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Occupational standards for the protection of employees in biotechnology

Abstract A growing number of employees are exposed to biological agents (BAs) at the workplace. Their handling can be associated with the risk of occupational illnesses like infections, allergic or toxic reactions. Several legal considerations are making requirements for the safe handling of BAs necessary. A specific risk assessment has to consider both the adverse health effects deriving from BAs and the exposure situation at the workplace. Industrial hygiene is of critical importance for safe handling, especially with regard to allergic reactions. Occupational surveillance programs can help to further minimize the risks, especially in preventing infections through vaccinations and in counseling persons with impaired immune systems. For accidental exposures medical emergency plans should be prepared. Occupational medical examination programs, vaccinations and counseling of employees must be adapted to the outcome of the risk assessment.

Key words Biological agents · Infections · Allergic reactions · Medical surveillance

Introduction

Biological agents (BA) are cells, microorganisms, or cell cultures, either of natural origin or genetically engineered. Natural BAs have been used in the production of food, wine, and beer for thousands of years. Over the last few decades, their technical use has spread: new recombinant DNA technology enables large-scale

production of enzymes and pharmaceuticals like hormones. So an increasing number of employees has intended use of BAs at workplaces in biotechnology. The new recombinant DNA technology in Germany is currently being used in 2475 projects.

In Germany, with a total workforce of about 35 million, an estimated 5 million workplaces are characterized by some use of BAs. Although the vast majority (more than 75%) works in traditional biotechnology fields of food production, farming, etc., there is a growing number of employees in new workplaces: New methods of waste treatment (recycling) are characterized by unintended use of BAs. For separated waste collection and biological waste processing in Germany 700 processing units were estimated for 1998.

With new groups of workers dealing with biohazards at the workplace and the development of new recombinant DNA technology, has led to several new legal initiatives in Europe. Several occupational laws and guidelines were published to improve and assure occupational standards in the field of biotechnology.

Legal considerations

Concerning hazards deriving from conventional BAs, the European Community passed the "Guidelines for Protection of Employees from Biological Risks at the Workplace" (1990), and in Germany the "Biohazard-Act" was issued in April 1999.

For recombinant DNA technology, the guidelines for safe handling go back to Asilomar, in 1975. Since then, several institutions and boards, and a wide range of public recommendations, guidelines and safety acts have addressed this topic. Although the WHO already stated, in 1983, "there are no specific safety risks associated with recombinant DNA-work", in Germany this new branch of biotechnology was subject to a special legal framework; part of the reason was that the above mentioned European Guidelines took so long to be transferred into national law.

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In 1990 the “Gentechnikgesetz” was issued, and revised in 1993. The standards for occupational surveillance are addressed in “Gentechnik-sicherheitsverordnung”. Thus recombinant DNA technology has a history of 20 years of safe handling.

The new legal considerations especially address the occupational risks of the unintended use of BAs. So in areas like waste treatment the efforts to improve safe handling have intensified as employees face high concentrations of BAs with often only partly known hazardous potential.

Biohazard Risk Assessment

Risk assessment can only be performed in a team consisting of an industrial hygienist, occupational physician and site manager. The team delivers the necessary basis of decision-making regarding all efforts to improve the safety of the workplace and gives advice concerning priority ranking. Risk assessment has to take into account two main aspects: (1) The risk deriving from the BAs in use; (2) The risk deriving from the specific handling of the BAs.

Biological agents

BAs, like viable cells, cell clusters or viruses, represent a great variety of possible hazards. The potential risk associated with every single sort of BA is determined by several qualities:

- Virulence
- Pathogenicity
- Infectious doses
- Routes of infection
- Tenacity
- Epidemiological situation
- Possibility of treatment/preventive measures

Taking into account these characteristics the BAs are classified into four different risk groups:

- Risk group 1: Unlikely to cause illness in humans, e.g. *E. coli* K 10, yeast.
- Risk group 2: May cause illness in humans, presenting a risk for employees, unlikely spreading of the disease in the population, and the need for effective treatment/preventive measures. Examples include staphylococcus, streptococcus, Candida, EBV.
- Risk group 3: May cause severe illness in humans, presenting a serious risk for employees, the risk of spread in the population, and the need for effective treatment/preventive measures normally available. Examples are anthrax, rabies, HBV, HCV, HIV.
- Risk group 4: Causes severe illness in humans, presenting a serious risk for employees. The risk of spreading in the population may be high. Effective treatment/preventive measures are not normally available, e.g., Ebola pox.

