Ciba Specialty Chemicals Corporation
USA

26 August 2003

Ciba

Via Next Day Courier

Dockets Management Branch
Food and Drug Administration (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852
(301) 827-2222

**Re: Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Health Care Antiseptic Drug Products; Reopening of the Administrative Record; (68 FR 32003, May 29, 2003); Docket No. 75N-183H**

Dear Sir or Madam:

Ciba Specialty Chemicals Corporation ("Ciba") Home and Personal Care Segment submits the following comments in response to the reopening of the administrative record for the subject rulemaking.

Ciba has provided FDA with information and formal comments supporting the Category I Safety and Efficacy of triclosan on various occasions since the last publication of the Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products on June 17th and November 15th 1994 (59 FR 31402 and 58799, respectfully). Specifically, Ciba submitted data and comments to FDA under Docket No. 75N-183H on the following dates:

- June 19, 1995 – in response to 59 FR 31402 (June 17 1994);
- December 14, 1995 – in response to 59 FR 58799 (November 15 1994);
- September 13, 2001 – as part of a Citizen Petition; and
- February 11, 2002 – as part of a Citizen Petition

Moreover, during this time period, Ciba has also been in touch with the FDA directly and indirectly with the Triclosan Industry Alliance (TIA) in an effort to support the reclassification of triclosan from Category III Safety/Efficacy (S/E) to Category I S/E in topical applications at concentrations up to 1.0 percent. However, Ciba has yet to receive any official feedback from the Agency regarding the adequacy of the data or requests for clarifications submitted.

It is Ciba's understanding that the Agency currently intends to finalize the monograph for topical antimicrobial healthcare professional products (comprised of pre-operative skin preparations, surgical scrubs and healthcare personnel hand wash products) and then address the remaining topical product categories (i.e., consumer hand and body and food handler products) under a separate or joint rulemaking sometime in the near future. As such, we request that the Agency continue to accept new data for consideration under this and future topical antimicrobial product rulemakings and also defer on the final classification of our active ingredient (if necessary) until we have

75N-183H C 85

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addressed all Agency concerns (based on feedback) and have completed any further testing deemed necessary to support the Category I S/E classification of triclosan.

Under this submission, Ciba is submitting additional safety and efficacy information supporting the classification of triclosan as Category I S/E at concentrations up to 1.0 percent as a single ingredient or combination with other active ingredients listed on the monograph.

Ciba requests that these data be used in support of the Category I status for triclosan in both the final Monograph for topical antimicrobial health-care products (comprised of products commonly described as pre-operative skin preparations, surgical scrubs and healthcare personnel hand wash products) and any planned Monograph for topical antimicrobial food handler, consumer hand, and consumer body products.

Furthermore, if the Agency determines that additional studies are needed, Ciba also requests that the FDA defer action on triclosan or make a provision in the final Monograph or rulemaking for the continued use of triclosan until official feedback has been transmitted to Ciba, we have had adequate time to respond, and any further necessary studies are completed and submitted to the Agency.

In the sections below, we describe what information has been submitted since the publication of the TFM for Health-Care Antiseptic Drug Products in June of 1994 and also provide a summary of the new data being conveyed under this transmittal.

## Safety

From a historical perspective, Ciba has developed a comprehensive toxicological database on triclosan that includes studies in the areas of:

- *Acute toxicity* (oral administration to rats, mice, dogs; dermal application in rabbits; inhalation exposure in rats);
- *Skin irritation and sensitization* (multiple studies in rats and guinea pigs);
- *Subacute toxicity* (oral administration to mice; inhalation and dermal exposures in rats; a neurotoxicity study in rats);
- *Subchronic toxicity* (oral administration in rats, mice, and rabbits; dermal administration in rats, rabbits, and monkeys);
- *Chronic toxicity* (oral administration to rats, hamsters, dogs, and baboons);
- *Reproductive toxicity* (teratology studies in mice, rats and rabbits; a multigeneration study in rats);
- *Genetic toxicity* (multiple bacterial and yeast systems; *in vitro* studies in mammalian cells; *in vivo* studies in mice, rats, and Chinese hamsters);
- *Metabolic fate and pharmacokinetic studies* (in rats, mice, hamsters, rabbits, monkeys, dogs, baboons, and humans);
- *Dermal absorption studies* (in rats, rabbits, monkeys, and humans); and
- *Clinical studies* documenting the pharmacokinetic fate of triclosan in humans following topical application and oral exposures.

