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Study results

Regulatory framework and Daily practices regarding Contained Use GMO licensing in several EU countries

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Colophon

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Contents

Summary

Contained use of genetically modified (micro)organisms is regulated in the European Union (EU) in Directive 2009/41/EC. In this Directive are defined:

- generic procedures for administrative processes;
- description of elements and the procedure to carry out an risk assessment of contained use activities;
- four classes of contained use and corresponding levels of biosafety and containment levels and other protective measures.

In the Netherlands, Dir. 2009/41/EC is implemented in the GMO Decree and GMO Order. Over the years a specific national daily licensing practice has been established based on this framework. Similarly, also in other EU Member States such daily practices have been established.

The focus of this study is to gain a better insight in the national implementation of the Directive and the daily practices of legal procedures (both for notifications and licenses) within other EU member States within the context of contained use. For this end we visited GMO Office-like organizations in Belgium, Denmark, France, Germany and Sweden. Significant differences were found in a number of areas regarding the implementation of Dir. 2009/41/EC and the daily execution of the licensing practice of contained use in the Netherlands and the visited countries. The most important findings are discussed in more detail grouped in the following categories:

- Regulatory oversight of contained use of GMOs
- Notification procedures, containment levels and risk assessment
- Information requirements and information management

This study confirms the initial assumption that besides general commonalities significant differences can be found in a number of areas regarding the implementation of Dir. 2009/41/EC and the daily execution of the licensing practice of contained use in the Netherlands and the visited countries. Two striking topics were identified when the frameworks and daily practices of the Netherlands and the other countries were compared. Firstly the legally binding standard set of classification rules applied in the Netherlands is unique. These classification rules aid the user to properly classify intended activities and moreover harmonizes the outcomes of risk assessments carried by different applicants. A disadvantage is a more inflexible system to cope with extraordinary types of activities. Secondly, the information requirements to notifiers differ among the countries. More particular, the Dutch GMO Office seems to require more detailed information in particular concerning applications for activities in containment level 2.
Finally, opportunities to intensify exchange of (daily) practical experiences between GMO-Office-like organizations in other Member States are discussed as well. Most of the people interviewed were supportive to the initiative to participate in an informal network with other GMO-Office like organizations across the EU. Such a network will promote the exchange of daily practical experiences and facilitate a better and detailed understanding of the various approaches and interpretations solidified in the day-to-day practices.

Introduction

1.1 Background of the study

The European Union Directive 2009/41/EC [1] *lays down common measures for the contained use of genetically modified micro-organisms (GMMs) with a view to protecting human health and the environment*.[1] In this directive common measures are laid down for the evaluation and reduction of the potential risks arising in the course of all operations involving the contained use of GMMs and to set appropriate conditions of use. Throughout this document this directive will be referred to as 2009/41 and contained use of genetically modified (micro-) organisms will be referred to as contained use. In 2009/41 the procedures are differentiated in record keeping, notifications and permits depending on the risk class. In addition, the principles for risk assessment and definitions for levels of biosafety and containment are specified.

Like all European Directives, each member state needs to implement 2009/41 in its national law. Directives are a form of legislation binding upon member states, but the 'leave to the national authorities the choice of form and methods' for implementation. This gives member states with a margin of maneuverability in their implementation, resulting in differing interpretations and requirements under the contained use laws and regulations across Europe. In the Netherlands the scope of 2009/41 is implemented in the Decree on Genetically Modified Organisms (GMO Decree)[2] and the Ministerial Order on GMOs (GMO Order)[3] and cover all genetically modified organisms (GMOs). Both pieces of regulation are recently revised and the revised regulations came into force at 1 March 2015. Among other changes, the procedures laid down in 2009/41 are fully transposed to Dutch law.

The Ministry of Infrastructure and Water Management is the competent authority (CA) that is responsible for the regulations and is tasked with developing policy and regulations. The CA is responsible for the assessment of the construction and use of GMOs, and for the issuing and control of contained use permits, on the basis of the GMO Decree. The GMO Office - part of the Centre for Safety of Substances and Products (VSP) of the National Institute for Public Health and the Environment (RIVM) – supports the CA in administrative and technical/scientific aspects by handling the applications and supporting policy development. The GMO Office receives all notifications and applications for contained use activities in the Netherlands, checks the risks to the environment and human health, and is mandated by the CA to grant permissions concerning contained use. The CA holds final responsibility for decisions made by the GMO Office.

1.2 Motivation for this study

With the recent entry into force of the revised GMO Decree in the Netherlands, other and/or new practical issues regarding the licensing practice emerged. The licensing practice of the past 20 years does not seem to fit well with the new procedural rules of the revised GMO Decree.

[1] Scope as defined in Article 1 of the directive

Technological developments in biotechnology seem to accelerate in recent years. This poses new challenges for the way in which the environmental safety of such products is assessed and whether the legislation is still suited and appropriate to accommodate these new developments. These developments are not confined to the Netherlands, but also concern other (EU) countries.

The EC regulatory committee tasked with the 2009/41 only meets very occasionally. In light of current technological developments the GMO Office feels the need to discuss these new developments and share experiences concerning the risk assessment of GMOs, regulatory challenges and daily practices with similar organizations in other EU Member States. With this in mind a number of EU member states were approached with a request to discuss these issues and topics informally and to collaborate more intensively in the future.

1.3 Purpose of the study

This study has been carried out for several purposes:

- Understand the way of the implementation of 2009/41/in a number of EU Member States;
- A more detailed understanding of the daily practice of GMO licensing in other member states;
- A more detailed understanding of the way of information management practices are implemented by other GMO Office-like organizations;
- Explore possibilities to create an informal network with other GMO Office-like organizations to exchange practical experiences.

The formulation of the purpose makes clear that this is not a study that aims to compare – and judge - implementation and/or practices between these countries. On the contrary, the study aims to find inspiration and to learn lessons from other EU member States that can help to improve the execution of the daily GMO licensing practice in the Netherlands. In all selected countries the implementation and execution of GMO regulations have evolved within specific national, historical, political and legal contexts. As such, national implementation and practices cannot be seen as more or less developed, as better or preferable, but first and foremost as different, originating from distinct national backgrounds. Consequently the findings of this study will be presented this way.

The focus of this study is to gain a better insight in the daily practices of legal procedures (both for notifications and licenses) in these countries within the context of contained use and what information is considered necessary at any level of detail to carry out an risk assessment and the subsequent decision making process. Furthermore we would like to learn more about how decisions are communicated to applicants and, if relevant, to the general public.

1.4 Method of the study

The selection of the countries to be invited into this study was based on the assumption that research activities concerning contained use are more or less comparable to the situation in the Netherlands. Another criterion was that those countries have longstanding experience regulating these types of activities. A final prerequisite was the availability to discuss these experiences in a bilateral face-to-face meeting. Belgium, Denmark, Germany, France and Sweden met these criteria.

The basic methodology followed was the same for the five selected countries. As a first step it was corroborated that the national legal framework concerning contained use is in conformity with 2009/41 and thus similar to the Dutch legal framework. National websites and an earlier conducted survey on the implementation of 2009/41[4] were used as basic sources of information. Although the latter report provides very valuable information concerning the implementation of the directive, this information is focused more on the formal and administrative implementation. Details on the daily practices and risk assessments within countries are scarcely available.

Upon request all five countries agreed to meet face-to-face to facilitate the exchange of more detailed information on the daily experiences of the GMO licensing practices. In the interest of this report efforts were made to conduct the interviews as much as possible with GMO Office-like organizations. That is, organizations that process notifications administratively and that carry out the risk assessment. Such a body does not exist in every country. In those cases, the interviews were conducted with people or organizations that perform the risk assessments. A list of topics to be discussed was prepared in advance, these topics have not been discussed in the same detail during the various semi-structured interviews.

1.5 Reading guide

Chapter 2 shortly introduces the key elements of 2009/41 and its implementation in the Dutch legal framework.
Chapter 3 presents the information collected during the interviews. The information is structured per topic. Where relevant notable differences are highlighted between the national frameworks and/or execution in the Netherlands compared to those in the other countries.
Chapter 4 contains a brief reflection and conclusion on the research process, outcomes and potential follow-ups.

A summary of the description of national frameworks based on the individual interviews is presented in annexes to this report.

2 European GMO regulation and its implementation in the Dutch legal framework

2.1 EU regulation on contained use of GMOs

In 1990 the European Union adopted two directives concerning the use of GMOs in order to harmonize existing national provisions for activities with GMOs:

- Council Directive 90/219/EEC on the contained use of genetically modified micro-organisms (GMMs);
- Council Directive 90/220/EEC on the deliberate release into the environment of GMOs. This directive has been recast and replaced by Directive 2001/18/EC.

Key elements of Directive 90/219/EEC:

- The legal basis for the Directive was the 'Environmental Protection article' of the Treaty of Rome;
- The objective was to lay down common measures for the contained use of GMMs with a view to protecting human health and the environment;
- The scope of the Directive was contained use of GMMs;
- The procedures were differentiated, based on levels of potential for risk:
    - Record keeping[2]
    - Notifications[3]
    - Permits[4]
- The description of the elements and the procedure to carry out an risk assessment of the contained uses;
- The definition of four classes of contained use and corresponding levels of biosafety and containment and other protective measures.

In 1998 an amending directive was introduced (98/81/EC). In this directive, the terms 'contained use' and 'GMM' were refined and the classification system was amended with the aim to simplify this system and subsequent procedures.
In 2009 a recast (2009/41) was adopted which incorporated necessary amendments and consolidated the earlier amended texts and included the adjustment of the comitology procedure as a new element.

2.2 Implementation of 2009/41 in the Dutch legal framework

EU member states have some leeway for their own initiative and interpretation of this directive. In the Netherlands, it has been decided to make GMO regulations part of the Environmental Protection Act. Furthermore the General Administrative Law defines generic procedures for administrative processes for issuing permits or other statutory decisions. These generic provisions also apply to procedures regarding contained use, unless specified otherwise in the specific GMO regulations.

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[2] Record keeping: Activities and/or GMOs do need to be notified in advance to the authorities. The user is required to keep record of the activities and/or GMOs only. The records always need be available for enforcement purposes.
[3] Notification: Written legal notice from applicant to authorities. The applicant declares (in advance) in a written legal notice the intended contained use of GMOs. The authorities will check the notification, but do not issue a specific authorization.
[4] Permit (also known as license): written permission issued by an authority to carry out contained use activities. Activities are only allowed to start after the permit is received. Applicants are required to request a permit by submission of an application.

2009/41 has been implemented in Dutch legislation as part of the GMO Decree, in Chapter 2, and in the GMO Order for more technical rules.
Besides 2009/41 also the provisions of other specific European GMO legislation are implemented as part of the GMO Decree, such as Directive 2001/18/EC on the deliberate release into the environment of GMOs [5] and Regulation EC/1946/2003 on the Transboundary Movement of GMOs (Biosafety Protocol)[6].

In the Netherlands the containment and other protection measures for each type and class of facility are implemented in as an annex of the GMO Order. However, the assessment and licensing of the GMO facility is independent from the assessment and licensing of the GMO activities. This results in two legally distinct frameworks and procedures concerning contained use of GMOs. Applications for the environmental permit for the classification of the facility are to be submitted at the local authorities under the General Administrative Environmental Law (Wabo). Optionally local authorities may consult the GMO Office for technical advice.
Furthermore, it is possible that in certain situations applicants cannot comply with the containment measures and working practice as specified in Annex 9 of the GMO Order and would like to conduct their activities in a different way. Or, alternatively, that the regulations described do not assure sufficient safety for the activities to be carried out. For these cases users may apply for alternative measures provided that an equal or higher level of safety is guaranteed.
In the Netherlands a distinction is made in class 2 activities in order to have better oversight and control on activities that are notified as class 2 , but which might have to be carried out at a higher containment level. This concerns mainly activities with a limited number of chimeric viruses[5]. Therefore, procedures for the containment level 2 are subdivided into two procedures and are dependent on the nature of the GMM; II-v requires a permit before activities are allowed to start and II-k for which a notification as described in Directive 2009/41/EC suffices.

[5] This concerns the following viruses:
- Enterovirus C poliovirus type 1, 2 or 3
- Human parechovirus type 1 to 5
- Viruses from the following families: coronaviridae, paramyxoviridae, flaviviridae and togaviridae.
For the above viruses when used as viral vector with donor sequences of viruses from the same family / group the activity will be classified as II-v.

