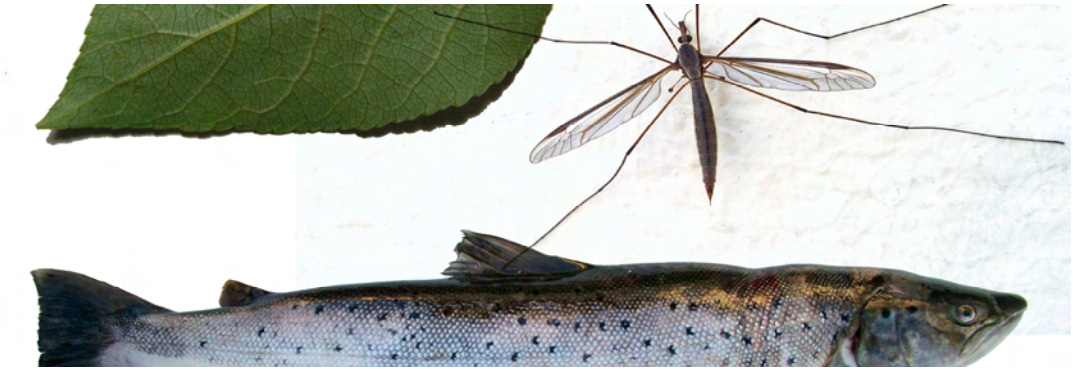
BIOSAFETY EXPERTISE AND EMERGING ISSUES

New GMOs

Until now, environmental and health risk assessments of genetically modified organisms have been limited almost exclusively, in Europe, to first generation GMOs, i.e. plant species that have been genetically modified for purely agronomical purposes, such as insects or phytopathogen resistance and/or herbicide tolerance.

We have already seen in Chapter 4 how risk assessments of these types of GMOs have had to be adapted to the increased development of "stacked event", obtained by means of traditional breeding between genetically modified lines. The SBB addressed this aspect in 2007 in a scientific publication, followed by the Biosafety Council and the EFSA, which developed guidelines specifying when and how the potential interactions resulting from the presence of multiple transgenes should be evaluated. It remains to be seen how these guidelines will make it possible to cope with the expected growth in the number and complexity of these stacked events over the next few years[143].

Another significant challenge that will face the bodies responsible for assessing biological risks in the coming years concerns the assessment of second- or third-generation GMOs, i.e. GMOs that, compared with current GMOs, have new functionalities or are developed from new host systems. There is a long list of these new GMOs, some of which are still at the laboratory development stage, while others have already reached the environmental experimentation stage. We cite, in particular, GMOs developed for the production of compounds for industrial or pharmaceutical use (for example transgenic plants used for the production of vaccines or medicines); plants resistant or tolerant to abiotic stresses (drought, salinity, etc.); GM food with improved nutritional quality (reduced saturated fatty acids, vitamin-enriched, etc.); GMOs for the production of biofuels or bioplastics; transgenic animals (cattle, poultry); transgenic insects (mosquitoes, etc.); transgenic fish (GloFish,



[143] As an example of complexity, we cite "SmartStaxTM", a variety of maize developed jointly by Monsanto and DowAgroSciences containing 8 different transgenes that provide insect resistance and herbicide tolerance.

salmon, etc.); transgenic trees (poplars, apple trees, etc.); or even genetically modified microorganisms (viruses, bacteria modified to be used in bioremediation, for example, and so on).

The assessment of these new types of GMOs is likely to raise new questions: are the current risk assessment methodology and principles appropriate for these types of GMOs? Is it necessary to develop guidelines specifically addressing the assessment of these GMOs? Is there sufficient scientific data on which to base the risk assessments? If not, how can such information be generated?
These questions have already been the subject of work by several bodies, both at the European level (the EFSA, for example) and the international level (in particular, work carried out within the framework of the Cartagena Protocol - see Chapter 5). They have also held the attention of the SBB and the BAC for several years, notably through their involvement in the work of the above-mentioned bodies. It is also recalled that some of these topics were discussed during the meeting of European biosafety committees organised in Belgium in 2009 (see Chapter 5). Finally, it should be noted that, from 2010, the SBB is participating in a COST Action (European project) on the biosafety of transgenic forest trees. These types of activities enable the SBB to share its expertise in GMO risk assessment while improving its knowledge through interaction with scientists specialising in the field.

