EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
C1 - Follow-up and dissemination of scientific opinions

OPINION ON TRICLOSAN RESISTANCE

ADOPTED BY
THE SCIENTIFIC STEERING COMMITTEE
AT ITS MEETING OF 27 –28 JUNE 2002

OPINION

BACKGROUND AND MANDATE

In the light of recent scientific papers discussing the possible impact of the use of Triclosan on the development of antimicrobial resistance, Commission Services requested the Scientific Steering Committee for an opinion on the following questions:

> *Is the use of Triclosan in cosmetic products safe, taking into account the risk of resistance development by certain micro-organism. Is it necessary in the safety assessment to take into account the fact that Triclosan is used in other consumer products?*

The Scientific Steering Committee (SSC) installed a working group of experts with the mandate to draft a scientific report that could be used as an input for the preparation for a scientific opinion of the SSC on the above questions. The report of this working group is attached to this opinion.

OPINION

The present opinion on Triclosan focusses on its use as biocide and the potential risks related to the induction of antimicrobial resistance. Other potential hazards, related to the extensive use of triclosan have not been considered.

The SSC considers that Triclosan is a useful and effective biocide which has been safely used for many years across a broad range of dental, medical, cosmetic and household products and is increasingly finding a use in clinically important applications.

At high (*biocidal*) concentrations, Triclosan is very effective and unlikely to produce a major problem of anti-microbial resistance. However, at sub-biocidal and bacteriostatic, concentrations, Triclosan is capable of penetrating bacteria and initiating changes related to important mechanisms of antimicrobial resistance including possibly transferable mechanisms of resistance, though the scientific evidence for transferability has been disputed. Sound scientific laboratory evidence exists for the development of Triclosan related mechanisms for antimicrobial resistance, but the evidence as to whether these mechanisms are shared by other antimicrobial agents or whether they are transferable to micro-organisms other than those used in the laboratory is limited and contradictory. No evidence of such resistance has been seen so far in clinical isolates, and there is no epidemiological evidence to suggest a problem in clinical practice. There are, however, very few targeted studies of resistance to Triclosan in relevant clinical or wider environments. Although, the stability and persistence of Triclosan resistance has not been widely studied, the limited information available points to it being stable over a three to ten year period.

The SSC therefore concludes that there is no convincing evidence that Triclosan poses an risk to humans or to the environment by inducing or transmitting antibacterial resistance under current conditions of use.

The SSC further recommends the following:

a. Taking into account the limited information available and the fact that any use of a biocide results in the availability of *sub-biocidal* concentrations in the wider environment[1], more information should be sought on:

   - The extent and uses of Triclosan and their comparative importance;
   - The prevalence of Triclosan resistant organisms in clinical environments;
   - The exact mechanisms and dose responsiveness of antibacterial action of Triclosan, especially at sub biocidal concentrations;
   - The kinetics of Triclosan antibacterial resistance mechanisms and their possible transferability;
   - The fate of Triclosan in the environment; the rate and extent of degradation of Triclosan and the anti-microbial activity of degradates or low concentrations in the environment;

   It is also recommended that the broader issue of the relationship between the use of biocides and the development of clinically relevant antimicrobial resistance be kept under continuous review.

   There are other issues related to the use of Triclosan, including exposure pathways, which may need further investigation. Some of them are addressed in the attached report.

b. If new scientific evidence were to indicate a significant risk of biocides causing anti-microbial resistance to antibiotics used in human medicines, then appropriate action to manage these risks might be needed.

c. Meanwhile, the recommendations of the SSC of 28 May 1999 on Antimicrobial resistance remain valid.

[1] According to the producer the use of Triclosan [as a biocide] in other consumer products is limited to 3% of the overall Triclosan production. These uses are not irrelevant as they represent a different route for the possible development of resistance (e.g., returnable containers to food processors, use in meat and poultry factories, …).

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Directorate C - Scientific Opinions
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REPORT ON TRICLOSAN ANTIMICROBIAL RESISTANCE:

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REPORT

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I. INTRODUCTION

I.1. BACKGROUND

Any exposure of a (micro-) organism, be it fungi or bacteria, to an antibiotic substance involves a risk of resistance developing through the process of selection. The rate and extent of development of resistant organisms (agents or strains), whether this resistance is reversible or not and whether it is a relevant issue in human medicine, depend upon a variety of factors and conditions, including the mechanism of action of the substance (frequently unknown), the target area(s) in the organism and their number, the risk of transfer of the resistance between individual organisms and species, and the mode of that resistance.