These studies, among others, have been previously submitted to the OTC Docket and serve as the basis for the agency's conclusion (under the 1991 TFM for first aid antiseptic drug products and restated under the current TFM) that triclosan, in concentrations up to 1.0 percent, is safe for short term uses.

Since, 1994, Ciba has submitted 24 additional studies of various types in support of the Category I Safety status of triclosan under this monograph. The submission date and title of each study submitted is presented in tables 1 to 5 below. Ciba believes that this comprehensive dataset supports the safety of not only short-term uses of triclosan, but long-term uses of triclosan as well. As mentioned previously, Ciba has not yet received any official feedback from the Agency on the studies or comments summarized below.

**Table 1. Triclosan Studies Submitted to FDA on September 12, 1994**

| OTC Volume Number | Date Safety Data Submitted to FDA: 75N-183H | Study Title |
|---|---|---|
| 101 | 12 September 1994 | Borzelleca, J.F., Frankos, V.H., Johnson, E.M., Jordan, W., Squire, R.A., and Weil, C., *Selected Portions of the Report of the Expert Panel on the Safety of Triclosan inToothpaste and Oral Rinse Products.* Environ Corporation Expert Panel Report. December 15, 1992. |
| 102 | 12 September 1994 | Goodman, D.G. *Pathology Working Group Report on Triclosan Chronic Toxicity/Carcinogenicity Study in Sprague-Dawley Rats.* Prepared by PATHCO, Inc. for Ciba- Geigy. January 23, 1990. Pathology Working Group members included: J.M.Cullen, D.G. Goodman, P.M. Newberne, R.M. Sauer, R.A. Squire, and J.M. Ward. |
| 103 | 12 September 1994 | Jones, E. and Wilson, L. *Ames Metabolic Activation Test to Address the PotentialMutagenic Effect of Triclosan.* Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Study No. KA 880169. September 9, 1988. |
| 103 | 12 September 1994 | Henderson, L.M., Produlock, R.J., Haynes, P., and Meaking, K. *Mouse Micronucleous Test on Triclosan.* Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Study No. KC 880168. August 12, 1988. |
| 105 | 12 September 1994 | Henderson, L.M., Ransome, S.J., Brabbs, C.E., Tinner, A.J., Davies, S.E., and Loyd, A., *An Assessment of the Mutagenic Potential of Triclosan Using the Mouse Lymphoma TK Locus Assay.* Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Study No. KM 880170. September 15, 1988. |
| 106 | 12 September 1994 | Riach, C.G., McBride, D., and M.L., O'Mailley. *Triclosan: Assessment of Genotoxicity in an Unscheduled DNA Synthesis Assay Using Adult Rat Hepatocyte Primary Cultures.* Inveresk Research International Limited. Project No. 738388. Report No. 4667. November 2, 1988. |
| 107 | 12 September 1994 | Heidemann, H.G. *Chromosome Aberration Assay in Chinese Hamster V79 Cells In Vitro with FAT 80'023/Q (Triclosan).* Cytotest Cell Research GmbH & Co. KG. Project No. 179100. December 17, 1990. |
| 108 | 12 September 1994 | Völkner, W. *Chromosome Aberration Assay in Bone Marrow Cells of the Rat with FAT80'023/Q (Triclosan).* Cytotest Cell Research GmbH & Co. KG. Project No. 218305. April 23, 1991. |
| 109 | 12 September 1994 | SanSebastian, J.R., et al. *Rat Hepatocyte Primary Culture/DNA Repair Test on 39317.* Pharmakon USA. Study No. PH 311-CP-001-93. June 24, 1993. |
| 110 | 12 September 1994 | Stankowski, L.F., et al. *Ames/Salmonella Plate Incorporation Assay on Test Article 39316 (CC# 14663-09).* Pharmakon USA. Study No. PH 301-CP-001-93. Dec. 2, 1993. |
| 111 | 12 September 1994 | Ciba-Geigy. *Summary of Current Available Safety Data on Triclosan.* Triclosan Industry Alliance. August 15, 1994. |

