

Federal Institute for Risk Assessment (BfR)

First results of the International Symposium on the Risk Analysis of Antibiotic Resistance

BfR Report of 13 November 2003

From 9 to 11 November 2003 the International Symposium "Towards a Risk Analysis of Antibiotic Resistance" was held in Berlin. This event was staged on the initiative of the Federal Ministry for Consumer Protection, Food and Agriculture (BMVEL) and the Federal Institute for Risk Assessment (BfR) with the support of the Federal Agency for Consumer Protection and Food Safety (BVL) and the Federal Agriculture Research Centre (FAL).

The Symposium was designed to record the current level of knowledge on the development and spread of antibiotic resistance in microorganisms. Individual themes were examined in working groups. The results are to serve as the basis for risk assessment and the elaboration of recommendations for active risk management. Management measures are to be discussed and decided on at a national follow-up conference.

The Symposium was intended for national and international experts in the field of antibiotic resistance research and consumer health protection. Interested guests were also welcome to attend as observers. Around 200 scientists from 16 countries attended the Symposium. On the first day 22 papers were presented in four sessions. They were based on the steps in the work plans on risk analysis adopted by the FAO/WHO CODEX Alimentarius Commission in 1995. According to them, the process of microbiological risk assessment is broken down into hazard identification, hazard characterisation, exposure assessment and risk characterisation. On the second day of the Symposium working groups were set up to examine the individual components of risk analysis. The main findings and the current level of knowledge were assessed and conclusions and recommendations were then formulated in the working groups. This report contains the first, summary overview of the results of the working groups.

Working group I: Hazard identification

This section involves the identification of the known and potential effects of a specific pathogen or specific agent on health.

The individual results of this working group were presented by the chairmen of the working group, Threlfall and Schwarz. The following conclusions are relevant for the risk assessment work of BfR:

1. Antimicrobial resistance spreads in bacteria of animal origin.
2. Resistant bacteria from animals can directly or indirectly infect man.
3. Resistant bacteria from animals transmit their resistance genes to bacteria of importance for human medicine.
4. This leads to the spread of resistant bacteria in food animals and in man.

These conclusions highlight the reasons for the failure of treatment of severe infections in man. The working group outlined the factors that lead to the selection and spread of resistant bacteria in animals. They include sub-therapeutic doses, mass medication, the lengthy treatment and use of antibiotics with a broad spectrum of action and their combination instead of using antibiotics with a narrow spectrum of action. Furthermore, prophylactic and metaphylactic use, without undertaking a suitable microbiological diagnosis that should also include an antibiogram, were mentioned as risk factors.

The following statements were made about the selection and spread of resistant bacteria in animals.

In general, it can be said that domestic food animals are given antimicrobial substances for therapeutic, metaphylactic and prophylactic purposes. Only a very small proportion was administered for growth-promoting purposes. It is a fundamental principle of microbiology that antimicrobial substances kill or prevent the spread of sensitive bacteria. Only resistant bacteria are then still able to multiply and spread. This selection leads to an accumulation of resistant bacteria. Commensal, zoonotic and animal pathogenic bacteria accumulate. Consequently, both resistance genes and resistance bacteria can be exchanged between individual animals in a herd or between herds.

Resistant bacteria from domestic animals can spread to man indirectly via the food chain or directly from the animal. Foods may be contaminated by the animal carcass during the slaughter process or during the production of foods. In the case of direct spread, contact with domestic food animals or their excrements is the main source. Farmers, vets and slaughterhouse workers are particularly at risk. The fate of resistant, animal pathogenic bacteria in man depends on various bacterial and host factors. Experts distinguish between long and short-term colonising pathogens. However, there may be a horizontal gene transfer of the bacteria from the animal to the human commensal flora or human pathogenic bacteria in the two groups.

In both cases this leads to the presence of resistance genes transmitted from bacteria in the domestic animal to bacteria in man. This colonisation can lead to disease in man. If these diseases are to be treated, resistant pathogens may lead to a prolongation of the illness. Furthermore, the course of the disease may be more severe. Resistance may lead to failure of the treatment and eventually to the death of the patient. The experts' discussions focussed on the situation with *Salmonella*, *Campylobacter*, *Escherichia coli* and *Enterococcus*. The working group endeavoured to discuss and find answers to the following main questions for these pathogens:

1. Does the use of antimicrobial substances in animals lead to the spread of resistant bacteria?
 - In the case of *Salmonella*, fluoroquinolone resistance, apramycin-gentamicin resistance and multi-resistance were considered to be particularly worrying.
 - In the case of *Campylobacter*, fluoroquinolone resistance and macrolide resistance are to the fore.
 - In the case of *E. coli*, fluoroquinolone, apramycin-gentamicin and streptothricine resistance.
 - In the case of *Enterococcus*, glycopeptide, macrolide and streptogramin resistance in particular is considered to be worrying.