New genetic modification techniques

As mentioned in Chapter 5, for the past two years, the European Union has been analysing the legal status of new genetic modification techniques. The objective is to determine whether or not these techniques fall within the scope of the existing GMO regulations. At the request of the Belgian authorities, the SBB is involved in this work. It is important to be able to inform the authorities about these new developments, which could lead to a modification of the regulatory framework, if necessary. This participation is also important in the context of risk assessment, as some of these technical developments constitute real challenges for the experts responsible for the assessment and management of biological risks.

These new developments include approaches aimed at modifying the gene expression profile without altering the nucleotide sequence. This field, which is still at the experimental stage, belongs to a rapidly expanding discipline known as "epigenetics"[144].

Another rapidly developing field is "synthetic biology". It is an approach whereby organisms can be created from any basic starting element, building blocks comprised of specific DNA sequences. This discipline is based on the basic principles of molecular biology, but combined with elements such as electronics, computer science, cybernetics and life sciences. Its feasibility has already been demonstrated in the *de novo* synthesis of viruses[145] or even bacteria with no cell wall[146] (in these cases, the complete genome of a species is adopted by the cytoplasm of another species) and the possible genetic combinations seem infinite.

[144] Epigenetics concerns any modifications that are not coded in the DNA sequence (examples: DNA methylation, histone acetylation). Their transmission during divisions may occur in a non-Mendelian fashion. It also involves the study of hereditary changes in gene function that take place without altering the DNA sequence.
[145] Cello J, Paul AV, Wimmer E. Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. Science 2002;297:1016-8.
[146] Gibson DG, Benders GA, Andrews-Pfannkoch C, Denisova EA, Baden-Tillson H, Zaveri J, Stockwell TB, Brownley A, Thomas DW, Algire MA, Merryman C, Young L, Noskov VN, Glass JI, Craig Venter J, Hutchison CA, III, Smith HO. Complete Chemical Synthesis, Assembly, and Cloning of a *Mycoplasma genitalium* Genome. Science 2008;319(5867):1215-1220.

Directly linked to synthetic biology, a recent discipline known as "xenobiology" aims to diversify nucleic acids (and the proteins that interact with them) by modifying their chemical structure (deoxyribose or ribose replaced by other radicals such as threose, hexose, glycol or cyclohexenyl, to obtain "XNA" or "xeno nucleic acids")[147]. According to some authors, this innovative approach could make it possible to develop potentially safer organisms in terms of health and the environment, as they are unable to exchange their genetic material with that of organisms present in the environment in their natural state[148]. Furthermore, organisms resulting from xenobiology that have enzymes specific to the management of their genome would not be able to use the biochemical pathways of natural organisms.

Without going into the technical details of these new applications, it is obvious that the assessment of the resultant organisms could open up new questions in terms of risks to human health and the environment (not to mention the ethical questions in the case of synthetic biology or xenobiology). To take just one example, in an environmental or health risk assessment, how can a comparative analysis be carried out for these types of organisms for which it is not always easy to identify a natural unmodified equivalent?

Pathogenic organisms responsible for (re-)emerging diseases

New microorganisms capable of causing human diseases continue to be detected and sometimes pose serious public health problems at the local, regional or global scale. For example, *Escherichia coli O157: H7,* a bacterium that is transmitted through contaminated food and was at the origin of outbreaks of hemolytic uremic syndrome in North America, Europe and Japan. As with any pathogenic microorganism, the health risks inherent to these new pathogens depend on factors such as the transmission potential between animals and humans and between human beings, the severity of the disease as well as the existence of effective identification, prevention and treatment methods.

In other cases, we are witnessing the re-emergence of known infectious diseases that are reappearing (sometimes after several years of extinction) with different pathologies or in new geographical regions. This situation particularly affects the African and American continents, although Europe is not entirely spared. One example is West Nile viral encephalitis in France.

