Risk assessment on the use of triclosan in cosmetics;

Development of antimicrobial resistance in bacteria - II

Norwegian Scientific Committee for Food Safety

Panel on Biological Hazards

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Contents

I. Summary

The Scientific Committee on Consumer Products (SCCP) of European Commission concluded in its Draft Opinion on triclosan (SCCP/1040/06) of October 10th 2006 that:

- On the basis of the available data, the SCCP is of the opinion that there is presently no evidence of clinical resistance and cross-resistance occurring from the use of triclosan in cosmetic products.

- Although probable, this link has not been fully demonstrated.

Since this conclusion differs from that made by The Norwegian Scientific Committee for Food Safety in its report of January 31st 2005, The Norwegian Food Safety Authority asked The Norwegian Scientific Committee for Food Safety, Panel on Biological Hazards to reconsider their conclusion in view of the SCCP draft opinion and recently published scientific literature.

The Norwegian Scientific Committee for Food Safety, Panel on Biological Hazards concludes in this report that:

- Neither the SSCP Draft Opinion on triclosan, nor recently published scientific literature, justifies rejection of our conclusions of January 31st 2005 (The Norwegian Scientific Committee for Food Safety, Panel on Biological Hazards report).
- If anything, recent scientific literature supports the conclusions stated in the The Norwegian Scientific Committee for Food Safety, Panel on Biological Hazards report.
- Triclosan use may elevate the risk of increased antimicrobial resistance (co- and/or cross–resistance) in clinically important bacteria.

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The dilemma posed by this issue is that if precautions are not observed, then at the time point when evidence of clinical resistance and cross-resistance becomes available, it may already be too late to contain the problem effectively. Accordingly, the use of triclosan, along with that of other antimicrobial agents, should be limited to situations for which scientific data are available demonstrating obvious health benefits.

II. Sammendrag (norsk)

Den Europa kommisjonens vitenskapskomité for forbruksvarer (SCCP) konkluderte 10. oktober 2006 med at det på grunnlag av tilgjengelige data ikke er funnet bevis for at triklosan i kosmetiske produkter kan føre til resistens – eller kryssresistensutvikling hos bakterier. Til tross for at en slik sammenheng kan være sannsynlig, finnes det ikke god dokumentasjon.

Siden denne konklusjonen ikke svarer til Vitenskapskomiteen for mattrygghets (VMK) konklusjon av 31. januar 2005, har Mattilsynet bedt VMK om på nytt å vurdere konklusjonen i lys av SCCPs rapport og nyere litteratur.

I denne rapporten konkluderer faggruppe for hygiene og smittestoffer ved VMK med at verken SSCPs rapport eller nyere litteratur gir grunnlag for å endre konklusjonen av 31. januar 2005. Tvert imot synes nyere litteratur å underbygge konklusjonen.

Dilemmaet er at den dagen det foreligger dokumentasjon på resistensutvikling hos klinisk relevante bakterier som en følge av triklosanbruk, kan det være for sent for å avgrense problemet på en effektiv måte. Antimikrobielle stoffer som triklosan bør derfor bare benyttes i tilfeller der vitenskapelig dokumentasjon bekrefter at bruken gir en klar helsegevinst. Slik dokumentasjon etterlyses.

III. Background

On October 10th 2006 The Scientific Committee on Consumer Products (SCCP) presented a Draft Opinion on triclosan (SSCP/1040/06). The SCCP Opinion on triclosan was prepared in response to a request from the Norwegian Food Safety Authority (Mattilsynet), asking for a re-evaluation of the safety of the use of triclosan in cosmetic products. This request was based on the report ”Risk assessment on the use of triclosan in cosmetics” (Norwegian Scientific Committee for Food Safety, 2005) which concluded:

- In some situations, particularly in clinical settings, triclosan is a useful, broad-spectrum biocide,

- However, widespread use of triclosan, including in cosmetic products, selects for development of triclosan resistance,

- Furthermore, such use represents a public health risk with regard to development of concomitant resistance to clinically important antimicrobial agents,

- The assessment regarding use of triclosan in consumer products from 2002 (Norwegian Institute of Public Health, 2000) seems strengthened by new evidence.

