

GUIDANCE ON CONTAINED USE OF GENETICALLY MODIFIED MICRO-ORGANISMS (GMMs)

This guidance is published by the Swedish Work Environment Authority on how to comply with the rules concerning contained use of GMMs.

The genetic modification of micro-organisms can entail hazards to both human health and the environment. The Swedish Work Environment Authority is the Competent Authority charged with supervising contained use of GMM in Sweden. The Authority's main task is that of a supervisory authority for the work environment, but in the present instance it is also tasked with supervising human health and the environment in general.

Under existing legislation, all contained use of GMMs must be subjected to a risk assessment and, with a few specified exceptions, must be notified to or permitted by the Swedish Work Environment Authority. The risk assessment forms the basis of the containment and other protective measures which the user need to apply for the prevention or counteraction of harm to human health or the environment.

Because the rules on contained use of GMMs are voluminous but scattered between a variety of instruments, the Swedish Work Environment Authority has compiled forms and an exhaustive guide in Swedish to simplify matters for those tasked with carrying out risk assessments, submitting notification or applying for permission. This English version is intended solely as an overview of the content of the more extensive guide in Swedish, [which can be accessed here](#).

Please note that this guide is information material and does not have the legal status of Provisions or General Recommendations.

Rules for contained use of GMMs

The national rules on contained use of GMMs are based on EC Directives. The Directives governing the legislation of the Member States on biological substances and contained use of GMMs are minimum Directives, which means that stricter rules are permissible. Implementation of Directive can vary somewhat from one legal system to another, depending on the individual legal traditions of the different Member States. A conspectus of Swedish legislation on gene technology can be accessed through the website of the Swedish gene technology authorities, <http://www.gmo.nu/>. English translations of rules issued by the Swedish Work Environment Authority (and the National Board of Occupational Safety and Health) [can be accessed here](#). The Provisions of the National Board of Occupational Safety and Health on Contained Use of Genetically Modified Organisms (AFS 2000:5) are available in translation. The Provisions of the National Board of Occupational Safety and Health on Biological Agents (AFS 1997:12) remains untranslated, pending their harmonisation with Directive 2000/54/EC. The rules issued by the Swedish Work Environment Authority are divided into Provisions, which are peremptory, and General Recommendations (Guidance), which do not have the legal status of Provisions. The Recommendations are not peremptory but are intended to



elucidate the Provisions, e.g. by explaining suitable ways of complying with their stipulations, by instancing practical solutions and procedures, and by making recommendations and providing background information and references.

Definitions

The Environmental Code (SFS 1998:808) defines **contained use** as: "an activity in which organisms are genetically modified, cultured, stored, used, transported, destroyed, disposed of or used in any other way, and for which specific containment measures are used to limit their contact with the general population and the environment."

The Genetically Modified Organisms (Contained Use) Ordinance (SFS 2000:271) defines a **genetically modified micro-organism** (GMM) as : "a micro-organism whose genetic material has been altered in a way not occurring naturally through mating or natural recombination."

Micro-organisms include, for example, bacteria, blue-green algae, virus, viroids, prions, micro-fungi, micro-algae, protozoa and cell cultures of superior organisms.

GMMs may not be released into the environment without permission. Failing such permission, specific containment and other protective measures have to be applied in order to limit contact between the organisms and the general public or the environment. It is neither reasonable nor necessary for maximum protective measures to be applied to all contained uses of GMMs. Every GMM use must therefore be subjected to risk assessment, so as to determine which containment and other protective measures are needed for the prevention of harm to human health and the environment.

What must be done?

The user (environmental legislation's equivalent of the employer in work environment legislation) is ultimately responsible within an organisation (e.g. a business undertaking or a university) and must see to it that the following steps are taken wherever GMMs are used within the organisation:

Each individual GMM use is assessed for risk and the assessment documented.

Containment and other protective measures have been chosen and applied according to the results of the risk assessments.

The activity has been classified by containment level (1-4) and category (F, L or R).

The activity involving the use is notified or permitted.

The individual use is notified or permitted, if notification or permission is needed.

Verification of these matters devolves on the Swedish Work Environment Authority.

Risk assessment of use

Under Chap. 13, Section 8 of the Environmental Code, contained use of GMMs must always be preceded by an investigation. This investigation shall form the basis of assessment concerning the harm which the organism is capable of causing to human health and the environment. The term risk **assessment** as used in this guide denotes the investigation and the assessment to be based on it.

