

**SUMMARY REPORT ON THE EXPERIENCE OF BELGIUM WITH DIRECTIVE 90/219/EEC AS AMENDED
BY DIRECTIVE 98/81/EC**

(TRISANNUAL REPORT UNDER ARTICLE 18 OF DIRECTIVE 90/219/EEC, AS AMENDED BY
DIRECTIVE 98/81/EC)

PERIOD JUNE 2003 - JUNE 2006

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Introduction

The regulatory framework concerning the contained use of genetically modified micro-organisms (GMMs) is implemented and enforced in Belgium at the regional level. It means that three different regional decrees are applied. These regional decrees fully implement the Directive 98/81/EC but also extend their scope to GMOs and pathogens. A juridical tool named "Co-operation agreement" has been set up to ensure that the transposition and practical implementation of the Directive 98/81/EC are done in a harmonised way between the three Regions at the administrative and scientific levels.

1. An overview of activities and installations particularly new ones and those involving GMOs (animals, fish and plants) as well as GMMs

During the period from June 2003 to June 2006, **300** biosafety dossiers of installations have been received by the SBB acting as the advisory body for the competent authorities. **283** of them have been reviewed. At time of report, 17 dossiers, involving 26 contained uses, are still under review by the SBB.

These dossiers have the following distribution :

- 1 dossier of request for exemption of GMMs under the criteria of Annex II, Part A of the Directive 98/81/EC
- **282** biosafety dossiers of installations, covering **723** contained uses of pathogens, GMMs and/or GMOs (transgenic plants and animals). 12 activities fell out of the scope of the regional decrees on contained use: those relates to the use neither of genetically modified (micro)organisms, nor of pathogens.
- Among the 723 reviewed contained uses, **266** of them exclusively concerned non-genetically modified, pathogenic microorganisms.
- With respect to contained uses of GMMs and GMOs, **445** activities have been assessed.

These contained uses are distributed as a function of :

- The procedure and the administrative year

Table 1: Distribution of the number of installations (number of contained uses) as a function of the procedure and the administrative year.

Procedure \ Year	June to December 2003	2004	2005	January to May 2006	Total
	First contained uses *	42 (82)	73 (245)	48 (90)	22 (32)
Subsequent contained uses	12 (45)	43 (112)	45 (122)	15 (21)	115 (300)
Total	54 (127)	116 (357)	93 (212)	37 (53)	300 (749)

* **Remark:** since 2002, the Walloon decree of 04/07/2002 regarding the contained use of GMOs and/or pathogens doesn't distinguish anymore between first and subsequent contained uses. In consequence, all notifications for this region are treated as new activities (or first contained uses).

The table 1 illustrates the evolution of the application of the regulations. In comparison with the previous 3 years period (1999-2002), the number of installations and contained uses has almost doubled.

- The Competent Regions

Brussels Capital Region : **39** dossiers, **164** contained uses
 Flemish Region : **209** dossiers, **430** contained uses
 Walloon Region : **52** dossiers, **155** contained uses

The number of dossiers submitted in the Flemish Region significantly increased in 2002 and remained high during the following years, reaching the highest level in 2004. In the two other Regions however, the process was reversed: the highest numbers of notified contained uses were reached during the period 1996-1997, decreased during the period 1999-2002 for then rejoining the average number of registered contained uses over 10 years.

The 445 contained uses of GMMs and/or GMOs are distributed as follows :

- GMMs and/or GMOs

- GMMs : **414** contained uses
 - GMOs : **99** contained uses
 - GMMs and GMOs : **68** contained uses

One single contained use can involve both GMMs and GMOs.

The large majority of GMMs are used by the university research laboratories or pharmaceutical companies in the aim of fundamental research. More rarely, GMMs are also used for teaching (practical work) or the production of enzymes, vaccines and therapeutic molecules.

- Types of GMOs

The 99 contained uses of GMOs are distributed as follows :

Transgenic animals : **68** contained uses

Transgenic plants : **31** contained uses

The majority of genetically modified animals are knockout or transgenic mice. The other types of animals met are rats, rabbits, and rarely zebrafish and drosophila's.

Some operations are simply knockout mice lodging. In the other cases, transgenic animals are used as tools in various fields of fundamental research or in preclinical studies of new drugs evaluation.

Genetically modified plants (*Arabidopsis thaliana*, maize, sugar beet, potato, rice, oilseed rape, chicory, cotton, ... and more rarely flowers and fruit trees) are used as research tools to study various topics like the resistance to herbicide or insects; the improvement of drought-, cold- or pest-resistance and nutritive properties; the characterization of genes involved in metabolism and photosynthesis.