3 An overview of the national policies and practices regarding contained use

3.1 Introduction

During the visits significant differences were found regarding the implementation of Directive 2009/41/EC and the daily execution of the licensing practice of contained use in the Netherlands and the visited countries. The most important findings for each identified topic is discussed in more detail. These topics are organized in the following manner:

- Regulatory Oversight of contained use of GMOs
  - Scope of national regulations on contained use
  - Regulatory structure, roles and responsibilities
  - Supervision on contained use activities within organizations
- Notification procedures, containment levels and risk assessment
  - Procedures regarding classification of activities and facilities
  - Specification of provisions and requirements for carrying out a risk assessment
  - Specification of provisions and requirements for containment
  - Lists of classified organisms, vectors or sequences
  - Customization and exemptions in authorizations
- Information requirements and information management
  - Information requirements for notifications
  - Information management to support the legal body
  - Public access and consultation
- Other topics
  - Gene therapy clinical trials

3.2 Regulatory Oversight of contained use of GMOs

3.2.1 Scope of national regulations on contained use

As noted earlier, the scope of 2009/41 is limited to genetically modified micro-organisms (GMMs). However, like in the Netherlands all the countries visited, have chosen to extend the scope of regulation to all genetically modified organisms (GMOs). Moreover in Belgium, Denmark and Sweden, the scope of national regulations does not only include GMOs but also wild-type pathogens (Directive 2000/54/EC)[7].

Furthermore, each country has made its own choice how to implement 2009/41 into existing national legislation. Like the Netherlands, France has implemented 2009/41 under French environmental protection regulatory framework. Germany has implemented 2009/41 into a separate law on gene technology. In countries that have implemented 2009/41 under environmental regulations like France, Germany and the Netherlands, the authorities more often tend to keep a tighter control on environmental safety of contained use and often request more details on the contained use on containment levels 1 and 2.

Belgium, Denmark and Sweden have implemented 2009/41 under environmental laws but have in their frameworks and/or daily practices linked the GMO regulation with occupational health and safety regulations (biological agents). Because the type of activities and the associated risks of GM and non-GM human pathogenic micro-organisms share many similarities the same competent authority and/or risk assessments body is assigned to minimize administrative burden for the GMO/GMM user. So in practice these governmental organizations

have (regulatory) oversight on the use of both wildtype pathogens as well as GMMs.

3.2.2 Regulatory structure, roles and responsibilities

In 2009/41 some general provisions are given to member states how to structure a national regulatory framework regarding contained use of GMMs. Different roles and tasks can be distinguished:

- Competent Authority (CA) who bears final responsibility for national implementation of 2009/41;
- An administrative body that receives and acknowledges the notifications for contained use (Article 10);
- (Scientific) reviews of the submitted risk assessments;
- Law enforcement (Article 16).

To comply with these provisions and to fulfill the requirements of the directive the following regulatory structure was set up in the Netherlands:

- The ministry of Infrastructure and Water Management is the Competent Authority (CA) who bears final responsibility for national implementation of 2009/41 into the GMO Decree and GMO Order;
- The GMO Office acts as the administrative body that receives and acknowledges the notifications for contained use and reviews the submitted risk assessments according the provisions and procedures laid down in the GMO Decree and GMO Order;
- The Human Environment and Transport Inspectorate is responsible for law enforcement regarding the contained use;
- The Netherlands Commission on Genetic Modification (COGEM) is the independent advisory committee on the biosafety of GMOs. The tasks and structure of COGEM are laid down in the Environmental Protection Act;
- Local and regional authorities, often represented by regional environmental protection agencies, are responsible for the permits for GMO facilities.

As mentioned in 3.2 in Denmark and Sweden the regulations on contained use of GMOs are closely linked to occupational health and safety regulations. As a result of this the work environment authorities are appointed as competent authorities in these countries. Here these authorities also have enforcement duties. This is in contrast with the other countries and the Netherlands where environment authorities are assigned as competent authorities and environment inspection agencies are charged with law enforcement.
In Belgium, Denmark, France and Germany administrative tasks and reviewing of the assessments are formally separated and executed by different bodies. In those countries the competent authority acts primarily as an administrative office that receives notifications and issues the final authorizations for contained use, whereas the review of the risk assessments is conducted by independent advisory bodies or agencies[6]. Although these countries have in common the division of administrative, executive and scientific tasks, in detail many national differences can be noted.

[6] For Germany, this is strictly true only for class 3, class 4 and class 2 operations which cannot be compared to operations already reviewed by the advisory body. See Annex 4 for more details.

Although in all visited countries four different regulatory roles and responsibilities can be distinguished, it may be concluded that the exact national implementation may differ considerably and seems to be strongly related to national administrative and regulatory structures. Also the form of government is an important factor how competences and duties are divided over governmental bodies or agencies. In Germany there are 16 different CAs (one for each federal state) and each federal state is completely free in delegating the administrative and enforcement duties, which results in considerate diversity regarding the administrative organisation of the agencies, which can be attached to the federal ministries. Furthermore, the federal agency BVL[7] acts as administrative office for the advisory board ZKBS[8] as well as the coordinating CA regarding 2009/41. In Belgium is a federal state, composed of communities and regions which all have their own responsibilities and duties. In order to avoid disparities between these different entities sharing competencies in the field of biosafety (in particular the federal state and the regions) a harmonised implementation of the European regulatory framework on biosafety has been necessary. As a result, the decisions of the different administrative bodies representing the different institutional levels (federal state, communities and regions) are taken on the basis of a single science-based advisory system on biosafety. In this system, all regulatory-related aspects of the uses of GMOs and pathogens are assessed in a coordinated way, independently of the specific (regional) regulation(s) involved.

3.2.3 Supervision of contained use activities within organizations

The overall aim of 2009/41 is the protection of human health and the environment from possible negative consequences of the contained use of GMOs. To achieve this goal not only the national regulatory framework is of importance but also the way how users of the contained use structure their internal supervision on biosafety within their organizations.

Directive 2009/41/EC has no explicit provisions or rules regarding the internal supervision of contained use activities within institutions or companies. It is important to note that countries interpret the provision '… *persons responsible for supervision and safety*…' in Annex V of 2009/41, on information requirements for the notifications, differently. Some countries consider this a formal requirement for users to appoint biological safety officers and/or project leaders (e.g. Sweden). Whereas other countries consider this provision only applicable if such a person is legally required by national law (e.g. Netherlands) because 2009/41 itself does not contain any other provision that obliges users or authorities to formally appoint persons responsible for supervision and safety. Nevertheless most countries have provisions in their national legislation for some kind of internal supervision system. These systems share many similarities in the roles of, whether or not legally prescribed:

- Operator / User / Responsible legal body;
- Biosafety expert (s) (BSO or internal biosafety committee);
- Principal scientist / project leader.

[7] BVL: Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, or Federal Office of Consumer Protection and Food Ssafety is an agency of the German federal government and is a national authority regarding the use of GMOs. BVL is also the office of the ZKBS.

[8] ZKBS: Zentralen Kommission fúr die Biologische Sicherheit or Central Commission for Biological Safety advises the German federal government and federal states.

Table 1: Summary of national provisions regarding roles and tasks within organizations to supervise contained use activities.

	User / Legal entity		BSO / IBC		Project Leader / Principal Scientist	
Requirements	**Provisions**	**Remarks**	**Provisions**	**Remarks**	**Provisions**	**Remarks**
Netherlands	Yes	• Detailed description of tasks	Yes	• Detailed description of tasks • Accredited by authorities	Yes	• Detailed description of tasks
•						
Belgium	Yes	• General description of tasks	Yes	• Detailed description of tasks • In large organization IBC required.	No	•
Denmark	Yes	• General description of tasks	Yes	• General description of tasks	Yes	•
France	No	•	Yes	• General description of tasks	No	•
Germany	Yes	• Detailed description of tasks	Yes	• Detailed description of tasks • Accredited by authorities	Yes	• Detailed description of tasks
Sweden	Yes	• General description of tasks	No	• In practice often BSO appointed	Yes	• In practice often appointed

For instance in the Netherlands the general obligations regarding the internal biosafety organization are laid down in the GMO Order. A distinction is made between the legal body (permit holder or applicant), the biological safety officer (BSO) and the 'responsible scientist':

- The legal body is the permit holder and is, for example, represented by the Board of Directors of an institution or company. The legal body has final responsibility and accountability for the execution the GMO activities in conformity with the GMO Decree and GMO Order.
- The GMO Order stipulates that a BSO is appointed by the legal body. This BSO has an independent position within the organization and is accredited by the GMO Office. Prior to the approval of a BSO, the level of education and experience of this person is reviewed by the GMO Office. The BSO is responsible for the internal biosafety management system and is the main contact person for the authorities.
- The GMO Order also stipulates that a 'responsible scientist' is appointed by the legal body. This person is an employee of the organization and is responsible for the daily affairs of the contained use within the notified and/or authorized contained use activities. The 'responsible scientist' must ensure that the GMO activities are carried out in conformity with the GMO Order and the permit that has been issued (only applicable for containment levels 3 and 4). His or her affiliation is known to and is registered by the GMO Office.

The exact roles and tasks of the actors and the way responsibilities are assigned to the actors differs from country to country. In all countries national regulations contain provisions regarding the internal organization of biosafety of the contained use. In Sweden however, not all these provisions are laid down in the GMO legislation. In Belgium, France and Germany users or operators are legally obliged to appoint a biological safety officer. In Belgium and France the tasks and responsibilities for such a BSO are stipulated only in general terms in the national regulations or provisions. In Germany these tasks are laid down in detail, similar to the Netherlands. Furthermore in Belgium (for the Walloon and Brussels regions only) large organizations are also required to appoint an internal biosafety committee (IBC) for technical coordination and support of the activities and to prepare the applications.
In Denmark a BSO as such is not required, but every organization needs to appoint a safety officer who is obliged to supervise on biosafety issues as well. This seems to be linked to the fact that in Denmark the regulations on contained use of GMOs are closely linked to occupational health and safety regulations.
In Sweden there are no specific provisions in the GMO legislation regarding an internal biosafety management system. Nevertheless almost all large organizations (mainly universities) have installed an internal biosafety committee and also have appointed a so-called work leader who is responsible for the general oversight of the contained use activities within the institution, because this is required for a notification (and to obtain approval). Like in Denmark such a person is also responsible for other occupational safety issues.

More details on the relevant provisions in national legislation in the Netherlands and the other five countries are shown in Table 1 and in the Annexes of this report.

3.3 Notification procedures, containment levels and risk assessment

3.3.1 Procedures regarding classification of activities and facilities

The outcome of the risk assessment of contained use activities consist of two components:

- the classification of the contained use activities based on defined risk classes and;
- the level of containment of the facility based on defined containment and other protective measures.

Depending on the national implementation of 2009/41, these components need to be notified, assessed and/or authorized separately or in combination. E.g. in some cases the level of containment and the outcome of the risk assessment of the contained use activities are notified and evaluated as a single package which is considered in its entirety as a notification of first use. Where in other cases authorities assess the facility as first use and regard the assessment of the activities as subsequent use.

3.3.1.1 Procedural requirements for classification of activities

The procedures as described in 2009/41 for applying and/or reporting activities under contained use as implemented in the various countries are summarized in Table 2.

As shown in Table 2 there are many commonalities in implementation of the procedural requirements for risk class 3 and 4 activities across the countries. However, there are many significant differences in the procedural requirements for the lower risk classes, in particular Class 1. For instance, Belgium and France require a full notification in case of both first use and subsequent use of class 1. Denmark issues also for first uses of class 1 contained use permits instead of notifications (Following notifications will only receive an acknowledgement of receipt). In Sweden regarding activities with GMOs other than GMMs, the applicant must always apply for a permit to use new facilities. Subsequently, GM plants and GM aquatic animals must be notified before use. Activities with GM animals have to be notified.

Finally, in the Netherlands a subdivision is made in class 2 activities. Procedures for this risk class are subdivided into two procedures and are dependent on the nature of the GMM; II-v requires a permit before activities are allowed to start and II-k for which a notification as described in Directive 2009/41/EC suffices. This subdivision was specifically made to ensure that activities with certain chimeric viruses would always be assessed by the authorities in detail.

Table 2: Summary of national procedures for first and subsequent GMO uses in different countries.

	Class 1 GMMs		Class 2 GMMs		Class 3 + 4 GMMs	
Use (Article)	**First use (Art. 6)**	**Subsequent use (Art. 7)**	**First use (Art. 8.1 + 8.3)**	**Subsequent use (Art. 8.2)**	**First use (Art. 9.1 + 9.2b)**	**Subsequent use (Art. 9.2 + 9.2a)**
Summary	Notify + start	Start	Notify + 45 days	Notify + start	Notify + permit (90 days)	Notify + permit (45 days)
Netherlands	Notify + start	Start; or when additional use* – Notify + start	Notify + 45 days	Notify + start	Notify + permit (Class 3: 45 days Class 4: 90 days)	Notify + permit (Class 3: 45days Class 4: 90 days) Small changes: 28 days)
Belgium	BR: Notify + start FL: Notify + start WA:	BR: Notify + start FL: Notify + start WA:	BR: Notify + 45 days FL: Notify + permit (45 days) WA: Notify + permit	BR: Notify + start FL: Notify + start WA: Notify + permit	BR: Notify + permit (90 days) FL: Notify + permit (90 days) WA: Notify + permit	BR: Notify + permit (45 or 90 days) FL: Notify + permit (45 or 90 days) WA: Notify + permit
Denmark	Notify + Permit (45 days) (facility *and* activity)	Notify + 45 days	Notify + Permit (45 days) (facility *and* activity)	Notify + permit (45 days)	Notify + permit (90 days) (facility *and* activity)	Notify + permit (45 days)
France	Notify + start	Notify + start	Notify + 45 days	Notify + start	Notify + permit (90 days)	Notify + permit (45 days)
Germany	Notify + start	Start	Notify + 45 days	Notify + start	Notify + permit (90 days)	Notify + permit (45 days)
Sweden	Notify + 45 days	Start; or when additional use* – Notify + start	Notify + 45 days	Notify + start	Notify + permit (90 days)	Notify + permit (45 days)

* additional use is defined as a change in the use of a new set of provisions (e.g. additional laboratory type).