The procedure for risk assessment is described in App. 1 to the Provisions AFS 2000:5. Further guidance on risk assessment is included in the Recommendations accompanying App. 1, AFS 2000:5.

Contained use of GMMs is subject to various stipulations concerning accounting, notification and permits. Some form of systematisation is required, enabling the user and

the authority to refer to what has been notified or permitted. The key terms in this connection are **use** and **activity**.

A use includes, not only a GMM but also the manner of its use. One and the same GMM can pose different risks, depending on how it is used. Use is the defining unit subjected to risk assessment. The containment and other protective measures taken on the basis of risk assessment are intended to prevent the use from causing harm. Relevant delimitation of use is therefore important.

[Read more about delimitation of a use and about risk assessments](#)

Containment and other protective measures and level of containment for contained use

The risk assessment forms the basis for determining which containment and other protective measures are needed. App. 3, AFS 2000:5 gives tabulated examples of containment and other protective measures at four containment levels for different types of activity. The level of containment is decided by comparing the containment and other protective measures determined for the use with those required at the different containment levels.

[Read more about containment and other protective measures and level of containment](#)

Activity – an administrative concept

A use always forms part of an activity, which in this context is an administrative concept. An activity belongs to an organisational unit, is conducted in a delimited facility at one single containment level and is of a certain type (e.g. laboratory activity or large-scale activity). A number of activities may occur under the direction of one and the same person, e.g. in a university department. If details of an activity have been submitted previously, notifications of new uses within that activity can be made simpler.

Classification into one of the administrative categories F, L or R activity

Once the containment level of the use has been determined, its activity category can be identified from the criteria in App. 2, AFS 2000:5. The activity category indicates the administrative procedure to be applied:

F (negligible risk) = cl 1	notification of the activity (new uses must be assessed for risk but need not be notified)
L (low risk) = cl 2	notification of the activity notification of every new use in the activity (can be started as soon as a complete notification has been submitted)
R (hazardous) = cl 3 and 4 and large scale cl 2	permit for the activity permit for every new use in the activity

Notification and permit applications

Apps. 4-6, AFS 2000:5, show the information to be provided in connection with notification or application for a permit. The Swedish Work Environment Authority has compiled forms to facilitate the structuring of information for risk assessment, containment and other protective measures, notification and permit applications concerning activities and uses. These forms are available in Swedish only, but the information can of course be provided in English. Note, however, that only the Swedish printed version of the AFS 2000:5 Provisions is legally valid. Before notifying or requesting a permit for contained use of GMMs, persons responsible need to be contacted within the organisation in which the activity is planned.

Continued contained use of GMMs

The person conducting activity with contained use of GMMs must continuously and systematically supervise compliance with rules of the Environmental Code, rules issued pursuant to that Code (AFS 2000:5, for example) and rules issued by authority of the Work Environment Act, so that no harm will be caused to human health or the environment.

Self check

The Environmental Code contains rules of self check for activities to which it refers. Activities notifiable or requiring a permit under the Code are also governed by the Managements Self-Check Ordinance (SFS 1998:901). Among other things, those rules require documented allocations of responsibilities, routines for the ongoing inspection of equipment and notice to the supervisory authority concerning any change of conditions which may be prejudicial to human health or the environment.

Systematic work environment management

Systematic work environment management is the equivalent of internal control in the work environment context. The rules on this subject are specified in the Provisions of the Swedish work Environment Authority ([AFS 2001:1](#)) on Systematic Work Environment Management.

Persons to contact at the Swedish Work Environment Authority

If you have any questions concerning contained use of GMMs, feel free to contact one of the following handling officers at the Swedish Work Environment Authority:

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Thorleif Joelson, tel. +46-8 - 730 90 66, thorleif.joelson@av.se

Each individual use of GMMs needs to be subjected to risk assessment, and the assessment documented. To facilitate risk assessment documentation, the Swedish Work Environment Authority has compiled form BA – Risk Assessment. That form will be found in section 7 of the Swedish guide.

RISK ASSESSMENT OF CONTAINED USE OF GMMs

What is “a use”?

One use may be distinguished from another by the use of a different GMM or by the same GMM being used in different ways.

Use is the defined unit which is assessed for risk. The containment and other protective measures taken on the basis of the assessment are designed to prevent the use from causing harm. Much therefore depends on a relevant delimitation of use. One and the same GMM can constitute different risks, depending on how it is used.

