Publication
of the work of the Central Committee
on Biological Safety in 2018

(BVL – German Federal Office of Consumer Protection and Food Safety 119/2019/4)

29. Report after entry into force of the Genetic Engineering Act

dated February 2019

The aforementioned 2018 report on the work of the German Central Committee on Biological Safety (ZKBS) will be published below.

Berlin, 5 February 2019

Federal Office

of Consumer Protection and Food Safety

By order

Dr. Anke S t e i n

Outline

Abbreviations

ATMP	pharmaceutical drug
BfN	Federal Agency for Nature Conservation
BfR	Federal Institute for Risk Assessment
BMEL	Federal Ministry of Food and Agriculture
BVL	German Federal Office of Consumer Protection and Food Safety
EFSA	European Food Safety Authority
EC	European Community
EMA	European Medicines Agency
EU	European Union
EuGH	European Court of Justice
FLI	Friedrich-Loeffler-Institut, Federal Research Institute for Animal Health
GenTG	Genetic Engineering Act
GenTSV	Genetic Engineering Safety Regulations
GMO	genetically modified organism
JKI	Julius Kühn-Institut
PEI	Paul-Ehrlich-Institut
RKI	Robert Koch-Institut
ZKBS	Central Committee on Biological Safety

Technical abbreviations are explained in the text.

1 Introduction

1.1 Basics of the ZKBS

The Central Committee on Biological Safety (ZKBS) is an expert committee composed of 20 members and 20 deputy members. The members are experts in various disciplines and are represented by experts in the same field. The areas of expertise represented are specified in the Genetic Engineering Act (GenTG). The ZKBS reviews and assesses safety-related questions about genetic engineering in accordance with the provisions of the GenTG and advises the Federal Government and the federal states. It provides position statements to the competent authorities, in particular on the risk assessment of micro-organisms, the biosafety classification of genetic engineering operations, the safety measures required in genetic engineering facilities and the possible risks of deliberate release or placing on the market of genetically modified organisms (GMOs). It considers international developments in the field of genetic engineering safety in its recommendations. The members of the ZKBS and their deputies volunteer their work in accordance with GenTG.

The ZKBS has its secretariat at the Federal Office of Consumer Protection and Food Safety (BVL), which is part of the Federal Ministry of Food and Agriculture (BMEL). The members of the ZKBS and their deputies are appointed for a period of three years by the BMEL in coordination with the Federal Ministries of Education and Research, Economy and Energy, Labour and Social Affairs, Health, Environment, Nature Conservation, and Nuclear Safety. Reappointment is permissible.

The ZKBS is headed by one chairperson, assisted by two deputies. It makes its resolutions either at a meeting or by written procedure. The members of the ZKBS and their deputies are obligated to maintain secrecy. The meetings are not public, but the ZKBS publishes general position statements and reports about their work to the public annually.

1.2 Development of genetic engineering in the Federal Republic of Germany and in other member states of the European Union

Genetic engineering operations and genetic engineering facilities

The term ‘genetic engineering operations’ refers in particular to the production and handling of GMOs. Genetic engineering operation, depending on its class, must be reported, registered or approved by the competent state authority and carried out in a genetic engineering facility, which must also be reported, registered or approved depending on the classification. Genetic engineering facilities may be laboratories, large scale facilities, greenhouses and/or animal facilities.

Generally, before deciding on a license permission, the competent authority shall obtain a position statement from the ZKBS on the safety-related classification of the planned genetic engineering operations and on the required safety measures. This mainly refers to genetic engineering operation of safety levels 3 or 4 and genetic engineering facilities with safety measures of class 3 or 4. However, the competent authority also asks the ZKBS to provide position statements on class 2 genetic engineering operations that are not comparable to other operations for which the ZKBS has already issued a position statement in the past, or on genetic engineering operations whose assignment to class 1 is uncertain.

Since the Genetic Engineering Act (GenTG) went into effect in 1990, the ZKBS recieved 2019 applications for biosafety classification of genetic engineering operations and/or evaluations of the required safety measures. In the year under review, 38 applications were submitted and the ZKBS issued 37 position statements.

In Germany, a total of 6,619 genetic engineering facilities are reported, registered or approved (as of December 2018). Table 1 lists the genetic engineering facilities based on the level of safety measures. Table 2 summarizes the reported, registered or approved genetic engineering operations in Germany by class.

