International Association for Soaps, Detergents and Maintenance Products

General appraisal of the risk of occurrence of resistance in target organisms through the use of disinfectants from main group 1

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Introduction

One pre-condition for the granting of an authorisation for a biocidal product under the requirements of the Biocidal Products Regulation EU No 528/2012 (BPR) (Article 19, Annexes II & III) is the proof of no unacceptable resistance or cross-resistance developing in target organisms following the use of biocides. Relevant data are demanded.

The issue of potential disinfectant resistance needs to be discussed, in particular, against the background of reports on biocide-induced antibiotic resistance (SCENHIR paper) and further literature reports on biocide-resistant micro-organisms (amphoteric surfactants, QAC, formaldehyde, glutaraldehyde).

Definition of the term "resistance"

In this paper, the term "resistance" is used based on a quote from an experience report by the German Federal Institute for Materials Research and Testing/BAM ("BAM Erfahrungsbericht: Resistenzen im Holzschutz"), in the meaning of the technical Notes of Guidance on the Biocidal Products Directive 98/8/EC (BPD) [Revision of Chapter 6.2 (Common principles and practical Procedures for the Authorisation and Registration of Products) of the TNsG on Product Evaluation, and a revision of Chapter 10 (Assessment for the potential for Resistance to the active substance) of the TNsG on Annex I inclusion, CA-Meeting 13-15 May 2009].

On the above basis, resistance is seen here as a genetically determined (congenitally) reduced sensitivity of target organisms to active substances / biocidal products which cannot be acquired during the lifespan of an organism. Resistance can be acquired by mutation or by uptake of relevant genetic material (e.g. bacterial plasmids), or resistance can pre-exist intrinsically.

In this context, it must be differentiated between phenotypic adaptation which leads to an increased biocide tolerance through adaptation (e.g. biofilm formation) and genetically inherent resistance which persists also after selection pressure is no longer given.

Furthermore, a differentiation is made between the naturally occurring resistance in certain species to certain active substances (intrinsic resistance) and acquired resistance, with individual strains of one species reacting with significantly different sensitivity to certain active substances. Here, only the minimum lethal dose according to accepted standards is examined for the efficacy testing of the relevant products – and not the minimum inhibitory concentration (as is usual for antibiotics).

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Can biocide use lead to an increase in antibiotic resistance?

Here, the nature of the biocide-induced antibiotic resistance needs to be discussed in some more detail. Sublethal doses of biocides select more tolerant strains which are essentially characterised by non-specific efflux pumps on/in the cell membrane. This answer constitutes an elementary capability of micro-organisms that was acquired in the course of evolution, in order to be able to respond flexibly to changing environmental influences. In this context, further going studies have shown that also other, non-biocidal chemicals trigger the same cell reactions and structural changes. At the same time, these non-specific changes in the layout of the cell membrane can lead to a faster removal of certain antibiotics, causing a specific antibiotic resistance. Nevertheless the conclusion of experts after thorough review of available information was that “even if each biocide represents a specific case, there is scientific evidence that biocides select for biocide resistance (note: defined as an increase minimum inhibitory concentration), but there is, so far, no conclusive evidence that this also determined or will determine an increase in antibiotic resistance”.

Practical relevance of resistance to disinfectants

A large part of the active substances commonly used in today’s disinfectants in the fields of private households, hospitals and industry have been applied for many years or even decades. In contrast to the well-known problem of antibiotic resistance, no resistance has become evident to commercial grade disinfectants. This is because of the different modes of action of both substance groups: unlike antibiotics, the active substances used for disinfection do not attack the individual components of micro-organisms; in a more general way they destroy the cell membrane, change functional groups of enzymes, or block the genetic information. In the usual use concentrations of disinfectants – which are normally determined by EN testing – these products react non-specifically with many target structures of the micro-organisms and thus prevent the development of real resistance. Many scientific articles have been published within the last three decades on “biocide resistance” with a particular focus on cationic agents. However, in all of these publications “resistance” is defined as an increase of minimum inhibitory (i.e. sublethal) concentrations. The usual use concentrations are 100-1000 times above the minimum inhibitory concentration. This ensures that intra- and interspecies tolerances in the natural or acquired sensitivity of micro-organisms cannot come to bear. By contrast, antibiotics react in a target-oriented manner with certain cell structures or metabolic pathways. If the structure of the target cell changes by mutation or by acquiring specific genetic material, then the antibiotic has no effect.

Laboratory studies in sublethal use concentrations (concentrations below the minimum inhibitory concentration) with various biocidal active substances show an increase in tolerance. This could be essentially attributable to the test design in the laboratory. For the usual use concentrations of biocides, one can speak of a real resistance only in a few exceptional cases. No development of resistance was observed in complex laboratory studies with a practice-oriented test design.

Generally, resistance develops under selection pressure in the range of sublethal biocide concentrations. This concentration range is not reached in use as instructed. The use of a disinfectant is normally followed by rinsing with a sufficient quantity of water, leading to a rapid dilution of the active substances to biodegradation level. Other active substances (e.g. alcohols) evaporate and no longer exert any selection pressure. In other cases surfaces are not rinsed,

but kept dry after biocide application. Hence, in the latter two cases there is no microbial growth on surfaces that are not rinsed. Consequently, no selective pressure for resistance is given here, either.

The risk of micro-organisms developing resistance to disinfectants of main group 1, which were tested according to international standards, is rated negligibly low in the intended and appropriate use of these products.

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