The description of use must be framed so as to make clear



what is included and sometimes also what is not included. It is essential for the risks assessed to be comparable in terms of probability, consistence and type. In research, for example, it is common for many genetic modifications to be made to the same micro-organism without the assessed risk of the use being affected. A biological system of this kind can be regarded as one GMM if it can be described in a clear and delimited manner. It is important for the risk assessment of complex uses to really include all cases which may exist within the delimitation. If a "worst case" deviating from the rest can be found within the delimitation, the delimitation has probably been made too broad.

Definition

Section 2 of SFS 2000:271 defines new use as:

"a contained use of genetically modified organisms in a previously notified activity which, compared with the activity notified, differs in a not insignificant manner with regard to the genetically modified organisms used or with regard to the methods for producing or using the organisms."

All uses included must be risk-assessed with sufficient competence

The user shall have access to the competence needed for an all-round risk assessment (Section 3 of AFS 2000:5). In larger organisations it may be appropriate to set up a biosafety committee or a network of experts within the organisation to meet this requirement. For risk assessment of uses where one's own competence is not sufficient, specialists may need to be consulted outside the organisation. See also the guidance on Section 3, AFS 2000:5.

Risk assessment methods

App. 1, AFS 2000:5, describes the procedure to be followed for risk assessment. The user of a GMM usually carries out some form of risk assessment, consciously or otherwise. Documentation of the risk assessment and procedure as shown in App. 1 enhances the structure of the assessment and awareness of different factors affecting the risk. See also the guidance on Apps. 1 and 5, AFS 2000:5.

The various components included in a GMM are described separately and collectively. This methodology applies regardless of whether one is using a "ready-made" GMM or constructing one. As the law now stands, the fact of a GMM being commercially available does not mean that it has been tested and proved harmless. Adequate information therefore has to be demanded and obtained from the supplier or seller of a GMM. Simple uses of well-characterised, frequently used organisms do not normally require such detailed risk assessments as complex uses involving less well-characterised and perhaps more hazardous organisms.

The complexity of a system can be illustrated with the following examples:

A cell is infected with a virus which has cloned nucleic acid in its genome. Here the virus appears in two capacities, namely as a GMM and as a vector for the cloned nucleic acid in the cell. The cell in turn becomes a GMM through the infection. Depending on the system, a new virus may be produced by the modified cell. If the cell genome is not modified, the cell can in certain cases be regarded as a substrate for the GMM virus, just like the nutrient solution in an agar plate for bacterial growth. If the nucleic acid of the cell is modified genetically and the cell subsequently used without the virus present, this modified cell is

regarded as a GMM in its own right, and its use has to be separately assessed.

In this example there are two “part-GMMs” with different host organisms: the virus which infects and the cell which is modified. Because virus GMMs often have far greater distribution capacity than the cell which is infected, it may be natural in the assessment of risk for greater importance to be attached to the modified virus. There are, however, instances of immunologically active cells from infected patients being expected to integrate with a virus GMM. In assessing the risk of such use, the risks associated with the cell may predominate, in such a way that the choice of containment and other protective measures will be dictated predominantly by the hazards of the infected cells.

Overall assessment and choice of GMMs for use

In the final assessment, all factors have to be balance together, e.g. potentially harmful effects of GMMs, including their constituent components, and the likelihood of those effects occurring. An important role is played by different procedures and conditions which use involves. The assessment is to be based on conceivable consequences of the GMM escaping beyond the primary or secondary containment, e.g. if someone pricks themselves or the GMM invades the immediate surroundings. If the potentially harmful effects are great, then in certain cases strict containment and other protective measures may be needed even if there is little likelihood of the effects occurring.

The possibility must also be considered of using a less hazardous GMM to the same end. Section 6, point (a) of AFS 2000:5 lays down that the first recourse in planning shall be to selected GMMs entailing as little risk to health and the environment as the activity permits.

The Swedish Work Environment Authority has designed a form, BA – Risk Assessment, to facilitate documentation. [The form and an accompanying guide are available here.](#)

It is important that everyone using a GMM should be aware of the limits of the use which has been subjected to risk assessment. The risk assessment documentation therefore needs to be available and to be continuously reviewed and updated. A new assessment may be necessary for every new use. If the new use differs in certain respects only from a use already subjected to risk assessment, the new assessment can be confined to the possible risk implication of the difference. It must also be borne in mind that there are risk factors which were not foreseen in the original risk assessment. Notes need to be kept, showing that comparisons with the original risk assessment are being made continuously.

See also Section 5 and App. 1, AFS 2000:5, and guidance on the same.