The SSC examined the phenomenon of emerging resistance to antibiotics and prepared a report together with recommendations in May 1998. In 2001, the SSC extended its opinion to encompass the use of antibiotics as growth promoting agents in the rearing of animals. Neither of these reports, however, considered the potential for biocides to influence the development of resistance to clinically useful antibiotics. That question has recently arisen in respect to the widespread use of the biocide Triclosan which is the subject of this report.

The development of antimicrobial resistance from the use of Triclosan is possible, and given its mode of action, is more likely to occur amongst bacteria, than amongst fungi. Importantly, however, the mechanisms by which it is effective are such that transferability of resistance is less likely than that which follows the use of conventional antibiotics.

I.2. MANDATE

In the light of recent scientific papers discussing the possible impact of the use of Triclosan on the development of antimicrobial resistance, Commission Services requested the Scientific Steering Committee for an opinion on the following questions:

> *Is the use of Triclosan in cosmetic products safe, taking into account the risk of resistance development by certain micro-organism. Is it necessary in the safety assessment to take into account the fact that Triclosan is used in other consumer products?*

The Scientific Committee for Cosmetic and Non-food Products will subsequently be asked whether there is a need for setting a new concentration limit for the use of this substance in cosmetic products.

The Scientific Steering Committee (SSC) installed a working group of experts with the mandate to draft a scientific report that could be used as an input for the preparation for a scientific opinion of the SSC on the above questions.

II. DEFINITIONS

II.1 Biocidal product

According to the Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on

the market, biocidal products are defined as "*Active substances and preparations containing one or more active substances, put up in the form in which they are supplied to the user, intended to destroy, deter, render harmless, prevent the action of, or otherwise exert a controlling effect on any harmful organism by chemical or biological means*."

It also has to be stated that "biocidal physical agents" such as radiation (UV, X, ionic, etc), heat, filtration among others are regularly used by industry, hospitals and laboratories to *destroy, deter, render harmless or prevent the action of infectious agents.*

Note[2]: The word biocide alone may have different meaning, depending on the expression or sentence. It may refer either to "biocidal agents (substances)", e.g. "biocides used in cosmetics", or to "biocidal products", e.g. "household biocides", or to both of them as a general term, e.g. "legislation on biocides". Apparently, in order to avoid ambiguity, the BPD* uses mainly the terms "biocidal product" and "active substance". "Biocide" alone, when used, seems to refer to "Biocidal Product".

II.2 Antibiotic

The opinion of 28 May 1999 of the Scientific Steering Committee on antimicrobial resistance, defines an antibiotic as a substance, produced by or derived from a micro-organism, which destroys or inhibits the growth of other micro-organisms. An antimicrobial is a drug, which, at low concentrations, exerts an action against microorganisms[3] and exhibits selective toxicity towards them.

The Working Group considers that both definitions are appropriate within the context of the current report.

III. CURRENT USES OF TRICLOSAN

Current consumer products containing Triclosan include cosmetics (including deodorants and toothpaste), household detergents, clothes, bedlinen, toys, and plastics intended for contact with food or feed.

Details on Triclosan volumes sold in various countries within the EU were provided on a confidential basis by the prime supplier of the substance. The sale of Triclosan to a particular European country does not necessarily reflect the usage of Triclosan-containing products in that country as many users of Triclosan export their finished goods to other countries within and outside the EU. Import/Export statistics indicate that more Triclosan-containing products are exported to countries outside the EU than are imported into the EU.

More than one third of the amount of active ingredient (Triclosan) appears to be used in products for oral care and a similar amount is used in products for skin care. Much less than one third of active ingredient is used in other ways, including household products.

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2 See also: EC (European Commission), 2001. An overview on biocides Terminology, Legislation, Progress in Procedures. Discussion paper adopted on 25 September 2001 by the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers.

3 It should be noted that the concept of antimicrobial applies equally to desinfectants, preservatives, sanitizating agents and biocidal products in general)

At the request of the SSC, industry (COLIPA, 2002c) has tried in a limited time span to trace the distribution of TCS-containing cosmetics within the EU Market. It became apparent that the user market of Triclosan is very fragmented. Since information from more than 20 companies would be needed in order to cover about 70-80% of this TCS usage in the EU, it was for instance impossible to obtain market information from the numerous manufacturers of TCS-containing skin-care products.

