EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Public Health and Risk Assessment
Risk assessment

Brussels,
SANCO.C7

EXPLANATORY NOTE FOR THE MODIFICATIONS OF THE SCCS OPINION ON TRICLOSAN (ANTIMICROBIAL RESISTANCE) FOLLOWING THE PUBLIC CONSULTATION ON THE DRAFT FINAL OPINION

This note sets out the rationale for the modifications made to the opinion of the European Commission Scientific Committee on Consumer Safety (SCCS) on triclosan (antimicrobial resistance) following a public consultation conducted between 29 March 2010 and 26 May 2010.

Introduction

In May 2009, the European Commission requested the Scientific Committee on Consumer Safety to assess the effects of triclosan on the emergence of bacterial resistance. A SCCS Working Group comprising of a member of the SCCS, a member of the Scientific Committee on Emerging and Newly Identified Risks (SCENIHR), a member of the Scientific Committee on Health and Environmental Risks (SCHER) and an expert from academia with experience on the subject was formed. The WG produced a draft opinion which was discussed and adopted by the SCCS plenary on 23 March 2010 as a preliminary opinion suitable for public consultation.

In line with its procedures for stakeholder dialogue, implemented in the Rules of Procedures of the new Scientific Committees set up by Commission Decision 2008/721/EC of 5 September 2008, the European Commission Health and Consumers Directorate General (DG SANCO) conducted a public consultation on the preliminary opinion of SCCS between 29 March and 26 May 2010.

Results/participation

By the deadline, DG SANCO received a total of 10 contributions. All of them were reviewed by the Working Group during its meeting on 8 June 2010 and appropriate modifications were introduced into the opinion which was then discussed and adopted as the final opinion by the SCCS at its plenary of 21 June 2010.

Modifications to the opinion

The opinion has been modified to take into account all submitted comments which were assessed by the Working Group to be pertinent and relevant for the subject matter and which were within

the competences of the Scientific Committees and respected the clear separation between risk assessment and risk management that underpins the Scientific Advisory structure of the European Commission. Comments on policy, risk management, legal clarification, ethics, the precautionary principle, were not considered as, although pertinent to the subject matter, they are outside the competences of the Scientific Committees.

Detailed explanations of the way the comments received were treated by the SCCS are provided below. The numbering of paragraphs and lines correspond to the sections of the final opinion adopted by the SCCS on the 21 June 2010 and published together with this document.

Changes to the opinion

1. On page 16, section 5.2, a sentence reporting on the reference Bojar et al. (2009) was added as a complement of information.

2. On page 26, section 6.3, a sentence reporting on the reference Bayston et al. (2007) was added. This reference reinforces the evidence base presented in the section on by-pass metabolic blockage.

3. On page 36, with respect to the negative results from the in situ studies, the text was amended as follows: "While these results are at first sight reassuring, the differences of methodologies used to measure "resistance" and to analyse the data make it premature at this stage to conclude that triclosan exposure never leads to developing microbial resistance. In addition, these useful in situ studies do not provide information on expression of genes involved in resistance, maintenance of resistance and virulence genes and transfer of resistance determinants. Thus this opinion strongly recommends to perform additional in situ studies looking at these aspects and bacterial phenotypes where known concentrations of triclosan have been found in the environment."

4. On page 30, section 6.6.2, text on the reference Pycke et al was added: "Pycke et al. (2010) observed that triclosan exposure of the environmental α-proteobacterium *Rhodospirillum rubrum* led to an increase in triclosan MIC. The extent of this increase as well as the generation of different antibiotic susceptibility profiles was triclosan-concentration dependent, indicating the expression of distinct resistance mechanisms." Triclosan resistance is rarely found in clinical strains because it is rarely looked for.

5. On page 27, section 6.3, the following text was added: "It is however interesting to note that Tabak et al. (2009) observed a synergistic action of sequential treatment of triclosan (500 μg/ml) followed by ciprofloxacin (500 μg/ml) against biofilm of *S. enterica* serovar Typhimurium. There is little information in the literature about the potentiation of activity between a biocide and an antibiotic and such a study is important and provides interesting application/effect of triclosan."