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| 112 | 12 September 1994 | Goodman, D.G. *Pathology Working Group Report on Triclosan 90-Day Subchronic Toxicity Study in Sprague-Dawley Rats.* Prepared by PATHCO, Inc. for Ciba-Geigy. January 23, 1990. Pathology Working Group members included: J.M.Cullen, D.G. Goodman, P.M. Newberne, R.M. Sauer, R.A. Squire, and J.M. Ward. |
| 113 | 12 September 1994 | Brooker, P.C., Gray. V.M., Howell, A. *Analysis of Metaphase Chromosomes Obtained from CHO Cells Cultured In Vitro and Treated with Triclosan.* Huntington Research Centre Ltd., ULR 214/88731. Unilever Test No. KC 880171. August 11, 1988. |
| 114 | 12 September 1994 | Trutter, J.A. *13-Week Subchronic Oral Toxicity Study of Triclosan in CD-1® Mice.* Hazleton Washington, Inc. Lab. Project I.D. No. 483-287. January 28, 1993. |
| 115 | 12 September 1994 | Trutter, J.A. *13-Week Subchronic Oral Toxicity Study of Triclosan in CD-1® Mice (Volume 2).* Hazleton Washington, Inc. Lab. Project I.D. No. 483-287. January 28, 1993. |
| 116 | 12 September 1994 | Trimmer, G.W. *90-Day Subchronic Dermal Toxicity Study in the Rat with Satellite Group with Irgasan DP 300 (MRD-92-399).* Exxon Biomedical Sciences, Inc. Lab. Project I.D. 139910B. July 14, |

## Table 2. Triclosan Studies Submitted to FDA in 1997 and 1998

| OTC Volume Number | Date Safety Data Submitted to FDA: 75N-183H | Study Title |
|---|---|---|
| None – Submitted by Triclosan Industry Alliance (TIA) | 23 June 1997 | Species Selection for Chronic Dermal Testing with Triclosan |
| None- Submitted by TIA | 6 March 1998 | Study protocol (13-week dermal subchronic study of triclosan in rats |

## Table 3. Triclosan Studies Submitted to FDA in 1999

| OTC Volume Number | Date Safety Data Submitted to FDA: 75N-183H | Study Title |
|---|---|---|
| 117 | 15 September 1999 | Chambers, P.R. *FAT 80'023/S (Triclosan) Potential Tumorigenic and Chronic Toxicity Effects in Prolonged Dietary Administration to Hamsters.* Huntingdon Life Sciences Ltd. Study Number CBG 756/972896. March 30, 1999. |

## Table 4. Triclosan Studies Submitted to FDA in 2001

| OTC Volume Number | Date Safety Data Submitted to FDA: 75N-183H | Study Title |
|---|---|---|
| 118 | 13 September 2001 | Burns, J.M., et. al, *14-Day Repeated Dose Dermal Study of Triclosan in Rats*, CHV 6718-102, Corning Hazelton, Inc., April 28, 1997 |
| 119 | 13 September 2001 | Burns, J.M., et. al, *14-Day Repeated Dose Dermal Study of Triclosan in Mice*, CHV 6718-101, Corning Hazelton, Inc., April 28, 1997 |
| 120 | 13 September 2001 | Burns, J.M., et. al, *14-Day Repeated Dose Dermal Study of Triclosan in CD-1 Mice*, CHV 2763-100, Corning Hazelton, Inc., April 29, 1997 |
| 121 | 13 September 2001 | Triclosan Industry Alliance Position Paper: Triclosan: Adequacy of Data to Support the Lack of Potential for Dermal Carcinogenicity, September 2001 |