In its draft opinion on triclosan, SCCP concluded that although probable, an association between increased occurrence of antibiotic cross-resistance and the use of biocides, including triclosan, has not been fully demonstrated (with reference to Aiello et al. 2004; and Cole et al. 2003).

Concern about triclosan use is not only related to development of antimicrobial resistance in bacteria, but also to the fact that triclosan has commonly been found in human milk and plasma samples both in European countries (Allmyr et al. 2006b;Allmyr et al. 2006a) and in the US (Dayan 2007). Triclosan has also been found in the bile of fish experimentally exposed to municipal wastewater and in wild living fish from the recipient waters of wastewater treatment plants (Adolfsson-Erici et al. 2002). The toxicity of low concentrations of triclosan to certain fresh water algae with further influence on fresh water ecosystems has been pointed out as a matter of concern (Orvos et al 2002; Wilson et al 2003).

IV. Terms of reference

Based on the overall conclusions presented in SCCP/1040/06, The Norwegian Food Safety Authority (Mattilsynet) asked The Norwegian Scientific Committee for Food Safety, Panel on Biological Hazards to:

Evaluate whether the 11 references included in the SCCP opinion of October 10th 2006, but not included in our opinion of January 31st 2005, as well as other relevant, recently published scientific literature, provided further evidence that might affect the conclusion of the risk assessment performed by The Norwegian Scientific Committee for Food Safety, January 31st. 2005. In particular, focus should be directed towards how this literature might affect the conclusions regarding aspects of resistance. With this basis, The VKM was additionally requested to comment on the SCCP Draft Opinion on triclosan, and the conclusions reached therein.

V. Opinion

Development of antibiotic resistance in bacteria involves complex processes that are not fully understood. Continuous exposure of a large human population to antibacterial agents and prolonged exposure to sub-inhibitory concentrations are particularly worrying. Use and misuse of antibiotics are obviously very important factors, but high-level resistance and multi-resistance development may be prolonged and involve various steps and events in different ecological niches. For instance, the development of vancomycin resistance in enterococci was not detected until 1986, 31 years after the introduction of this antibiotic into clinical use. Likewise, penicillin-resistant pneumococci have developed over decades, from being reported from a few locations in the 1960s and 70s, to emerge as a worldwide clinical problem in the 1980s, significantly affecting patients with respiratory tract infections. Mobile genetic elements may carry various resistance factors. In addition to inducing resistance to the drug itself, a substance may also select bacteria with resistance to other, clinically more important drugs. Even low-grade resistance may entail such effects by giving the insensitive bacteria in normal flora selective advantages. Many members of the normal flora, such as *Escherichia coli*, *Bacteroides* spp., *Stenothrophomonas maltophilia,* and the pneumococci, are potential pathogens and under particular circumstances may give rise to clinical infections.

VI. Remarks on SSCP's opinion, - evaluation of recently published scientific literature

Is there a rationale for adding triclosan to cosmetic or common household products?

The rationale for using triclosan-containing products is based on whether beneficial effects can be anticipated, e.g. reduced incidence of contagious infectious diseases, or improved general or oral health. Any potentially beneficial effects must be considered against potential harmful effects, such as the risk of increase and/or spread of antimicrobial resistance.

Are there any documented beneficial effects of adding triclosan to cosmetic products?

Proper hand hygiene is widely acknowledged as a critical element in an adequate infection control program. In a randomized, 48-week, double blind trial, intervention families were allocated use of triclosan-containing liquid soap and various house-cleaning products containing antimicrobial agents. As no difference in prevalence of infectious disease symptoms was observed between the control and intervention groups, there was no obvious benefit of using triclosan (Larson et al. 2004). In a recent meta-analysis of six-month studies of antiplaque and antigingivitis agents, toothpastes containing triclosan (0.3 %) and Gantrez copolymer (2 %) had a significant beneficial effect on plaque and gingivitis. However, it was notable that triclosan combined with soluble pyrophosphate or zinc citrate showed no significant effect. Mouthrinses with 0.12 % chlorhexidine were most efficacious, and showed the most consistent results (Gunsolley 2006). The ultimate goal of dental plaque control is to maintain oral health and to prevent periodontal disease and dental caries. However the level of plaque reduction required to prevent development, or to slow the progression of periodontitis or dental caries has not been fully ascertained, and the documentation for an additional beneficial effect of triclosan on periodontitis or dental caries has been reported as weak (Edwardsson et al. 2005).