- Biological risk class (art 5, 3 of Directive 98/81/EC)

The number of activities using GMMs of class of biological risk 1 and 2 is predominant. Only six class 3 contained uses involving GMMs have been notified from June 2003 to June 2006. There are no contained uses of biological risk class 4. A detailed description of the risk class 3 contained uses involving GMMs is given in annex 1.

2. Risk assessment and classification of contained uses (including effectiveness of the risk assessment guidelines)

No significant changes have been made since end of 2002; please refer to the previous Belgian summary report covering the period of 1999-2002.

3. Notification and approval systems (and relevant changes)

For an overview of the regulatory and advisory systems, please refer to the previous Belgian summary report (1999 - 2002) and to the "Belgian Biosafety Server" (<http://www.biosafety.be>).

Directive 98/81/EC, already transposed into the Belgian legislation at the regional level for the Brussels-Capital Region in 2001 and the Walloon Region in 2002, has been transposed in the Flemish Region in April 2004 (decree of 4 February 2004). The notification procedures adopted in the Flemish Region are similar to those in force in the Brussels-Capital Region. For a detailed description we refer to the previous Belgian summary report covering the period 1999-2002. A brief description of the notification procedures in the three Regions can also be found on the Belgian Biosafety Server, contained use chapter:

<http://www.biosafety.be/CU/EN/CUMenu.html>

4. Accidents

During the period 2003 - 2006, no accident has been declared in Belgium.

5. Inspections and enforcement issues (including requests by competent authorities for assessment of class 1 contained uses)

As already mentioned in the previous Belgian summary report (1999-2002), following a series of trainings given in 2002 and 2003, inspections were organized in the three regions on a regular basis. They concerned contained uses with GMOs as well as with pathogens.

The three Regions adopted a different approach for inspection: whereas the Flemish Region aimed at visiting installations of containment level 2 and 3, the Brussels Capital Region decided to inspect first premises with containment level 3 and secondly the containment levels 2. Up to now, all installations of containment level 3 have been inspected. The Walloon Region planned to visit all installations concerned by the contained use regulation, also those who didn't notify their activities yet.

Inspections can also be undertaken in case of complaints or incidents. If the inspection reveals serious gaps in the application of containment measures, either during visits before or after an authorisation has been delivered, a delay is imposed for fulfilment of special conditions with regard to these shortcomings. At the same time a follow up is put in place.

As part of the conventions with the three regional competent authorities, the SBB took part in inspection visits organized by the inspectorates of each Region and offered scientific and technical support.

In the Flemish Region inspections were done by 2 inspection bodies, the Health Inspection branch of the Flemish Community and the Environmental Inspection Department of the Flemish Competent Authority, respectively concerning Public Health and Environment. The inspections are performed either in the frame of the environmental permit, either during authorisation procedures for contained uses as such, since both are delivered by different bodies.

In the frame of a separate agreement with the Health Inspection branch, the following tasks were assigned to the SBB : scientific and technical support during inspection visits, advice on specific questions, training, participating in reporting and promoting contact with other inspectorates at the European level (this was realized through participation at the annual congress of the European Enforcement Project (EEP)).

An audit campaign was set up whereby risk class 2 contained uses would be inspected once and risk class 3 contained uses twice over a period of 5 years. The Health Inspection team focused hereby on 5 themes: administration (did the installation have the requested permits and authorizations?), prevention (biosafety policy of the installation, secondary containment and work practices), waste management, animal facilities and transport. Although transport falls out of the scope of the contained use regulation it was considered as an important biosafety issue.

A report was written on the results of a first health inspection round of the Health Inspection branch, covering the period 2003-2005. During this period, 35 visits of installations occurred and the SBB took part in 22 of them. In terms of contained uses, these audits concerned 62% of contained uses of risk class 2 and 82% contained uses of risk class 3 of all authorised installations in the Flemish region. This first round showed several positive points with regard to biosafety, such as organizing biosafety through biosafety committees and biosafety coordinators, biosafety courses and internal audits, working in a higher containment than needed, performing double inactivation of biological waste. It also revealed some negative points: some installations still didn't have the requested authorizations or permits, control of biosafety equipment was not done at a regular basis and waste inactivation was often not validated. Some of the problems were due to difficulties with interpretation of containment measures and showed the need for guidelines.

Finally, it can be said that the inspection rounds resulted in a heightening people awareness involved in biosafety of contained use as a lot of efforts were done to improve containment measures.

6. Problems with interpretation of the provisions (possibly with conflict in defining work use with respect to Directive 2001/18/EC)

Medicinal GMOs dossiers related to clinical trials in humans submitted under the provisions of the Directive 2001/18/EC, part B, also require in some instances an authorization based upon the contained use decrees (Directive 98/81/EC), causing a double authorisation regime. The interpretation of the Directive 2001/18/EC in the medical area remains an unsolved problem at the European level.

