ZKBS
Zentrale Kommission
für die Biologische Sicherheit

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Position statement of the ZKBS on the draft of the VDI Guideline VDI 6300 – Genetic engineering operations in contained use systems

Foreword

The Association of German Engineers (VDI) plans to publish a guideline on genetic engineering operations in contained use systems (VDI 6300). The first draft of the guideline (official draft) was published in January 2012. In May 2012, on its 172th meeting, the ZKBS passed a statement on the draft and brought it to the knowledge of the VDI using the objection portal of the association. In April 2014, the ZKBS in turn received a comment on its objections from the VDI. In November 2014, a second official draft was released with the notice: objections until Feb. 28, 2015. The revised draft of the VDI 6300 was discussed on the 191th meeting of the ZKBS on Feb. 3, 2015. The following concerns and ideas were formulated (numeration in accordance with the VDI Guideline):

General considerations

The VDI accepted some of the changes of the first official draft inspired by the ZKBS and promised a revision of the pertinent text passages. However, the ZKBS wants to point out that, in various cases, these corrections have not been made in the revised official version. This concerns, for example, drawing upon Art. 13 and Annex III of the German Genetic Engineering Safety Regulation (GenTSV) as the legal foundation for proposals and guiding values for test intervals, the type of tests to be carried out and the requirements applicable to the auditor who is to test the technical installations and the equipment as presented in Table 1. It also concerns the withdrawal of the demand of sampling the work environment in Section 5.3.1. Determination of Surface Contaminations; here, areas in recreation spaces are still listed as sampling sites.

2 Normative references

This section is supposed to make clear that the VDI Guideline 6300 merely possesses informative character and is not legally binding.

4 Requirements for technical and analytical tests

4.1 Testing technical installations and equipment

According to the VDI Guideline, testing technical safety measures pursuant to Art. 10 of the Industrial Safety Regulation (BetrSichV) must be carried out exclusively by authorized personnel and persons commissioned by external companies must be instructed on potential biological hazards and required measures of protection.
It should be specified that commissioned persons from external companies must be instructed by the contracting authority (operator, project leader) on potential hazards, necessary protective safety measures and rules of conduct prior to the onset of their work (compare LASI Publication LV 23 "Guidelines on Working with Biological Agents").
In this context, it is pointed out that the revision of the Industrial Safety Regulation (BetrSichV) will enter force on Jun. 1, 2015 and the pertinent references and terminology in the VDI 6300 shall be updated and, if necessary, adapted.

4.2 Identification and characterization of organisms

According to the VDI Guideline and with reference to Annex III, Part A Level 1 No. 11 of the German Genetic Engineering Safety Regulation (GenTSV), identification and characterization of the applied organisms might be necessary in order to evaluate their hazard potential.
According to Annex III, Part A Level 1 No. 11 of the German Genetic Engineering Safety Regulation (GenTSV), the purity and identity of the organisms used must be regularly verified should this be necessary for the evaluation of the hazard potential.
The terminology of the German Genetic Engineering Safety Regulation (GenTSV) should be used for reasons of disambiguation.

5 Execution of testing activities (biosafety level 1 to biosafety level 3)

5.3 Confirmation of safety and hygiene (primary containment)

5.3.1 Determination of surface contaminations

Pursuant to the VDI Guideline, the work areas in which genetic engineering operations of biosafety level (BSL) 1 are carried out must usually not be sampled.
Pursuant to Art. 12 Paragraph 7 of the German Genetic Engineering Safety Regulation (GenTSV), taking a sample from the work area is only necessary when the occurrence of human pathogenic GMOs in a concentration which either is or could constitute a risk to

human health cannot be excluded according to the current state of science and technology. Since organisms assigned to risk group 1 are not human pathogenic, BSL 1 genetic engineering operations will not require sampling of the work area.

The word group "under normal circumstances" should therefore be deleted.