In a recent clinical study supported by Colgate-Palmolive, the antimicrobial effect of one week's tooth-brushing with toothpaste containing triclosan, was still evident in saliva at 12 h after brushing (twice daily) (Fine et al. 2006). The implication from this data is that a triclosan-containing dentifrice with such a formulation may exert a persistent selective pressure on the oral flora.

Several studies have demonstrated that in ordinary use triclosan is, to some extent, absorbed and distributed to human tissues. As it is highly lipophilic, triclosan reaches the systemic circulation through the mucosal membranes of the oral cavity (Lin 2000), and the gastro-intestinal tract (Sandborgh-Englund et al. 2006). Toothpaste is the main source of the triclosan in human blood and milk samples (Adolfsson et al. 2002; Allmyr et al. 2006a; Allmyr et al. 2006b; Dayan 2007), and concentrations vary considerably in the population. Studies of triclosan pharmacokinetics show an average half-life of 21h in plasma, which suggests that twice-daily tooth-brushing with a triclosan toothpaste will result in constant elevation of triclosan plasma levels. The finding that 24 to 83 % of an oral triclosan dose was excreted via the urine (Sandborgh-Englund et al. 2006) is also indicative of this elevation. These data suggest that when toothpaste contains triclosan, it will occur in various tissues of the user and the normal flora will be exposed to a range of triclosan concentrations.

Resistance against triclosan, a reality not only in laboratory mutants

Fan and co-workers (Fan et al. 2002) found that clinical isolates of *Staphylococcus aureus* with triclosan minimum inhibitory concentrations (MICs) of above 0.016 μg/ml showed an increase, of between three to fivefold, in their levels of enoyl-acyl carrier protein (ACP) reductase (Fab1). Thus, in addition to a mutation in the *fabI* gene, these altered genes were over-expressed in comparison to that observed in susceptible

strains. This publication is the first elucidating the mechanisms of triclosan resistance in clinically-derived isolates of this important pathogen.

Schmid and Kaplan (Schmid and Kaplan 2004) examined reduced triclosan susceptibility among methicillin-resistant *S. aureus* and *Staphylococcus epidermidis* (CNS) strains. Decreased susceptibility to triclosan was found to be more prevalent among methicillin-resistant *S. epidermidis* isolates than among methicillin-resistant *S. aureus* isolates and the authors speculated that the mechanisms and frequencies of resistance might differ between *S. epidermidis* and *S. aureus*. Alternatively, this difference might be explained by greater exposure of *S. epidermidis* to triclosan, due to frequent skin contact with triclosan-containing antimicrobial products. *S. epidermidis* is considered a predominant resident skin bacterium, and is also a major nosocomial pathogen associated with implanted medical devices. *S. aureus* is most frequently carried in the nasal vestibulum in humans.

Aiello et al. (2004) reported increased MICs in some isolates from household, clinical and industrial settings. Among them were *S. aureus* and coagulase-negative staphylococci, *Staphylococcus capitis*, *S. epidermidis* and *Staphylococcus warneri*. Some of the isolates (*Acinetobacter baumannii*, *Enterobacter agglomerans*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Pseudomonas fluoresecens* and *Pseudomonas putida*) had triclosan MICs in the concentration range commonly used in consumer products.

In a recent report (Wisniewska et al. 2006), triclosan MIC values were assayed in 100 methicillin-resistant (MRSA) and 100 methicillin-sensitive (MSSA) clinical *S. aureus* isolates derived from 18 hospital laboratories in Poland between 2000 and 2004. The MRSA isolates also demonstrated a diverse background of resistance patterns to other clinically important antibiotics. Methicillin resistance was confirmed by *mecA* PCR. The results show (Table 1) that the MIC_{50} and MIC_{90} to triclosan of the MRSA isolates were much higher than that of the MSSA isolates, and of the control strain.