COLIPA (2002c) therefore focuses on the major manufacturers of finished oral-care products containing TCS. In this segment, a limited number of companies (4) accounts for 60% of the TCS usage. The results of the enquiry on this use of Triclosan are presented in the **Table** below. Given the higher fragmentation, the market situation on skin-care can be reasonably assumed to be more homogeneous.

It should be noted that this information has been obtained within the severe time constraints and represents an estimate to facilitate the SSC in its review. The figures provided should not be considered as exact or comprehensive for all industries. They represent sales of the major oral-care companies to wholesale and retail outlets and as such it cannot be guaranteed that further export does not take place once out of the manufacturer's control.

Table: Illustration of the percentage (%) of the oral-care uses of triclosan per individual EU Member State.

EU country	**%**	**EU country**	**%**
Austria	2.64	Italy	17.03
Belgium	1.23	Norway	0.82
Denmark	1.46	Portugal	1.42
Finland	0.27	Spain	2.72
France	16.54	Sweden	2.46
Germany	19.74	Switzerland	1.66
Greece	3.02	UK	27.12
Holland	1.87	**Total**	**100 %**

Note : It may be noted that the distribution of uses of Triclosan in oral-care among the different EU Member States becomes quite homogeneous if one normalises these % values for the population size of the countries.

III.1. CLINICAL USES (PRESCRIBED OR ON ADVICE FROM A CLINICIAN)

Triclosan is available as the active ingredient in a number of licensed medicinal products where it is mainly used in soaps, creams and solutions in concentrations of up to 2% for disinfection of the hands and wounds and for disinfection of the skin prior to surgery, injections, or venepuncture. It is also present in some licensed preparations for the treatment of acne.

Triclosan is also used as a whole body wash in some clinical circumstances in environments where infections with MRSA pose difficult treatment problems. Control of MRSA infection in surgical units involving handwashing and bathing with Triclosan has been reported by Bartzokas *et al* (1984) and Bartzokas (1985). Other studies have demonstrated the use of triclosan-containing products in the same clinical setting, for example: Zafar *et al*

(1995); Marshall *et al* (1997); Webster (1991); Webster (1992); Tuffnell et al (1987); Brady *et al* (1990).

There exist a large number of medical ('over the counter' rather than prescription) products that contain Triclosan.

III.2. COSMETIC USES (NOT TAKEN ON CLINICAL ADVICE)

Triclosan is permitted for use at up to 0.3% cosmetic products. In the oral care market, Triclosan is mainly used in toothpastes and to a minor degree in mouthwashes. Within the skin care segment, Triclosan is used predominantly in rinse-off products, such as bar and liquid soaps (handsoaps and shower products) underarm deodorants, facial lotions or cleansers, anti-acne products, hair care and other products such as foot care, skin lotions.

Triclosan has been shown to reduce body odour when applied in deodorant products. See Cox (1987) and Furia and Schenkel (1968).

The addition of an antimicrobial, such as triclosan, to a fluoride-containing toothpaste may be of benefit in the prevention of plaque (Addy, and Renton-Harper, 1996) but robust clinical evidence of efficacy is not available.

III.3. HOUSEHOLD USES

Triclosan is used in consumer household products and in the manufacture of textiles (i.e. sport clothing, socks, sponges, etc.) and plastics (i.e. cutting boards, kitchen or bathroom utensils, etc.). There is no evidence available to demonstrate the efficacy of Triclosan as an antimicrobial when combined in plastics and textiles. Another household application is in detergents for dish washing and for the manufacture of industrial or institutional hand soaps (ie for use in hospitals).

IV. MICROBIOLOGICAL CONSIDERATIONS

IV.1. MODE OF ACTION

Triclosan is a general biocide with broad-spectrum antibacterial and anti-fungal activity (MIC's ranging from 0.1 mg/ml to 33 mg/ml). It is generally more effective against gram positive, than gram negative bacteria or moulds except when used in enhanced formulations, eg, with EDTA. It acts by a number of different mechanisms, but at biocidal concentrations it acts predominantly by disruptive effects on the cytoplasmic membrane. At lower bacteriostatic concentrations it uncouples oxidative phoshorylation by trans-membrane proton conduction and inhibits substrate transport processes. At bacteriostatic and sub-bacteriostatic concentrations it affects enoyl reductase-mediated fatty acid synthesis. Some organisms such as *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa* and *Malassezia* species are intrinsically extremely resistant (100 mg/ml, >1000 mg/ml and >1000 mg/ml respectively).