Finally, it is worth adding the increase in the number of bacteria that are becoming resistant to an increasingly broad range of antibiotics, due to the improper use of antibiotics in animal farming and their over-consumption in human medicine. In many regions, first generation antibiotics have lost their efficacy against infections linked to microorganisms such as *Escherichia coli, Mycobacterium tuberculosis, Neisseria gonorrhoea, Pneumococcus, Shigella, Staphylococcus aureus.*

It should be noted that the above-mentioned phenomena do not only concern human pathogens. Indeed, the last few years have been marked by the emergence or re-emergence of infectious animal diseases, such as prion diseases or foot-and-mouth disease epizootics. Of course, these situations are potentially detrimental to global food safety and the industry sectors concerned. However, the examples of SARS (severe acute respiratory

[147] Herdewijn P, Marlière P. Toward safe genetically modified organism through chemical diversification of nucleic acids. Chemistry and Biodiversity 2009;6:791-807.
[148] Schmidt M. Xenobiology: a new form of life as the ultimate Biosafety tool. BioEssays 2010;32:322-331.

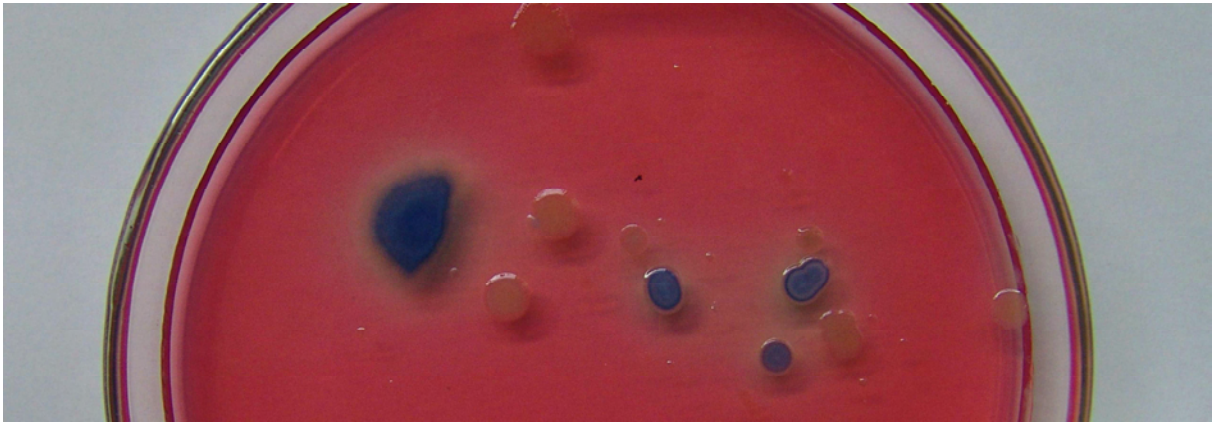
syndrome) and avian influenza also demonstrate the reality of the threat that infectious animal diseases pose to human health (zoonoses).

First of all, the emergence and re-emergence of infectious diseases represent a public health problem. Several national and international initiatives (WHO) have been set up to improve surveillance operations and the fight against these diseases. But of course, they also have impacts in terms of biosafety. The scientific assessment of microbiological risks must be adapted to the handling of these new pathogens in the laboratory in order to be able to rigorously determine appropriate risk management measures (working practices, containment, waste management).

Finally, we highlight the possibility of these infectious and/or transmissible emerging (or re-emerging) agents being used for terrorist purposes, which is currently a threat that cannot be ignored (see below).

Biosecurity

At present, there is some confusion between the terms "biosafety", "biosecurity" and "biorisk". Furthermore, there is still no international agreement on the definition of biosecurity[149]. However, it is clear that existing or future actions for the preparation of a possible bioterrorist threat (linked to the malicious use of pathogenic organisms, whether genetically modified or not) will partly depend on what is done in the field of biosafety. We have already addressed this topic in Chapter 5, illustrating through various concrete examples how, in this context, the expertise of the SBB has already been integrated into a wider scope for several years.



[149] New Security Challenges: Biosecurity. Origins, Transformations and Practices. B Rappert and C Gould. Ed. Palgrave Macmillan. pg. 250 ISBN 13:978-0-230-22356-1.