3.3.1.2 Procedure for classification of facilities

Directive 2009/41/EC specifies for each type and class of facility the containment measures such as for GMMs in laboratory, glasshouses and growth-rooms, animal units or large scale production plants. This framework for classification and appropriate containment is mainly based on the pathogenic properties of micro-organisms and consists of 4 risk classes. Furthermore 2009/41 distinguishes between first use and subsequent use. However, several countries have different provisions and/or procedures on what is regarded first and subsequent use in relation to the classification of the facility.

In the Netherlands, first and subsequent use is only used for GMO activities and is not applicable to permits for use of the facility. Permits for use as a GMO facility are issued separately by local authorities within the framework of the General Administrative Environmental Law (see also 2.2).
Also in Denmark a permit for the use as a GMO facility is required but may be submitted as a notification for first use together with a description of the proposed contained use activities.
In Germany one may notify the containment level of the facility as part of the notification for first use, but the facility may also be notified separately. In Belgium and France the notification of the facility may be submitted as part of a notification for first use and will be assessed by the authorities separately from the proposed contained use activities. In Sweden, a (GMM)[9] activity is considered within the physical and organisatory frames of the GMM work at one containment level (one or more activities may be conducted at one site). Thus the combination of the nature of the activities and the (physical) containment and protective measures of the facility are taken into consideration when the notification is assessed by the authorities. Consequently, the consent applies to the specifics of both the notified activities and facility. In Germany the procedure is more like in Sweden, as it is also examined if the safety measures taken in the facility are suitable to perform the proposed activities. Only in a few cases (as part of a construction permit) the activities are not exactly known yet.

3.3.1.3 Term of validity and renewal of authorized contained use

2009/41 contains provisions for the periodical review of the containment and other measures applied to contained uses[10]. In Belgium, Denmark, France and Sweden this provision is implemented into national legislation and decisions are issued in these countries with a validity term. In Belgium and Sweden only permits for Class 3 and Class 4 have a limited validity term. In the event of renewals the activities need to be fully notified again and will be fully reassessed. Germany implemented this provision as well as an option for authorities to authorize contained use for a limited time period, but it is not common practice. In the Netherlands this provision is implemented in such a manner that operators need to review their risk assessments at least once in every five year. See table 3 for further details.

[9] In Sweden contained us of other GMOs than GMMs are notified by other systems:
- Facility needs permission
- GMOs needs notifications, but must be assigned to permitted facility

[10] See preamble 17 and Article 10 para 3 (b) of 2009/41.

Table 3: Summary of legal validity terms of contained use authorizations in different countries

	Netherlands	Belgium	Denmark	France	Germany	Sweden
Facility	No validity term	No validity term	5 years	Not issued separately	No validity term	Permission up to 10 years for other GMOs than GMMs
Class 1 + 2 Activities	No validity term, periodic review of RA every 5 years	First use: 5 (or 10*) years Subs. Use: 5 years (or no validity term*)	5 years	5 years	No validity term	Optional, if there are risks that require a time limit
Class 3 + 4 Activities	No validity term, periodic review of RA every 5 years	5 (or 10*) years	5 years	5 years	No validity term	Up to 5 years

*In case this concerns only routine activities, such as diagnostics

3.3.1.4 Legal fees

In addition, in Belgium, France and Germany legal fees are demanded when applicants submit a notification or application. These fees vary by country and on the type of application.

3.3.2 Specification of provisions and requirements for carrying out a risk assessment

In 2009/41, in particular in Annex III, the general steps and requirements for conducting a risk assessment are prescribed. According to these provisions the user assesses the risks for the human health and environment before starting the contained use activities. Based on this risk assessment, the user assigns the appropriate risk class and containment level. The containment level is indicative of the type of work space or installation that provides adequate protection for human and environmental health, whether or not accompanied by protective measures considered in the risk assessment.
In all countries users are required to carry out their risk assessment according to these provisions and some guidance to support is provided to the users how to conduct the risk assessment. Most countries provide this guidance in structured notification forms and/or guidance notes.

In the Netherlands a risk assessment is carried out in accordance with the principles as set out in Annex III 2009/41, like in other European countries. However the Netherlands is the only country that provides a legally binding risk assessment scheme as an aid to the user to properly classify the intended activity. To this end the Dutch legislator prepared Annex 5 of the GMO Order which summarizes, in the form of classification rules, the outcome of different risk assessments for groups of similar GMOs and activities. These classification rules are in accordance with the risk assessment principles set out in Annex III of 2009/41. These rules accommodate both the most frequently occurring activities at the regular containment level as well as certain activities downscaled to a lower containment level (e.g. activities with 3rd generation lentiviral vectors).
The purpose of the classification rules is that the user focuses on those elements that are relevant from a risk assessment perspective to classify the contained use activities appropriately. The user determines which article of the

classification rules in Annex 5 apply to the intended activity with a certain GMO or group of GMOs.
The systematics of the classification rules has the advantage that the user has a lower effort in performing an appropriate risk assessment, thus making less mistakes and thereby ensuring biosafety. Sets of specific restrictive measures that apply to defined activities with GMOs are linked to the classification rules. Potential disadvantage of the prescribed use of classification rules is that some users apply the rules and fully rely on them, without thinking through properly the relevant risk assessment aspects for their particular situation. In other words those users follow the rules without appropriate knowledge and understanding of the relevant biosafety issues. Another disadvantage is that the classification rules may not be suited to classify all intended activities. In particular extensive and complex experiments may not fit well within the classification rules.

3.3.3 Specification of provisions and requirements for containment

Annex IV of 2009/41 lists containment and other protective measures for laboratories applicable to contained use in tables. These tables present the minimum requirements and measures necessary for each level of containment and are specified for laboratory activities, glasshouse/growth-room activities involving GMMs, activities with animals involving GMMs and finally other than laboratory activities. The measures listed in the tables concern both physical requirements for the facility/installation as well as working instructions. These measures are formulated as goal setting regulations and there is room for interpretation and/or further specification of those measures.

In all countries the containment and protective measures for each class and type of laboratory as specified in Annex IV of 2009/41 are implemented into national legislation. The way these tables are transposed into national legislation varies: countries like Belgium, Denmark and Sweden have almost literally taken over these tables in their national provisions whereas other countries, such as France, Germany and the Netherlands, have added more differentiation and more detailed additional rules in their national provisions. Examples of such provisions are specific requirements to prevent spread by aerosols or to prevent contact to the skin.
The classification of an organism determines for a large part which containment level and in particular which protective measures are to be applied. In France there is a comprehensive system of organism classifications and each classification type is linked to specific protection measures.

3.3.4 Lists of classified organisms, vectors or sequences

In Belgium, Denmark, France and the Netherlands lists of pathogenicity classes of micro-organisms are available, often as legally binding lists. However, only in the Netherlands these lists are frequently updated (every 3 months), while in the other countries such a list might be updated only once in several years. In Germany, new classifications of organisms issued by the advisory committee ZKBS are published on their website after each meeting (6 – 7 times/year) in a database. Also, dossiers on most newly classified organisms are made available on the website. Users are legally bound to take into account the classification of

organisms issued by ZKBS. Sweden has a list in AFS 2005:1 (biological agents 2000/54/EC). AFS 2005:1 also includes criteria for classification[11].
In France, where such a list is not mandatory, the classification of pathogenicity of a particular organism is often leading and acting as a starting point for the risk assessment of the GMO activities. Special attention is paid in all countries when activities are planned with new organisms that have not yet been classified. Such organisms need to be classified first in a risk class, often based on the degree of pathogenicity, before the risk assessment for the contained use of the GMM can be carried out.

In addition in France and Germany also other and often non-mandatory lists are available:

- Databases for cell lines;
- Oncogenes and other hazardous sequences;
- Vectors and / or viral vectors;

All the above mentioned lists, whether these are mandatory or not, are tools to facilitate and/or harmonize risk assessments for contained use. As scientific progress advances researchers may expand their activities to other specific organisms, vectors and/or donor sequences that are not yet listed or classified. In most of such cases authorities demand on a case-by-case basis a full risk assessment in accordance with the principles set out in Annex III of 2009/41. In case of mandatory lists the classification needs to be carried out before the contained use activities can be granted (e.g. like in Germany and the Netherlands).

3.3.5 Customization and exemptions in authorizations

Most countries have implemented the generally defined containment and other protective measures of Annex IV of 2009/41 (almost) literally into national regulations. This makes it feasible for notifiers/applicants and authorities to devise and apply customized containment measures to particular activities if needed. In many countries such specialized activities are notified and assessed on a case-by-case basis without the need of specific procedures.
In some countries, in particular Sweden, the risk assessment and corresponding authorization for Class 3 and Class 4 takes into account the nature of the contained use activities as well as the containment measures which need to be applied during those activities. Such a framework allows for an even more customized approach to accommodate specialized containment measures

In particular the Netherlands have codified special procedures and requirements to accommodate these specific activities and apply appropriate customized containment measures. As mentioned above users are legally bound to apply the classification rules described in a separate annex the GMO Order which accommodate most frequently occurring activities at the regular containment level as well as certain activities downscaled to a lower containment level. This is in contrast to other countries where most requests for downscaling of specific activities are assessed on a case-by-case basis.
Secondly detailed containment and other protection measures are prescribed in a separate annex of the GMO Order. In the Netherlands these provisions are also laid down in the environmental permit of a GMO facility. This permit is issued

[11] The EU is currently working to change and update the list of organisms in the Directive 2000/54/EC. This exercise should take care of discrepancies due to earlier national translations that have led to errors regarding some classifications and could also be of help for risk assessments of contained use of GMOs.

under a different law than the GMO Decree. Users may apply for exemptions of specific measures or may propose alternative protection measures that provide an equivalent (bio)safety level. If granted, this will result in an amendment of the environmental permit of the facility.

3.4 Information requirements and information management

3.4.1 Information requirements for notifications

Annex V of 2009/41 lists for the different containment levels the (minimum) information requirements for the notifications for contained use as referred to in Articles 6, 8 and 9. These information requirements do not prescribe the required level of detail. As a result of this in each country a national practice or standard has been developed concerning the required information and the required detail of the submitted information. The national practices or standards for information requirements of applications vary considerably:

- The level of detail required for risk class I and risk class II notifications may vary considerably between countries. In some countries a global description of the GMO, or group of GMOs with a similar risk profile, suffices. (This is probably also the case for permit applications). In other countries the GMO and its components need to be described in detail irrespective of the class of contained use.
- In countries like Belgium, Denmark, France and Sweden a similar level of detail is requested for risk class I and risk class II notifications. The Netherlands is exceptional that it does not request specific details at risk class I, while at risk class II detailed information is required.
- In general, the information requirements for risk class 3 and 4 activities are reasonably comparable between countries.
- Registration of activities is generally applicable per project or per class of contained use. In Belgium, several classes of contained use can be notified as a single application. In Germany contained use of Class 2, 3 and 4 are combined into a single application form (Class 1 activities are always notified separately). In those cases the procedure and deadline corresponding to the highest class of contained use is applied.
- In general, permissions are issued to a research group or faculty. Administration and licensing is therefore generally more segmented and limited to specific research projects than in the Netherlands (see also the last bullet).
- In countries where the GMO facilities are not assessed and/or approved separately, the facility and its containment measures must be described in detail as well.
- In every country (except the Netherlands) each applicant must describe in every notification in detail the waste disposal measures. In the Netherlands, this is not required since these requirements are listed in Annex 9 of the GMO Order and applicable to the notified activities.
- Notifications covering institution-wide activities with GMOs are not common. In general, the scope of notifications is limited to specific research projects. This includes activities carried out at class 1 of contained use. In contrast to (most) other countries in the Netherlands authorizations for contained use are issued to the legal entity and is not restricted to a specific research group within for instance a university. This in contrary to many other countries. Merging activities with GMOs with an equal risk profile across a number of research projects seems to be applied generically in the Netherlands only. This provides a lot of flexibility since research materials can be exchanged freely within the

institution without the need of submitting or amending notifications and reducing administrative burdens.