Table 1 Reported, registered or approved genetic engineering facilities in Germany (as of December 2018)

Level	Quantity
S1	4,702
S2	1745
S3	105
S4	5

Compared to the past five years, the total number of 6,000 to 7,000 genetic engineering facilities of class 1 to 4 has remained largely stable. The largest part is occupied by class 1 and 2 facilities (see Figure 1).

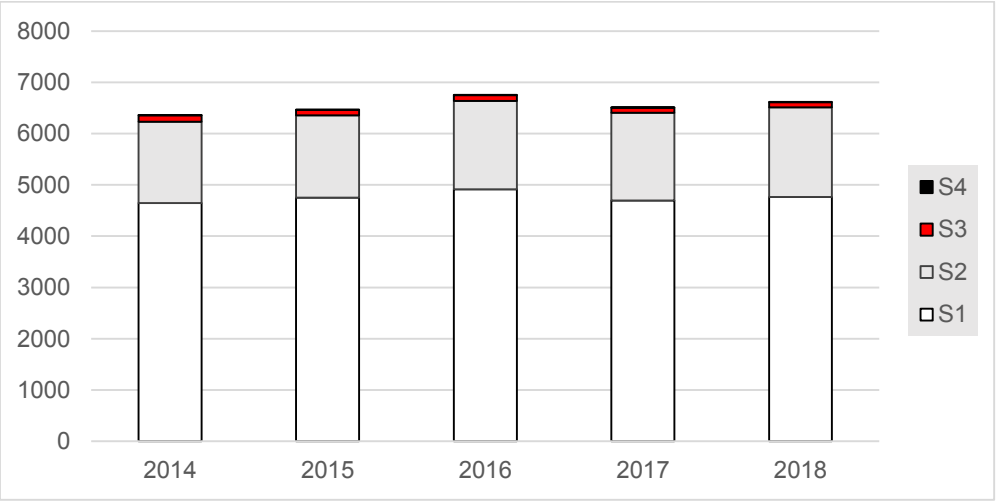

Figure 1 Number of reported, registered or approved genetic engineering facilities in Germany from 2014 to 2018

Table 2 Currently reported, registered or approved genetic engineering operations in Germany (as of December 2018) *

Level	Quantity
S2	7,724
S3	333
S4	13

* Precise specification is not possible for the performed genetic engineering operations of class 1, since the operators are obligated according to § 9 GenTG to record subsequent class 1 projects, however they are not obligated to notify or report to the competent state authority. Thus, further S1 work is not recorded in the regulatory databases.

Further information on genetic engineering operations and genetic engineering facilities is available on the ZKBS website: http://www.zkbs-online.de.

It is not possible to compare the number of genetic engineering operations or genetic engineering facilities between Germany and other Member States of the European Union (EU) as there is no information available in that regard. General information on the implementation of the underlying Directive 2009/41/EC are made available to the European Commission at regular intervals by the Member States. They are summarized by the European Commission and published on its website[1].

Deliberate releases of GMOs

If GMOs are released into the environment for a limited time and space during an experiment, it is referred to as 'deliberate release'. For each intended deliberate release, permission must be obtained from the BVL in accordance with GenTG, which can only be granted if the planned deliberate release does not have any harmful effects on humans, the environment in its causal network, animals, plants and material assets. If the GMOs to be released already have permission to be placed on the market, no separate permission is required.

In Germany, the BVL, as the higher federal authority, is responsible for permission for deliberate releases of GMOs since April 1, 2004; previously it was the RKI. The BVL makes the decisions in consultation with the BfN, the BfR and the RKI. The ZKBS, the JKI and the competent authority of the respective federal state issue position statements on the deliberate release intent. In case of a deliberate release of genetically modified vertebrates or genetically modified micro-organisms used on vertebrates, the FLI will also be involved. The other EU Member States are notified about deliberate release applications and can comment on them.

As in the years from 2013 to 2017, no deliberate releases of genetically modified organisms were requested in Germany in 2018, nor was permission granted for such releases. A comparison of the submitted release applications from the different EU Member States shows that in 2018 individual applications have been submitted in Great Britain, Sweden, the Czech Republic, Spain, Finland, and Belgium. Details can be found in the register maintained on behalf of the Commission[2].