**Table 5. Triclosan Studies Submitted to FDA in 2002**

| OTC Volume Number | Date Safety Data Submitted to FDA: 75N-183H | Study Title |
|---|---|---|
| None – Submitted as part of Citizen Petition | 13 February 2002 | Human Dermal Pharmacokinetics (PK) Study – A Pilot Study for the In-Vivo Evaluation of the Percutaneous Absorption of Triclosan; Arizona Clinical Research Center (ACRC); January 17 2002 |

Given the absence of any substantive comments from the Agency regarding the safety information already submitted, Ciba has decided to submit 27 additional studies (see Table 6) to the docket in support of the reclassification of triclosan from Category III to Category I for safety for short and long-term topical application uses at concentrations (single or in combination) up to 1.0 percent. It is our belief that the enclosed studies will fill any perceived data gaps or confirm the results of older non-GLP compliant studies.

In general, the following types of safety data are being submitted:

- Developmental toxicity studies in rats, rabbits, and mice;
- Skin sensitization;
- Human pharmacokinetics after using various TCS-containing products;
- Hamster, rat, and mouse pharmacokinetics after administration of TCS;
- Effects of TCS on various biochemical and morphological liver parameters in hamsters, rats, and mice;
- Subchronic toxicity in hamsters; and
- Acute oral and inhalation toxicity

These studies, in conjunction with the studies already in the docket, show that TCS is not a developmental toxicant, is not a skin sensitizer, does not bioaccumulate and is readily eliminated from man and animals, and exhibits moderate subchronic and acute toxicity. In addition, the enclosed studies show that TCS exhibits a species-specific peroxisome proliferative effect in the liver of mice, which is not observed in hamsters and is only slightly apparent in rats. Furthermore, these studies demonstrate that:

- Triclosan does not have the profile of biological activities of any known human skin carcinogen or skin cancer risk factor;
- Triclosan is nongenotoxic and is unlikely to be a rat skin carcinogen since these agents appear to be predominantly genotoxic;
- Triclosan does not cause skin hyperproliferative changes such as acanthosis at typical use levels;
- The available data from the rat and hamster cancer bioassays with oral dosing of triclosan are adequate to assess the carcinogenic potential of triclosan; and
- Extensive human experience with triclosan through both controlled clinical studies and over 30 years of safe product use support the dermal safety of this material.