2. Which resistances are transmitted from animals to man?
 - In the case of *Salmonella*, fluoroquinolone, apramycin-gentamicin resistance and multiresistant pathogens.
 - In the case of *Campylobacter*, fluoroquinolone resistance. Macrolide resistance was deemed to be questionable.
 - In the case of *E. coli*, apramycin-gentamicin resistance and streptothricine resistance. Fluoroquinolone resistance was deemed to be questionable.
 - In the case of *Enterococcus*, glycopeptide, macrolide and streptogramin resistance.

3. Which resistance determinants of these bacteria can be transmitted to other human pathogenic bacteria?

The experts quoted the following examples:

- In the case of *Salmonella*, apramycin-gentamicin and multiresistance.
- In the case of *Campylobacter*, fluoroquinolone and macrolide resistance.
- In the case of *E. coli*, apramycin-gentamicin and streptothricine resistance.
- In the case of *Enterococcus*, glycopeptide, macrolide and streptogramin resistance.

In general, the group was of the opinion that the question about transmissibility cannot be clearly answered for other resistance genes since the same resistance genes are found in bacteria of animal and human origin. Hence, at present the origin of widespread resistance genes in human pathogens cannot be clearly identified. It is, however, clear that the use of antimicrobial substances in human beings, in veterinary medicine, in agriculture and aquaculture has frequently led to the transfer of genes from human pathogenic, plant and animal pathogenic organisms and of bacteria which live in the environment.

4. Do resistant strains of animal origin trigger clinical diseases in man?

- The expert group concluded that there are well-documented studies for *Salmonella* and *Campylobacter* which prove infections in man caused by resistant or sensitive strains of animal origin.
- Human infections were also described from bacterial *vanA*-gene bearing *Enterococcus faecium* and uropathogenic *E.coli* strains. These resistance genes are probably of animal origin.

5. What effects do resistant strains have on cases of disease in man?

- In the case of *Salmonella* therapy failure occurs, e.g. when fluoroquinolones are administered.
- In the case of *Campylobacter* antibiotic treatment is only necessary in the case of a very lengthy or very severe course of gastroenteritis or generalised infections. In this context, macrolides are the preferred treatment. Fluoroquinolones are only in second place.
- In the case of *Enterococcus* infection is triggered specifically in immunocompromised patients. Treatment failures occur in the case of multi-resistant strains.

Furthermore, the experts named the following five aspects as being of importance for the increase in or spread of resistance:

1. The import of resistant strains or resistance genes through commerce, open markets without any global control.
2. Use of disinfectants and heavy metals which exert selection pressure on the microorganisms.
3. Residues and their potential to select resistance.
4. Clarification of the question whether hazard identification should be undertaken only for individual species (*Salmonella*, *Campylobacter*) or whether a general approach should be adopted for all zoonotic bacteria.
5. The slow reversibility of resistant strains to sensitivity.

The experts deemed the transfer of resistant pathogens from domestic food animals to man to be a central factor in hazard identification.

Working group II: Hazard characterisation

Hazard characterisation encompasses the quantitative and/or qualitative assessment of the properties of adverse effects. A dose-effect relationship should be established, as far as possible, for biological agents.

The individual results of this working group were presented by the chairpersons of the working group, Tollefson and Tschäpe.

The following conclusions are of importance for the risk assessment of BfR:

There are several sources for studies confirming the causal link between the incidence of resistant bacteria in man and their selection in domestic food animals. Mention should be made of epidemiological surveys of food-borne infections and ecological studies about the trend towards resistance development. Moreover, studies on outbreaks and outbreak descriptions amongst farmers, their families and other persons, who come into direct contact with resistant bacteria, as well as the typing of the isolates confirm that there is a close link between resistant microorganisms of animal origin and those in man. According to a study by Mead et al. (1999) 95% of the infections caused by enteritis *Salmonella*, 80% of the infections caused by *Campylobacter*, 85% of the infections caused by verocytotoxic *E. coli*, 70% of the infections caused by enterotoxigenic *E. coli* and 30% of infections caused by other diarrhoeal *E. coli* can be attributed to food.

There are numerous studies that were able to trace back infections with resistant *Salmonella* to their origin in the farms. The experts pointed to studies which showed that the mortality rates were far higher in outbreaks with resistant *Salmonella*. Furthermore, they pointed out that there are at least 13 publications which report complications that occurred during the treatment of *Salmonella* with MIC values in respect of fluoroquinolones which were below the 4 µg/ml breakpoint laid down by NCCLS. The negative effects of this infection include the failure to eliminate the pathogen from the patient, a prolongation of the feverish illness and fatalities. There are also studies documenting a prolongation of diarrhoea disease in the case of *Campylobacter* infections. This has been described for the USA and Denmark.

A new, as yet, unpublished study by Varma et al. shows that Danish patients infected with resistant *Salmonella* are more likely to develop an invasive infection and also have to be treated more frequently in hospital. The length of treatment is longer for these infections. Another study by Helms et al. from 2002 shows that patients, infected with quinolone resistant *Salmonella Typhimurium*, ran a greater risk of dying within the next two years than patients infected with sensitive *Salmonella*. Compared to the general Danish population the corrected relative mortality rates for sensitive *Salmonella* were 2.3, for *Salmonella* with the resistance type ACSSuT 4.8, with the resistance type nalidixine resistance (Nx) 10.3, and with the resistance type ACSSuTNx 13.1. Similar results were described by Molbak et al. for *Campylobacter*.