3.4.2 Information management to support the legal body

In the visited countries research activities concerning contained use are more or less comparable to the situation in the Netherlands. As a consequence in all countries there is need to process effectively the numbers of submitted notification for contained use of GMOs. To this end in many countries some kind of IT system is developed and/or used to support the administrative processes to handle notifications for contained use of GMOs efficiently. This IT support ranges from rather straightforward Excel sheets to (relatively simple) databases and may support one or more of the following functionalities:

- Administrative registration of notification;
  - operator/legal entity
  - biosafety officer
  - responsible scientist/project leader
  - title of notification
  - address of GMO facility.
- Status of the notification, including decision.
- Details on the GMO activities:
  - Host organism
  - Vectors
  - Donor sequences
  - Global description of the operations
  - Conclusion of the risk assessment

As described in detail in chapter 3.4, in many countries different agencies are charged with the administrative handling of the notification and the actual risk assessment often results in two or more (for Germany) relatively simple IT-systems. In Sweden the Swedish WEA processes the notifications administratively and reviews the notifications to determine whether the notification requirements are fulfilled and that the safety measures seem legitimate. Sweden has a public access policy. All GMM notifications are kept in an (digitalized) archive at SWEA. To keep track of individual contained use activities at different users (e.g. a university may have over 50 new notifications or updates for a single activity) SWEA has another system to distinguish the uses, activities and users/applicants/employers. That system is not public. In Denmark different systems are used for the processing of notifications for activities under contained use and for the authorization process for the classification of facilities. In most countries the IT supports the monitoring of the licensing process, and to keep proper record of what is when authorized in general terms.

In Sweden and Denmark the full process (including submission of notifications and sending authorizations) is completely digitized[12]. Recently also in the Netherlands applicants are now able to submit notifications electronically on a voluntary basis and receive correspondence electronically.

In Germany BVL as the federal authority is responsible for the registration of all notified and authorized GM activities in Germany. The competent state authorities are obliged to inform the BVL on each prepared statement or decision concerning risk assessment which is stored in a web-based database, and can be

[12] In Sweden notifications for Class 3 are occasionally submitted on paper, but digitalized when received by SWEA.

accessed and record management by staff of competent state authorities and BVL.

Compared to these findings the Dutch IT system seems to be unique in its kind. The IT system is used by the GMO Office for both administrative purposes as well as to support a consistent and harmonized evaluation of risk assessments. To this end the IT system has several functional modules, such as case management, process flow management, custom relation management and knowledge database. In general similar types of data are registered in the various IT systems. However the level of detail of the technical data on GMOs and their components, as registered in the GRIP system, is rather exceptional. In the other countries IT systems are generally less complex and extensive due to the implemented licensing practice. Those IT systems are generally used as administrative tool or as knowledge base only and consist of less functional modules.

3.4.3 Public access and consultation

Article 18 of 2009/41 has provisions regarding public access to (environmental) information on the contained use and confidentiality of information. This article defines what kind of information may be treated as confidential, if verifiably justified. The same article states that some data of an application can never be kept confidential, namely:

- the general characteristics of the GMOs;
- name and address of the applicant;
- the location of use;
- the class of contained use and the containment measures;
- the evaluation of foreseeable effects, in particular any harmful effects on human health and the environment (the outcome or conclusions of the risk assessment).

In the Netherlands licensing of the GMO contained use facilities and the authorization of contained use activities are two distinct legal processes (see also §3.4). The contained use facilities for GMO's are part of a general environmental permit for the premises and the public is consulted during this licensing procedure. During the consultation process details concerning the number and containment level of the various rooms destined for contained use of GMO's, are made publicly available. Once such a general environmental permit for the facility is obtained users may start their authorized GMO-activities. The GMO-notifications are not subject to public consultation, but the general public may access a public web-based database to obtain general information on the notifications (such as user, title, municipality of the facility and authorization date).

In all countries passive disclosure of GMO files is applied. This means that members of the public may have access to non-confidential parts of a GMO file upon request. The way submitted notifications of contained used activities are disclosed to the general public differs among the visited countries.
E.g. in Belgium applicants are required to submit a technical part of the notification and a public part. The technical part is not publicly accessible by definition. In Germany the advisory body ZKBS issues upon request opinions on specific notifications. These opinions are not made publicly available and it is up to the competent authorities (the individual Federal States or Bundesländer) to disclose these ZBKS opinions to the applicants. In Sweden, anyone can search

among archive records online, including notifications etc. concerning GMMs. These documents are not available online, but by request.
In the Netherlands GMO files are passively disclosed since 1994 as these files should be treated as other regular environmental permits. Since 2004 a register of all permits for GMO activities under contained use is available at the website of the GMO Office. This register shows the permit holder, the title of the project and the address of the facility where the activities are carried out. Currently preparations are ongoing to actively disseminate the underlying documents of the GMO files by means of a web-based database. When in operation such a web-based database would be the first compared to other EU-countries.

3.5 Other topics

3.5.1 Gene therapy clinical trials

Throughout the EU consider clinical or gene therapy trials are considered differently to be contained use or to be deliberate release or both. During the various interviews, the national policies regarding clinical or gene therapy trials were discussed briefly with some of the visited agencies and also what the general goals are of these national policies. The risk assessment procedures and data requirements for the risk assessments at a national level were also briefly discussed. However this topic was not explored in much detail as the interplay between the GMO legislation and the legislation on medicinal products and the harmonization how to regulate such applications are now under discussion at the European level.
Denmark considers gene therapy clinical trials under the framework of 2009/41. In France and Sweden until recently all gene therapy studies were considered to be contained use but deliberate release is also applicable nowadays.
Depending on the nature of the trial Belgium considers such trials under contained use and only incidentally as deliberate release (Dir. 2001/18/EC) and makes specific guidance on this issue available (more details are presented in Annex 1). In Germany, gene therapy clinical trials are regulated under the German Ordinance on the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for use in humans (GCP Ordinance - GCP-V). Due to the application/use on humans this part of GMO regulation is completely separate from the regulation of other GMOs (e.g. different competent authority = the Federal Institute for Vaccines and Biomedicines). The BVL takes part in one aspect, the environmental risk assessment, which is conducted according to the principles and provisions of Directive 2001/18/EC. In the Netherlands all gene therapy trials are regulated under the deliberate release framework.

4 Conclusions and options for further exploration

Findings and observations

This study confirms the initial assumption that 2009/41 is implemented differently across the various visited EU member states. It is apparent that the national regulatory context influences the way the Directive is implemented in national legislation and the daily practice of executing the regulations on contained use. Some important generic factors that shape the national regulations are:

- A distinction can be made between countries that have linked the provisions of the 2009/41 with the existing legislation for occupational health and safety (e.g. Denmark and Sweden) or in the existing legislation for protection of the environment (e.g. Belgium, France and the Netherlands), or have set up a new separate legislative framework on gene technology (e.g. Germany);
- Whether or not the GMO regulations are linked or combined with regulations on (wild type) biological agents (e.g. Belgium, Denmark and Sweden);

Some factors that shape the daily practice of executing the regulations are:

- Daily practices regarding permit applications for contained use at containment level 3 seem to be rather similar across the countries.
- In contrast, the daily practices for notifications for contained use at containment levels 1 and 2 differ among the countries. In particular the practices for containment level 1 are quite divergent.
- Most countries apply lists of (a)pathogenic organisms acting as a starting point for the risk assessment of the GMO activities. The use of these kind of lists is most often mandatory. In Belgium, Denmark, France and the Netherlands these lists are legally binding.
- In all countries procedures and/or practices exist for applicants and authorities to devise and apply customized containment measures to particular activities.
- Most countries (except Sweden) have provisions in their national GMO legislation for some kind of internal biosafety management system. In many cases this involves appointing a biological safety officer (BSO). In Sweden responsibility for safety is regulated by other legislation.
- The operator and BSO have a responsibility to ensure the biosafety of the contained use activities. On the other hand the regulatory oversight by authorities also ensures the biosafety. The allocation of responsibility to ensure biosafety between different actors within national frameworks is different in every country.

Viewed from a general perspective, the implementation of the overall structure of the directive shows many commonalities across all countries. However, when looking at a more detailed level many differences exist between the countries which in turn may affect the day to day practice significantly. This is also due to the different legislative / administrative approaches. For example, due to historical reasons, much more administrative duties are decentralized in Germany and Belgium compared to other countries and are performed by the German Federal States and the Belgian regions.

Also, it is to be expected that daily practices (including enforcement) within the different countries varies already due to the different sizes of the countries and the number of genetic engineering operations. Despite these differences all

countries stated during the visits that the regulatory framework and the daily practices function rather well. The procedures and technical requirements for contained use of GMMs and GMOs in their country do not pose serious challenges. There is nevertheless a general consensus amongst the interviewed that the execution of the regulations may benefit from further clarification, updating to technical and scientific advancements, and/or further harmonization on the European level.

Noticeable differences between the Netherlands and other countries
In comparison to the regulatory frameworks and daily practices in the other countries some noticeable differences can be identified in the Netherlands:

- In the Netherlands, the principle of first and subsequent use is only used for GMO activities and is not applicable to permits for use of the facility. Permits for a facility to be used as a GMO facility are issued separately;
- Special procedures were designed to accommodate for the possibility to apply for appropriate alternative protection measures of the facility related to the intended contained use activities specified in the notification;
- Notifications for contained use activities in containment level 1 may be merged in a single notification covering all class 1 activities within an institution and are therefore not limited to the scope of a specific research project or research group;
- Moreover the information and reporting requirements for notifications for class 1 activities are very minimal compared to most other countries. The required information focusses on the type of facility (laboratory, glass house, etc.);
- Procedures for containment level 2 are subdivided into two procedures and are dependent on the nature of the GMO: II-v requires a permit before activities are allowed to start and II-k require a notification only. This concerns mainly activities with a limited number of chimeric viruses. None of the other regulatory frameworks in the EU seems to have this subdivision.
- In the Netherlands the information requirements for notification for class 2 activities are significantly more detailed compared to the requirements for class 1 activities. This is in contrast to the practices in other countries;
- In the Netherlands the information requirements for class 2 activities share a similar level of detail as required for class 3 activities;
- The Netherlands is the only country that obliges applicants the use of legally binding classification rules for the risk assessment of contained use activities in the Netherlands;
- The Netherlands seems to be the only country that informs the general public concerning contained use activities with GMOs by means of a public internet database and that includes non-confidential documents.

Reflections and recommendations for further exploration
The goal of this study was to get a better insight in the national frameworks and daily practices on contained use of GMOs in a number of EU Member States. During the visits attention was also given to information requirements considered necessary to carry out a risk assessment and the subsequent decision making process. As such, national implementation and nationally developed daily practices cannot be seen as more or less developed, as better or preferable. Even in this relatively limited set of countries visited a wide diversity of approaches was observed. This diversity provides an excellent basis to explore in

further detail opportunities to optimize the execution and/or implementation of the Dutch framework on contained use of GMO.
Based on the findings described above two striking topics may be identified. Firstly, the uniqueness of a standard set of classification rules applied in the Netherlands is unique in comparison to other frameworks. These classification rules aid the user to properly classify intended activities and also harmonize the outcomes of risk assessments and subsequent decisions making of similar or identical activities carried out by different applicants. However, inherent in applying the structured classification rules is the inflexibility of the system to cope with extraordinary and/or complex activities, despite the specific procedures in the GMO Decree in case the standard classification rules cannot be applied. It is recommended to adapt the Dutch framework in such a way that it is sufficiently flexible to also accommodate the risk assessment of extraordinary activities, but in which the current advantages are retained, such as the support to applicants to properly classify those activities.
Secondly, during the visits it became apparent that the information requirements to notifiers differ among the countries. More particular, the Dutch GMO Office seems to require from applicant more detailed information to substantiate the outcome of the risk assessment compared to daily practices in other countries. This applies in particular to applications for activities in containment level 2.

The findings of this study provide valuable insights to be able to understand and interpret the various approaches in the different countries. Although this outcome is a given fact, it is exactly this level of practical interpretation of the general provisions of 2009/41 that much can learned from daily practices in other countries. It is therefore recommended to explore options for a new balance between the level of detail of the required information in relation to the relevant risk and/or containment level.

Opportunities for intensified exchange of (daily) practical experiences
As already indicated in the introductory section the GMO Office has a need to exchange views and experiences concerning new (bio)technological developments and its challenges as well as to discuss issues encountered during the daily execution of its duties with similar European organizations.
One of the goals of these visits was to explore the possibilities to collaborate more intensely on this topic and to establish an informal network with other GMO Office-like organizations. Such a network will promote the exchange practical experiences and dilemma's regarding challenges posed by new (bio)technological developments. But this will also establish a better and detailed understanding of the various approaches and interpretations solidified in the day-to-day practices. Most of the people interviewed were very supportive to such an initiative and indicated that they would like to actively participate in such a network. Also a number of people referred to the European Enforcement Project on GMOs (EEP) as a potential working model. Analogous to the aims of the EEP an informal network of GMO Office–like organizations could be useful:

- To promote the exchange of knowledge and expertise regarding the execution and daily practices of the provisions of 2009/41;
- To "guarantee" the longer term exchange of knowledge and expertise by creating an information network on the contained use of GMMs/GMOs;
- To identify and discuss regulatory challenges resulting from the Directive and/or new technological developments within the context of contained use of GMOs;
- To stimulate collaborative activities across the EU;

- To establish, maintain, and expand a network of contacts among the risk assessors and/or administrative offices in different Member States.
- To promote an EU-wide harmonized interpretation and understanding of the aims and provisions of 2009/41.