[1] https://ec.europa.eu/food/plant/gmo/reports_studies_en

[2] http://gmoinfo.jrc.ec.europa.eu/gmp_browse.aspx

Placing on the market of genetically modified organisms

'Placing on the market' refers to the distribution of GMOs and products containing or produced from GMOs to third parties, usually for marketing purposes.

The placing on the market of GMOs requires an EU-wide approval procedure. This procedure distinguishes whether the GMO should be used as food or feed [Regulation (EC) No. 1829/2003] or not (Directive 2001/18/EC). Products from GMOs that fall outside the scope of the aforementioned regulation or directive, such as cotton clothing, do not require permission to be placed on the market. After processing the EU-wide procedure, the permission applies to all EU Member States.

The BVL is the competent German authority and issues a national position statement on applications for the placing on the market of GMOs in consultation with the BfN, the BfR and the RKI. Prior to this, a position statement of the JKI and, if the GMOs are vertebrates or micro-organisms to be applied to vertebrates, a position statement from the FLI and the PEI will be obtained.

In addition, the BVL asks the ZKBS for a position statement on such applications under Directive 2001/18/EC, which were filed in Germany. For applications under Regulation (EC) No. 1829/2003, the BVL will seek the position statement of the ZKBS if Germany has been commissioned by EFSA to carry out an environmental risk assessment of an application for cultivation.

Currently, events (number in parentheses) of the following plants are mostly approved for importation as a GMO capable of reproduction and its processing or as feed and food.

- Cotton (12)
- Maize (82)
- Oilseed rape (15)
- Soya (19)
- Ornamental plants (5)
- Sugar beet (1)

Further details can be found on the BVL[3] website and in the entries of the register of the European Union[4].

In contrast to local and time-limited deliberate release experiments, the agricultural cultivation of genetically modified plants is not limited to specific locations or trial years. Cultivation of genetically modified crops by farmers can only take place once the placing on the market of the genetically modified seed has been approved for the purpose of exposure to the environment. A permission is usually valid for ten years and must be renewed thereafter. The EFSA is responsible for the scientific evaluation.

Decision of the European Court of Justice (ECJ) that plants produced with new mutagenesis techniques are considered to be GMOs

Following a complaint by French (agricultural) associations to the French State Council, the ECJ in its judgement dated 25/07/2018 found that plants produced by both conventional and new mutagenesis methods are genetically modified organisms. Thus they fall under the regulations of EU Directive 2001/18/EC on the deliberate release of GMOs into the environment (GMO Directive). However, GMOs produced by conventional mutagenesis are excluded from the applicability of the Directive. As a result, genomically identical organisms are regulated differently.

[3] https://www.bvl.bund.de/DE/06_Gentechnik/02_Verbraucher/03_Genehmigungen/01_Inverkehrbringen/gentechnik_GenehmigungenInverkehrbringen_node.html

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

In addition to numerous international scientific evaluations and position statements on the ruling, the ZKBS has also dealt intensively with this legal interpretation of the GMO Directive and its consequences. As a result, it has published an article under the Focus Topics section on its website[5]. It is the opinion of the ZKBS that the European Genetic Engineering Act, which is essentially based on 1990 state of knowledge, urgently needs to be adapted to the current state of knowledge.

Clinical trials with GMO-containing investigational drugs and use of GMO-containing medicines in humans

According to § 2 (3) GenTG the application of GMO-containing investigational drugs in humans is excluded from genetic engineering regulations in Germany. The permission for clinical trials with investigational medicinal products consisting of, or containing, a genetically modified organism or a combination of genetically modified organisms is regulated in the regulation on the application of good clinical practice in the conduct of clinical trials on medicinal products for human use (GCP regulation). In Germany, the PEI is responsible for granting the permission as the upper federal authority. The BVL is involved as an advisory authority in the assessment of the risk to the environment and in determining the delineation of certain activities to the GenTG and reports to the ZKBS. In some cases, the ZKBS assesses the hazard potential of the GMOs in a position statement.

There has been a significant increase in the number of applications for permission of clinical trials in recent years (34 applications in 2018 compared to 25 applications in 2017 and 18 applications in 2016). In total, 20 permissions were issued by the PEI in 2018 involving the BVL. The investigational drugs were potential advanced therapy medicinal products (ATMPs), such as the treatment of cancers with reprogrammed endogenous cells for immunostimulation or gene therapy approaches to serious diseases due to monogenic genetic defects, or novel infectious disease vaccines. An overview of approved clinical trials in the EU can be found in the Register of the European Union[6].