BAs used in recombinant DNA work are classified in the very same categories. Experience has shown so far that there is no specific risk associated with genetic engineering. The legal framework in Germany addressing genetic engineering nevertheless tends to be stricter, and so biological risk assessment has to be supervised by a public scientific board (ZKBS).

In addition to the infectious risks the toxic and allergic potential of the BA has to be considered.

Workplace characteristics

After the specific properties of the BAs, the procedures for handling them is the second most important determining factor in risk assessment. Special risks derive from procedures with increased likelihood of direct contact or with procedures involving a corresponding risk of accident:

- The use of glass tubes, pipettes, syringes, with the risk of injury
- Direct contact with BAs in great volumes (waste treatment)
- Handling of infected animals/treatment of infected patients
- Risk of inhalation of bioaerosols

With BAs of risk group 2 or higher in use, it has to also be considered if vaccinations are available and if they should be offered to the employees.

As with other workplace stressors, there is an established ranking of control measures:

- Substitution: Is the use of BAs of a lower risk group possible?

Table 1 Risk assessment for handling of BAs

Health effects/ risk groups						
4	X		O	O	O	O
3		X		O	O	O
2			X	O	O	O
1				X	X	X
Exposure rating	A	B	C	D	E	

A = No exposure: No contact (remote operations)

B = Low exposure: Infrequent contact, low concentration of biological agents (closed systems)

C = Moderate exposure: Frequent contact at low concentration/infrequent contact at high concentration, engineering control in place (biological safety cabinet)

D = High exposure: Frequent contact at high concentration, limited engineering control in place (bioaerosols)

E = Very high exposure: Frequent contact at very high concentration (waste water, waste product handling) or increased risk of accidental exposure

Insignificant: No need of action, documentation

Low: Counseling, documentation

X Moderate: Counseling, evaluation if medical surveillance is necessary

O High: Counseling, medical surveillance

- Technical solutions: Are there ways to minimize exposure to the BAs?
- Organization: Is it possible to reduce risky procedures and/or the number of exposed employees?

As supplementary control measures the following have to be considered:

- PPE: Are personal protection devices available to reduce the risks?
- Medical surveillance: Are medical examination procedures, vaccinations reasonable?

Industrial hygiene

The classification of BAs involves addressing their infectious potential, neglecting allergic or toxic effects. So we know about serious allergic reactions after contact with several risk group 1 species (especially well-known for fungi like mould).

This history of work-related allergic skin and airways diseases with BAs from all risk groups is one important reason to place great emphasis on good industrial hygiene, especially avoiding or minimizing every ambient air contamination.

Threshold values at this time can only be provided for a few BAs. There are no exact dose/response relations as with chemical or physical hazards, due to the individual allergic disposition. But the risk of work-related airways diseases caused by exposure to BAs such as “organic dust toxic syndrome”, “farmers lung”, etc., is related to the level of ambient air contamination. There is an increased risk for already sensitized persons, so that very low exposures to mould species, e.g., *Alternaria* with 100 spores/m³, may trigger allergic responses. Several limiting values have been discussed for endotoxin concentration and mould (spores/m³).

Again, it should be outlined that the main challenge for occupational medicine and industrial hygiene is in those areas of unintended use of BAs. Work-related illnesses derive almost exclusively from these kind of workplaces.

The basic requirements for appropriate industrial hygiene in handling BAs include: minimizing exposure; easy-to-clean facilities; avoiding aerosols; no mouth pipetting.

Corresponding to risk groups 2–4, increasing precautionary measures are required and are described with respect to the corresponding degree of containment. For biotechnological workplaces with intended use of BAs they are well-established. They include demands for: laboratory facilities, laboratory ventilation, laboratory equipment, and laboratory operations.

In-detail requirements are for: biohazard signs; restricted access; low pressurized atmosphere; HEPA filter systems; protective clothing; cleaning; waste disposal; etc.

Occupational medical surveillance

What are the specific occupational risks associated with BAs?

We know about occupational risks associated with the handling of BAs: infectious diseases; allergic reactions; intoxications.

These occupational risks are well-known, especially the risk associated with infectious diseases in health services.

In Germany, 1,153,412 occupational health examinations were administered in 1997, mainly addressing occupational risks of infections caused by BAs of natural origin. The main concern is the prevention of hepatitis infections in health services.

The number of occupational health examinations for employees working in recombinant DNA technology is far lower. The statistics in Germany list 4,871 examinations in 1997.