Other guides on risk assessment in connection with contained use of GMMs

Further guidance on the risk assessment required under the Directive on Contained Use of Genetically Modified Micro-Organisms is obtainable from the European Commission guidelines (2000/608/EC). http://europa.eu.int/eur-lex/pri/en/oj/dat/2000/l_258/l_25820001012en00430048.pdf

The Belgian website <http://biosafety.ihe.be> has links to several sites offering useful guidance on matters of biosafety, such as the British Health & Safety Executive (HSE), whose Advisory Committee on Genetic Modification (ACGM) has uploaded a compendium on implementation of the British rules concerning GMMs. Those rules, like Sweden's, are partly based on Council Directive of 23 April 1990 on the contained use of genetically modified micro-organisms (90/219/EEC), as amended by Council Directive 98/81/EC. It is possible for the EU Member States to have stricter legislation. Sweden's legislation on

contained use of GMMs and Britain's are not identical, but the compendium is nonetheless extensively applicable to Swedish conditions, especially those parts of it relating to risk assessment.

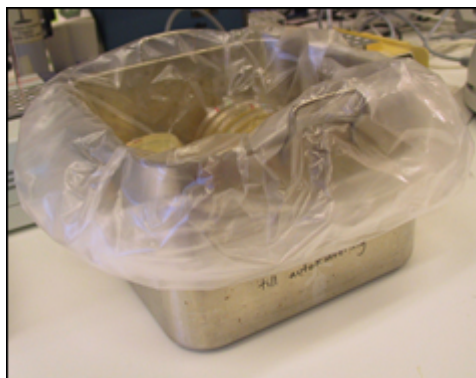
The compendium can be downloaded in PDF format from:
<http://www.hse.gov.uk/infection/gmo/acgm/acgmcomp>.

CONTAINMENT AND OTHER PROTECTIVE MEASURES AND CONTAINMENT LEVEL

Assessment of containment and other protective measures needed

The Ordinance (SFS 2000:271) defines a protective measure as a containment measure or other precaution taken to avert, prevent or counteract the harming of human health or the environment by the activity.

All GMMs, unless a permit has been granted for their release into the environment, must be contained by means of containment and other protective measures adapted to the potential risk of harm to human health or the environment. Since it is not a realistic proposition for all use to proceed at a maximum level of containment, containment and other protective measures have to be chosen which are appropriate to the specific use. In order to arrive at an objective and, from the viewpoint of risk, appropriate choice of containment and other protective measures, a preliminary choice should be made solely on the basis of the risk assessment and with no regard for administrative stipulations or established containment levels.



App. 3, SFS 2000:5 contains various tables indicating containment and other protective measures for different types of activity. Those containment and other protective measures comprise primary measures for the protection of persons coming into contact with the organisms in the course of the work, and secondary measures for the protection of the general public and the environment outside the work zone. The containment and other protective measures comprise the design of premises, technical equipment, work routines and organisation.

An account of containment and other protective measures can be given by completing form [S – Choice of Containment and other protective measures](#), which is based on the tables in App. 3. It is important that reasons for choosing (or not choosing) a containment or other protective measure should be given in the form, or else a description of how that measure is applied. Certain measures may sometimes be applied for reasons other than protection of workers or the environment.

Other containment and other protective measures than those stated in the table may sometimes be needed. In certain cases these may be apparent from handling and safety instructions. In the final choice of containment and other protective measures it must also be considered that there are general rules in the Provisions of AFS 2000:5 and good microbiological practice in App. 3 A which have to be complied with. Templates have yet to be provided for certain kinds of activity, e.g. clinical trials with gene therapy.

Determination of containment level for a particular use

A consensus view regarding suitable “packages” of containment and other protective measures at various containment levels for work with micro-organisms in activities of a similar nature has crystallised out of experience of such activities. These templates can simplify the selection of containment and other protective measures while still affording a reasonable margin of safety.

The tables in App. 3, AFS 2000:5, contain four columns, one for each of four containment levels. The column for each containment level indicates a number of obligatory containment and other protective measures and other measures which need to be applied on the basis of individual risk assessments. The column also indicates which measures do not normally need to be applied at the containment level concerned.

Containment level means that all obligatory containment and other protective measures at the containment level in question are applied as per the table in App. 3. Exceptions to the rule are subject to permission from the Swedish Work Environment Authority.