7. Clinical trials using the provisions of the Directive

Clinical trials activities can be authorised within the contained use Regional biosafety regulations as soon as they involve GMMs and if the treatment occurs in a contained area (hospitals).

Between June 2003 and June 2006, four human clinical trial protocols have been approved in Belgium within the Regional biosafety regulations and one application is presently under review. In new cases, the risk assessment has always involved meetings of an ad hoc scientific expert group.

All these trials were multicentric. They were carried out in academic and non-academic hospitals. The five protocols intended to test viral vectors. Two of them aimed at treating cardiovascular disease, two of them involved cancer therapy and one was aimed at treating an infectious disease.

More information on the regulatory parameters of these protocols and the most relevant clinical data of the authorised trials can be found on the "Belgian Biosafety Server" (<http://www.biosafety.be/GT/Regulatory/GTtrials.html>).

8. Public consultation and information

Public consultation is performed, when relevant, through the general procedures established under the regional environmental laws.

The procedures for public consultation aim at providing general information to the neighbourhood regarding the contained uses. In the Flemish and Brussels Capital Regions, this information is given via a "public dossier", which is a short summary of the full notification drafted by the notifier and containing information written in standard language and without any reference to confidential information. A similar procedure of public consultation is established in the Walloon Region during the course of the environmental permit demand to the competent authority.

The consultation also gives the public the possibility to express comments, observations or objections regarding the contained uses. The competent authorities take these comments, observations or objections into account when drafting their final decision.

All decisions are made available to the public for a time-limited period. Appeals against decisions may be submitted to the competent authority within that period.

In the Flemish Region, public consultation occurs only in the frame of the environmental permit demand. To that purpose, a copy of the public dossier is joined to this demand.

Public information is provided primarily in two ways. Firstly, general information (in French and/or in Dutch) focusing on legal and administrative aspects can be found on the websites of the three regional competent authorities :

- Brussels Capital Region: <http://www.ibgebim.be>
- Flemish Region: <http://www.mina.be>
- Walloon Region: <http://environnement.wallonie.be/>

On the other hand, scientific and technical information (mainly in English, Dutch and French) is provided through the "Belgian Biosafety Server" (<http://www.biosafety.be>), an Internet site maintained by the SBB. This website also provides full texts of regional laws and EU Directives.

9. Accident and emergency plans

According to article 14 of the Directive, an emergency plan must be drawn up for contained uses where failure of the containment measures could lead to serious danger, whether immediate or delayed, to humans outside the premises and or to the environment.

In Belgium, this article has been partly transposed at the regional as well as at the federal level. Since the regional contained use regulation extended the scope to GMOs and pathogens, emergency planning applies in this case also to non genetically modified pathogens. This is in contrast to the federal regulation, which transposes the Directive as such, so that emergency planning is limited to GMMs.

Regional level

Accident

The three regional regulations mention that the user must declare immediately to the competent authority an accident that occurs in an installation. The information that must be provided in such a case is listed in annex of these regulations.

Emergency plans

The Brussels regional regulation (Brussels Decree of 8/11/2001) mentions that the user must submit the information needed to establish emergency plans outside the installation in case of contained uses of risk class 2, 3 or 4. Before the start of a contained use the regional authority consults the competent federal authority (Federal Public Service Home Affairs) in order to set up emergency plans outside the installation.

The Walloon regional regulation (Walloon Decree of 4/7/2002) mentions that the user must submit an emergency plan (project) outside the installation for contained uses of risk class 2, 3 or 4.

The Flemish regional regulation (Flemish Decree of 6/2/2004) mentions that the user must submit the information needed to establish emergency plans outside the installation in case of contained uses of risk class 3 or 4.

Federal level

During the meeting of 19/12/2003, the Council of Ministers decided to invite the local and provincial authorities to draw up an emergency plan, for the contained use of GMMs. The legal frame is the ministerial Circular of Federal Public Service Home Affairs of 4/08/2005.

A distinction is made between "internal" (inside the building) and "external" (outside the building) emergency plans: whereas an internal emergency plan is needed for all contained uses except

contained uses of risk class 1, an external emergency plan is needed for all contained uses of risk class 3 and 4, and only large scale contained uses of risk class 2.

Accidents

In case of an accident, the external intervention organizations and the "Coordination and Crisis Centre of the federal government" are alerted.

Following information's have to be reported :

- The circumstances of the accident;
- The identity of the GMMs or organisms, and their released quantities;
- The requisite information to evaluate the consequences on the public health and the environment;
- The measures that have already been taken.