The authorization for the use of human medicinal products consisting of, or containing, a genetically modified organism or a combination of genetically modified organisms is subject to a centralized procedure by the European Commission in accordance with Regulation 726/2004/EC. The application is submitted to the European Medicines Agency (EMA), which prepares guidelines for evaluation as part of its mission and handles the scientific coordination of the procedures. The environmental impact assessment must involve the competent authorities of the Member States in accordance with Directive 2001/18/EC, which in Germany is represented by the BVL. Same as with clinical trials, there has been an increase in applications for market authorizations for ATMPs. The requested products are increasingly reprogrammed endogenous T cells for the treatment of cancer and vaccines. An overview of already approved ATMPs is provided on the website of the PEI[7]. Again, the ZKBS is regularly kept up-to-date.

[5] https://www.zkbs-online.de/ZKBS/DE/03_Fokusthemen/Genome%20Editing/Genome%20Editing_node.html

[6] http://gmoinfo.jrc.ec.europa.eu/gmo_browse.aspx

[7] https://www.pei.de/DE/arzneimittel/atmp-arzneimittel-fuer-neuartige-therapien/atmp-arzneimittel-fuer-neuartige-therapien-node.html

2 Structure of the ZKBS

The ZKBS brings together experts from different fields. This way, a broad range of expertise is institutionalized and made available for the tasks of the ZKBS, which are specified in the GenTG, namely the evaluation of micro-organisms as donor and recipient organisms for genetic engineering operations, the biosafety classification of genetic engineering operations, the assessment of safety-related measures of genetic engineering facilities, and the evaluation of deliberate releases and placing on the market of GMOs. Table 3 shows the composition of the ZKBS.

Prof. Dr. Sigrun Smola, member of the Virology Division since 2012, is Chair of the ZKBS since June 2016. Vice Chairmen are Prof. Dr. Uwe Groß and Prof. Dr. Dr. Thomas Vahlenkamp (as of December 2018).

Prof. Dr. Patrick Schweizer, member of the Plant Cultivation Division since 2009, fell victim to a fatal accident in March 2018, much to the dismay of all ZKBS members.

The appointment periods for Prof. Dr. Stefan Vidal, who has been a member of the Ecology Division since 2000, and Prof. Dr. Friedhelm Taube, member of the Agricultural Council since 2015, and member of the Consumer Protection Division since 2006, expired in 2018.

New appointments include:

in April 2018:	Prof. Dr. AnDr.ea Hartwig as a member of the Toxicology Division
in August 2018:	Prof. Dr. Martin Hasselmann as a deputy member for Ecology
in August 2018:	Prof. Dr. Ulrich Schurr as a deputy member for Agriculture
in August 2018:	Ms Annette Neuhaus as a deputy member in the field of Consumer Protection

The composition of the ZKBS shown in Table 3 corresponds to the specifications of the GenTG in the currently valid version.

Table 3 Speciality fields and members of the ZKBS (as of December 2018)