Participation in these meetings should preferably not be limited to the visited organizations and should be extended to similar organizations in all EU countries.

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[6] Regulation (EC) No 1946/2003 of the European Parliament and of the Council of 15 July 2003 on transboundary movements of genetically modified organisms; *OJ L 287, 5.11.2003*.
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https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000L0054&qid=1541176651790&from=EN

Other information sources:

Belgium:

- Belgian legal framework on contained use of GMOs and pathogens; Contained Use of GMOs and Pathogens | Belgian Biosafety Server
- Details on the notification procedures for contained use in the 3 Belgian regions; https://www.biosafety.be/content/contained-use-gmos-andor-pathogenic-organisms-notification-procedures
- Details on procedures for clinical trials; Notification procedures: Clinical Trials with GMOs for human or veterinary use | Belgian Biosafety Server

Denmark:

- Executive order on genetic engineering and the working environment; Bekendtgørelse om genteknologi og arbejdsmiljø - Arbejdstilsynet

France:

- Decree No. 2011-1177 on the contained use of GMOs; Version électronique authentifiée publiée au JO n° 0223 du 25/09/2011 | Legifrance
- HCB manual on contained use notifications; http://www.hautconseildesbiotechnologies.fr/fr/system/files/file_fields/2015/06/30/manuelduconfine.pdf
- Manual Ministry of Higher Education and Research regarding contained use of GMOs; http://cache.media.enseignementsup-recherche.gouv.fr/file/OGM_en_milieu_confine/16/1/OGM_150713_v2_262161.pdf

Germany:

- Overview of national regulations on genetic engineering in Germany; https://www.bvl.bund.de/EN/06_Genetic_Engineering/03_Applicants/08_LegalFramework/01_Germany/legal_basis_national_node.html
- Contained use of GMOs in federal states – Bund/Länder – Arbeitsgemeinschaft Gentechnik; http://www.lag-gentechnik.de/
- Examples of contained use of GMOs in a German federal state (Berlin – LaGeSo); https://www.berlin.de/lageso/gesundheit/gesundheitsschutz/gentechnik/
- Databases on micro-organisms, oncogenes, vectors and cell lines published by ZKBS; https://www.zkbs-online.de/ZKBS/EN/05_Databases/datenbanken_node.html

Sweden:

- Contained Use of GMOs Ordinance SFS (2000:271); https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/forordning-2000271-om-innesluten-anvandning-av_sfs-2000-271
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Annex 1: List of topics intended to be discussed during interviews

Topics organized by theme:

- Legal framework of national implementation directive
  - Implementation of 2009/41 (as law / decision / regulation / guidance)
  - Scope Contained Use regulations (GMM, also plants and/or animals, gene therapy)
  - Level of detail of prescription of risk assessment
  - Use of supporting lists of classified (micro-)organism, vectors and/or donor sequences. To what extent are these lists legally binding?
  - Request for authorization as notifications, permits or a combination thereof
  - How is supervision on contained use activities internally organized and/or prescribed within institutions?

- Regulatory structure, roles and responsibilities within the national framework
  - What are the different actors within the framework?
  - Definition of roles and responsibilities and duties of those actors defined
  - Advisory committees

- Daily practices
  - Procedures and conditions for first use and continued use of activities
  - Procedures and conditions for first use and continued use of facilities
  - Assurance of correct classification of activities assured within the framework
  - Detail level of imposed regulations
  - Is customization in authorizations possible? How is this implemented?
  - Procedures for applying contained use of complex (research) activities comprising multiple containment level
  - Large-scale / process installations
  - Storage and waste processing

- Information management
  - Application forms
  - Obligation for applicants to use predefined formats
  - What is the level of detail of requested data in applications
  - What does an application look like in detail?
  - IT support of administrative processing of applications

- Public access / confidentiality
  - Decisions / authorizations
  - Level of details that are publicly accessible

Annex 2: Belgium

Short description of the organization

- The **Service Biosafety and Biotechnology** (SBB) is the Belgian focal point responsible for assessing biological risks for human and animal health and the environment linked to activities involving (pathogenic) and /or genetically modified organisms (GMOs)[13] or products containing them. It advises the federal and regional authorities regarding all aspects of biosafety linked to the use of these organisms.
- SBB is part of the Belgian scientific institute Sciensano (formely Scientific Institute of Public Health - WIV-ISP).
- SBB acts as a scientific and technical expert for the authorities. This includes the following aspects:
    - The contained use of GMOs and/or pathogens (including gene therapy when applying)
    - The dissemination of GM plants into the environment
    - Clinical trials with medicinal GMOs
    - Commercial applications of GMOs in livestock farming and food, and in medicine
    - The SBB reviews the biological risk assessments for human and animal health, and the environment of activities involving the use of GMOs and/or pathogens.
    - Furthermore, the SBB also acts as the secretariat of the Belgian Biosafety Advisory Council.

Legal framework and structures concerning Contained Use

- The **contained use** of genetically modified micro-organisms (GMMs) or organisms (GMOs) and/or pathogens is regulated in Belgium at the **regional level** and is based on the implementation of **European Directive 90/219/EEC & 98/81/CE to** regional Decrees (respectively in November 2001 for the Brussels Region, in July 2002 for the Walloon Region, and in February 2004 for the Flemish Region). Directives 90/219/EEC and 98/81/EC have 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. The exact procedural details may vary between the Belgian regions.
- To employ contained use in Belgium two authorizations are needed independently; an environmental permit valid for the facility, which has no validity term provided no new changes are needed that are legally required to be notified to the authorities, and one for the activities with the GMOs (with limited validity, but dependent on the region). Both authorizations are issued by the region.
- Also in Belgian legislation several lists are made available as annexes regarding the classification of various organisms (not limited to GMMs

[13] Pathogens are also included in the scope for Contained Use in Belgium.

only). These lists/annexes are compulsory. The lists published online on the Belgian Biosafety Server website may show some discrepancies with the officially published legal list but has the same legal status. The lists were revised in 2008 and were reviewed occasionally by experts depending on the evolution of research and knowledge. In the future the lists will be reviewed every two years. Classification of novel organisms is carried by SBB with sometimes help from external experts. The risk classification of the listed organisms guide the risk assessment but does not necessarily determines to the conclusion at which containment level the GMO need to be operated (e.g. HIV is class 3 but may be operated at risk level 2)

- In general the scientific infrastructure and the type of (GMO) activities conducted are similar between Belgium and NL. There are no L4 labs in Belgium.
- The Belgian legislation contains provisions regarding the duties of the organizations and the internal organization concerning the oversight of GMO activities within facilities.
- In Belgium activities with GMO's as well as (wild type) biological agents are considered equally important and need to be assessed consistently. This consistency has also its effect on how the risk assessments are conducted.
- Clinical trials may be considered as deliberate release and/or contained use of GMO's depending on the characteristics of the GMO and the (planned) activities. In general, when there is no possible release of the GMO in the environment (GM medication taken at home; probability of shedding, spreading,…) that may confer a risk to human health or the environment or if proper management procedures and/or working practices are taken to prevent any possible release conferring a risk, then a 'contained use' procedure is sufficient. The opposite, when there is a probability of possible release that may confer a risk to human health or the environment which cannot be avoided by proper management procedures or working practices, a notification under 'deliberate release' will additionally be required. Clinical trials under contained use need to be authorized per site, whereas permits for clinical trials authorized under deliberate release may concern also multicenter studies. See also specific guidance[14].

Procedural aspects and processing of applications for contained use

- General characteristics of procedures in the three regions Belgium[15]:
    - The procedure for submission of an application is dependent of the region. See the link https://www.biosafety.be/content/notification-procedures-clinical-trials-gmos-human-or-veterinary-use for more details.

[14] See also Notification procedures: Clinical Trials with GMOs for human or veterinary use

[15] Details for each Region; see also procedures in Flemish Region - Brussels-Capital Region – Walloon Region)

    - The notifications of contained use operations, in 2015 about 250, are registered by the CA and the SBB for a scientific advice.
    - In general SBB staff examines the notifications/applications, reviews the risk assessments and draws up the advice. Dependent on the procedure this advice is sent back to the CA or to the applicant directly.
    - If needed the procedural clock can be stopped for requests for additional information.
    - The CA sends the decision to the applicant.
- In Belgium the decisions have a limited validity; are valid for 5-10 years[16] depending on the region. Requests for renewal require a full notification. For more details on the procedure see Contained use of GMOs and/or pathogenic organisms: Notification procedures.
- In case of complex applications, activities are not always separated into the different applicable containment levels as is done in NL, instead a permit may be provided involving all activities at the highest applicable containment level. However each of the separate activities described in the notification will be assessed individually and risks will be classified and additional risk management measures may be imposed if relevant.[17] Not all details of GMO's coming from lower levels (e.g. level I organisms like GM mice or cell lines) have to be provided when these are combined with GMO's that have to be handled at a higher containment level. The necessary level of detail depends on the application, when the assessor is convinced of the correct containment level, based on the supplied information, less detail is necessary.
- Storage of GMOs is allowed outside of the classified room. Apparatuses may also be present in the building outside of the classified room (levels I and II) or has to be within the classified room (level III)

IT-systems, information sharing and public access

- SBB does not process the notifications (only the assessment) no extensive IT-support is necessary. Nevertheless electronic submission of notifications is already implemented for the Flemish region.
- The provisions article 18 of Dir. 2009/41 regarding information that in no case can be kept confidential are implemented in Belgian law. Each dossier consists of a public part and a technical part. The technical part is not actively publicly accessible ,but may be accessed according to the EU regulation on access to environmental information. Upon request and during the procedure, the public part may be accessed. In practice such request are very rare. The decision for access to a specific notification is

[16] In case of a renewal of the environmental permit, the validity term may be extended to 20 years (in conformity with the validity term of the environmental permit under which the notification resides). This is only possible for activities with risk classes 1 and 2.
Currently the regulations are under revision and this may also impact the validity terms.

[17] Example: Activities with viral vectors of risk class 2 that are used for the replication of the viral plasmids necessary for viral production using the standard *E.coli* laboratory strains. These type of activities are classified at containment level 2 but that the storage and manipulation of these GM *E. coli* cells are allowed to be carried out under containment level 1.

in the hands of the competent authorities (i.e. the regions). Only people living in the direct neighbourhood are actively notified.

- There is a memorandum of understanding between the SBB the Belgian Biosafety Professionals (BBP) that ensures communication and documents sharing. Furthermore SBB host the Belgian Biosafety Server which contains extensive information regarding biosafety and contained use and have the task to support users in case of questions or other requests for information. Occasionally SBB hosts round table meetings on specific topics or to validate/discuss new initiatives.

Annex 3: Denmark

Legal frameworks and structures concerning Contained Use

- In Denmark the legal framework for gene technology under contained use is organized alongside that for biological materials. Therefore the focus of the legislation is worker safety. Directive 2009/41/EC is implemented in Executive Order No. 910 on Genetic Engineering and the Working Environment of 11 September 2008 and supplemented by WEA guidelines on risk assessment of gene technological research projects, and classification of laboratories, premises for production, etc.
- The Danish Working Environment Agency (WEA) together with the Danish EnvironmentalProtection Agency (EPA) are assigned as the competent authority.
- The GMO safety is ensured at several levels:
    - Approval of research project, large scale and production
    - Approval of laboratories, premises/facilities for GMO work
    - Inspection visits at laboratories (e.g. prior to permission as laboratory GMO class 2-4)
- Two types of notifications can be distinguished;
    - Classification of the laboratory, stable or greenhouse
    - Approval of research project, large scale production
- A list is available of micro-organisms of which the level of pathogenicity is classified. The Danish list is limited to micro-organisms which are known to infect humans. Also this list of pathogens is applicable for activities with both GMMs and wild type micro-organisms. The list can be found at URL http://arbejdstilsynet.dk/da/regler/bekendtgorelser/b/biologiske-agenser-57/bilag-8-klassifikation-af-biologiske-age.
- In Denmark gene therapy clinical trials are considered as contained use activities.
- The Danish framework offers the possibility to schools/universities to notify and use defined GMOs under GMO-BSL1 conditions without a notification/permit for the premises. Only GMO's generally considered to be safe may be used in these instances, such as the pGLO kit from Biorad. Within WEA it is discussed which other GMO's may also be appropriate for this purpose.