## Table 6. Triclosan Studies Submitted on August 27, 2003

| OTC Volume Number | Date Safety Data Submitted to FDA: 75N-183H | Study Title |
|---|---|---|
| 122 | 27 August 2003 | Schroeder, R.E., et al. *A Segment II Teratology Study in Rabbits with Igacare MP (C-P Sample No. 38328).* Bio/dynamics, Inc. Project No. 91-3666. Colgate-Palmolive Study No. 91-006. April 16, 1992. |
| 123 | 27 August 2003 | Schroeder, R.E., et al. *A Range-Finding Study to Evaluate the Toxicity of Irgacare MP (C-P Sample No. 38328) in the Pregnant Rat.* Bio/dynamics, Inc. Project No. 91-013. Colgate-Palmolive Study No. 91-3654. May 6, 1992. |
| 124 | 27 August 2003 | Schroeder, R.E., et al. *A Segment II Teratology Study in Rats with Irgacare MP (C-P Sample No. 38328).* Bio/dynamics, Inc. Project No. 91-3665. Colgate-Palmolive Study No. 91-005. April 16, 1992. |
| 125 | 27 August 2003 | Hoberman, A.M., et al. *Dosage-Range Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of C-P Sample No. 38328 Administered Orally Via the Diet to Crl:CD®-1(ICR)BR Presumed Pregnant Mice.* Argus Research Laboratories, Inc. Protocol Number 403-010P. July 22, 1992. |
| 126 | 27 August 2003 | Hoberman, A.M., et al. *Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of C-P Sample No. 38328 Administered Orally Via the Diet to Crl:CD®-1(ICR)BR Presumed Pregnant Mice.* Argus Research Laboratories, Inc. Protocol Number 403-010. October 22, 1992. |
| 127 | 27 August 2003 | Denning, H.J., Sliwa, S. and Wilson, G.A. *Triclosan: Effects on Pregnancy and Post-Natal Development in Rats: Volume 1.* Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Document No. D92/105. December 1992. |
| 128 | 27 August 2003 | Denning, H.J., Sliwa, S. and Wilson, G.A. *Triclosan: Effects on Pregnancy and Post-Natal Development in Rats: Volume 2: Appendices 1-17.* Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Document No. D92/105. December 1992. |
| 129 | 27 August 2003 | Wnorowski, G. *Acute Oral Toxicity Limit Test for Triclosan (Irgasan® DP300) Lot No. 5.2.0211.0.* Product Safety Labs. Study No. 2800. March 11, 1994. |
| 130 | 27 August 2003 | Wnorowski, G. *Dermal Sensitization Test - Buehler Method for Triclosan (Irgasan® DP 300, Lot No. 5.2.0211.0.* Product Safety Labs. Study No. 2635. April 4, 1994. |
| 131 | 27 August 2003 | Schmid, H., Dotti, B., Keller, B., et. Al. *13-Week Oral Toxicity (Feeding) Study with FAT 80'023/R (Triclosan) in the Hamste: Part 1.* RCC Project Number 356490. October 20, 1994. |
| 132 | 27 August 2003 | Schmid, H., Dotti, B., Keller, B., et. Al. *13-Week Oral Toxicity (Feeding) Study with FAT 80'023/R (Triclosan) in the Hamste: Part 2.* RCC Project Number 356490. October 20, 1994. |
| 133 | 27 August 2003 | Schmid, H., Dotti, B., Keller, B., et. Al. *13-Week Oral Toxicity (Feeding) Study with FAT 80'023/R (Triclosan) in the Hamste: Part 3.* RCC Project Number 356490. October 20, 1994. |
| 134 | 27 August 2003 | Van Dijk, A. *$^{14}$C-Triclosan: Absorption, Distribution, Metabolism and Elimination After Single/Repeated Oral and Intravenous Administration to Hamsters.* RCC Project 351707. November 11, 1994. |
| 135 | 27 August 2003 | Thomas, Rer. Nat., H. *The effect of FAT 80'023/R (triclosan) and the model inducers: phenobarbitone, 3-methylcholanthrene, pregnenolone-16alpha-carbonitrile and nafenopin on selected biochemical and morphological liver parameters in the Syrian hamster.* Ciba-Geigy Limited. Laboratory Reprot No. CB 93/40. September 16, 1994. |
| 136 | 27 August 2003 | Persohn, E. *FAT 80'023/R (triclosan): assessment of replicative DNA synthesis in the course of a 13-week oral toxicity study in the hamster.* RCC Project 356490. Ciba Laboratory Report No. 93/47. September 19, 1994. |