Area of Expertise	Member	Deputy Member
Experts according to § 4 (1) No. 1 GenTG		
Microbiology	Prof. Dr. Petra Dersch Helmholtz-Zentrum für Infektionsforschung GmbH, Braunschweig	Prof. Dr. Kai Matuschewski Humboldt University, Berlin
Cell biology	Prof. Dr. Bernd Gänsbacher Munich	Prof. Dr. Michael Meisterernst University of Münster
Virology	Prof. Dr. Dr. Thomas W. Vahlenkamp University of Leipzig	Prof. Dr. Edgar Maiß University of Hannover
Virology	Prof. Dr. Sigrun Smola Saarland University	Prof. Dr. Stefan Pöhlmann Deutsches Primatenzentrum GmbH Göttingen
		Prof. Dr. Anja Ehrhardt University of Witten/Herdecke
Genetics	Prof. Dr. Jürgen Wienands University of Göttingen	Prof. Dr. Alfons Gierl Munich
Genetics	Prof. Dr. Uwe Sonnewald University of Erlangen-Nuremberg	Prof. Dr. Uwe Völker University of Greifswald
Hygiene	Prof. Dr. Uwe Groß University of Göttingen	Prof. Dr. Werner Solbach University of Lübeck
Ecology	Dr. Walter Durka Helmholtz-Zentrum für Umweltforschung GmbH Halle	Prof. Dr. Ilona Leyer University of Geisenheim
Ecology	Prof. Dr. Rainer Waldhardt University of Gießen	Prof. Dr. Martin Hasselmann University of Hohenheim
Plant cultivation	Prof. Dr. Karl Schmid University of Hohenheim	N.N.
Security technology	Dr. Sven Deutschmann Roche-Diagnostics GmbH Penzberg	Dr. Jürgen Vorlop Marburg
Toxicology	Prof. Dr. Andrea Hartwig Karlsruhe Institute of Technology (KIT)	Prof. Dr. Edmund Maser University of Kiel
Specialists according to § 4 (1) No. 2 GenTG		
Occupational safety	Frank Gerschke State Office for Occupational Safety Potsdam	Dr. Beatrice Spottke Trade Association for Raw Materials and Chemical Industry, Hamburg
Unions	Prof. Hon. Dr. Wilfried Wackernagel University of Oldenburg	Dr. Brigitte Dreiseikelmann University of Bielefeld
Agriculture	Prof. Dr. Joseph-Alexander Verreet University of Kiel	Prof. Dr. Ulrich Schurr University of Düsseldorf
Nature conservation	N.N.	N.N.

Area of Expertise	Member	Deputy Member
Research funding organizations	Dr. Ingrid Ohlert German Research Foundation (Deutsche Forschungsgemeinschaft DFG), Bonn	Dr. Jan-Wolfhard Kellmann University of Marburg
Environmental protection	Dr. Gerd Neemann BLaU-Umweltstudien (environmental studies), Göttingen	Dr. Gesine Schütte University of Hamburg
Consumer protection	Sigrid Lewe-Esch Deutscher Evangelischer Frauenbund e. V., Duisburg	Annette Neuhaus District Chemicals Council – District Lippe Detmold
Economy	Dr. Siegfried Throm vfa Die forschenden Pharmaunternehmen, Berlin	Dr. Anja Matzk KWS SAAT SE Einbeck

3 Advisory activities of the ZKBS in 2018

3.1 Mode of operation

The working method of the ZKBS is set out in its rules of procedure, which was adapted in 2018 to current standards for legislation. In 2018, seven meetings of the ZKBS (212th - 218th meeting sessions) took place at the BVL in Berlin. Most of the position statements of the ZKBS were adopted at these meetings. However, further decisions were also made using the written procedure, mainly if there were simpler questions that did not require a detailed discussion between all members.

3.2 Task forces/work groups

In 2018, several topics were handled in work groups.

Upon request of the BMEL for a position statement on the amendment of the GenTSV by the ZKBS, the work group 'GenTSV' was reconvened. The members prepared a position statement, which was adopted by the ZKBS at its 215th meeting in July and subsequently submitted to the Federal Ministry.

The efforts of the work group 'influenza viruses', which had already developed criteria for a risk assessment in the previous years, were continued in 2018. The outcome of the discussions was the adoption by the ZKBS of an update of the position statement on the risk assessment of genetic engineering operations on recombinant influenza A viruses, ref_ 45310.0113.

In the context of applications for permission for the establishment or operation of class 4 genetic engineering facilities, discussions were also held with the applicant prior to the meetings of the ZKBS or work groups were set up. In one case, an on-site visit was also carried out.

3.3 Advising the Federal Government, the competent state authorities and the BVL

At its 214th meeting, the ZKBS was visited by the Federal Minister of Food and Agriculture, Julia Klöckner. The Minister stressed the importance of fact-based information exchange as the basis for broadly accepted policy-making and will draw on the expertise of her committee in the field of genetic engineering.

At its 214th session, the ZKBS also adopted its 2nd Synthetic Biology report. The report summarizes the international literature on research conducted under the term Synthetic Biology. It describes the progress in each of the fields of Synthetic Biology and examines whether the activities give rise to hazards that are not regulated by the Genetic Engineering Act or the European legislation on genetic engineering. The report was made available to the BMEL, but also distributed as a printed brochure and published on the website[8].

In addition, the BMEL asked the ZKBS for a position statement on the amendment of the GenTSV. After questioning her work group, it was made available to the Federal Ministry.