Procedural aspects and processing of applications for contained use

- WEA issues a permit when a GMO-BSL 1 project is notified for the first time. Applicants cannot start the work until they have received a permit from the WEA. The permit is send within 45 days. This is comparable to the provisions of the old GMO Decree in NL, and deviates from the provisions of Dir. 2009/41/EC.
- The companies are the prime responsible for making the risk assessment.

- Since 2015, all notifications are to be submitted electronically via Virk/e-Boks (comparable to DigiD/berichtenbox in NL).
- Notifications for activities/projects with GMOs are sent to WEA and processed by an inspector. The inspector does not assess the notification in detail, the company is responsible for an appropriate and correct risk assessment. The Danish EPA is involved also when animals or plants are part of the project (EPA is able to log into IT system of WEA). Inspections of e.g. animal facilities are performed together with EPA.
- In rare cases the risk assessment may be sent to an independent advisory body for review. It is only sometimes done by the EPA when concerning GMO class 2 activities with animals.
- Until to date, no GMO BSL 3 or 4 are notified in DK.
- The information requirements to describe the GMO activities on GMO BSL-1 are comparable between DK and NL. Although not discussed into details, in NL the data requirements for GMO-BSL 2-4 seems to be more strict than in DK.
- In DK notifications for complex activities with GMOs are always processed as notifications for first use.
- Additional provisions may be imposed to notifications with complex experiments.
- During inspections the Danish authorities inspect the premises/facilities, but not the GMO activities.
- In Denmark it is possible to use a classified GMO laboratory also for non-GMO activities with wild type organisms (but not simultaneously). In those cases laboratories approved for GMO BSL 2 correspond to wild type BSL 3 (not airborne), and laboratories approved for GMO BSL 1 correspond to wild type BSL 2. In case of an airborne wild type BSL 3 a specific judgement will be made.
- Storage of GMOs classified in containment level BSL1 or BSL2 is allowed outside of the classified rooms.

IT-systems and public access

- WEA uses one IT system to both process notifications concerning premises/facilities and (research) projects. This IT system supports process flow / case management but does contain in contrast to the Dutch IT system no technical data on the GMOs or activities.

Annex 4: France

Short description of the organization HCB and HCB Office

- Established by law in 2009, the High Council for Biotechnology (HCB) is the federal expert advisory body. HCB is mandated to inform the government on all questions concerning biotechnologies including GMOs and of formulating opinions and advice regarding the evaluation of risks for the environment and public health. It gives advice on each notification to the CA, regarding the granting of permits. HCB members, researchers and representatives of civil society, are split into two committees:
    - A Scientific Committee (SC) comprising 40 experts - with expertise in genetics, molecular biology, microbiology, health assessment, agronomy, statistics, ecology, ecotoxicology and social science – assesses the impact of biotechnology on the environment and public health, including issues relating to contained use (dealt by a sub-committee);
    - An Economic, Ethical and Social Committee (EESC) comprising 33 members (representatives of consumer, health and environmental protection associations, of farmers' unions, of trade associations for the seed, food and pharmaceuticals industries, elected representatives, and specialists in economics, sociology, law and ethics) examines and debates the social, ethical and economic aspects of biotechnology and its applications.
- HCB is competent to give an opinion on:
    - Applications for authorization to use GMOs
    - Environmental monitoring reports
    - Biotechnology regulation
    - Wider issues raised by biotechnology
- Notifications for the contained use of GMOs are evaluated by the Scientific Committee (SC). The SC is supported by a scientific secretariat or Bureau that, amongst others, deals with many of the administrative matters and screen all applications before these are forwarded to the SC.

.Legal frameworks and structures concerning Contained Use

- French framework: Directive 2009/41 is implemented in the Decree 2011-1177. This decree regulates reporting procedures and applications for approval of contained use of genetically modified organisms for research, development, education and industrial production. In a public or private facility, any use of GMOs in contained use is subject to declaration or authorization. The Ministry of Higher Education and Research is the competent authority in the field of contained use of GMOs.
- To employ contained use in France only one assessment and authorization is needed for the facility/premises and the activities with the GMOs.

- Several lists are made available as annexes of the Contained use manual. These lists/annexes are not compulsory and comprise of the following:
    - Classification method of microorganisms prepared by the EFB (European Federation of Biotechnology;
    - Lists of human pathogens, animal pathogens and plant pathogens (all including classification to risk groups);
    - Method of determining the class of B-type inserts (potentially harmful sequences)
    - List of viral vectors, including risk classification in relation to activities
    - Furthermore the manual contains the description of the containment measures laboratories, animal/plant/industrial production facilities, as well as for clinical trials, and waste treatment.
- In general the scientific infrastructure and the type of (GMO) activities conducted are similar between France and NL. In France there are also S4 labs present.
- The French control system relies strongly on self compliance and on the own responsibilities of institutes and companies to carry out regular internal checks, hence the obligation to implement strict Internal Biosafety Systems.

Procedural aspects and processing of applications for contained use

- General procedure in France:
    - In France a so-called application kit is made available consisting of a set of applications forms for general information and for specific activities e.g. micro-organisms, plants, animals, viral vectors, adenoviral vectors, retroviral vectors etc.
    - The application is sent to the competent authority. In almost all cases this is the Ministry for Research in case of contained use activities for R&D purposes. The CA may also be the Ministry of Defense for defense research activities or “prefectures (counties federal authority)” in case of commercial production under contained use.
    - The notifications (100-200 each month) are registered by the CA and forwarded to the HCB (in batch). When sent to the HCB a procedure time of 35 days starts (75 days for notifications for first uses on containment level 3 or 4). All notifications are screened by the HCB-Bureau and if considered to be complete two (relevant) experts of the Council are appointed as assessors of the notifications and examine the notification in detail.
    - The HCB-SC subcommittee on contained use convenes every month. Only notifications with diverging opinions of the two experts are discussed in plenary.
    - After the meeting the HCB secretariat analyses the outcomes of the assessments and prepare the advice for the CA.

    - The CA sends the decision to the applicant.
- In France the decisions are valid for 5 years. Requests for renewal require a full notification.
- In general the risks of similar types of activities with GMOs are assessed in a similar way in France and NL resulting in comparable risk classifications of those GMOs and activities.

IT-systems and public access

- In France a distinction is made between public consultation and public information. When an authorization covers the first contained use of GMOs at containment level 3 or 4, the application comprises an information package to the public. This package includes:
    - The information cannot be considered confidential pursuant to article 18 of Dir. 2009/41 regarding information that in no case can be kept confidential;
    - The address of the High Council of biotechnology, from which the public can communicate any comments.
    - After the approval to this dossier shall be granted all relevant information on the classification of the GMOs which may be used in the installation as well as on containment measures, means of intervention in the event of a disaster and technical requirements to which the approval is subjected.

  Upon issuance of the approval, the operator transmits the information package for the public to the mayor of the borough or district where the installation is located and to the prefect of the department. A public notice is posted at the town hall for 1 month, at the expense of the operator of installation and care of the mayor.
- All notifications/applications for contained use of GMOs need to be submitted electronically using the so-called DUO (***Demande d'Utilisation d'Organismes génétiquement modifiés***) portal of the Ministry for Higher Education and Research.
- As HCB and the HCB-Bureau do not process the notifications (only the assessment) no extensive IT-support is necessary. All basic functions are supported by an Excel sheet.

Annex 5: Germany

Short description of the organization ZKBS / ZKBS office (BVL):

- The ZKBS is established by law (§4 and §5 of GenTG) and advises the competent federal authorities concerning safety recommendations for genetic engineering and their facilities.
- Meetings and sessions of the ZKBS are not open to the public and specific recommendations (on applications) are confidential.
- On the ZKBS website several lists / databases are published to support the applicants when conducting a risk assessment and authorities processing applications and notifications. The ZKBS published the following lists (https://www.zkbs-online.de/ZKBS/EN/05_Databases/datenbanken_node.html):
    - List and database of (micro)organisms, including bacteria, fungi, viruses, parasites and some single cell eukaryotes, to be used as donor and/or recipient organism, classified by ZKBS (compulsory);
    - List of oncogenes (supportive to users and (local) authorities);
    - List of vectors and *Escherichia coli* strains already known and assessed by ZKBS (supportive to users and (local) authorities);
    - List of cell lines, to be used as donor and/or recipient line, already assessed and classified by the ZKBS (supportive to users and (local) authorities);
    - Recommendations and classifications contained in the databases have to be taken into account, but they are not compulsory.
- Besides specific opinions on applications, the ZKBS also issues general recommendations and opinions. These are made publicly available via the ZKBS website:
    - Genetic engineering operations carried out frequently, based on criteria of comparability, e.g.:
        - Gene transfer using adenoviral vectors
        - Gene transfer using retroviral vectors
        - Operations with of alpha virus derived expression systems
        - Operations with recombinant measles virus vaccine strains
    - Issues of common interest, e.g.:
        - On the classification of genetic engineering operations with highly pathogenic avian influenza A viruses (HPAIV) which possess the potential for efficient airborne transmission between mammals
        - On new plant breeding techniques
        - On Gene drive technologies
        - On Synthetic Biology
    - On current scientific literature (Séralini et al.)
- BVL is responsible for a federal database management system StellDB for the registration of all notified and authorized GMO activities of contained use in Germany.

- When an opinion by the ZKBS is required the following procedure will be followed by BVL/ZKBS:
    - Participation needed when notification concerns uncertain S1, new S2 (not comparable to other ZKBS recommendations), S3, S4
    - Office of the ZKBS (BVL) receives the application
    - File / reference number attached (different form file / reference number by competent state authority by administrative support workers)
    - Check for completeness (scientific officer) – additional demands necessary?
    - Examination of content (scientific officer)
    - Preparation of draft opinion / recommendation (office)
    - Organization of the ZKBS decision making procedure (scientific officer, administrative support workers)
    - Primary examination of the application by two experts (or more, if required by the complexity of the topic)(leads)
    - Plenary consultation/discussion of the conclusions of the two leading experts. For simple questions, alternatively a written procedure can be chosen.
    - Forwarding of the opinion to the requesting competent (state) authority.
    - The requesting state considers the ZKBS opinions when drafting the permission and may make the ZKBS opinion available to the applicants.

Legal frameworks and structures concerning Contained Use

- German framework: Directives 2009/41 and 2001/18 are both implemented in the Gene Technology Act (GT Act), and practically implemented in several (6) ordinances. The GT Act not only covers contained use of GMMs but all types of GMOs with the exception of applications to humans. The GT Act is aimed at the protection of human health and the environment and for further development and promotion of genetic engineering.
- Berlin is one of the 16 federal states and the regional offices are the competent authorities regarding contained use and the execution of the law and legal rules. The competent state authorities decide autonomously concerning S1 and S2 on the basis of comparability of earlier notifications. Notifications concerning uncertain S1, new S2, S3 and S4 are always forwarded for an opinion of the ZKBS.
- All federal states participate in the German Working Group on genetic engineering of the Federal States and the Government (www.lag-gentechnik.de). Two formal meetings per year are organized to discuss practical and legal issues relating to GMO legislation enforcement. This can e.g. relate to issues in the interplay of GM/Pharma legislation, the harmonization and collection of results of seed sampling and detection or the monitoring of Do-it-yourself biology kits intended for amateur users.

- To employ contained use of GMOs in Germany a single authorization suffices for both the facility/premises and the activities with the GMOs. This authorization is issued by the Federal States (e.g. LAGeSo for the state of Berlin)
- In general the scientific infrastructure and the type of (GMO) activities conducted are similar between Germany and NL. In Germany there are also S4 labs present. In the state of Berlin 1 S4 facility is located and 15 S3 facilities.
- The internal organization within institutions or companies regarding GMOs is regulated by law.
- An operator is defined as an entity (university or company) or a legal person. The entity is represented by the president (of a university) or the managing director (of a company), i.e. a representative who has the overall responsibility for the genetic engineering facility or facilities. The contact person can be any person named by the representative. Usually he or she belongs to the administrative staff.
- Each genetic engineering facility holds an operator (+ contact person). The operator is responsible for appointing a project leader who plans and organizes the projects and instructs the co-workers. Furthermore a biosafety officer (BBS) is appointed who controls the project leader and advises the operator. The BBS should be independent, but usually the BBS is employed by of the entity.