It is more than likely that this issue will remain relevant for the SBB. Firstly, it is on the agenda of international organisations (UN) and professional associations active in the field of biosafety (such as the ABSA or the EBSA). Secondly, in response to pressure from North American regarding the problem of bioterrorism, some initiatives have also been undertaken at the European and, therefore, Belgian levels, with which the SBB has been associated. In particular, we note the discussions that have been underway since the publication of the "Green paper on bio-preparedness"[150] in 2007.

The Commission has invited Member States to consult each other on ways to reduce biological risks and improve preparation for and responses to biological threats. In particular, the Commission has suggested setting up a European Bio-Network (EBN), an advisory structure that would pull together European expertise on bio-preparedness from various sectors. The idea is that any new measure aimed at tackling biological threats should be based on those measures already in place to guarantee the safety food and products.

BIOLOGICAL RISK ASSESSMENT: A CONSTANTLY EVOLVING DISCIPLINE

The methodology, general principles and basic criteria for the assessment of biological risks have not fundamentally changed in the last twenty years. Nevertheless, as we pointed out in Chapter 1, biological risk assessment is a constantly evolving discipline. As advisory bodies in this field, the Biosafety Council and the SBB will continue to be associated with these developments.

In particular, these developments translate into suggestions of new approaches to complete or refine the current risk assessment methodology. A recent example that is still being debated by European experts concerns the 'problem formulation' approach (see text box next page).

The scientific data on which risk assessments are based is also evolving. This data is increasing in volume and can be generated via new experimental protocols or methods. By way of example, there are new analytical methods known by the term "omics" (proteomic, transcriptomic, metabolomic or interatomic analyses) which, although still being developed, could constitute new tools for biological risk assessments concerning food or environmental safety.

The evaluation of data also calls for increasingly specialised expertise. In this context, we stress the importance, for both the BAC and the SBB, of having access to external expertise. As we have already mentioned several times in this book, the BAC and the SBB have a long tradition of collaborating with scientists from academia. In future, the structures and procedures that make it possible to call upon these scientists will need to be sufficiently flexible to ensure access to the appropriate expertise at any given time. It will also be necessary to have the largest and most representative pool of experts possible in the disciplines concerned by risk assessment, although this already poses a challenge (it is already difficult to find expertise in certain fields).

[150] Brussels, 11.7.2007, COM(2007) 399 final.

Possible changes to the environmental risk assessment methodology for GMOs

In the EU, the GMO risk assessment approach is based on a set of principles applied throughout the world that are largely inspired by the work of international organisations such as the OECD, the FAO and the WHO. Nevertheless, beyond these similarities, there are differences in risk assessment methodology between countries. In the EU, GMO risk assessment is currently carried out using the approach described in Annex II of Directive 2001/18/EC, which begins with identification of the hazards (see Chapter 1). In other countries (for example, the United States), 'problem formulation' is the first stage of the risk assessment process. Problem formulation partly overlaps with hazard identification, although it differs in the sense that it indicates more clearly the hypotheses underlying the risk assessment, namely what needs to be protected from damage. This is done by taking into account the protection objectives defined in local environmental legislation.
In the preliminary draft of its scientific opinion on the environmental risk assessment of genetically modified plants (which is currently in the process of being evaluated[151]), the EFSA included 'problem formulation' as the first stage of the risk assessment process. If this approach is ratified, in the near future, problem formulation will become a key element in the GMO environmental risk assessment process in the EU.

In future, the accumulation of scientific data and knowledge in the field of GMOs and pathogenic organisms, the monitoring of technological innovations (such as new genetic modification techniques) and adaptation to the constant improvements in biological risk assessment tools will certainly require more forward-planning and creativity, rather than simply "monitoring". To meet this need for proactivity, Belgium should be represented on the various bodies that address issues relating to biosafety both at the European and international levels. In Chapter 5, we saw how the SBB, as a Belgian focal point for biosafety, has actively contributed to this work. The increased involvement of Belgian scientists in international forums should also be considered beneficial in this context as it helps improve the quality of the network of experts available in Belgium.

COMMUNICATION: AN ESSENTIAL STAGE IN RISK ANALYSIS

Communication between risk assessment specialists, risk management specialists and all other interested parties is an essential aspect of improving understanding of the scientific processes involved in risk assessment.

For information to be regarded as credible, it is important for the various groups concerned to be able to recognise the competence, reliability, honesty and impartiality of the information source. In this book, we have shown how the SBB has contributed to this through different communication activities. These activities must be continued or even stepped up in the future.