5.3.1.1 Testing intervals and time points of sampling

The third sentence of this passage should be extended as follows: "Relevant factors in this regard are, for example, cleaning and disinfection programs (hygiene plan), the transmission routes of the GMOs, their survival and infection capacity outside the primary containment and the potential amount of released GMOs in relation to the minimum infectious dose."

5.3.1.2 Sampling sites

This section presents a list of the surfaces from which samples are to be taken. In order to encounter the impression that it is a checklist to be worked off completely, the first sentence should be rephrased as follows: "Surfaces to be sampled in genetic engineering facilities may be:...."

5.3.2 Sampling of airborne GMOs – bioaerosols

According to statements made in the VDI Guideline, contaminations in the laboratory spaces might usually be sufficiently detected and evaluated on the basis of surface sampling, for which reason methods to determine the microbial load in ambient air are not described. It is also stated in Table 2 that sampling of airborne GMOs is not necessary; however, for the safety levels 2 and 3 this is limited by means of a footnote reference a) stating "depending on the hazard potential and the type of work".

The representation of the VDI implicates that in certain cases the sampling of biological aerosols is indicated in BSL 2 or 3 genetic engineering facilities in order to determine a contamination of ambient air. Sampling of biological aerosols usually proceeds with an air sampler. These instruments are cost-ineffective and hardly available in research laboratories. In addition, a contamination can only be determined with this method if the measurement is made immediately after the release from the primary physical containment, since airborne microorganisms are usually bound to dust particles or water droplets and rapidly sediment (calculation of the sedimentation velocity depending on the particle size, cf. W. C. Hinds "Aerosol Technology", 2nd edition, 1999 John Wiley & Sons). Identifiable would merely be a

GMO of known identity, which had been released into ambient air in a close temporal relation to the measurement and can reproduce under the culture conditions selected in (nutrient medium and incubation conditions). However, such determination does not provide any new information and is therefore redundant. The ZKBS is also unaware of scenarios applying to safety levels 2 and 3, in which the identification of contaminations by sampling airborne GMOs would be recommendable.
The footnote a) should therefore be removed from the respective sites in Table 2.

5.3.3 Testing safety workbenches

The VDI Guideline states that for BSL 1 genetic engineering operations the use of a microbiological safety workbench (MSW) might become necessary if the generation of aerosols cannot be avoided.
According to Annex III, Part A Level 1 No. 8 of the German Genetic Engineering Safety Regulation (GenTSV) it is necessary to ensure that the formation of aerosols is avoided as far as possible. When working with GMOs with sensitizing or toxic properties, respective measures must be taken to minimize the exposure of the persons employed (e.g. MSW or respiratory protection). Consequently, the law does not require a general application of an MSW in safety level 1 should the generation of aerosols be inevitable.
This falsely represented connection between aerosol avoidance precept and a binding use of MSWs in safety level 1 situations should be dissolved. The third sentence of the passage should therefore be deleted.
The VDI Guideline also states that an inactivation of the filter before its removal and disposal may be usually dispensed with in case of MSWs which are applied for BSL 1 genetic engineering operations. However, this could be necessary in case of work steps with considerable aerosol formation with GMOs requiring inactivation according to Art. 13 Paragraph 1, 2 and 3 of the German Genetic Engineering Safety Regulation (GenTSV).
Pursuant to Art. 13 Paragraph 3 of the German Genetic Engineering Safety Regulation (GenTSV), solid waste derived from BSL 1 genetic engineering facilities, to which Paragraph 2 does not apply, must be inactivated to an extent that the GMOs it contains are no longer able to reproduce and, if applicable, are no longer infectious. In certain cases, the filters must therefore be inactivated prior to their disposal until rendered innocuous (e.g. by autoclaving). By no means, however, not even in cases of work steps with considerable aerosol formation with GMOs requiring inactivation, must the filters be fumigated prior to