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| 137 | 27 August 2003 | Van Dijk, A. *$^{14}$C-Triclosan: Absorption, Distribution, Metabolism and Elimination After Single/Repeated Oral and Intravenous Administration to Mice.* RCC Project 337781. March 1, 1995. |
| 138 | 27 August 2003 | Van Dijk, A. *AMMENDMENT: $^{14}$C-Triclosan: Absorption, Distribution, Metabolism and Elimination After Single/Repeated Oral and Intravenous Administration to Hamsters.* RCC Project 351707. February 14, 1995. |
| 139 | 27 August 2003 | Duchosal, F. and Thevenaz, Ph. *4-Hour, Acute Inhalation Toxicity Study with FAT 80'023/Q.* RCC Project Number 254597. June, 1990. |
| 140 | 27 August 2003 | Eldridge, S. *Cell proliferation in rodent liver.* Pathology Associates, Inc. January, 13, 1993. |
| 141 | 27 August 2003 | Molitor, E., Persohn, E., and Thomas, H. *The effect of FAT 80'023/Q (Irgasan DP300) on selected biochemical liver parameters following subchronic dietary administration to male and female mice.* Ciba-Geigy Limited, Switzerland, Report CB 91/18. May 22 1992. |
| 142 | 27 August 2003 | Molitor, E. and Persohn, E. *The effects of FAT 80'023/Q (Irgasan DP300) on selected biochemical liver parameters following dietary administration to male rats.* Ciba-Geigy Limited, Switzerland. August 2, 1993. |
| 143 | 27 August 2003 | Sagelsdorff, P. and Buser, G. *Investigation of the binding of Irgasan DP300 to human, hamster and mouse plasma proteins in vitro.* Ciba-Geigy, Switzerland Report No. CB 95/07. July 19, 1995. |
| 144 | 27 August 2003 | Van Dijk, A. $^{14}$C-Triclosan: Absorption, distribution and excretion (ADE) after single oral and repeated oral administration to male rats. RCC Umweltchemie AG, Itingen, Switzerland. RCC Project 341998. Sponsored by Ciba-Geigy AG, Grenzach-Wyhlen, Germany. July 17, 1996. |
| 145 | 27 August 2003 | Henderson, L.M., Ransome, S.J., Brabbs, C.E., Tinner, A.J., Davies, S.E., and Lloyed, A. An assessment of the mutagenic potential of triclosan using the mouse lymphoma TK locus assay. Huntingdon Research Centre Ltd., Cambridgeshire, England. HRC Report Number ULR 216/88644. Sponsored by Unilever Research Laboratory, Bedfordshire, England. September 15, 1988. |
| 146 | 27 August 2003 | Frankos, V.H., Goodman, D.G., Lake, B.G., Rodricks, J.V., and Ward, J.M. Implications for human health of the triclosan animal bioassay data. ENVIRON International Corporation, Alrington, Virginia, USA. December, 2000. Sponsored by Colgate-Palmolive Company, Piscataway, New Jersey, USA. |
| 147 | 27 August 2003 | Beiswanger, B.B., and Tuohy, M.A. *Analysis of Blood Plasma Samples for Free Triclosan, Triclosan-Glucuronide, Triclosan Sulfate and Total Triclosan From Subjects Using a Triclosan Dentifrice or a Dentifrice, Bar Soap and Deodorant.* Indiana University School of Dentistry, Oral Health Research Institute Study No. 89-A-111. October 17, 1990. |
| 148 | 27 August 2003 | Schroeder, R.E., et al. *A Range-Finding Study to Evaluate the Toxicity of Irgacare MP (C-P Sample No. 38328) in the Pregnant Rabbit*. Bio/dynamics, Inc. Project No. 91-014. Colgate-Palmolive Study No. 91-3655. May 6, 1992. |

## Efficacy

Ciba believes that sufficient data exist demonstrating triclosan's efficacy. Ciba, as well as the Soap and Detergent Association (SDA), Cosmetic Toiletry and Fragrance Association, and numerous other companies, have made several submissions to the docket in support of the efficacy of triclosan as an active ingredient and in combination with other ingredients listed on the Monograph.

Since 1994, Ciba has submitted 21 studies of various types in support of the Category I Efficacy status of triclosan under this monograph. The submission date and title of each study submitted is presented in tables 7 to 8 below. Ciba believes that these

comprehensive *in-vitro* and *in-vivo* efficacy data fully support the use of triclosan for the various topical antiseptic applications described in the TFM (i.e., healthcare professional, consumer and food handler products) for short and long-term use and at concentrations up to 1.0 percent.