IV.2. MECHANISMS OF RESISTANCE SHARED WITH CLINICALLY USEFUL ANTIBIOTICS

IV.2.1 Laboratory Evidence

The mode of action of Triclosan is such that antimicrobial resistance to Triclosan is more likely to occur amongst bacteria, than amongst fungi. Because Triclosan is effective through multiple mechanisms of action, however, it might be supposed that this would provide protection against the development of resistance. This is not necessarily so and laboratory evidence of Triclosan resistance has now been reported in the literature by several authors (Russell *et al*, 1999). Similarly, the mechanisms by which it is effective are such that transferability of resistance should be less likely than that which is associated with the use of conventional antibiotics. This has also been questioned and both Cookson *et al* (1991) and Sasatsu *et al* (1993) have published on the possibilities of transferability of Triclosan induced resistance but with contradictory opinions.

Two important questions therefore need to be addressed with respect to this particular consideration of Triclosan.

- does the extensive use of Triclosan result in the selection of resistant organisms that are clinically relevant or deleterious to the environment.?
- is the antimicrobial resistance induced by Triclosan at sub-biocidal concentrations transferable to organisms that may be of clinical relevance or that are deleterious to the environment?

The evidence for development of resistance and for the mechanism by which that resistance occurs has so far been exclusively laboratory in origin. In laboratory studies using specific selection methods and in-vitro development of mutants, several authors have reported on bacteria with elevated MICs to Triclosan (McMurry *et al*, 1998). The mechanisms involved are principally those of decreased cell wall permeability, interference with efflux mechanisms, and modification or upregulation of the Enoyl Acyl Carrier Protein Reductase target.

At concentrations below those which are bactericidal, Triclosan can inhibit the uptake of essential nutrients and it has been proposed that divalent ions and fatty acids may limit accessibility to its site of action. Divalent ion dependent E.coli have been produced experimentally with MIC values for Triclosan which are substantially greater than those for wild type *E.coli*, though the MBC values for these organisms are not different indicating that Triclosan has multiple target sites for bactericidal activity (Russell, 1999, McDonnell and Russell, 1999). This may even be considered as conferring advantage.

Laboratory studies have also shown that bacteria are capable of developing resistance to Triclosan by means of common mechanisms linking biocide exposure to the development of both biocide and antibiotic resistance. Data at laboratory level for experimentally produced *E.Coli,* MRSA, MSSA and *Mycobacterium smegmatis* show that Triclosan can cause the development of resistance amongst bacteria that are pathogenic to humans. For example, Triclosan is one of the biocides capable of causing increase in MICs for plasmid mediated methicillin resistant *Staphylococcus aureus* (McDonnell and Russell, 1999). There is also evidence (McMurray et al 1999), that

mutations in the inhA gene of *Mycobacterium smegmatis* result in resistance both to Triclosan and to isoniazid. There is also evidence that exposure to low concentrations of Triclosan can induce resistance mechanisms mediated through multi-drug efflux pumps which has relevance to tetracycline and fluoroquniolone resistance. These examples have all been laboratory generated and not derived from studies using clinical isolates. They demonstrate that it is possible under experimental conditions for Triclosan to generate or be associated with mechanisms that can lead to antibiotic resistance. The one that probably has most relevance and may warrant further investigation is the development of resistance in *Mycobacterium smegmatis*.

The stability and/or persistence of resistance to Triclosan under normal conditions of use could be an important indicator but has not been widely studied. The information that is available from studies of manufacturing sites (Lear *et al*, 2001), and clinical follow up studies points to resistance patterns being stable over periods of three to ten years which is modestly reassuring.

IV.2.2 Clinical evidence

At present there is neither clinical nor epidemiological evidence that the use of Triclosan has caused the development of antibiotic resistance in clinical practice, indicating that antibiotic use is a more significant causative factor in the development of antibacterial resistance. However, the evidence available is sparse and a more detailed assessment would be necessary to draw meaningful conclusions. This would require the availability of substantial data, for which new research would be necessary as outlined later.