6. The reference of Cottell et al is already mentioned in the text, page 30.

7. On pages 37-38, the text of the opinion (section 12) has been modified to clarify the use of *in situ* data in relation to *in vitro* investigations.

8. On page 29, section 6.6.2, text referring to Pycke et al (2010) on the characterization of triclosan-resistant mutants was added

9. On page 26, section 6.3, text referring to Yu et al (2010) on the signature gene expression

profile of triclosan-resistant Escherichia coli was added.

10. On page 25, section 6.3, text referring to Zhu et al (2010) on triclosan resistance of *Pseudomonas aeruginosa* was added.

11. On page 27, section 6.3, text referring to Tabak et al (2009) on the synergistic activity of triclosan and ciprofloxacin on biofilms of Salmonella Typhimurium was added.

12. The conclusion of the opinion has been clarified to reflect comments received suggesting additional clarity.

Comments for which no changes could be made

In addition to the comments received which resulted in the above changes, the following comments were received and were evaluated by the SCCS but no changes were introduced in the opinion. The main reasons for this are : 1) comments were outside the scope of the terms of reference for this opinion; 2) comments were outside the competences of the Scientific Committees (and SCCS in this case) as they concerned policy and risk management; 3) in the scientific judgement of the SCCS, the submitted scientific evidence and argumentation were not of sufficient quality and strength to support changes and modifications in the opinion and its conclusions. For reasons of clarity, a brief rationale underpinning its evaluation of each comment is provided for each comment.

1. Regarding the comment on stability and solubility of triclosan, the normal storage conditions are not defined in the submission. Quantitative data on the solubility of triclosan in DMSO are not available. The SCCS considers that triclosan is soluble in DMSO. This opinion is not dealing with the ecotoxicity of triclosan.

2. Regarding the comment on **evidence of the potential of triclosan to induce or transmit antibacterial resistance** stating that since 2006 *"there do not appear to be any compelling reasons or scientific data to support different conclusions regarding the potential for triclosan to induce or transmit antibacterial resistance. In fact, there are several studies that provide support for a lack of antibacterial resistance in situ (Cole et al. 2003; Jones, 2000; Ledder et al. 2006; McBain et al. 2004; Sullivan et al. 2002)",* the WG agrees. This is actually in the text of the opinion in section 5.5.2.

3. The WG agrees on the **lack of standardized methods for MIC determination**. These points are covered in the document. There is no recognized bacterial model for the study of biocide resistance (SCENIHR, 2009).

4. Regarding the comment **on the in situ clinical and environmental studies** that "the 2010 SCCS draft document should give more consideration to the *in situ* clinical and environmental studies of triclosan and its impact on antimicrobial resistance as recommended by Russell (2004)", the SCCS considers that the information provided by Russell (2004) is limited and largely agrees with the data and conclusion of the opinion.

5. The SCCS considers that number of **in situ studies conducted** is limited. In addition, the methodologies used in these studies differ, notably in the measurement of resistance and although useful, the data provided by these studies showing a lack of correlation between triclosan usage and selection of triclosan resistance are limited. In particular, they do not incorporate any genetic aspect of resistance. Therefore, the SCCS concluded that it is still not possible to quantify the

genetic risk associated with triclosan usage (and any other biocide) and recommended in its opinion that additional studies be performed.

6. The in situ studies focused on measuring triclosan resistance and antibiotic resistance following triclosan exposure. They **did not look into the expression of genes involved in resistance**, maintenance of resistance and virulence genes and transfer of resistance determinants (SCENIHR 2010). The six in situ studies reported in this opinion showed no increase in bacterial resistance following exposure to triclosan. However, in these studies, not all hazards (e.g. genetic aspects) have been measured.