The statistics for occupational infections in Germany are dominated by the incidence of hepatitis and tuberculosis with declining trends. One of the most powerful instruments of occupational medicine is vaccination. In the handling of some BAs vaccination has the greatest influence on health protection. Since the beginning of HBV vaccination programs the rate of work-related hepatitis B has dropped dramatically. Everywhere it was administered, the infection rates of employees at risk were reduced to approximately 10% of the previous numbers. The absolute number of occupational infectious diseases for the chemical industry in Germany is very low (nine suspected cases announced in 1998).

What are the strategies of occupational medical surveillance?

Occupational medical surveillance generally has two objectives: (1) medical contribution to the safety program; (2) detection of work-related diseases.

The personal nature of the response is of unusual great importance with biohazards. In contrast, chemical or physical hazards tend to follow a dose response-related risk, with few individual factors involved in the process of possible work-related diseases. Regarding BAs, the infectious and allergic risk is very much influenced by the immunological responses of the individual person.

About one third of the population has a history of allergic diseases – most common is pollinosis. It is not possible under the category “fitness for duty” to deny this part of the population access to every workplace with BAs that have allergic potential, although in individual cases medical concerns might be justified.

There is a great variety of different personal susceptibilities to infections. The underlying process of infection is determined by the individual interaction between the infected person and the infecting microorganism.

Following the stress versus strain concept of occupational medicine, one of the objectives of the surveillance program is to identify those employees who are at higher risk when exposed to BAs because of an impaired immune system or weakened resistance, and thus an increased risk of infectious diseases. The tools to achieve this goal are occupational health examination programs:

- **Preplacement examinations:** Employee medical history with special regard to immunological diseases, illnesses and medications that may impair the immune system; physical examination including urine sample, WBC, RBC, BSR, SGOT, SGPT, and blood sugar.
Employee counseling should be provided.
Vaccinations, if available against the BAs in use, should be administered.
The first medical examination, prior to work with BAs, establishes a baseline for further surveillance and detects employees with impaired immune responses.
- **Periodic examinations:** These accompanying examinations are to monitor the unimpaired immune response and to detect work-related diseases. The recommended frequency is different between the European countries. In Germany, yearly examinations are demanded for workers in DNA technology, with other BAs the recommended frequency is every 3 years after the first annual repeated examination.
- **Final examinations:** After more than 1 year of occupational exposure to BAs, a final examination is recommended. To detect delayed occurrence of diseases (the incubation periods of various viral infections may last several months) the dates of the final examinations should be adapted to these time frames.

With the development of improved diagnostic tools in the last decade (PCR), it is no longer necessary to store away frozen serum samples of employees. This had been a legal obligation for some time in the recombinant DNA technology field. Every different BA may require special adaptations and enlargements of the examination program, as in the case of vaccinations. The different aspects of the BAs in use are taken into consideration in the new examination program of the German Workers Compensation Act (G 42). Specific information, addressing 43 different microorganisms, is listed, advising the occupational physician what to consider with every special germ and how to best advise the employees. In a similar way the TRBA 310 published by German state authorities deals with the special aspects of 17 different recombinant DNA organisms.

The specific risks associated with BAs in use call for specialized and adapted occupational programs: the trend is towards *case-by-case* management for every BA in use. It is therefore a prerequisite to have a close and open cooperation between industrial hygienists and occupational physicians in order to produce these specific medical and organizational control measures.

- **Crisis management:** The challenge for occupational medicine with regard to biohazards is: **BE PREPARED!** Other than with most physical or chemical hazards, the occupational physician may provide effective medical preventive measures (vaccination), and there exist effective treatments in case of most infections. Even in cases of accidental exposures to viruses like HIV or herpes B, post-exposure management, including drug therapy, reduce the risk of virus transmission. This means information about the BA should be at hand, including:
 - Antibiotic/antiviral treatment possible? Antibiotics!
 - Effective disinfectants?
 - Vaccinations available?
 - Diagnostic tracking tools available?
 - Knowledge of allergic/toxic properties?

Conclusions

In the fields of biotechnology, including genetically engineered BAs, there are well-established control measures and surveillance programs. These have guaranteed a high standard of safety. Further improvements have to be achieved in the areas of unintended use of BAs, new legal considerations specially address this topic.

The occupational standards show a tendency towards management adapted to the specific BAs in use, to assure the best possible health protection.

Therefore, to protect employees handling BAs, the competence of the occupational physician and the industrial hygienist is of critical importance. They have to provide appropriate counseling of both workers and the community affected by the safety of the workplace.

Currently, rates of occupational illnesses are low and vaccination programs of the past, have been successful. There is a need to further improve the training and safety motivation of workers. Unselected screening procedures should be replaced with medical programs tailored to the outcome of the specific risk assessments.