AGENCE FRANÇAISE
DE SÉCURITÉ SANITAIRE
DES ALIMENTS

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Contribution

LE DIRECTEUR GÉNÉRAL

de l'Agence française de sécurité sanitaire des aliments à la consultation publique de l'Autorité européenne de sécurité des aliments (EFSA) sur le document : « Revision of the joint AFC/ BIOHAZ guidance document on the submission of data for the evaluation of the safety and efficacy of substances for the removal of microbial surface contamination of foods of animal origin intended for human consumption"

L'Agence française de sécurité sanitaire des aliments s'est autosaisie le 12 février 2010 pour répondre à la consultation publique de l'Autorité européenne de sécurité des aliments (EFSA) concernant la révision d'un document d'orientation réalisé par les groupes scientifiques BIOHAZ/ AFC concernant la soumission des demandes d'autorisation des substances destinées à éliminer la contamination microbienne de la surface des aliments d'origine animale.

L'Afssa avait fait part de ses commentaires lors de la première consultation publique sur ce document en mai 2006. Elle s'est autosaisie sur ce nouveau document soumis à consultation, très largement développé par rapport à la version précédente.

Le document d'orientation inclut des données et des exemples de plans d'étude relatifs à l'évaluation de ces substances en termes de sécurité pour les consommateurs et pour l'environnement et en termes d'efficacité pour la réduction du niveau de contamination microbienne. Le document d'orientation indique également comment évaluer le développement éventuel d'une résistance aux antimicrobiens pouvant être déclenchée par ces agents de décontamination.

Suite à la consultation de son comité d'experts spécialisé « Microbiologie » réuni le 11 février 2010, l'Afssa a élaboré des commentaires sur le document « Revision of the joint AFC/ BIOHAZ guidance document on the submission of data for the evaluation of the safety and efficacy of substances for the removal of microbial surface contamination of foods of animal origin intended for human consumption ». Ces commentaires, figurant en annexe, ont été transmis à l'Efsa via leur site internet le 22 février 2010.

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Afssa comments on "Revision of the joint AFC/ BIOHAZ guidance document on the submission of data for the evaluation of the safety and efficacy of substances for the removal of microbial surface contamination of foods of animal origin intended for human consumption"

General comments

Afssa underlines the net improvement of this guidance document compared with the first version due to the inclusion of examples of study designs and precisions on the type of data that a dossier should include for the evaluation of the potential emergence of antimicrobial resistance;

However, the document contains certain number of terminological and methodological inaccuracies that are detailed below:

- Many recommendations in this document are not clearly delineated:
  - Example 1: it is written on Line 387 that non-pathogenic microorganisms should be counted. The reader has no information on the basis for the choice of these microorganisms or on the number of genus/species/strains.
  - Example 2: when comparing numbers of bacteria, what level of statistical significance is to be used to consider there is a difference, and is just a significant difference enough to conclude there is an effect?

Inexplicit requirements could lead to information being judged differently by different experts, agencies or Member States, and to some degree of arbitrariness.

- While it was repeatedly written that the text applied to different animal species at different stages of production, the text is biased towards poultry. It seems that guidelines defined for application to carcasses in a slaughterhouse cannot be fully compatible with guidelines that should be put into practice for finished products.
- On the subject of efficacy, the whole document focuses on efficacy as such, including immediate efficacy, maintaining efficacy over time and the risk of microorganisms persisting due to lower susceptibility, but:
  - What about evaluating the effects on spoilage flora with possible risks to human health?
  - What about the impact of sub-lethal concentrations on the expression of virulence genes? While this is a relatively new subject of exploration (Kastbjerg, 2010; Ryan, 2008; Galice, 2006; Matja, 2002), it is important to integrate this point in the requirements straight away, asking for at least a bibliographic review.
- The terms "microbial" (in the title), "microorganisms", "pathogenic bacteria" and "pathogenic microorganisms" are employed indifferently throughout the document., These generic terms may cover contaminants other than bacteria such as viruses or mould. To take the example of viruses, such as noroviruses, are these to be considered to lie within the scope of this guidance document? This point should be specified in a foreword.
- Throughout this document, a variety of terms are used. These include "substance" (in the singular and plural), "product", "formulated product", "decontaminating agents and "decontamination agent". Furthermore, the term "substances" appears in the title while in the "Definitions" chapter (pp. 27-28), only the term "formulated product" is defined ("The ready-to-use product for which authorisation is sought"). This definition assumes that the products are not diluted before use, yet line 317—which describes the application method—specifies "the intended doses to be used", and lines 407-410 "justification of the concentration of the product formulation proposed should be experimentally demonstrated". This needs to be clarified as specidied in chapter 7.