If a particular use requires application of a containment or other protective measure which is obligatory at a certain containment level, then normally the other obligatory containment and other protective measures at this containment level will also be needed. In cases where one of the obligatory containment and other protective measures at a certain containment level is judged unnecessary for the use intended, solidly founded arguments need to be presented in the application or notification to show why this protective measure is unnecessary.

Handling and safety instructions

Workers need to be issued with handling and safety instructions, to ensure that the containment and other protective measures are put into effect. These instructions need to be given in a language which the workers understand. Other persons doing work – such as cleaning or repair work, for example – which can entail exposure to GMMs also need to be informed about the risks and how to avoid them.

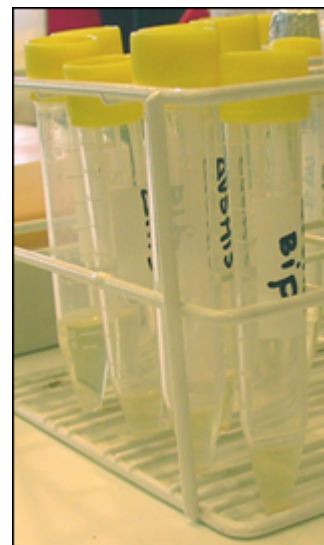
Large organisations may have standardised handling and safety instructions at different levels. For example, there may be certain routines of waste disposal which apply generally throughout the organisation, while there may be instructions common to a particular activity or activities within the organisation. In addition, supplementary, specially adapted instructions may often be needed for the individual use, depending on the risks which it specifically entails.

Written handling and safety instructions are obligatory at containment level 2 and upwards, but they may be needed in other cases too. Compilation of written instructions offers many advantages and can very well be made a part of regular quality management.

The recommendations accompanying Section 16 of AFS 2000:5 gives examples of important elements of handling and safety instructions, as well as further guidance.

EXPLANATIONS OF TERMS USED IN FORM BA – RISK ASSESSMENT

This is a guide to completion of the form [BA – Risk Assessment](#) for documenting risk assessments of contained use of GMMs. It is vital for the form to be completed in such a way that the most relevant components of the risk entailed by the use will be adequately illuminated. It is impossible to design a form containing completely fixed alternatives for every biological system. When describing complex systems it may sometimes be possible to use the same risk assessment form, with or without modifications, but otherwise separate forms are needed for different parts of the system.



The recipient organism (Mottagarorganismen)

Section 2 of AFS 2000:5 defines the recipient organism as:

- (a) an organism which has received foreign genetic material,
- (b) each of the organisms jointly contributing to a GMM in cases where it is impossible to tell which organism is the donor or recipient.

It is the properties that decide what can be counted as “one and the same recipient organism”. The possibility of different strains of one and the same species entailing very different risks is clearly instanced by the bacterium *Escherichia coli*. The designation *E. coli* is applied to everything from specially weakened *E. coli* K12 and *E. coli* B to enterohaemorrhagic *E. coli* O 157:H7 (EHEC), which requires specific containment and other protective measures at containment level 3. In this case, accordingly, the risk assessment has to include a strain definition of the recipient organism. In other cases, what are classified as two different species may on the whole be identical, as for example with *Mycobacterium avium* and *M. intracellulare*. The recipient organism must be unambiguously describable with regard to properties and identity.

It is important in GMM risk assessment to take account of harmful properties and properties with a bearing on the contexts or likelihood of manifestation of the harmful properties. Other properties such as disease mechanism, transmission routes and infection dose have a bearing on infection risk, while capacity for colonising many different animal or plant species is important in other connections.

It matters whether the recipient organism is a plant or animal pathogen, and also whether it is parasitic. The life cycle of the organism can be important, e.g. for retrovirus or sporulating bacteria. It is also useful to know where the organism occurs naturally and how resistant it is in different connections. One also needs to consider how and to what other organisms genetic material could spread from the recipient organism.

It needs to be ascertained whether the recipient organism is classified in a system of human, animal or plant pathogens. Classification under the Provisions of the National Board of Occupational Safety and Health (AFS 1997:12) on Biological Agents is always mandatory.

If the recipient organism used for the genetic modification is already a GMM, a documented risk assessment of that GMM is needed.

Genetic modification (Den genetiska modifieringen)

Genetic changes can be achieved through a variety of methods. Some of these have been in use for a long time and are considered to occur naturally, e.g. mutations caused by chemical or physical agents or conjugation. Genetic changes only involving “natural” methods of this kind do not come under the regulations applying to gene technology, but

of course may still need to be considered when assessing the risk entailed by contained use of GMMs. App. A to the General Recommendations in AFS 2000:5 offers guidance on the definition of GMMs, with examples of methods considered or not considered to result in GMMs.