their removal, since GMOs belonging to risk group 1 do not impose a health hazard to the people employed or the maintenance personnel.
The VDI Guideline further states that in case of MSWs, which are used for BSL 3 genetic engineering operations, a thermal sterilization of the filters shall not be required, provided that a validated fumigation method has been carried out before pursuant to Section 5.3.4 Fumigation of Safety Workbenches. The ZKBS expressly welcomes this proposal of the VDI. If a method of validated efficacy is applied, a subsequent thermal treatment of the filters will not be necessary.
In summary, it is recommended to revise the section and to render it more precisely in order to avoid false interpretations. It should be made clear that in BSL 1 genetic engineering facilities fumigation of the filters prior to their removal from the MSW is never required, at most an inactivation before disposal. The footnote c) in Table 2 should also be revised in this context.

5.4 Testing the efficacy of the containment measures (secondary containment)

5.4.1 Evidence for the efficacy of sterilization procedures designed to inactivate microorganisms /GMOs in solid waste

For safety level 2 and higher, the VDI Guideline mentions thermal exhaust air treatment by means of an incinerator as an alternative to the filtration of the exhaust air with HEPA filters for autoclaves whose exhaust air is returned to the working area.
As far as the subsequent treatment of exhaust air is concerned, the ZKBS recommends thermal treatment (alternatively: installation of a second sterile filter) only for safety level 3 and higher (cf. also ZKBS statement on VDI 6300 from May 2012). In its comment as of April 2014, the VDI rejected this objection with the information that there would be a contradiction in this point between the ZKBS and the Committee on Biological Agents (ABAS) and it would decide in favor of the higher safety level. The ZKBS refers to the fact that the ABAS according to its Decision 03/2009 "Installation recommendations for new installations, retrofitting or extension, on selecting treatment of exhaust air from autoclaves" also recommended the subsequent thermal treatment only for safety level 3 and higher. ABAS recommends the installation of a second sterile filter for autoclaves used in safety level 2.
An revision of the section in accordance with the recommendations given by the ZKBS and ABAS is recommended.

5.4.4 Testing the efficacy of exhaust air filtration – methods designed to test filter integrity

5.4.4.2 Supply and exhaust air filters of room ventilation systems (in safety level 3 and higher)

The VDI Guideline recommends an annual integrity test for ambient air exhaust filters.
The ZKBS considers an annual integrity test for ambient air exhaust filters not to be necessary, instead, it recommends a test when the filter is put into operation the first time, after filter changes and after reconstruction work on the ventilation system, during which the filters might have been damaged (cf. also ZKBS statement on the VDI 6300 from May 2012).
In its comment in April 2014, the VDI rejected this objection with the information that there would be a contradiction between the ZKBS and the ABAS Decision 16/2010 and that it would assume the higher safety requirement. The Decision 16/2010 explicates that test intervals are not unequivocally determined and should be integrated into the operation instructions after a hazard assessment relative to each facility. Furthermore, it is stated that an annual test interval has been established in practice.
In summary, it is recommended to revise the section and to represent the recommendations of the ZKBS and the ABAS with precision.

Summary

In its comment as of April 2014 the VDI refers to the fact that it does not intend any tightening of the standards for operators and project leaders. The VDI Guideline is supposed to serve as a directing, practical work document which gives experts the security to orient themselves to the accepted rules of engineering.
The ZKBS ascertains that the content of the current official draft (taking into consideration the limitation of the purview) is almost identical with the first draft issued in January 2012. Only few suggestions of the ZKBS were taken up, and the mentioned tightening has hardly been loosened. The remaining points of criticism in the ZKBS statement from May 2012 are therefore maintained.
In summary, the ZKBS refers to the fact that the requirements and provisions made in the VDI 6300 do not agree in many points with the statements and recommendations of the expert committees such as the ZKBS and the ABAS which have been particularly established for this field of expertise. The aspired goal of the guideline, i.e. to give operators and project leaders more security concerning the accepted rules of engineering, has therefore not been achieved.

As a result, it is proposed to thoroughly revise the VDI Guideline and to limit it to the description of technical specifications and test procedures.