V. CLINICAL CONSEQUENCES OF USE

V.1. POTENTIAL FOR CROSS-RESISTANCE BETWEEN TRICLOSAN AND OTHER ANTIMICROBIAL AGENTS

There is evidence from in vitro studies discussed previously that some bacteria, including *Staphylococcus aureus*, isolated from clinical samples may be found to have increased MIC values to Triclosan. The increased MIC's so far observed are still well below the local concentrations of Triclosan likely to be found at sites of bacterial carriage or infection if biocidally effective concentrations of the compound are used. Importantly, however, Cookson *et al* (1991) have shown that this resistance can be transferred through a plasmid-mediated mechanism though these findings have been disputed by others. Unfortunately, very few studies have been undertaken in this area and further evidence would be required adequately to resolve the issue. According to Cookson *et al* (1991), in MRSA strains with low-level resistance to Triclosan, the transferability always included mupirocin transfer. However, Suller and Russell (2000) did not find important changes in MICs to Triclosan associated with mupriocin resistance and did not observe transferable resistance to Triclosan in their studies. The latter authors showed some modest changes of in vitro sensitivity amongst *Staphylococcus aureus* but reported that the bacteria were still inhibited by biocidal concentrations of Triclosan. The mechanisms of resistance have been partially delineated and include the involvement of a specific locus such as the inhA gene pathway (McMurry *et al,* 1998) and the promotion of efflux pumps. The latter mechanism is also

theoretically important as the intracellular concentrations and, by implication, capacity for cell killing with other antibiotics such as ciprofloxacin and other fluoroqunilolnes as well as tetracyclines may be compromised if bacteria are conditioned by exposure to Triclosan. Such cross-resistance micro-mechanisms have been described for other organisms.

V.2. CLINICAL ENVIRONMENT

Despite the laboratory observations described above no studies conducted in using clinical isolates have yet established that the variations observed in in vitro sensitivity amongst a range of different bacteria to Triclosan have clinical implications. There is no evidence that exposure to Triclosan either in biocidally effective or sub biocidal concentrations, in clinical use, results in the emergence of strains of bacteria that are resistant to Triclosan or show cross resistance to other antibiotics. There are to our knowledge, no convincing studies that demonstrate that exposure to Triclosan can affect the spectrum of antibiotic resistance amongst commensal bacteria in the gastrointestinal tract or on the skin. However, there are studies of dental plaque flora which have failed to show biologically significant changes in MIC values to commonly used antibiotics in patients using Triclosan long term (Walker *et al*, 1994; Dunford, 1998). There is also no data on the clinical significance of exposure to low doses of Triclosan at levels that would reflect non-therapeutic uses of this biocide.

Further studies to establish these points should not be difficult to accomplish using modern technologies but they have not been conducted to date.

VI. FATE OF TRICLOSAN AND ENVIRONMENTAL CONSEQUENCES OF USE

Triclosan (2, 4, 4'-tricholo-2'- hydroxydiphenyl ether) is a chlorinated compound with pK_a of 7.9. Its bio-availability is dependent on the ambient pH which may explain some of the variation in conclusions drawn from data regarding environmental fate and toxicity.

VI.1. FATE AND TOXICITY OF TRICLOSAN

The classic risk assessment of Triclosan in humans and animals is not an issue for this report. Its chemical and biological fate are, however, important in consideration of its availability in the wider environment where it might influence antimicrobial resistance.

Triclosan is absorbed from the gastrointenstinal tract and also possibly from the skin and has been identified in most human body fluids, including human breast milk. Continuous use of Triclosan containing products results in steady state plasma concentrations of Triclosan (including conjugates) up to 127 ng/ml serum within a few days. Studies with volunteers show that it is rapidly conjugated in the body into glucuronides and sulfates and excreted in the urine and no long-term or large scale accumulation occurs.

Bioaccumulation by aquatic organisms does occur as may be expected from the Log $P^{o}w$ (4.66) for non-ionised Triclosan. In a study with *Brachidanio rerio*, bioaccumulation was measured at pH-values between 6 and 9 (Schettgen, 2000). The BCF equilibrium values in this study were between

7.900 and 3.700 based on whole body weight and 163.000 – 49.000 based on average lipid content. Both Triclosan and a methylated metabolite (4-chloro-1-(2,4-dichlorophenoxy)-2methoxybenzene) has been found in fish.