**Table 7. Triclosan Efficacy Data submitted on June 19, 1995.**

| Date Efficacy Data Submitted to FDA: 75N-183H | Study Title |
|---|---|
| 19 June 1995 | Vischer W.A., Regos J., Antimicrobial Spectrum of Triclosan, a Broad Spectrum Antimicrobial for Topical Application (1974); Zbl. Bakt. Hyg., I Abt. Orig. A 226, 376-389. |
| 19 June 1995 | Marsh P.D., Dentifrices Containing New Agents for the Control of Plaque and Gingivitis: Microbiological Aspects , Journal of Clinical Periodontology (1991); 18: 462-67. |
| 19 June 1995 | Stensby P.S., "Letter to W.E. Gilbertson responding to Triclosan effectiveness issues (1983). |
| 19 June 1995 | Larson E., Mayur K., Laaughon B.A., Influence of Two Handwashing Frequencies on Reduction in Colonizing Flora with Three Handwashing Products used by Health Care Personnel, Am. J. Infect. Control (1989); 17:83-8. |
| 19 June 1995 | Bartzokas C.A., Corkill J.E, Makin T., Evaluation of the Skin Disinfecting Activity and Cumulative Effect of Chlorhexidine and Triclosan Handwash Preparations on Hands Artificially Contaminated with *Serratia Marcescens*, Infect. Control (1987); 8: 163-7. |
| 19 June 1995 | Butz A.M., Laughon B.E., Gullette D.L., Larson E.L., Alcohol Impregnated Wipes as an Alternative in Hand Hygiene, Am. J. Infect. Control (1990); 18: 70-6. |
| 19 June 1995 | Bartzokas C.A., Paton J.H., Gibson M.F., Graham R., McLoughlin G.A., Croton R.S., Control and Eradication of Methicillin-Resistant *Staphylococcus aureus* on a Surgical Unit, The New England Journal of Medicine (1984); 311: 1422-25. |
| 19 June 1995 | Webster J., Handwashing in a Neonatal Intensive Care Nursery: Product Acceptability and Effectiveness of Chlorhexidine 4% w/v and Triclosan 1% w/v, J. Hosp. Infect. (1992); 21: 137-41. |
| 19 June 1995 | Webster J., Faoagali J., Cartwright D., Elimination of Methicillin-Resistant *Staphylococcus* from a Neonatal Intensive Care Unit after Washing with Triclosan, J. Paediatr. Child Health (1994); 30: 59-64. |
| 19 June 1995 | Tuffnell D.J., Croton R.S., Hemingway D.M., Hartley M.N., Wake P.N., Garvey R.J., Methicillin-Resistant *Staphylococcus aureus*; the Role of Antisepsis in the Control of an Outbreak, J. Hosp. Infect. (1987); 10: 255-9. |
| 19 June 1995 | Brady L.M., Thompson M., Palmer M.A., Harkness J.L., Successful Control of Endemic MRSA in a Cardiothoracic Surgical Unit, Med. J. Aust. (1990); 152: 240-5. |
| 19 June 1995 | Russell A.D., Bacterial Resistance to Antiseptics and Disinfectants, Journal of Hospital Infection (1986); 7: 213-25. |
| 19 June 1995 | Masanori S., Shimizu K., Noguchi N., Kono M., Triclosan-Resistance *Staphylococcus aureus* The Lancet (1993); 341: 756. |
| 19 June 1995 | Uhl S., Reply to Triclosan-Resistance *Staphylococcus aureus* The Lancet (1993); 342. |
| 19 June 1995 | Cox A.R., Efficacy of the Antimicrobial Agent Triclosan in Topical Deodorant Products: Recent Developments In-vivo, J. Soc. Cosmet. Chem. (1987); 38: 223-31. |
| 19 June 1995 | Volpe A.R., Petrone M.E., DeVizio W., Davies R.M., A Review of Plaque, Gingivitis, Calculus and Caries Clinical Efficacy Studies with a Dentifrice Containing Triclosan and PVM/MA Copolymer, The Journal of Clinical Dentistry (1993); IV: Special Issue: 31-41. |

**Table 8. Triclosan Efficacy Data submitted on December 14, 1995**

| Date Efficacy Data Submitted to FDA: 75N-183H | Study Title |
|---|---|
| 14 December 1995 | *In-vitro* Efficacy: Determination of Triclosan Minimum Inhibitory Concentrations (MIC) as required under 330.470, section (a)(1)(ii) of 59 *FR* 31444 (June 17, 1994), Ciba-Geigy Limited, R&D Labs, Grenzach, Germany |
| 14 December 1995 | *In-vivo* Efficacy: Efficacy Evaluation of Triclosan Handwashing Products for Use in the Health Care Environment using modified ASTM method E1174, Hill Top Biolabs, Miamiville, Ohio |
| 14 December 1995 | Cited Resistance Studies: Michna-Bednarek and Czorniawski (no date); Cookson et al., Lancet (1991); Jones (1988) and Stephen (1990) |