The following questions of the responsible state authorities were discussed and evaluated by the ZKBS:

- Evaluation of *Halomonas elongata* with altered ribosome binding site or altered σ38 promoter

[8] https://www.zkbs-online.de/ZKBS/SharedDocs/Downloads/01_Allgemeine Stellungnahmen/01_Allgemeine Themen/2. Bericht der ZKBS zur Synthetischen Biologie (2018)

- Recognition of chemical sterilization procedures in genetic engineering facilities of class 3
- Safety assessment of the Digestor operation in an S4 animal facility
- Request to identify to what extent influenza A viruses produced through genetic engineering are GMOs
- Risk assessment of the influenza A virus deletion mutant VH244
- Assessment of genetic engineering operations with pigs injected with recombinant lentiviruses

3.4 Risk assessment of donor and recipient organisms

The following micro-organisms, which are used as donor or recipient organisms in genetic engineering operations, were assigned to a risk group in 2018 in accordance with § 5 in conjunction with Annex I GenTSV, or their classification was checked:

Table 4 Newly classified micro-organisms

Organism	Risk Group
Viruses	
Adeno-associated viruses (AAV) types 4, 7, 10, 11, 12 and 13	2
Adeno-associated viruses (AAV) types 1, 2, 3, 3b, 5, 6, 8, 9 and rh-10	1
Apple latent spherical virus (ALSV)	1
Batken virus (BatV)	2
Black medic leaf roll virus (BMLRV)	1
Bourbon virus (BRBV)	3
Dandenong virus	2
Enterovirus C, poliovirus serotype 2	3
Enterovirus C, poliovirus serotype 1 and 3	2
Foxtail mosaic virus (FoMV)	2
Fusarium graminearum virus China 9	1
Hepacivirus A	2
Human alphaherpesvirus 1 5dl1.2	1
Jos virus (JosV)	2
Madariaga virus (MADV)	2
Middelburg virus (MIDV)	2
Modified vaccinia virus Ankara-HBV	1
Papiine alphaherpesvirus 2	2
Porcine endogenous retrovirus (PERV), subtype C	1
Salmon pancreas disease virus (SPDV)	2
Simian adenovirus group C virus 155	2
Simian adenovirus group C virus 155-hli-HBV	2
Soil-borne wheat mosaic virus	1
Southern elephant seal virus (SESV)	1
Tobacco vein mottling virus (TVMV)	2
Turnip mosaic virus (TuMV)	1

Organism	Risk Group
Bacteria	
Acinetobacter junii	2
Acinetobacter ursingii	2
Elizabethkingia miricola	2
Enterococcus mundtii	2
Escherichia albertii, non-Shiga toxigenic strains	2
Escherichia albertii, Shiga toxigenic strains	3**
Escherichia fergusonii	2
Lactobacillus reuteri	1
Mycobacterium bovis BCG	2
Parabacteroides goldsteinii	2
Rhodococcus erythropolis	1
Spiroplasma citri	2
Trabulsiella guamensis	1
Parasites and eukaryotic protozoa, except fungi/oomycetes	
Angomonas deanei	1
Globodera pallida	1
Polymyxa graminis	1
Fungi and oomycetes	
Alternaria tenuissima	1
Candida auris	2
Candida viswanathii	2
Candida viswanathii ATCC 20336, ATCC 20913, ATCC 20962	1
Cochliobolus carbonum (teleomorph)	1
Cochliobolus sativus (teleomorph)	1
Melampsora lini	1
Microbotryum lychnidis-dioicae	1
Moniliophthora roreri	1
Penicillium coprobium	1
Phytophthora cryptogea	1
Serendipita vermifera	1

The allocation to risk groups can be found in the ZKBS organism database[9]. General position statements on the risk assessment of organisms are published on the ZKBS website[10].

3.5 Biosafety classification of genetic engineering operations and assessment of safety measures of genetic engineering facilities

In 2018 (as of December), the ZKBS issued 37 position statements on the biosafety classification of genetic engineering operations and/or required safety measures. The evaluated genetic engineering operations and facilities concerned the topics listed in Table 5. For most of the genetic engineering operations that were evaluated, only a reference to the GenTSV was made for the safety measures. However, a detailed assessment was issued for a few of them regarding the technical and organizational security measures available or planned in the genetic engineering facility.