7. The points regarding dental plaque and gingival health and the lack of resistance found in a number of environmental isolates are already covered by the opinion. The SCCS considers that:

- The status of gingival health is not an indication of the lack of bacterial resistance.
- While the Walker study and the other studies cited were state-of-the art at the time they were performed, they did not have the modern tools (e.g. proteomic or genomic analysis) available today to investigate the complete bacterial population and the bacterial response to biocides.

8. **Regarding the comment according to which triclosan-induced antibacterial resistance has not been convincingly demonstrated in the group of in situ studies** discussed, the SCCS is of the following view. Only few *in situ* studies have been conducted. Through the use of different methodologies and analysis of data, these studies did not find a correlation between triclosan exposure and emerging resistance. This contrasts with studies performed *in vitro* and emphasizes the need for translational research. The development of bacterial resistance through well-defined mechanisms, notably following triclosan exposure, has been very well-described. *In situ* studies have only focused on MIC and cross-resistance to antibiotics and demonstrated a lack of both following triclosan exposure. These studies have however not looked at the phenotypic expression of these mechanisms, nor at the maintenance of the gene pool and transfer of resistance determinants. With this in mind, the information obtained in situ is limited, and it is premature at this point to conclude that triclosan is not of any concern. It must be emphasized that, although this opinion focuses on triclosan, the conclusion and observation drawn in this document are also valid for other biocides.

9. Regarding the comment that the statement that environmental concentrations in selected geographical regions are high enough that "triggering of bacterial resistance could also occur in the environment" is speculative and not supported by the studies conducted by Ledder et al. (2006) and McBain et al. (2004), the SCCS is of the following view. The McBain et al. (2004) study is an *in vitro* study. The Ledder et al. (2006) is an *ex situ* study and actually showed that bacterial microcosm exposure to triclosan did not result in widespread high level resistance, except for enteric bacteria, especially *E. coli*. The McBain et al. (2003) *ex situ* investigation actually highlighted a change in bacterial microcosm composition although the overall microcosm resistance to triclosan as measured by an increase in MIC did not change. Again, this is not unique to triclosan. Where a selective pressure exerted by a biocide is present, then alteration of a microcosm is to be expected.

10. The SCCS considers that **reports investigating triclosan low level resistance** in clinical *Acinetobacter* strains (Chen et al. 2009) should be taken seriously and further research should be conducted on the mechanisms and conditions leading to increase of resistance in the environment

is already mentioned in the text (reference to Chen et al, page 25).

11. The SCCS considers the comment that **environmental conditions favourable for induction of triclosan resistance** is an interesting point and that it should be considered in future research projects as previously mentioned in the SCENIHR (2010) opinion on biocides research.

12. The SCCS agrees with the comment on **limiting the use of triclosan without proven benefit for human health** but also accepts however, that where evidence exists that triclosan use in beneficial in e.g. preventing disease in humans, it should be encouraged. Hence prudent use is mentioned in the conclusion of the opinion: *When used appropriately, biocides, including triclosan, have an important role to play in disinfection, antisepsis and preservation*.

13. Concerning the comment on **the difference between the previous SCCP opinion and this one by the SCCS** , the main difference is the scientific information available on proteomic and genetic aspects of triclosan resistance.

14. This opinion is based on the weight and quality of the available scientific evidence regardless of its source. On that basis, the SCCS notes that the **lack of resistance reported in some in situ studies** did not take into account the recent developments in genetic and proteomic methodologies.

15. Concerning the comments **on the value of the comparative study by Lambert (2004)** with clinical isolates of methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* and *Pseudomonas aeruginosa* which showed no indications for a connection between triclosan resistance and antibiotic resistance under real-world conditions, the views of the SCCS are the following: this was a retrospective study looking at the MIC profile of various clinical isolates to a range of biocides. There were indeed no differences in susceptibility of the clinical isolates to various biocides over time. This study confirmed that antibiotic resistant bacterial isolates might not necessarily be less susceptible to a range of biocides. However, in the view of the SCCS, this study did not inform on the continuous use of biocides on antibiotic resistance in the clinical settings. This view was first formulated by Russell in 2002.