The SBB continues to maintain and develop exchanges of information with other biological risk assessment experts, academic scientists and other biosafety professionals, particularly biosafety managers. This book has shown the extent to which the SBB is already involved in these networks. It actively participates in working

[151] EFSA (2010) http://www.efsa.europa.eu/en/consultationsclosed/call/gmo100305a.htm

meetings, seminars and conferences, at both the national and international levels, through posters and oral presentations. It also continues to develop tools available to users such as training, recommendations, reports, risk assessment sheets and case studies. The underlying idea behind the majority of these initiatives is to apply or illustrate the biological risk assessment methodology through real examples in order to facilitate the work of the competent authorities and target organisations (universities, scientific institutes, pharmaceutical companies, etc.). The "Belgian Biosafety Server" should remain a key tool for the distribution of this information.
The SBB also aims to step up the organisation - in collaboration with the BAC, where possible - of activities (seminars, working parties, etc.) to enable the exchange of opinions or ideas about various scientific issues relating to GMO or pathogen risk assessment. These activities will be supplemented by the publication of scientific articles.

The Cartagena Protocol and other initiatives (for example, the TAIEX network in which the SBB is already involved - see Chapter 5) offer the possibility of training aimed at improving capacities in certain countries. The SBB is, of course, available to contribute expertise in this context, within the limits of its human resources and budget.

Finally, the SBB must also meet the expectations of non-specialist groups in terms of biosafety information. This will primarily be done by supporting the competent authorities (which are responsible for public information), but also through various initiatives designed to make the language, scientific terminology or even the methodology linked to the risk assessment process accessible to the general public.

BIOLOGICAL RISK ASSESSMENT: WHAT ARE THE TOOLS OF THE FUTURE?

This book has extensively referred to the European directives and regulations on which the implementation of biosafety in Belgium is largely based. 2010 could be a pivotal year in the implementation of the European regulatory framework for GMOs. Indeed, the presentation by the European Commission of the results of the evaluation of the current regulatory framework, added to the awaited conclusions of the work on new genetic modification techniques, could lead to certain adaptations, or even thorough overhauls, of European legislation, in the short or medium term. We cite, for example, a possible revision of the definition of GMO, modification of decision-making procedures (increased use of the subsidiarity principle for the cultivation of transgenic plants), or the taking into account of socio-economic aspects (although none of these possible changes is certain to occur).
The new EFSA guidelines could also give rise to certain changes in the methodology and particularly the criteria to be taken into consideration in health or environmental risk assessments.

Although these are changes that would take place at the European level, they would of course have repercussions in Belgium. At the Belgian level, the revision of the 1997 Cooperation Agreement concerning biosafety is one of the main tasks for the future. This revision is sought by the majority of the actors concerned and, moreover, its principle was the subject of a political agreement in 2008, following discussions held during the

Printemps de l'Environnement/Lente van het Leefmilieu process[152]. The working party set up at the time confirmed the relevance and usefulness of a common biosafety assessment system (composed of the Biosafety Advisory Council and the SBB). It did, however, suggest certain improvements to the cooperation process to overcome limits of the current system (increase in the number of applications to be processed, short deadlines, insufficient financial and human resources, insufficient availability of the necessary Belgian scientific skills, etc.). The proposed changes include:

- Restricting the composition of the Council to members performing (or that have performed) a scientific role in a public body. The delegates of government bodies concerned would be present during Council discussions as observers and no longer as members;
- Avoiding associating a scientist with a given political authority (currently, the members are appointed by the different authorities) to further guarantee their freedom of action and enable more balanced representation of the different scientific disciplines necessary for the assessments;
- Freeing up additional resources so that all areas of expertise are represented, not only among the members of the Council but also among external experts working for the Council;
- Confirming the SBB in its role as scientific and administrative secretariat of the BAC and reinforcing, if necessary, its function as the centre of expertise to meet the needs of the competent authorities and the Council.

Although the federal and regional ministers concerned agreed at that time to review the Cooperation Agreement by June 2009 at the latest, no concrete action has been taken to date.