Procedural aspects and processing of applications for contained use

- General procedure in Germany: In general an application contains a section for general administrative data (e.g. operator / project leader), a section describing the GMO and the activities (short description of the genetic modification, activities with the GMOs, donor, recipient and description of GMO), and the final risk assessment (proposal / assessment biosafety level, description of safety measures, appropriate GM facility available? (if not, also a description of the facility is required)). The application is sent to the competent state authority. When the application is received a file / reference number will be attached and a check for completeness is conducted. The content is then examined and considered whether participation of ZKBS is required (application comparable to previous ZKBS recommendations S2; or S1-> no ZKBS). Whether or when the participation of the ZKBS is required is stipulated by law (§12 para 4 GenTG). In biosafety level 3 and 4 this participation is always required, while it is not required in biosafety level 1. In case of biosafety level, 2, the participation of the ZKBS is only required for projects that are not comparable to previous position statements of the ZKBS. Here, the local authority decides about the comparability and whether the ZKBS shall be consulted. When a notification is sent to the ZKBS, the procedural clock will be stopped. In general competent state authorities act on ZKBS opinions, but are not obliged to do so. (Also the ZKBS opinions are not available to the applicants in any case). After these

steps the notification will be taken under consideration and processed. The notification will be registered / authorized by preparation of a statement or decision concerning the risk assessment. The applicant is informed of the decision.

- In general the risks of similar types of activities with GMOs are assessed in a similar way in Germany and NL resulting in comparable risk classifications of those GMOs and activities.
- In Germany operators need to archive their notifications/applications after the experiments have been terminated and keep them for a number of years.
- All GMOs (level S1 to S4) must be stored within containment of the corresponding biosafety level.

IT-systems and public access

- LAGeSo uses IT systems for the registration of GMO activities but are focused on the legal duties of the agency. The IT system is accessible to authorized users only.
- BVL is as the superior federal authority responsible for the registration of all notified and authorized GM activities in Germany. The competent state authorities are obliged to inform the BVL on each prepared statement or decision concerning risk assessment which is stored in the Stell-DB system. Stell-DB is a web-based (Oracle) database, and can be accessed and record management by staff of competent state authorities and BVL. The dataset plus the attached statement is stored in Stell-DB. A problem of Stell-DB is that it also contains information originating from its predecessor FileMaker-DB. Some of the information consists of input based on the filled out datasheets which were forwarded to the BVL and processed by administrative support workers of the BVL. This information may contain errors or is not complete.
- The provisions article 18 of Dir. 2009/41 regarding information that in no case can be kept confidential are implemented in German law. The applications and decisions on contained use of GMOs are not actively disclosed to the public. However, the general public can request access to specific notifications and permissions.

Annex 6: Sweden

Short description of the organization SWEA Office

- The Swedish Work Environment Authority (SWEA) is an independent and non-political executive body acting under and financed by ministries. The SWEA consists of 7 departments and is a so-called Central Government Authority and is mandated to issue provisions, amongst others concerning Contained Use (CU) of GMMs. These provisions are detailed binding provisions and general recommendations which apply to the contained use of GMMs. Furthermore, besides GMMs SWEA is also the responsible authority regarding biological agents and other work environment and other occupational health issues.
- The unit dealing with contained use of GMMs has a variety of duties:
    - Act as experts: Regulatory Committee of Competent Authorities on Dir. 2009/41, other (Inter)national groups, negotiations (represent Government);
    - Provisions (biological agents, GMM directive)
    - Handling notifications and applications
    - Inspecting premises
    - Information
        - Website
        - Mail, telephone service
    - Swedish informal network of GMO officers, inspectors and officers at the authorities
        - Meetings twice yearly
        - Website https://genteknik.nu/genteknikmyndigheter-i-sverige/ (only in Swedish)

Legal frameworks and structures concerning Contained Use

- In Sweden GMOs are regulated under the Environmental Code (1998:808), Chapter 13. The Directive 2009/41/EC is implemented in Swedish law in the Ordinance (2000:271) Contained use of GMO and in the Provisions (AFS 2011:2) Contained use of GMMs.
- Provisions for contained use of genetically modified organisms other than microorganisms are contained in the Swedish Board of Agriculture (SJVFS 2003: 28) and (SJVFS 2009: 89) and in the regulations of the agency forMarine and Water Management (FIFS 2004: 2).
- In Sweden there are several authorities in the GMO area. The SWEA are the responsible authority concerning GMMs. GM plants and GM animals (including for instance GM mice and nematodes) are regulated by other authorities (the Swedish Board of Agriculture (Jordbruksverket) or the Swedish Agency for Marine and Water Management (specifically for activities involving GM fish). When GMMs are used in association with GM plants or GM animals, an authorization is issued by the Jordbruksverket for the plants or animals. SWEA authorizes the use of GMMs only.

Furthermore, SWEA is all responsible for enforcement of the provisions of the CU of GMM. In case GMMs are used in association with non-modified as well as GM plants or animals the Jordbruksverket receives the first confirmation letter in copy. In some cases (a (new) moss, fungus/mushroom or worms/nematodes) the authority will be assigned based on the most appropriate containment for that specific organism.

- All GMO detailed regulations are scattered between different authorities that have expertise in the respective field (see above); thus, contained use of GMMs is handled by SWEA simply because notification of unmodified microorganisms (biological agents) are handled by SWEA. But the rules of AFS 2011:2 still fall under the Environmental law. AFS 2011:2 has a wider scope than other occupational health/work environment regulations. There are similarities, but in the occupational rules, only human pathogens are covered. The GMM rules on the other hand, covers also animal and plant pathogenic GMMs as well as GMMs not pathogen to any organism or dangerous for environment when the GMM can cause harm to workers. The purpose to include GM as well as non-GM at the different authorities is to minimize administrative burdens to the GMM/GMO user.
- Contained use of other GMOs than GMMs are often notified by other systems/frameworks:
    - Facility needs always a permission or permit;
    - GMOs need to be notified, but must be assigned to a permitted facility.
- For gene therapy, clinical trials and authorization of other GM medical products, the responsible authority is the Läkemedelsverket (MPA – Medical Products Agency). Most clinical trial applications are handled as deliberate release since about 10 years ago. Sweden has no laws that allow keeping a person or patient contained during a gene therapy/clinical trial. SWEA is consulted for parts related to contained use and/or workers protection (e.g. preparation and administration of the GMM).
  There may be cases where contained use is more appropriate (in veterinary medicine) in Sweden. Animals can be kept in containment according to law.
- In general the scientific infrastructure and the type of (GMO) activities conducted are similar between SW and NL.
- In AFS 2011:2 it is stated that, when notifying contained use of GMMs, the names and qualifications of person's) responsible for (bio)safety and health must be included. These persons are not allowed to start contained use activities if these details are not included in the notification (or when asked for). The level of detail is dependent on the request class: the higher, the more details are needed.
- The exact roles and tasks of actors and the assignment of corresponding responsibilities are not stipulated in detail in AFS 2011:2. In Sweden a wide diversity among the (types of) users/employers exists. According to Swedish legal tradition there are no detailed rules how an employer should organize its work. But the requirements on roles/tasks/functions

are laid down; someone must be designated as responsible (if not delegated, it is the CEO).
Other regulations, on a basic level, stipulates that the employer must have sufficient knowledge, either within the organization or with help from experts outside the organization (Work environmental laws). All responsibility, also within the Environmental law, is on the user/employer or “licence holder”, i.e. the organization that usually has delegated internal responsibilities appropriate to its organization.
For GMMs, three distinct cases of organizations can be distinguished:

- Universities and other research institutes
- Small/intermediate biotech or medical companies
- Schools

The organizations differ both in size, available resources and purpose for the contained use of GMMs.
For any work, the responsibility is on the user/employer how to organize its internal responsibilities. The responsibilities are in the different laws and regulations, but how to organize is up to each employer/user.

- In Sweden there are no specific provisions regarding an internal biosafety management system. Nevertheless in general all large organizations (mainly universities) have installed an internal biosafety committee and also have appointed a so-called work leader who is responsible for the general oversight of the contained use activities within the institution. This is required for a notification. Other laws covers the requirements and obligations for responsibilities and knowledge.
  Different GMM users have solved the responsibilities in different ways, depending on their own organization. Sometimes, two persons have different responsibilities; one can have direct, delegated, employer responsibility as “work leader” and the other can have more (bio)safety responsibilities. Sometimes a central responsibility for environmental issues are assigned, and this person is usually not the same as the person responsible for occupational health/work environment.

Procedural aspects and processing of applications for contained use

- In Sweden an activity is defined as the total of all physical and organisatory frames for the work with GMMs. This system is closely linked to the different tables of activities in Annex IV of Dir. 2009/41. Within this framework a notification for first use consists of a combined assessment of both the facility (premises) and the planned activities with the GMM(s).
- One or more activities may be conducted at a site:
  - Same or different containment level
  - Same or different nature of activity
  - Same, or partly same or different (part of) premises where different organization parts use the same facilities such as a cell

lab, a freezer, an autoclave, a dish room. Also getting rid of GMMs is included in the "activity" (or "verksamhet"[18]).

- A GMM-use consists of
  - one (type of) receiver/GMM
  - one (type of) vector
  - one (type of) insert
  - one (type of) use
- SWEA considers as a new GMM use[19] when another receiver/GMM or type of vector (e.g. lentiviral vectors instead of adenoviral vectors) or type of insert will be used OR another type of activity or safety measures needed. If a GMM is used in a "laboratory activity" and then will be used in an animal, a new notification of the GMM in animal must be submitted. The notification can be either a new "GMM in animal activity" or a new use in an already notified "GMM in animal activity". When a GMM will be applied in association with a GM animal two separate notifications need to be submitted to different authorities[20]. A GMM that will be applied in association with a GM animal, needs to be notified to SWEA as a "GMM in animal"-activity/use. The animal facility must be permitted from Jordbruksverket, and GM animals needs a permission as well as non-modified, both for research and for breeding. Swedish animal welfare rules also include ethical permission for animal research projects.
- Sweden has a list in AFS 2005:1 (biological agents 2000/54/EC), which is planned to be updated and into force November 2018. The criteria for classification are also included in AFS 2005:1. Both are legally binding. In AFS 2011:2, the user is obliged to determine whether the GMMs are still in the wild type risk group or not, due to the different modifications that may be included for each unique contained use of GMM.
- In Sweden separate application forms are available for each safety level. The risk assessment[21] should contain the appropriate documentation and a description of the safety and containment measures. All notifications

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[18] SWEA may not use "activity" in the same way: In Sweden "verksamhet" is the facilities/premises + the organization part (responsible person) that is adapted to the GMM uses within the "verksamhet". The GMM uses may belong to the same research project or different projects, especially in containment level 1 where SWEA allows a whole department to notify only one "F-verksamhet" (laboratory activity) for all work – if they do it in the same premises. In some cases, even large departments do this and in other cases, they notify one "F-verksamhet" (laboratory activity) for each research group. In the latter case an overlap of the premises/facilities is unavoidable regarding autoclave, cold storage, apparatus rooms and other "common shared" rooms at the department.
SWEA also allows a department to notify only one "L-verksamhet" (containment level 2) serving the whole department, but each research group then will notify their own "GMM uses". This is common when it comes to an "animal activity" (GMM in animals), where the animal facility usually has one responsible person not belonging to a specific department but when the facility serves the whole university. Each researcher must then notify their GMM in animal within the already existing "L-verksamhet". This provides a tool for better internal control of who performs GMM work in the animal facility.

[19] A "first notification" can come with one GMM use or 20 GMM uses, depending on the notifier. In some very rare cases the notifier has notified the facility without a first use. But a notification is limited to one type of activity; EITHER laboratory activity OR animal activity OR plant activity OR large scale activity OR "other" acitivity (mostly waste companies).

[20] Jordbruksverket has information about this, but in Swedish. Please follow this link:http://www.jordbruksverket.se/amnesomraden/djur/olikaslagsdjur/forsoksdjur.4.7850716f11cd786b52d80001724.html.

[21] The risk assessment part of the form includes:
-risk analysis
-risk assessment
-conclusions of risk assessment i.e. what safety measures are necessary, as well as assignment to containment level and activity type.
Assignment to a containment level/activity class F-verksamhet, L-verksamhet or R-verksamhet.
Assignment to activity type: GMM in laboratory activity, GMM in animal acitivity, GMM in plant activity, GMM in large scale activity, GMM in other activity.

will be confirmed by the authorities whether the notifications were correct. If needed additional provisions may be imposed in the same document.