The results may indicate that MRSA isolates have a selective advantage over MSSA isolates during triclosan challenge. Although these findings need further confirmation, they are considered important in that they demonstrate increased triclosan resistance among clinical bacterial isolates.

Table 1. Sensitivity of methicillin-resistant (MRSA) and methicillin-sensitive (MSSA) clinical *S. aureus* isolates towards triclosan (Wisniewska et al. 2006). (Translated from Polish)

Isolates	**No.**	**Triclosan MIC (mg/L) given as % of examined isolates**									
		0.03	**0.06**	**0.12**	**0.25**	**0.5**	**1.0**	**2.0**	**MIC_{ST}**	**MIC_{50}**	**MIC_{90}**
MRSA	100	30	0	0	0	4	4	62	1.3	2	2
MSSA	100	93	4	0	0	0	0	3	0.09	0.031	0.031
Total	200	61.5	2	0	0	2	2	32.5	0.7	1.02	1.02

Small-colony variants (SCVs) of *S. aureus* are the cause of recurring and persistent infections, and often refractory to antimicrobial chemotherapy. This mode of antimicrobial resistance is poorly understood, but *in vitro* SCV evolution is observed in both MRSA and MSSA on Mueller-Hinton agar containing 1 mg/L triclosan (Seaman et al. 2007). Sequencing of the *fabI* gene excluded mutation in this target molecule. Triclosan selected for *S. aureus* colonies with low-level triclosan resistance and concomitant reduced susceptibility to penicillin and gentamicin. Further, the SCVs were shown to have increased tolerance to the bactericidal effect of triclosan. Such SCVs may have a selective advantage when exposed to triclosan. However, the extent to which isolates with decreased susceptibility to triclosan would develop and have the fitness to survive under clinical conditions, is as yet unknown.

In one study (Brenwald and Fraise 2003), mentioned neither in our opinion nor in the SCCP's opinion, two triclosan-selected mutants had a 4-fold and a 16-fold increase in triclosan MICs (1 mg/L and 4 mg/L, respectively). Four clinical isolates of MRSA were also detected with similar susceptibilities as these mutants. One selected mutant and one clinical isolate showed changes in their *fabI* genes. The other mutant and three clinical isolates lacked such changes, suggesting that genetic loci other than *fabI* may be involved in triclosan resistance.

VII. Evaluation of 11 reports/scientific papers mentioned in the Draft opinion of SCCP /1040/06

See Appendix 1 and Conclusions

VIII- Conclusions

Several publications on triclosan resistance have indicated the apparent lack of resistance development in clinical isolates after triclosan exposure *in vivo*. Emergence of bacterial resistance has repeatedly been shown to involve a substantial delay following introduction of new antimicrobial compounds. As testing for triclosan resistance is not routinely conducted in clinical laboratories assessing microbial therapy, triclosan resistance in clinical isolates may be less restricted than the data suggest.

Toothpastes are the main source of triclosan exposure in humans. The use of triclosan in every day consumer products (including cosmetics) has questionable health benefits. Available data on beneficial health effects of triclosan-containing cosmetics or household products are not convincing. None of the 11 articles/reports mentioned in the SCCP opinion recommends use of triclosan in consumer products for general use.

Scientific assessment of the potential consequences associated with triclosan use should also consider possible detrimental environmental and ecotoxicological effects. These are well documented, but not further discussed in this report.

In vitro studies have repeatedly revealed that several bacterial species have the potential to develop triclosan resistance. In addition, information on increased triclosan resistance in clinical isolates is emerging. These data should be considered in assessing the potential long-term effects of widespread triclosan use. The dilemma posed by this issue is that if precautions are not observed, then at the time point when evidence of clinical resistance and cross-resistance becomes available it may already be too late to contain the problem effectively. Accordingly, the use of triclosan, along with other antimicrobial agents, should be limited to situations for which scientific data are available demonstrating obvious health benefits.

The main conclusions are:

- Neither the SSCP Draft Opinion on triclosan, nor recently published scientific literature, justifies rejection of our conclusions of January 31st 2005 (The Norwegian Scientific Committee for Food Safety, Panel on Biological Hazards report).
- If anything, recent scientific literature support the conclusions stated in the The Norwegian Scientific Committee for Food Safety, Panel on Biological Hazards report.
- Triclosan use may elevate the risk of increased antimicrobial resistance (co- and/or cross–resistance) in clinically important bacteria.