Another aspect addressed during the *Printemps de l'Environnement/Lente van het Leefmilieu* discussions was the possibility of having an independent socio-economic review of GMOs. The idea of setting up a specific body responsible for socio-economic and ethical assessments of GMOs was mentioned. However, the political authorities chose to wait for the result of the discussions currently underway on this topic at the European level before taking any concrete measures at the Belgian level. Of course, the BAC and the SBB are keeping a close eye on future developments in this area. Indeed, the implementation of an assessment of the socio-economic impact of GMOs in addition to the human health and environmental risk assessment would require links to be established between disciplines that although complementary are little used to sharing their knowledge.

Currently, the links between the BAC and the SBB on the one hand, and scientific research on the other hand, are limited almost exclusively to the contributions of academic scientists to the assessment of biosafety applications. It would be desirable for the 'worlds' of the risk assessors and the researchers to be further integrated. Some initiatives in this respect have been undertaken recently, such as scientific publications bringing together members of the Council and/or the SBB and researchers from universities, or even the recent organisation by the SBB of a symposium focussing on the contribution of scientific research to the risk assessment process

[152] "*Printemps de l'Environnement/Lente van het Leefmilieu*" is a political process aimed at obtaining firm agreements to secure the commitment of different levels of powers to environmental matters. It was initiated in April 2008 by the Prime Minister, Regional Ministers and Federal Minister of Climate and Energy, and ended in July of the same year. Some 200 people representing civil society, business, trade unions, NGOs and so on were split into working groups to produce opinions on different topics (including GMOs). Those opinions served as the basis for the representatives of the Ministries concerned to define a road map with specific political commitments. Further information is available at http://www.printempsdelenvironnement.be/.

(Symposium on Contributions from Scientific Research to the Risk Assessment of GMOs", 21-22 October 2010, Brussels, Belgium). These kinds of initiatives should be repeated in the future.

Other possible synergies could also be developed. For example, obtaining further experimental data through collaborations with universities and other scientific institutions, to support biological risk assessments of both GMOs and pathogenic organisms. Scientific doubts or questions identified during risk assessments should ideally serve to stimulate new research, either by the notifiers themselves within the framework of their experimental tests (it would then be necessary for the design of those tests to contribute to answering biosafety questions), or within the framework of fundamental research in general, while highlighting the difficulty of obtaining public funding for this type of research.

CONCLUSIONS

For 20 years, Belgium has been present and even sometimes a forerunner in matters of biosafety. Belgium is unique in that is has both significantly contributed to the invention of genetically modified plants and to the development of the scientific foundations of biosafety, while actively participating in international scientific cooperation in this field. The implementation throughout Belgium of a common biological risk assessment system has enabled the harmonious management of biosafety in an institutionally complex context. The scientific quality of the work of the Biosafety Council and the SBB is widely recognised at the national, European and international levels.

Emerging questions about biosafety and biosecurity straddle different disciplines and are addressed by various bodies at the Belgian, European and international levels. This diversity merely underlines the importance for the competent authorities and other actors involved in biosafety of having a permanent, flexible focal point for information and scientific expertise. Furthermore, during the *Printemps de l'Environnement/Lente van het Leefmilieu* process, the participants highlighted the importance of having a permanent expertise unit such as the SBB. Such a focal point ensures the consistency, coherence and harmonisation of scientific work carried out during biosafety assessments on behalf of the various public authorities. It also promotes interaction between all the actors concerned.

Through numerous concrete examples, this book has illustrated how, over the last twenty years, the Biosafety and Biotechnology Unit of the Scientific Institute of Public Health has developed knowledge and expertise in the field of biosafety. In this last chapter, we have outlined some of the challenges that the expert appraisal work will have to overcome in the coming years. Because biosafety expertise will have to continue to adapt to the evolution of biotechnological innovations and society in general, just as it has done since 1990 and the publication of the first European Directives on GMOs. Beyond the analytical approach, expertise will have to become increasingly dynamic, multidisciplinary and accessible. The SBB, in partnership with the Biosafety Advisory Council, is determined to rise to these challenges, through proactive support for the authorities, reciprocal collaboration with the scientific world, increased interaction with other types of expertise and greater openness to the general public.