[9] http://apps2.bvl.bund.de/organismen/organisms.jsf

[10] https://www.zkbs-online.de/ZKBS/DE/04_Allgemeine_Stellungnahmen/Allgemeine_stellungnahmen_node.html

Table 5 Risk assessed genetic engineering operations and facilities in 2018

Class 1

- Technology transfer and GMP production of Master Cell Bank (MCB) seed, drug substance and lyophilized drug product for recombinant (huCXCL12-1a) *Lactobacillus reuteri* R2CL bacteria (*L. reuteri*-huCXCL12-1a)
- Genetic engineering operations with coronaviral replicons *

Class 2

- VSV pseudotype vectors (sentence 2) for oncolytic virotherapy
- Orf virus vector TRP-2 for anti-tumour vaccination
- Studies of the gene products of influenza viruses using reverse genetic methods
- Expression of transgenes in *Leishmania major*, here: Search for BH3 domain-interacting proteins in Leishmania and their effect on reactive oxygen species (ROS) in *L. major* parasites expressing different superoxide dismutases during their differentiation and in the infection process
- Working with recombinant influenza virus H7N9
- Reversible protein synthesis inhibition in the mouse brain
- VSV-$Gx_{Dandenong}$ for oncolytic virotherapy
- Process development and GMP drug substance production of recombinant rNDV-LS-L289A-HuIL12
- Co-infection of recombinant influenza A and B viruses with *Staphylococcus aureus*
- Identification and further studies of regulatory networks in *Fusobacterium nucleatum*
- The use of recombinant virus vectors as antigen carrier system
- Molecular studies on alphavirus replication and studies on inflammasome activation by alphaviruses (SINV and CHIKV-VRPs)
- Studies of mVOCs from a catheter isolate of the genus Myroides
- Cloning of replication-competent porcine polytropic endogenous retroviruses and analysis of recombinants
- Cloning and overexpression of staphylococcal enterotoxins and staphylococcal enterotoxin-like proteins (SEs and SEIs)
- Production of recombinant measles viruses from cDNA
- Classification of recombinant influenza viruses of strain WSN with mutations in the polymerase complex genes *

Class 3

- Investigation of recombinant immunodeficiency viruses for pathogenesis and host-virus interactions in human and other mammalian cell lines (facility permission)
- Production of recombinant herpes B viruses and their analysis in recombinant cell lines
- Molecular biological analysis of coronaviruses using reverse genetics (including major modification of the genetic engineering facility)
- Application for permission of the essential modification of a class 3 genetic engineering facility (handling recombinant mycobacteria)
- Evaluation of kinetics of the HIV reservoir using an HIV-1 EGFP-transfected Jurkat cell line

- Functional studies of the gene products of influenza viruses using reverse genetic methods (requested as S2 operation)
- Study of the adaptive immune response towards zoonotic influenza A viruses and influenza B viruses (applied for as S2 operation)
- Establishment of reverse genetics for thogotoviruses
- Operation of a class 3 genetic engineering facility
- Identification of MxA escape mutation in avian influenza A viruses
- Establishment of AAV (adeno-associated virus) based vector systems to modulate HIV expression: Use of pBR43IeG-nef+ and replication-defective derivatives of pBR43IeG-nef+ to produce HIV-positive cells
- Study of recombinant immunodeficiency viruses for pathogenesis and host-virus interactions in human and other mammalian cell lines – Request for extension
- Operation of a class 3 genetic engineering facility, barn and laboratory buildings
- Establishment of a total genomic hepatitis C virus replicon based on the HCV strain Ad78 and study of the biological properties in a cell culture system – significant change in the genetic engineering facility*

Class 4

- Construction and operation of a class 4 genetic engineering facility, stable
- Construction and operation of a class 4 genetic engineering facility, laboratory
- Analysis of virus replication and functional characterization of African swine fever virus (ASPV) gene products through targeted mutagenesis of genomes of avirulent and virulent strains

---

* updated position statements on already requested/performed genetic engineering operations or facilities

3.6 General position statements and reports

The ZKBS issued or revised the following general position statements in 2018:

- Ref_ 6790-03-05 General position statement on the classification of genetic engineering operations in which genes for immunomodulating or apoptosis-regulating proteins are inserted into the genome of replication-competent micro-organisms *
- Ref_ 6790-10-41 General position statement of the ZKBS on frequently performed genetic engineering operations with the underlying criteria of comparability: Gene transfer using retroviral vectors *
- Ref_ 6790-10-65 General position statement on porcine endogenous retroviruses *
- Ref_ 6790-10-73 Risk assessment of human adeno-associated viruses and AAV-derived vectors *
- Ref_ 6790-10-74 Risk assessment of the recombinant vaccinia virus MVA *
- Ref_ 45310.0113 Position statement on the risk assessment of genetic engineering operations with recombinant influenza A viruses *
- Ref_ 45310.0117 General position statement on genetic engineering operations with rabies viruses

* Updates

All general position statements can be found on the ZKBS website[11].