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IX-Appendix I

Brief review of literature referred to by the Scientific Committee on Consumer Products (SCCP) in the Draft Opinion on triclosan (SSCP/1040/06), with focus on risk assessment on use of triclosan in cosmetics:

1. BfR, Federal Institute for Risk Assessment, Germany. 2006. Triclosan nur im ärztlichen Bereich anwenden, um Resistenzbildungen vorzubeugen, Stellungnahme Nr. 030/2006 des BfR vom 08. Mai 2006.

and

2. BfR (Federal Institute for Risk Assessment, Germany). 2006. Triclosan only belongs in the clinic and doctor's surgery! (Press release).

These two publications give an overview on triclosan and its applications, the mechanisms and epidemiology of triclosan resistance, and possible implications. A statistically significant increase in resistance among pathogens isolated from the environment is not demonstrated after the application of triclosan in household products. However, a tendency to increased resistance towards quinolones and tetracyclines is indicated. According to the risk assessment by BfR, triclosan should be used very restrictively and with the necessary degree of caution. Furthermore the precautionary principal regarding consumer safety, as recommended by WHO, should be enforced.

3. Braoudaki, M and A.C. Hilton. 2005. Mechanisms of resistance in *Salmonella enterica* adapted to erythromycin, benzalkonium chloride and triclosan. International Journal of Antimicrobial Agents. 25:31-37.

Adaptation of the *Salmonella enterica* serovars Enteritidis, Typhimurium and Virchow to sub-MIC concentrations of the antimicrobial agents included different active efflux systems and increased cell surface hydrophobicity, which could contribute to antimicrobial resistance. The response is dependent on the specific strain/antimicrobial involved and is therefore difficult to predict.

4. Champlin, F.R., M.L. Ellison, J.W. Bullard and R.S. Conrad. 2005. Effect of outer membrane permeabilization on intrinsic resistance to low Triclosan levels in *Pseudomonas aeruginosa*. International Journal of Antimicrobial Agents 26, 159-164.

The outer membrane of *P. aeruginosa* has an intrinsic resistance mechanism to low concentrations of triclosan. The impermeability of the outer cell envelope of *P. aeruginosa* is suggested to play a role in resistance to higher concentrations of triclosan.

5. Cookson, B. 2005. Clinical significance of emergence of bacterial antimicrobial resistance in the hospital environment. Journal of Applied Microbiology, 99, 989-996.

This review article outlines antimicrobial resistance among microorganisms causing hospital infections. The author emphasizes: “Although resistance to antibiotics has been addressed in many strategies and publications, the complex issue and importance of biocide resistance has not achieved as high a profile...” The author states: “There are many confounding factors that plague any discussions relating to biocide resistance”. As “There is no international consensus on biocide efficacy tests or approved product registers...”, , “Unlike antibiotic resistance, the issue relating to biocide resistance has a very low profile and priority... This low priority is also reflected in the lack of funding of biocide research projects in most countries.

”Another deficiency is that studies often fail to identify the biocide resistance mechanism, its genetic nature or location. This is no doubt related to the lack of investment outlined above.“

6. Cole, E.C., R.M. Addison, J.R. Rubio, K.E. Leese, P.D. Dulaney, M.S. Newell, J. Wilkins, D.J. Gaber, T. Wineinger and D.A. Criger. 2003. Investigation of antibiotic and antibacterial agent cross-resistance in target bacteria from homes of antibacterial product users and nonusers. Journal of Applied Microbiology 95, 664-676.

The aim of the study was “…to describe the relationship between antibiotic and antibacterial resistance in environmental and clinical bacteria from home environments across geographic locations, relative to the use or non-use of antibacterial products, with focus on target organisms recognised as potential pathogens”.

Among a total of 1238 bacterial isolates, 197 isolates were from clinical sites, hands or oral cavities, and two samples were collected from one to two individuals of each family.