MAIN RELEVANT OFFICIAL TEXTS[153]

Belgium

General provisions

Cooperation Agreement of 25 April 1997 between the Federal State and the Regions on the administrative and scientific co-ordination concerning Biosafety.
=> Ministère des Affaires sociales, de la Santé publique et de l'Environnement - Loi du 3 mars 1998 portant assentiment à l'accord de coopération / Ministerie van Sociale zaken, Volksgezondheid en Leefmilieu - Wet van 3 maart 1998 houdende instemming met het samenwerkingsakkoord (Belgian Official Journal, 14.07.1998, p. 22773)
=> Ministère de la Région de Bruxelles-Capitale - Ordonnance du 20 mai 1998 portant assentiment à l'accord de coopération / Ministerie van het Brussels Hoofdstedelijk Gewest - Ordonnantie van 20 mei 1998 houdende instemming met het samenwerkingsakkoord (Belgian Official Journal, 14.07.1998, p. 22850)
=> Ministère de la Communauté flamande - Décret du 17 décembre 1997 portant approbation de l'accord de coopération / Ministerie van de Vlaamse Gemeenschap - Decreet van 17 december 1997 houdende goedkeuring van het samenwerkingsakkoord (Belgian Official Journal, 31.01.1998, p. 2890)
=> Ministère de la Région wallonne - Décret du 5 juin 1997 portant approbation de l'accord de coopération / Ministerie van het Waalse Gewest - Decreet van 5 juni 1997 houdende goedkeuring van het samenwerkingsakkoord (Belgian Official Journal, 14.07.1998, p. 22790)

Loi du 20 juillet 1991 portant des dispositions sociales et diverses / Wet van 20 juli 1991 houdende sociale en diverse bepalingen (Belgian Official Journal, 1.08.1991, p. 17002).

Loi du 22 février 1998 portant des dispositions sociales / Wet van 22 februari 1998 houdende sociale bepalingen (Belgian Official Journal, 3.03.1998, p. 5683).

Contained use of GMOs and pathogens

Arrêté du Gouvernement de la Région de Bruxelles-Capitale du 8 novembre 2001 relatif à l'utilisation confinée d'organismes génétiquement modifiés et/ou pathogènes et au classement des installations concernées / Besluit van de Brusselse Hoofdstedelijke Regering van 8 november 2001 betreffende het ingeperkt gebruik van genetisch gemodificeerde en/of pathogene organismen en betreffende de indeling van de betrokken installaties (Belgian Official Journal, 26.02.2002, p. 7209).

[153] A complete list of official reference documents related to biosafety is available on the "Belgian Biosafety Server" (www.biosafety.be).

Arrêté du Gouvernement flamand du 6 février 2004 modifiant l'arrêté du Gouvernement flamand du 6 février 1991 fixant le règlement flamand relatif à l'autorisation écologique et modifiant l'arrêté du Gouvernement flamand du 1er juin 1995 fixant les dispositions générales et sectorielles en matière d'hygiène de l'environnement / Besluit van de Vlaamse regering van 6 februari 2004 tot wijziging van het besluit van de Vlaamse regering van 6 februari 1991 houdende vaststelling van het Vlaams reglement betreffende de milieuvergunning, en van het besluit van de Vlaamse regering van 1 juni 1995 houdende algemene en sectorale bepalingen inzake milieuhygiëne (Belgian Official Journal, 01.04.2004, p. 18362).

Arrêté du Gouvernement wallon du 5 juin 2008 modifiant l'arrêté du Gouvernement wallon du 4 juillet 2002 déterminant les conditions sectorielles relatives aux utilisations confinées d'organismes génétiquement modifiés ou pathogènes / Besluit van de Waalse Regering van 5 juni 2008 tot wijziging van het besluit van de Waalse Regering van 4 juli 2002 tot bepaling van de sectorale voorwaarden inzake het ingeperkte gebruik van genetisch gemodificeerde of pathogene organismen (Belgian Official Journal, 26.06.2008, p. 32957).

Arrêté du Gouvernement wallon du 5 juin 2008 modifiant l'arrêté du Gouvernement wallon du 4 juillet 2002 relatif à la procédure et à diverses mesures d'exécution du décret du 11 mars 1999 relatif au permis d'environnement / Besluit van de Waalse Regering van 5 juni 2008 tot wijziging van het besluit van de Waalse Regering van 4 juli 2002 betreffende de procedure en diverse maatregelen voor de uitvoering van het decreet van 11 maart 1999 betreffende de milieuvergunning (Belgian Official Journal, 30.06.2008, p. 33316).