According to standard tests on aquatic toxicity, Triclosan is classified as "toxic to aquatic organisms and may cause long-term adverse effects in the aquatic environment". Acute toxicity for *Brachidanio rerio* is LD50 = 0.5 mg/l, for trout 2 mg/l, *Daphnia magna* EC50 = 0.4 mg/l. Algae are the most sensitive species with an EC50 of 0.2 mg/l.

VI.2. DEGRADABILITY OF TRICLOSAN IN THE ENVIRONMENT

The major pathway of Triclosan into the environment is via wastewater and therefore aquatic degradability, biologically and photochemically are the most important questions regarding Triclosan stability and occurrence in the environment. Triclosan can also be present is solid municipal waste.

The majority of Triclosan used in consumer products ultimately ends up in low concentration in wastewater, and Triclosan is not readily degradable in aquatic environments. There is no degradation at 100 mg/l in the MITI-Test and only 37 % and 18 % in the Sturm-Test at concentrations of 10 and 20 mg/l respectively. In Continuous Activated Sludge Tests, however, removal rates of up to 99 % were found at concentrations of up to 2.000µg/l. Depending on the study, mineralisation was between 70% and 90 %, the remainder being sorption to the sludge or unchanged parent material. The inhibitory concentrations of Triclosan varied by a factor of more than 10 (20 mg/l, 239 mg/l) in these studies.

Field studies, sewage treatment plants, rivers and a lake have shown that despite the high elimination of Triclosan during activated sludge treatment, effluent concentrations may be in the µg/l range. The highest sorption to sludge was found in a wastewater treatment plant showing 80 % biological degradation, 15 % sorption to sludge and 5 % discharge. No information is available on the further fate of the sludge sorbed Triclosan. These data show that despite efficient elimination of Triclosan in acclimatised sewage treatment systems, significant amounts of Triclosan are released into surface waters.

Occurrence of Triclosan in surface waters has been studied recently. In an U.S.-Study (Furlong, *et al*., 2002) 58 % of the water samples contained detectable concentrations of Triclosan, the medium of the positive samples being 0.14 µg/l and as high as 2.3 µg/l. In surface waters further degradation is possible, biologically and photochemically. Direct photolysis in laboratory experiments is in the order of several hours half-life, indirect photolysis with half-lifes of days to years. In the real environment photolysis half-lifes have been calculated between 2 and 2.000 days (Tixier, *et al*, 2000). For a lake, it has been estimated that 80 % of disappearance during the summer period was due to photodegradation (Singer *et al*, 2000).

Although soil is not a receiving compartment, degradability in soil may give an indication on the further fate of Triclosan sorbed to sludge and may be important, when sewage sludge is used on soils. Half-lives on soils were found to vary between 17 and 35 days in an US study (COLIPA, 2002b).

V1.3 IMPLICATIONS FOR THE WIDER ENVIRONMENT

It can not be excluded that Triclosan is present in the aquatic environment and could influence microbial ecology. The concentrations likely to be present are a factor of 500 below the MIC for relevant organisms, but this cannot necessarily be considered safe since there is no information on effects at these low concentrations.

Attempts to isolate naturally occurring bacteria resistant to Triclosan are needed to assess the environmental impact as well as the environmental relationship between Triclosan and antibiotic resistance. Finally, since triclosan is a "predioxin", its potential to influence environmental health should be assessed.

The extensive use of Triclosan results in its widespread presence in the environment. This wider environment, however, is the final reservoir of genes that codify for antimicrobial and biocide resistance and at sub biocidal concentrations Triclosan has mechanisms of antimicrobial action which are shared with antibiotics and which may be capable of inducing resistance to antibiotics. If irreversible genetic change were to result as a consequence of the use of Triclosan, then it could phase out possible beneficial species or bacterial consortia with important roles, for example, during oil spills or more usual regular xenobiotic release.

According the U.S. Geological Survey published in the 2002 March issue of Environmental Sciences & Technology, Triclosan is one of the more frequently detected organic waste-water contaminants in susceptible water resources. Considering that environmental concentrations have been determined in the range of 1 μg/l and taking further into consideration its well established bioaccumulation in aquatic organisms there may be a risk for aquatic organisms from the present use of Triclosan. Further studies would be needed to quantify this chronic or life-cycle toxicity. A further toxicological aspect of Triclosan use is that it belongs to the pre-dioxin class of chemicals.