“The results showed lack of antibiotic and antibacterial agent cross-resistance in target bacteria from homes of antibacterial product users and non-users, as well as increased prevalence of potential pathogens in non-user homes.” The authors judged the significance and impact of the study as follows: “It refutes widely publicised, yet unsupported, hypotheses that use of antibacterial products facilitate the development of antibiotic resistance in bacteria from the home environment”.

Although the study included 30 families that used antibacterial products and 30 non-user families, and a large number of bacterial samples were collected, the number of clinical isolates investigated was relatively low. Furthermore, it is unclear how previous exposure to triclosan was controlled.

Whilst the study revealed no association between use of antibacterial products and the prevalence of resistant bacteria, the high number of resistant strains detected in both groups is worrying. In both study groups, 75-77 % of environmental bacteria were resistant to one or more antibiotics, and among the clinical isolates, 52-57% strains were resistant. Could this possibly reflect a universal, inadvertent, high exposure to triclosan and other antibacterial products? Regarding which bacterial groups were resistant, differences between the product users and non-users were not detected, except with respect to viridans streptococci, with three times more resistant viridans

Streptococcus isolates among users than non-users (19.6% versus 6.3 %). Viridans streptococci constitute a major proportion of the oral flora and represent an important reservoir of antimicrobial resistance genes that might be transferred to other bacteria, e.g. the clinically important pneumococci (Spratt 1993,Bryskier 2002).

7. Dixon, B, 2005. Selective agencies. ASM News, 71:310-311. A commentary/ review note.

Agents (culinary herbs, chemotherapeutic drugs and copper) other than antimicrobials can exert selective pressures, favouring the proliferation of organisms insensitive to antimicrobials.

8. Glaser, A. 2004. The ubiquitous Triclosan. A common antibacterial agent exposed. Pesticides and You. 24, 12- 17.

Glaser raises the concern of resistance development and concludes that triclosan in cosmetic and household products is unnecessary and adds no health benefits.

9. Kampf, G. and A. Kramer. 2004. Epidemiologic background of hand hygiene and evaluation of the most important agents for scrubs and rubs. Clinical Microbiological Reviews. 17:863-893.

This review article from 2004 gives an extensive overview on the epidemiology of hand hygiene and important agents used in this respect. Triclosan is one of the agents covered. Several of the original scientific publications included in this review article demonstrate development of cross-resistance to other clinically significant antibacterial agents occurs after *in vitro* exposure to triclosan. The authors conclude that no conclusive link between triclosan usage and antibiotic resistance development in clinical isolates has been shown. However, the article also refers to studies that show high prevalence of triclosan resistance in samples of compost, water and soil, in which the widespread use of triclosan in consumer products is proposed as the probable explanation.

10. Russel, A.D. 2004. Whither Triclosan ? Journal of Antimicrobial Chemotherapy. 53, 693-695.

The basis for this Leading article is that environmental surveys to date have not demonstrated any association between triclosan usage and antibiotic resistance. There are many unanswered questions regarding the consequences of widespread use of triclosan, and the future aim should be to retain the important and valuable applications of triclosan, whilst eliminating the unnecessary ones.

The author states: …there is no convincing evidence to support the contention that triclosan usage has resulted in the clinical development of antibiotic-resistant (…) bacteria (…). Nevertheless, it would be wise to restrict the use of triclosan to areas where it has been shown to be effective."

11. Sánchez, P., E. Moreno and J.L. Martínez. 2005. The biocide Triclosan selects *Stenotrophomonas maltophilia* mutants that overproduce the SmeDEF mutidrug efflux pump. Antimicrobial Agents and Chemotherapy. 49, 781-782.

Triclosan can select triclosan-resistant mutants of the opportunistic human pathogen *Stenotrophomonas maltophilia.* These mutants over-express the multi-drug resistance pump SmeDEF. *S. maltophilia* is a problematic microorganism in patients suffering from cystic fibrosis, and in transplantation patients. *In vitro* studies are useful for predicting the capability of an organism to develop resistance in the future. The authors refer to (Russell 2004): ”there remain concerns about the unnecessary use of triclosan and other biocides in the home and in clinical setting.”

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XI. Scientific Panel Members

Panel on Biological Hazards
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