16. Concerning comments on the continued use of triclosan, due to the limited number of *in situ* studies of resistance induced by triclosan to date, the SCCS can only recommend the prudent use of triclosan, for example in applications where a health benefit can be demonstrated. However, the SCCS considers that conclusions from *in vitro* studies cannot be ignored, notably, the role of triclosan (and other biocides) in triggering resistance and in the dissemination (or lack of) resistance determinants. Hence, the SCCS appreciates that research investment from industry will be maintained to contribute to a better understanding of the potential risks associated with triclosan applications. Research in triggering mechanisms of resistance, maintenance of the gene pool and the transfer of resistance and virulence determinants, and improving the translational application of laboratory results to situations *in situ* are needed. In that spirit, the SCCS appreciates the comments received that product manufactures are taking approaches which limits the use of triclosan to a limited number of products with a demonstrated health benefit.

17. Comemnts **on ecotoxicity** were not considered as they are out of the scope of this opinion.

18. With respect to comments on the **essential differences between the concepts of resistance to antibiotics and resistance to disinfectants** (Cerf et al 2010), the SCCS will point to the 2009 SCENIHR opinion on the antibiotic resistance effect of biocides.

19. Concerning the comments on the **significance of the Chen et al (2009), and Stickler and**

Jones (2008) studies the views of the SCCS are the following: These are not *in situ* studies. Chen et al. 2009 observed that the majority of the *A. Baumannii* was susceptible to triclosan with only 3% showing reduced susceptibility (max. 16 mg/L). They further observed that all triclosan resistant isolates were also resistant to important chemotherapeutic antibiotics while the susceptible isolates showed a resistance percentage between 40% and 55%. Stickler and Jones (2008) has been cited several times in the opinion.

20. Concerning comments on the link **between triclosan exposure and resistance to important antibiotics in vitro** this has been made clear in the opinion. The role of biocides, including triclosan, in emerging resistance to clinically effective antibiotics and their impact in clinical settings needs to be clarified. In the views of the SCCS, this is certainly of a lesser concern than the improper use of antibiotics in clinical settings triggering resistance as mentioned in the SCENIHR 2009 opinion.

21. Concerning the comments on **the use concentrations of triclosan,** the information available to the SCCS for the elaboration of its opinion are from 2007. The SCCS has no information on the triclosan use patterns before 2007 and therefore is not in a position to establish a link between the environmental concentrations of triclosan and its use in cosmetic products only.

22. Concerning the comment on soil bacteria, the opinion (section 10.2) makes clear that the exposure to some biocides favours the dissemination and maintenance of genetic mobile elements. However, there is no such information available concerning triclosan. On that basis, the SCCS in it opinion (section 10.3), formulates a number of questions that need to be answered to be able to perform a risk assessment on this issue.

23. The comment that the **environmental concentrations of triclosan depend upon the efficiency of WWTPs** is already stated in the opinion (section 5.5, page 18) so no further revision was deemed necessary.

24. Concerning the comment on **the relevance of the Beier et al. (2008) study on triclosan resistance**, the SCCS is of the view that the study investigated the susceptibility profile of vancomycin-resistant *Enterococcus faecium* isolates from community wastewater. One third of the isolates showed MICs of up to 8 μg/ml. This confirms that there was no correlation between antibiotic susceptibility profile and biocide susceptibility. In the view of the SCCS the study showed a specific mechanism of high resistance to vancomycin and is not correlated to any known mechanism of biocide resistance.

25. Concerning the comment on the possibility to **predict changes in antibiotic resistance of bacteria following exposure to triclosan**, the SCCS agrees with the view of the SCENIHR (2010) that, on the basis of the available evidence in the scientific literature, it is not possible at present to predict changes in the antibiotic resistance profiles of bacteria following exposure to triclosan or to any other of the biocides currently used in various applications.