The genetic material introduced (Det insatta genmaterialet)

There are instances of harmless recipient organisms being turned into pathogens by the introduction of plasmids or phages with virulence factors.

Genes which, for example, code for peptides with hormonal effects or other biologically active substances, receptor-binding sequences in virus or bacteria and toxins and carcinogenic factors are examples of harmful properties which can be added through the genetic material inserted.

If parts of cloned nucleic acid sequences are unknown, the likelihood should be assessed of the material containing genes which could impart harmful properties to GMMs.

Vectors (Vektorer)

Factors which may be relevant to the assessment of risk include, for example, the type of vector, how well it is characterised, its origin, the function planned, marker genes, copy number, transferability to other micro-organisms, recombination properties, host spectrum and integration properties in the host's nucleic acid. It should also be noted that a vector with genetic material inserted can in itself constitute a GMM.

Plasmids are also regarded as GMM when they are used for transferring genetic material. In a risk assessment of a plasmid-carrying bacterium, they will generally be presented as "vector". If so, an adequate description of the properties of the plasmid must be given under this heading.

Antibiotic resistance (Antibiotikaresistens)

Antibiotic resistance is a growing problem. It is imperative not to use genes which code for resistance to antibiotics which may be of importance in the treatment of diseases, and especially to avoid using genes which confer resistance to preparations of last resort in the treatment of multi-resistant bacteria. A certain resistance gene can imply different risks, depending on which host organism it is inserted into. It is important to consider the possibility of removing resistance genes which have been used in the production of a GMM used as a production organism in large-scale production.

Further information concerning, for example, which antibiotics are used in human medicine for different infections as first-line treatment, second-line treatment or not at all, can be accessed on <http://www.ltkronoberg.se/ext/raf/raf.htm>.

Donor organism (Givarorganism)

If nucleic acid sequences inserted in GMMs are of biological origin, one may need to know which species or strains they come from. When the donor organism is a pathogen, the occurrence, for example, of genes for virulence factors and the proportion of the genome cloned have a bearing on risk. In shot gun experiments there is great uncertainty as to which of the donor organism's genes are inserted. The donor organism as such sometimes occurs within the activity, in which case it needs to undergo separate risk assessment.

Other biological factors (Andra biologiska faktorer)

How well characterised the biological material is has a bearing on the risks entailed by use. The factor of uncertainty will be greater if the material is taken directly from nature or patients, if there is a risk of contaminated micro-organisms or a risk of other unknown

factors. In certain cells or laboratory animals there may be factors present which make possible complementation, so that a replication-incompetent virus, for example, could become replication-competent. It is also important to indicate whether genes of importance, say, for virulence and colonisation remain or have been removed.

The resultant genetically modified micro-organism, GMM (Resultande GMM)

When assessing the resultant GM it is important, just as with the recipient organism, to take into account its harmful properties and properties which may influence the connections in which those harmful properties may come to expression, or the likelihood of their doing so.

It may also be necessary to judge whether any harmful properties which were present in the initial material for constructing the GMM remain in the resultant GMM, and whether other harmful properties could arise as a consequence of the genetic material having been recombined or changed.

Genetic modification can mean that the risks entailed by the final GMM are not the same as with the original material. Since the classification of the unmodified recipient organism does not automatically apply to GMMs, the classification as per AFS 1997:12 has to be repeated. Note that classification under AFS 1997:12 applies only to infections in humans.

Other harmful effects may occur, e.g. allergy or the influence of harmful substances. Harmful effects on flora and fauna and the environment generally must also be taken into account. It may be appropriate to factor in properties of similar GMMs if experience exists concerning them. If there is great uncertainty, the caution principle requires the risk to be considered a major one until more knowledge and experience are available. App. 1 B, AFS 2000:5, contains examples of potentially harmful effects.

Outward factors affecting the risk (Yttre faktorer av betydelse för risken)

In addition to the inherent properties of the biological material, there are other factors which can influence the risk, e.g. different modes of use and the type of activity to which the use belongs. The risks associated, for example, with large-scale activity or use of GMMs on animals are different from those of laboratory activity. Different procedures and conditions, such as cultivation volumes, mode of cultivation, concentration of organisms or substances, special working operations etc. need to be gone over so as to make the risks identifiable. Outward factors of this kind affecting the risk are instanced in the guidance on App. 1, AFS 2000:5.