- A notification for F- or L-activities may be sent back and forth between SWEA and the applicant until it is considered as fulfilled regarding the requirements in AFS 2011:2 (Annex 3 or 4).
- No “uses” or GMMs are notified for F- or L-activities, neither before first use or subsequent use. Only a designation to what “organism group” (bacteria/viruses/fungi etc.) a GMM belongs is required. The user must always keep record on every contained use risk assessment and the records must be available on request, either when notified or when inspected.
- The risk assessment needs to be in conformity to the provisions laid down in AFS 2011:2Annex III of Dir. 2009/41. The documentation of the risk assessment should be kept “in-house” and is not to be submitted with the notification. Only for permission (containment level 3 and 4), the documentation must be included in the application.
- The level of detail of the required information in the notifications/permits is dependent on the proposed level of containment. In general a broader description of the GMMs or its components (parent organisms, vector or insert) is accepted. For example, it is acceptable to describe that E1/E3 deleted adenoviral vectors are applied without supplying maps of all plasmids and cell lines involved in the production. Recently new forms were made available that ask for more detailed information regarding the inserts and vectors used in order to limit the number of requests for additional information, in particular for Class 2 notifications.
- In Sweden a permit is valid for 3-5 years, notifications can be indefinite. The procedure for class 3 and 4 authorisations takes a maximum of 90 days.
- Contained use of genetically modified micro-organisms (GMMs) is divided into F, L and R activities depending on risks. The different activities have different requirements for authorization and notification and are regulated by the Regulation (2000: 271) on the contained use of GMOs:
    - F activity concerns contained use of GMM with negligible or no risk to human health or the environment. The operation must be reported, but new use within the business need not be reported;
    - L activity concerns contained use of low-risk GMM for human or environmental damage. The operations must be reported, as well as any new use in activities that have previously been reported;
    - R activities include contained use of GMM with moderate or high risk to human health and the environment. The operations must be licensed, as well as any new use in activities previously granted.
- The application forms used in SW in more detail:
    - For class 1 activities the so-called F-form is used. For F activities no specific risk assessment needs to be submitted, only the conclusions/outcome of the risk assessment. The focus is on

protective measures when F activities are notified, and to the actual GMMs. The applicant has full responsibility for a proper classification of the GMMs. Contact details and competence must be provided for the responsible person(s) for supervision and safety.

- For class 2 activities a so-called L-form is used. In addition to the information required for F-activities, in case of notifying a L activity, the applicants needs to include contact details of the person responsible for supervision and/ or safety for each GMM use[22],[23]. Furthermore details of the GMM (recipient organism / vector / insert) and its use need to be included.
- For classes 3 and 4 a so-called R form is used. Again the information requirements for the L activities also apply for R activities. In addition information and detailed description of the R activity is required as well as a more detailed description of the protective measures and a contingency plan where necessary.

IT-systems and public access

- In SW the full process (including submissions of notifications and sending authorizations) is almost completely digitalized. Only occasionally a notification for a R-activities or uses (Class 3) is submitted on paper. These will then be digitalized upon receipt by the SWEA.
- SWEA reviews risk assessments. It is the users/notifiers responsibility for assess risks properly. SWEA only review the notifications to determine whether they fulfil notification requirements and that the safety measures seem legitimate.
  Sweden has a public access policy; all official documents are public unless law states something else. For this purpose, all notifications are kept in an archive, like any other (GMM) issue reaching or going out from authorities. All these records are digitalized since 2015 at SWEA. However, to keep track of all individual Contained use-activities at different users (usually the employer, such as a university), that may have over 50 new notifications or updates for a single activity, the archive system is not enough. Therefore, SWEA has another system to distinguish the uses, activities and users/applicants/employers. That system is not public.
- SWEA use IT systems to support the registration, processing and archiving notifications and applications. These IT-system are custom

[22] The Work environment law (occupational health) and the Environmental Code prescribe the general responsibility for anyone doing something potentially environmental or health damaging. To get a functional organization, the user/employer may want to assign all environmental responsibility to one person or office. How it is done depends on the organization. A university with many departments using GMMs may have one central BSO-like/biosafety committee function. A small startup biotech company may assign the CEO for all responsibilities.

[23] In Sweden a researcher may have several GMM uses in his/her project. All may be notified when a new L activity is notified, but can also be notified subsequently in an already notified L-activity. It is not necessary that each researcher has his/her own L-activity. The department can notify an “umbrella L-activity” where the head of the department is responsible for supervision and safety in general and the project leaders are responsible for his/her own GMM uses within that activity. It usually comes along with responsibilities under the work environment legislation

made. One system concerns a GMM register, only accessible by the GMM officers at SWEA. The system is designed for keeping track of all GMM-activities and GMM-uses that has been notified and those with permission. It is both a tool for the GMM officer/inspector and a surveillance register. GMM activities or GMM-uses that are notified/applied for but the handling is not finished can be tracked, as well as ongoing and closed activities or uses. The register allows easy updating of minor changes and addition of subsequent uses. It is searchable and a list of non-confidential information may be provided by request.

- In SW in conformity to laws on openness and public access notifications need to be registered in a system and archived. The basis is that everything is public, unless a law states otherwise. SWEA uses a 100% electronic web based system which is based on the commercially available platform Public 360 and what is adapted to the needs of SWEA. The general public has no direct access to this system, but access to individual notifications may be granted upon request. Anyone can search among archive records online[24], including notifications etc. concerning GMMs. The documents are not available online, but on request (provided that these documents are not deemed as secret by law).

[24] https://www.av.se/om-oss/sok-i-arbetsmiljoverkets-diarium/

Annex 7: The Netherlands

Short description of Bureau GGO (GMO Office)

- Dutch GMO Office / Bureau GGO (BGGO) is based at the National Institute for Public Health and the Environment (RIVM) and is part of the Centre for Safety of Substances and Products.
- BGGO is the executive office for the Ministry of Infrastructure and Water management (IenW) concerning the environmental safety of GMO's. BGGO carries out some legal tasks within the framework of national and European legislation and international conventions on genetically modified organisms (GMOs) as commissioned by the ministry
- BGGO assesses the notifications for contained use and carries out the licensing of activities with GMOs. For the deliberate release of GMOs as field or clinical trials and market applications, BGGO is charged with all substantive preparations such as the risk assessment. In addition, BGGO is the focal point for all parties involved in work with GMOs, and supports the Ministry of IenW in the development and execution of their policies on biotechnology. BGGO functions as the link between policy / regulation and organizations conducting activities with GMOs and provides information to stakeholders.
- BGGO also acts as the gene therapy office and the Food Feed office for GMO market permits. The aim of the gene therapy office is to coordinate and streamline licensing and licensing procedures for clinical gene therapy research in the Netherlands and to make the procedures for the researchers insightful. The purpose of the Feed Food office is to act as focal point for all European market applications submitted in the Netherlands. In addition, the office is the national contact and information point for applicants for market access.
- BGGO is authorized to issue permits/decisions on contained use of GMO's. Furthermore BGGO also advises local authorities when they handle an application for classification of a facility for GMO activities. BGGO has no enforcement mandate.
- Within BGGO 9 risk assessors are involved in handling and assessing contained use, and 5 people with deliberate releases (plants and clinical/veterinary uses). Furthermore, 2 people are involved in information management and IT management support and 2 secretaries.

Legal frameworks and structures concerning Contained Use

- Dutch framework: In the Netherlands European Directives 2009/41 and 2001/18 are implemented in the GMO Decree and GMO Regulation (Ordinance) and covers all types of GMOs (not only GMMs). The Ministry for Infrastructure and the Environment is the competent authority on the biosafety of GMOs and has final responsibility for the laws and execution of the legal rules. The GMO Office is mandated to issue decisions on

contained use (600-800 first use and subsequent use combined annually).

- The Commission on Genetic Modification (COGEM), established by law, advices on request the competent authority on biosafety issues and safety recommendations. The COGEM is requested for an opinion for assignments of risk groups of donor and recipient organisms, novel applications and/or developments or general safety recommendations (40-50 requests annually). All COGEM publications are made publicly available. In principle meetings/sessions of the (sub)committee(s) are open to members of the public, but only upon request. Summary records of those meetings are also in principle non-confidential, but are not actively publicly available (only upon request).
- In principle all decisions on contained use in NL have no specific expiry date.
- To employ contained use in NL two permits are needed independently, one for the facility/premises issued by the local authority and one for the activities with the GMOs issued by BGGO.
- Besides the regular risk assessment procedure as laid down in Annex III of 2009/41, NL also prescribes a standardized risk assessment. This standardized RA is part of the GMO Ordinance as Annex 5 and its use by applicants is obligatory. Linked to this Annex 5 are additional appendices (2, 4, 7). The outcome of this RA determines the risk group and therefore also the legal procedure. If a particular GMO and/or activity cannot be classified according to Annex 5, a full general RA in conformity of Annex III of 2009/41 is needed.
- The Dutch GMO Ordinance contains several lists: a list of apathogenic microorganisms (Annex 2-list A1), a list of microorganisms and their risk (pathogenicity) group (Annex 4) and a list of plants grouped according their characteristics for dispersal (Annex 7). Furthermore Annex 2 – list A2 contains a list of vectors that are classified safe for general use (Class 1) and Annex – list A3 that consists of criteria for donor sequences classified as safe for general use (Class 1). The combination of lists A1-A2-A3 results in GMOs with risk group 1 and applications are no longer obliged to conduct a RA for these GMOs (internal registration of specific GMOs is still required for enforcement purposes).
- Specific GMOs are listed (Annex 11) for educational purposes (e.g. pGLO in the Biorad education kit) which are exempted from a permit for the GMO facility. Thus only a notification on level 1 is required.
- The internal organization within companies or institutions carrying out contained use activities is regulated in the Ordinance. The board of directors has the final legal responsibility and is required to appoint a biological safety officer (BSO) and a responsible scientist or project leader (VM). BSOs are accredited by BGGO and VM for level 3 and 4 are registered by BGGO. Besides being the most important contact person for BGGO, the BSO has an independent position within the organization and is responsible for the internal biosafety management system. In this

capacity the BSO controls the responsible scientists and advises and reports to the operator.

- In NL there is no legal link between activities with GMO's or (wild type) biological agents. In general the provisions for GMO's are considered to be more strict than for biological agents.
- Gene therapy clinical trials are considered as deliberate releases of GMO's and thus fall under the scope and procedures of Directive 2001/18/EC. The rationale is that although the patients themselves are not subjected to genetic modification, the cells or viruses that are administered to the patients are GMO's. Currently naked DNA applications in a clinical setting are considered as deliberate release as well.

Procedural aspects and processing of applications for contained use

- General procedure in NL:
    - All applications (500-800 annually) are sent to BGGO.
    - All received applications are given a file number and are acknowledged upon receipt. The content is then examined and considered whether all information is delivered and specified to conduct the risk assessment.
    - If needed the procedural clock can be stopped for requests for additional information. The procedural clock cannot be stopped in case (also) COGEM will be requested for a scientific opinion.
    - BGGO is not obliged to follow COGEM's advices. However, in general BGGO acts on their advice or need to clearly substantiate when BGGO acts against a specific advice or particular recommendation.
    - BGGO will register the notification and the risk assessment and prepares a decision on application (and no notifications).
    - BGGO sends the decision to the applicant. If COGEM was requested for an opinion on a particular application, the related COGEM advice will be included.
- Several GMO-uses may combined in a single notification or application as long as these activities can be classified in the same safety class (e.g. class 2).
- Separate application forms are available for each safety level.
- The application form(s) used in NL in more detail:
    - GMOs and their components and their use need to be described in relatively detail. GMOs to be used in containment class 1 or 2 GMOs with an identical risk profile may be combined and submitted as a group. For activities on class 1 a broad description of the GMO activities suffices. Neither is necessary a full description of all GMOs since for class1 the responsibility of a complete registration leis with the operator.
    - The applicants need to submit data on the GMOs (recipient organism / vector / insert / use) in all forms. In all forms this information is registered in a set of tables which setup is identical

for all application forms. Depending of on the safety class of the activities more detailed information on the biological materials and/or use is needed in the form on additional questions.

- All application forms need to be signed by a person legally authorized to act on behalf of the company, the BSO and in case of permits also the principal scientist.
- For activities on class 1 on class 1 only exemplary GMOs need to be submitted as it is the responsibility of the applicant to have a complete registration of all GMOs used on safety level 1. All physical containment classes (CFI) need to be notified, also when in subsequent use work other CFI's will be conducted.
- For activities on safety levels 2 and higher details of all GMOs and their use needs to be submitted and will be checked by BGGO. The risk assessment focusses on the safety of the resulting GMO and if the relevant CFI ensures sufficient containment or whether additional protective measures may be needed.

IT-systems and public access

- The provisions article 18 of Dir. 2009/41 regarding information that in no case can be kept confidential are implemented in the GMO Decree. Besides this information, in principle all non-confidential information on GMO dossiers are passively publicly accessible (upon request). In the near future this information will probably also be made accessible on the BGGO webpages.
- In NL non-confidential information and documents in dossiers in the IT system GRIP are exported to a website with database with public access. BGGO is currently updating this system. When updated all contained use notifications and applications will be publicly accessible.
- Since 2015, all notifications are to be submitted electronically via DigiD/Berichtenbox. This is a general
- BGGO uses an IT system based on the Sharepoint 2007 platform which is heavily adapted called GRIP. Because GRIP is also used as a case management system for a consistent semi-automated processing and evaluation of notifications and applications, it also has some important additional functions, such as case management with process control, document management, account management. All these modules are interlinked with the central module dossier management.
- BGGO has a good understanding with the biosafety professionals and interacts with this group frequently. Due to the IT system there is an actual and accurate overview of active biosafety professionals. In cases of important developments (e.g. the new rules on gene drives) the group of BSO's are actively informed. BGGO also has frequently meetings with biosafety professionals regarding the daily practice and discusses (general) practical and procedural issues.