In addition to this need for clarification, harmonisation and consistency, there is the problem of the integral composition of a product that could contain a single substance or, several substances declared as active plus one or more co-formulants. The latter can play a role not only with respect to the product's intrinsic activity but can also contribute to lowering susceptibility (e.g.: acid or alkaline pH, surface active agents).

- The word "antimicrobial" has been used in the past to designate a decontamination agent (EFSA, 2005, 2008). To avoid confusion, we suggest, as seen in some places in the document (including the definition section), systematical use of the adjective "therapeutic" before "antimicrobials".
- With regards to resistance, only the expression "antimicrobial resistance" appears in the chapter on definitions and linking this term to conditions of use in practice is quite acceptable. However, in the body of the document, we often find the expression "potential occurrence of acquired reduced susceptibility" which is distinct from the expression "development of resistance to antimicrobials". All these terms relating to "resistance" should be carefully defined and distinction should be made between adaptation to inhibitory concentrations and resistance to killing concentrations of decontamination agents.

  There are several definitions of resistance in the literature. To avoid confusion between the impact on growth inhibition and the impact on killing of decontamination agents, we suggest as in Lear et al (2002), in the Afssa opinion (Afssa, 2007) and in Cerf at al. (2010), the use of the word "resistance" in the context of micro-organism killing and "tolerance" in the context of adaptation to inhibiting concentrations.

  Moreover, there is an agreement between EU Member States relating to Biocides directive 98/8/EC in the TNG (Technical Notes for Guidance, in support of annex VI of directive 98/8/EC of the European parliament and the Council concerning the placing of biocidal products on the market – ECB, February 2008 - chapter 6 "Assessment of other unacceptable effects" revised in 2009). Whatever the vocabulary chosen, it must be included in the Definitions section.

Comments on different chapters/sections

INTRODUCTION

A few lines explaining the words "remove" and "removal" before "surface contamination" should be added to the introduction. Whereas decontamination agents may remove some microbial cells, their effect is mainly to inactivate bacterial cells that are not all detached from the meat surface.

Whatever chemical decontamination process is used, one is faced with the tailing off phenomenon that characterizes the decontamination kinetics: a fraction of the initial population escapes the decontamination process. Furthermore, it is highly improbable that the number of decimal reductions (log kills) obtained on a high population level could be reached when the initial population level is low. In any case, the outcome is the survival of a low number of pathogenic bacteria on the food surface. For this reason, decontamination may be acceptable when the probability of infection by low doses is low. But it is certainly not a good measure against pathogenic micro-organisms when the probability of infection by low doses is high (e.g. *E. coli* O157:H7 or other STEC). For such pathogenic micro-organisms, the best protection of consumers is through the application of good hygienic and HACCP principles. Furthermore, as natural prevalence of STEC is low, the only possible trials to judge decontamination efficacy would have to be made after artificial contamination, with no guarantees to reproduce the physiological state and attachment strength of naturally contaminating cells. This point should be specified in introduction.

It is said that the efficacy of a technique must be assessed by comparison with a control treated with water (lines 57, 147 and 151 among others), in compliance with Regulation 853/2004. Hot water is actually used as a decontamination technique, so it obviously cannot currently be considered as a control. This point should be specified.

Comments on the performance of a chemical treatment (lines 189 and on)

It is one thing to demonstrate a statistically significant reduction in contamination and quite another to accept this amount of reduction. To put it succinctly, a 20% reduction in bacteria during experimentation may not be acceptable in the light of the risks linked to the nature of the microorganisms tested. It is difficult to establish a performance criterion in such a reference system.

However, the applicant should develop an argument based on the results obtained with respect to risks. This argument would then be analyzed to decide on its pertinence by the experts responsible for examining the application.

CHAPTER 3: SUBMISSION OF AN APPLICATION

3.2: Summary document:

Line 270: It would be useful to be more accurate and add to the "intended use" point the level of performance and action spectrum claimed.

CHAPTER 4: TECHNICAL DATA

4.1: Identity of the substance(s) and specifications:

Line 291: It is important to add an additional point on the chemical reactivity of each ingredient, knowing that this information would need to be related to point 4.4 (Reactions and fate on the treated foods of animal origin after rinsing).

4.3: The treatment and its purpose:

- Lines 308-309 i. c: Draw up an argument for the relationship between a reduction in contamination and a lower risk.
- Lines 310 and 311: The aims d and e should be removed.
- Lines 315-316: iii: Give more specific information on the relationship between the quantity of product (or substance) and the surface area (or weight) of the foodstuff especially when spraying the carcass.