In case of an accident, the SBB will provide technical and scientific support to the fire brigade and to the operational units of the civil protection for GMMs and/or pathogens.

A permanent duty is organized whereby the SBB is on call 24h/24h.

Emergency plans (procedure)

The user (person responsible for a contained use of GMMs), must submit all information needed to establish an emergency plan to the local authorities, on whose territory the installation is located with a copy to the provincial authorities. This information is accompanied by an advice of the Scientific Institute of Public Health (IPH), more precisely its Division of Biosafety and Biotechnology (SBB).

To simplify the procedure, the SBB has established a form with additional guide for the users; based on annex V, part A, B and C of Directive 98/81/EC. Relying on the submitted information, the local and provincial authorities will establish a local or provincial emergency plan. The local emergency plan has to be approved by the provincial governor. On the other hand, the provincial emergency plan must be subjected to advice of the SBB and the Minister of Home Affairs. These emergency plans must be transmitted to the authorities and emergency services, which can be involved in case of an accident.

At the same time, the user must transmit an internal emergency plan to the mayor. This must also be accompanied by an advice of the SBB.

More detailed information on emergency plans can be found on the "Belgian Biosafety server" at the following addresses:

In Dutch: <http://www.biosafety.be/CU/Rampenplannen/rampenplannen.html>

In French: <http://www.biosafety.be/CU/Rampenplannen/PlansUrgence.html>

10. Protection of confidential information

In accordance with article 19 of Directive 98/81/EC, the regional decrees transposing the Directive now, including the Flemish decree of 6 February 2004 as well, give the possibility to the notifier to indicate, when necessary, the information in the notifications submitted pursuant to the decrees that should be treated as confidential.

For any further information, we refer to the previous Belgian summary report covering the period of 1999-2002.

11. Waste disposal

In the Belgian Regional regulation implementing Directive 98/81/EC, there is an explicit legal requirement to inactivate all types of GMOs - even of risk class 1- to be disposed of in wastes by appropriate and validated means.

In each region, these requirements are completed by specific regulations on waste originating from medical care and dangerous waste in general, imposing rules for storage, for incineration and for collection by an approved company.

ANNEX 1

Contained uses of GMMs of risk class 3 (According to art. 18.1 of Directive 98/81/EC)

Six class 3 contained use activities involving GMMs have been notified in Belgium from June 2003 to June 2006:

Contained use 1 :

Description : this contained use activity implies the use of recombinant adenovirus derived from serotype 5 and carrying as inserts human and murine genes from cDNA libraries.

Purpose : to study tumor rejection gene functions

Risk : the risk associated with this contained use activity is potential production of infectious adenoviruses in cell cultures coding for unknown genes.

Contained use 2 :

Description : this contained use activity implies the use of the bacteria *Brucella melitensis* (pathogenic for humans and animals, class of risk 3) genetically modified by mutation.

Purpose : to study molecular mechanisms of *Brucella melitensis* such as transcriptional regulation, virulence and quorum sensing.

Risk : the risk associated with this contained use activity is potential contamination and transmission of infectious bacteria.

Contained use 3 :

Description : this contained use activity implies the use of a chimeric retrovirus constructed from SIV and HIV.

Purpose : research on vaccine development for human use.

Risk : the risk associated with this contained use activity is potential production of infectious genetically modified retroviruses in used cell cultures.

Contained use 4 :

Description : this contained use activity implies the use of recombinant retroviral and lentiviral vectors carrying oncogenes of human origin, known genes or unknown genes of human or viral origin.

Purpose : to study of the role of oncogenes and known or unknown genes of human or viral origin in the differentiation process of haematopoietic stem cells or T-cell progenitors.

Risk : potential production of genetically modified retroviruses and lentiviruses in cell cultures coding for oncogenes and known or unknown genes from viral, mouse or human origin.

Contained use 5 :

Description : this contained use activity implies the use of strains of genetically modified *Brucella* sp. (pathogenic for humans and animals, class of risk 3) carrying either a deletion or complemented with genes implied in virulence mechanisms.

Purpose : to study the virulence in vitro (cell culture) and in an in vivo mouse model

Risk : the risk associated with this contained use activity is potential contamination and transmission of infectious bacteria.

Contained use 6 :

Description : this contained use activity implies the use of genetically modified *Mycobacterium tuberculosis* (pathogenic for humans and animals, class of risk 3) whose some genes implied in virulence mechanisms were knocked-out by gene silencing.

Purpose : to study the role of some target genes in the infectious capacity and the virulence mechanisms

Risk : the risk associated with this contained use activity is potential contamination and transmission of infectious bacteria.