Based on these facts, the experts came to the following conclusions:

1. The food chain contains a multitude of antimicrobial pathogenic microorganisms, including *Salmonella* and *Campylobacter*. There is considerable evidence that they have a significant impact on general public health.
2. The hazards include a greater risk of
 - death
 - invasive diseases
 - hospitalisation
 - prolongation of the duration of an illness

- higher transmission frequencies of disease as a consequence of impaired resistance
- outbreaks in areas in which antimicrobial substances are used

The experts formulated the following recommendations:

1. A preventive approach should be selected instead of waiting for a completely sound scientific chain of evidence. The general selection pressure through the use of antimicrobial substances should be reduced through careful use.
2. The use of fluoroquinolones and third and fourth generation cephalosporins should be reserved for the treatment of individual animals and only undertaken when the pathogens are resistant to other antibiotics.
3. Improvement of animal production and animal husbandry in order to reduce the need to use antimicrobial substances.
4. The ultimate goal is to restrict the use of antimicrobial substances in domestic food animals if no diagnosis of the infectious agent has been undertaken and if there are signs of a threat to public health.

Working group III: Exposure assessment

Exposure assessment means the qualitative and/or quantitative assessment of the degree and probability of the intake of a pathogen.

The individual results of this working group were presented by the chairmen of the working group, Angulo and Baquero.

The following conclusions are of importance for the risk assessment of BfR:

The third working group considered the dissemination paths by means of which resistance determinants in human pathogenic microorganisms can reach man and estimated the scale and the frequency of this exposure. At the same time, attention was drawn to the importance of the monitoring programmes and also to how changes in the use of antimicrobial substances influence exposure. The working group came to the following conclusions:

The exposure paths for man are food, water, human beings themselves and animals. In the case of foods chicken, turkey, beef, pork and the resulting products are to the fore. In the case of water, sewage and contamination caused by waste are considered to be critical. Human exposure can occur at many points, e.g. within the community, in hospitals or amongst workers involved in food production. In the animal realm exposure occurs through food animals, pets (dogs, cats, etc) and wild animals. For the individual pathogenic agents, the exposure paths needed to be ranked in respect of the incidence and scale of exposure for municipalities and hospitals. To this end, it is important to determine the occurrence of the pathogens at the individual locations, the incidence of resistance determinants, the scale of bacterial contamination and the degree of interaction in respect of the volumes used and contact frequencies. These parameters have a major impact on the development of monitoring programmes.

Working group IV: Risk characterisation

Risk characterisation involves the summarising of hazard identification, hazard characterisation and exposure assessment. The goal is to estimate adverse effects and the probability of their occurrence in a population also bearing in mind uncertainties.

The individual results of this working group were presented by the chairmen of this working group, Wegener and Witte.

The following conclusions are of importance for the risk assessment of BfR:

The working group focussed on the model of quinolone resistance (reduced sensitivity to fluoroquinolones) in *Salmonella* and *Campylobacter*.

1. For the risk characterisation of *Salmonella* 250 cases of therapy failure with 20 fatalities were calculated for the Federal Republic of Germany.
2. For *Campylobacter* the number of therapy failures is lower and there are also fewer fatalities.

When assessing exposure the experts came to the following conclusions:

1. It is estimated that around 20% of the cases of disease are caused by travel.
2. Water was deemed to be an insignificant source of infection.
3. Cases of food-borne disease can also be attributed to imported foods.
4. 50% of the cases of disease in the country can, however, be attributed to foods produced in the country.

The recommended risk management option involved improved animal and food production hygiene. At the same time, the restrictive use of fluoroquinolones was recommended through a voluntary undertaking of livestock breeders. One alternative is the ban on the use of fluoroquinolones. Attention is drawn to the importance of training schemes for producers, consumers, veterinary surgeons and physicians.

BfR assessment

Based on the situation outlined above, BfR considers the following statements on the status quo of current expert knowledge to be particularly relevant and they should be taken into account on the management level:

1. The use of antimicrobial substances in domestic animal production leads to problems in the treatment of human beings. They range from a serious and prolonged course of the disease to fatalities.
2. Compared to sensitive pathogens, resistant pathogens lead to a higher morbidity and number of fatalities.
3. These effects are particularly noticeable in the case of zoonotic pathogens.
4. To avoid delays, preventive approaches should be chosen instead of waiting for a completely sound scientific chain of evidence. The general selection pressure through the use of antimicrobial substances could be reduced through careful use.
5. The use of fluoroquinolones and third and fourth generation cephalosporins should be reserved for the treatment of individual animals and only be undertaken if the pathogens are resistant to other antibiotics.
6. No further marketing authorisations should be granted for the use of fourth generation cephalosporins in veterinary medicine.

Further, up-to-date information can be accessed on:

<http://www.who.int/foodsafety/micro/meetings/nov2003/en/>