Circulaire du 4 août 2005 relative aux plans particuliers d'urgence et d'intervention concernant les micro-organismes génétiquement modifiés / Ministeriële omzendbrief van 4 augustuis 2005 aangaande het bijzonder rampenplan voor hulpverlening betreffende het ingeperkt gebruik van genetisch gemodificeerde micro-organismen (Belgian Official Journal, 21.12.2005, p. 54623).

Environmental release en marketing of GMOs

Arrêté royal du 21 février 2005 réglementant la dissémination volontaire dans l'environnement ainsi que la mise sur le marché d'organismes génétiquement modifiés ou de produits en contenant / Koninklijk besluit van 21 februari 2005 tot reglementering van de doelbewuste introductie in het leefmilieu evenals van het in de handel brengen van genetisch gemodificeerde organismen of van producten die er bevatten (Belgian Official Journal, 24.02.2005, p. 7129).

Loi du 7 mai 2004 relative aux expérimentations sur la personne humaine / Wet van 7 mei 2004 inzake experimenten op de menselijke persoon (Belgian Official Journal, 18.05.2004, p. 39516).

European Union

Contained use of GMOs

Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (Recast) (Official Journal L 125, 21.05.2009, p. 0075).

Environmental release en marketing of GMOs

Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (Official Journal L 106, 17.04.2001, p.1).

Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed (Official Journal L 268, 18.10.2003, p.1).

Regulation (EC) No 1830/2003 of the European Parliament and of the Council of 22 September 2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms and amending Directive 2001/18/EC (Official Journal L 268, 18.10.2003, p.24).

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Official Journal L 121, 01.05.2001, p.34).

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Official Journal L 136, 30.04.2004, p.1).

Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Official Journal L 324, 10.12.2007, p. 121).

Diverse

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 (seventh individual directive within the meaning of Article 16(1) of Directive 89/391/EEC) (Official Journal L 262, 17.10.2000, p. 21).

Regulation (EC) No 1946/2003 of the European Parliament and of the Council of 15 July 2003 on transboundary movements of genetically modified organisms (Official Journal L 287, 05.11.2003, p. 1).

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ABBREVIATIONS

ABSA	American Biological Safety Association
AMINAL	"Administratie Milieu-, Natuur-, Land- en Waterbeheer"
BAC	Belgian Biosafety Advisory Council
BBS	Belgian Biosafety Server
BBP	Belgian Biosafety Professionals
BCH	Biosafety Clearing-House
BSE	Bovine Spongiform Encephalopathy
CCIEP	Co-ordinating Committee for International Environmental Policy
CEN	European Committee for Standardization ("Comité Européen de Normalisation")
DG	Directorate-General
DNA	Deoxyribonucleic acid
EBSA	European Biosafety Association
EC	European Community
EEC	European Economic Community
EEP	European Enforcement Project
EFSA	European Food Safety Authority
EMA	European Medicines Agency (formerly EMEA)
ERA	Environmental Risk Assessment
EU	European Union
FASFC	Belgian Federal Agency for the Safety of the Food Chain
FPS	Federal Public Service
GMM	Genetically Modified Micro-organism
GMO	Genetically Modified Organism
IHE	Institute of Hygiene and Epidemiology (currently WIV-ISP)
JRC	Joint Research Center

LMO	Living Modified Organism
LNE	"Leefmilieu, Natuur en Energie"
NGO	Non-governmental organization
NIH	National Institutes of Health
NRL	National Reference Laboratory
OECD	Organisation for Economic Co-operation and Development
OJ	Official Journal of the European Union
PCR	Polymerase Chain Reaction
RGPT	"Règlement Général pour la Protection du Travail"
SBB	Division of Biosafety and Biotechnology
SNIF	Summary Notification Information Format
ToVo	"Toezicht Volksgezondheid"
UN	United Nations Organization
VLAREM	"Vlaams Reglement bretreffende de Milieuverguning"
WIV-ISP	Scientific Institute of Public Health (formerly IHE)
WHO	World Health Organization

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