In summary, Figure 2 displays the number of position statements issued by ZKBS in 2018 graphically compared to the number of position statements issued in the past five years. Overall, it can be seen that the overall annual number of position statements during this period has been largely constant.

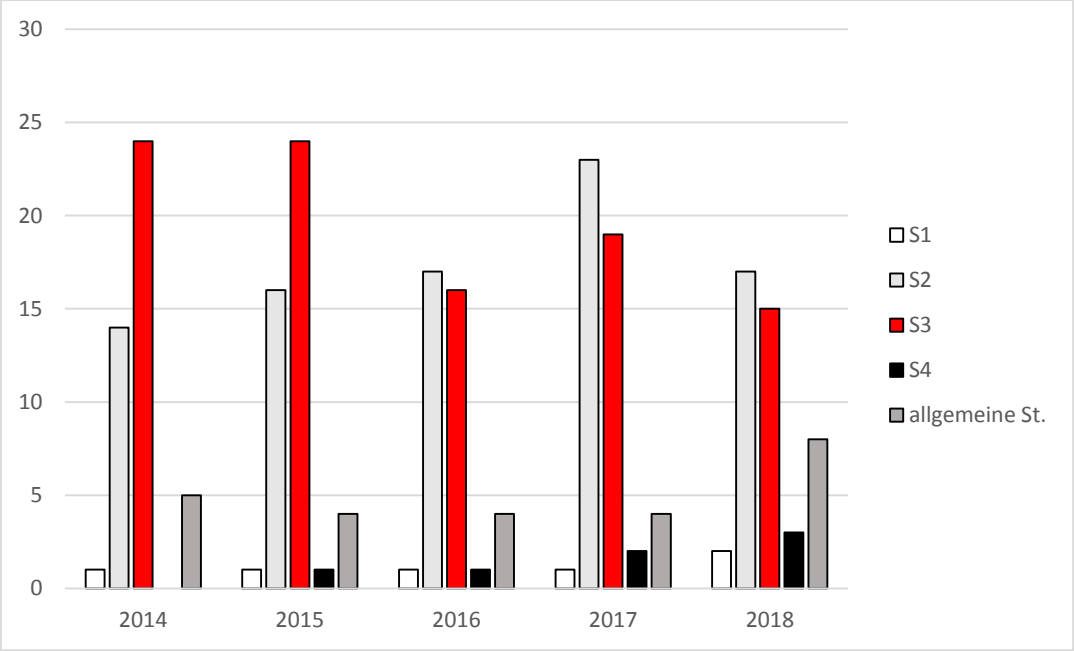

Figure 2 Number of position statements issued by the ZKBS in the past five years on genetic engineering operation in the genetic engineering facilities of the corresponding class and the general position statements

3.7 Position statements on deliberate releases

Position statements on deliberate release applications for GMOs were not submitted by the ZKBS in the reporting period.

3.8 Position statements on placing on the market

Position statements on applications for the placing on the market of GMOs were not submitted by the ZKBS in the reporting period.

[11] https://www.zkbs-online.de/ZKBS/DE/04_Allgemeine_Stellungnahmen/Allgemeine_stellungnahmen_node.html

3.9 Reports on topics of general importance

With the help of the newly established website (http//www.zkbs-online.de), the ZKBS also wants to use the opportunity to inform the public in a suitable way about topics of general importance. In 2018, the following three topics were presented and commented on by the ZKBS[12]:

'*Gene Drive Systems* - Tools for Accelerated Dissemination of Genetic Modifications'

'Synthetic Biology'

and

'Genome Editing - Impact of European Court of Justice (ECJ) Judgement on Plant Breeding'

[12] https://www.zkbs-online.de/ZKBS/DE/03_Fokusthemen/DIY-Biologie/DIY-Biologie_node.html