CHAPTER 7: INFORMATION REQUIRED TO ASSESS THE EFFICACY OF A FORMULATED PRODUCT

As far as the methodological approach is concerned, for this particular area we cannot currently refer to standardised protocols recognised by the European scientific community. The approach suggested in this document has a number of defects and omissions, such as:

- In the Laboratory phase, inoculation is very brief (20 min, as confirmed by appendix A) and not credible. For this flora to grow on the food matrix, a Laboratory simulation would require one night at 4°C-8°C.
- Different levels of contamination would be necessary, not just one, to establish a correlation with the risk assessment.
- Prior to this simulation of tests in laboratory conditions, it would be useful to provide preliminary information:
    - On the product's intrinsic activity and its basic action spectrum according to current European standards,
    - An assessment of the product's ability to maintain this activity in the presence of representative organic media such as proteins and fats, and this at one or more temperatures corresponding to the usage claimed,
    - An assessment of the product's ability to lower bacterial susceptibility, an evaluation of the stability of this drop in susceptibility and a study of the impact on bacterial susceptibility to antibiotics,
    - An assessment of the product's impact on the expression of virulence genes, at least from a bibliographical viewpoint.

Once these data has been analysed, it will be possible to fully analyse the product's conditions of application and their consequences.

Lines 382-383: the end of the sentence should be removed, because at the end of shelf-life, it is not possible to know whether the new detected cells are repaired cells or daughter cells from CFUs that were not detectable (below the detection limit) after application of the decontamination solution.

8. INFORMATION NECESSARY FOR THE EVALUATION OF THE POTENTIAL EMERGENCE OF ANTIMICROBIAL RESISTANCE:

- Lines 437 to 439: This type of research must be carried out even if the product is already used and authorized in the framework of other regulations. Setting aside the fact that conditions of use would probably be different, we need to consider knowledge development. Consequently, the applicant should at the very least justify the fact that further research is not necessary.
- Line 511-514: to test susceptibility for (therapeutic) antimicrobials and decontamination agents, two types of methods are suggested: determination of the MIC and MBC. It must be noted that MIC and MBC of decontamination agents are not always correlated as shown for instance for Chlorhexidine Gluconate-Containing Mouthwash by McBain et al. 2003. Those authors suggested that, for several studied strains, "growth inhibition and lethality are related to interaction with different targets". Thus if a decontamination agent has for instance an increased MIC and a non-modified MBC, the bacteria in question could be declared as having a "reduced susceptibility". The decontamination agent could consequently be rejected although its MBC is adequate for its intended used, which is to kill bacteria, not to inhibit their growth.

APPENDIX A: EXAMPLE OF AN EXPERIMENTAL PROCEDURE FOR TESTING THE EFFICACY OF CHEMICAL SOLUTIONS IN REDUCING THE NUMBER OF CAMPYLOBACTER ON BROILER MEAT

Line 770:

– Different levels of contamination should be studied, which would be consistent with what is written in line 399.
- The conditions of inoculation of microorganisms are not sufficiently representative: prefer a night at 4-8°C to 20 min at an ordinary temperature,

Line 774

- The volume of product sprayed should be specified for comparison with the surface area treated.
- After contact, the product should be rinsed off with a suitable validated neutralizing agent so as to stop residual activity. This is consistent with line 405.

APPENDIX B: EXAMPLE OF AN EXPERIMENTAL PROCEDURE FOR TESTING THE EFFICACY OF CHEMICAL SOLUTIONS IN REDUCING CAMPYLOBACTER ON BROILER CARCASSES AT SLAUGHTER

Line 811: After treatment, add a rinsing stage with the neutralizing agent validated previously.

DEFINITIONS

Lines 926- 933: For the definitions of "co-resistance", "cross-resistance" and "multidrug resistance", it would be useful to refer to the technical Notes for Guidance, in support of annex VI of directive 98/8/EC of the European parliament and the Council concerning the placing of biocidal products on the market .

Line 941: As regards "Decontaminating agents", it is written that "These are substances applied to remove or reduce surface contamination"; a definition repeated in point 2, Objective (line 226). Reducing contamination is obviously a consequence of elimination. It would be more accurate to write "remove and/or destroy surface contamination" or "inactivate and possibly remove surface microbial contamination".

This definition is to be compared with line 65 defining decontamination as a reduction in the level of microbial contamination of carcasses and with line 83 (+ lines 189-190) introducing another approach, this time the reduction in prevalence and/or number of targeted pathogenic bacteria. In other words, the text needs to be made consistent.

Line 946: For the definition of disinfection", it would be useful, to be consistent with other European texts, to refer to European standard EN 14885 (February 2007) "Application of European standards for chemical disinfectants and antiseptics".

The term "residue" needs to be defined. There is already a clear and thorough definition in Biocides directive 98/8/EC.

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