VII. CONCLUSIONS AND RECOMMENDATIONS REGARDING USES OF TRICLOSAN

The Working Group considers that Triclosan is a useful and effective biocide which has been safely used for many years across a broad range of dental, medical, cosmetic and household products and is increasingly finding a use in clinically important applications. It has several mechanisms of action but as a biocide it acts principally by disruption of cell membranes. It also possesses specific modes of action at lower (sub-biocidal) concentrations, with similarities to the mode of action of some clinically important antibiotics.

At high (biocidal) concentrations, Triclosan is very effective and unlikely to produce a major problem of anti-microbial resistance.

At sub-biocidal concentrations, however, Triclosan may be capable of penetrating bacteria and initiating changes related to important mechanisms of antimicrobial resistance. It may induce mechanisms of resistance which are transferable to other bacteria, though the scientific evidence for this has been disputed. Sound scientific laboratory evidence exists for the development of Triclosan related mechanisms for antimicrobial resistance, but the evidence as to whether these mechanisms are shared by other antimicrobial agents or

whether they are transferable to micro-organisms other than those used in the laboratory is limited, not final and contradictory. No evidence of such resistance has been seen so far in clinical isolates, and there is no epidemiologic evidence to suggest a problem in clinical practice. That there are, however, very few targeted studies of resistance to Triclosan in relevant clinical or wider environments. Although, the stability and persistence of Triclosan resistance has not been widely studied, the limited information available points to it being stable over a three to ten year period, which is modestly reassuring.

The Working Group therefore concludes that there is no convincing evidence that Triclosan poses a risk to humans and the environment by inducing or transmitting antibacterial resistance.

However, taking into account the limited information available and the fact that any use of a biocide results in the availability of sub-biocidal concentrations in the wider environment[4], the Working Group recommends that more information is sought on:

- The extent and uses of Triclosan and their comparative importance;
- The prevalence of Triclosan resistant organisms in clinical environments;
- The exact mechanisms and dose responsiveness of antibacterial action of Triclosan, especially at sub biocidal concentrations;
- The kinetics of Triclosan antibacterial resistance mechanisms and their possible transferability;
- The fate of Triclosan in the environment; the rate and extent of degradation of Triclosan and the anti-microbial activity of degradates or low concentrations in the environment;
- The toxicological relevance of the presence of Triclosan in human milk.

It is also recommended that the potential for biocides, in general, to induce antimicrobial resistance of importance to clinical medicine, or management of the wider environment be kept under continuous review.

If new scientific evidence were to indicate a significant risk of biocides causing anti-microbial resistance to antibiotics used in human medicines, then appropriate action to manage these risks might be needed. Meanwhile, the recommendations of the SSC of 28 May 1999 on Antimicrobial resistance remain valid.

The present report on Triclosan focussed on its use as biocide and the potential risks related to the induction of antimicrobial resistance. Other potential hazards, related to the extensive use of triclosan have not been considered.

[4] According to the producer, the use of Triclosan [as a biocide] in other consumer products is – as claimed by - limited to 3% of the overall Triclosan production. These uses are not irrelevant as they represent a different route for the possible development of resistance (e.g., returnable containers to food processors, use in meat and poultry factories, …).

VIII LITERATURE CONSULTED

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COLIPA (The European Cosmetic, Toiletry and Perfumery Association), 2002a. Antimicrobial resistance and Triclosan. Dossier submitted on 4 April 2002to the Working Group of the Scientific Steering Committee. (3 Volumes + summary).

COLIPA (The European Cosmetic, Toiletry and Perfumery Association), 2002b. Antimicrobial resistance and Triclosan. Second dossier submitted on 7 May 2002 to the Working Group of the Scientific Steering Committee, covering the following topics:

I. Bacterial resistance (answers to specific questions raised by the Working Group on 19 April 2002)
II. Triclosan usage data (provided on a confidential basis)
III. Environmental aspects
IV. Human metabolism / bioaccumulation
V. Effectiveness of triclosan and benefits from its skin and oral care uses

Note: *Most of recent work related to Section V is in press or in preparation for publication so that abstracts provided by COLIPA have been used in addition to the safety data sheet of different manufacturers.*

COLIPA (The European Cosmetic, Toiletry and Perfumery Association), 2002c. Triclosan contribution III. Letter of 24 June from COLIPA to the SSC secretariat, containing a Table illustrating the percentage (%) of the **oral-care uses** of Triclosan per individual EU Member State. Provided in confidence.

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