**Table 9. Triclosan Efficacy Data submitted on February 11, 2002**

| Date Efficacy Data Submitted to FDA: 75N-183H | Study Title |
|---|---|
| 11 February 2002 | *In-vitro* Efficacy: Determination of Triclosan Antimicrobial Activity in a Time Kill Suspension Test, T.J. Stephens and Associates (Study No.: L00-D047), Dallas, TX, November 30, 2000. |
| 11 February 2002 | *In-vivo* Efficacy: Efficacy Evaluation of Triclosan Health Care Personnel Handwash Products, Hill Top Research, Inc. (Study No. 00-105877-11, Miamiville, Ohio, January 10, 2001 |

## Resistance Surveillance

Since our submissions of January 22, 1995 and December 14, 1995, the following information regarding topical antimicrobial ingredient resistance has become available:

- On January 22, 1997 a joint meeting of the FDA's Nonprescription Drug Advisory and Anti-Infective Advisory Committees ("Advisory Committees") agreed that the evidence to date indicated that topical antimicrobial wash products do not contribute to antimicrobial resistance. They further suggested that on-going surveillance for the possible development of resistance to these agents is prudent.

- On June 27-28, 2002, the European Commission's Health & Consumer Protection Directorate-General the Scientific Steering Committee met and published its findings on triclosan resistance (European Commission, 2002). It was concluded that: although "sound scientific laboratory evidence exists for the development of Triclosan related mechanisms for antimicrobial resistance, ... 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."

  Furthermore, it was stated that: "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."

  It was concluded 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. There is no convincing evidence that Triclosan poses a risk to humans or to the environment by inducing or transmitting antibacterial resistance under current conditions of use."

A copy of the European Commission's opinion on Triclosan resistance is included with this submission.

## Concluding Remarks

Triclosan, (2,4,4'-trichloro-2'-hydroxydiphenyl ether), has broad-spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria. It has been safely utilized in health-care professional and consumer products including deodorants, soaps and dentifrices for over 30 years. As seen in this transmittal, the favorable safety and efficacy profile of triclosan has been well established in numerous laboratory and clinical studies and through extensive human experience.

Under this submission, Ciba has transmitted additional safety and efficacy information supporting the classification of triclosan as Category I S/E at concentrations up to 1.0 percent as a single ingredient in or combination with other active ingredients listed on the monograph.

Ciba requests that these data be used in support of the Category I S/E status for triclosan in both the final Monograph for topical antimicrobial health-care products (comprised of products commonly described as pre-operative skin preparations, surgical scrubs and healthcare personnel hand wash products) and any planned Monograph for topical antimicrobial food handler, consumer hand, and consumer body products.

Furthermore, Ciba requests that if FDA determines that additional studies are needed, FDA defer action on triclosan or make a provision in the final Monograph or rulemaking for the continued use of triclosan until official feedback transmitted, we have adequate time to respond, and any further necessary studies are completed and submitted to the Agency.

Ciba looks forward to working with the agency on resolving any unanswered questions.

Sincerely,

Carl D'Ruiz, MPH
Head, Regulatory Affairs and Product Safety
Home and Personal Care

Attachments: OTC Docket Transmittal

CC via e-mail: C. Ganley
D. Lumpkins
R. Osterberg

# TRANSMITTAL DOCUMENT

## 1. NAME AND ADDRESS OF SUBMITTER

Ciba Specialty Chemicals Corporation
Home & Personal Care Segment
4090 Premier Drive
High Point, NC 27265

## 2. REGULATORY ACTION OF SUPPORT FOR WHICH THIS PACKAGE IS SUBMITTED

The contents of this package are being submitted to the U.S. Food and Drug Administration for inclusion into OTC Docket Number 75N-0183H (triclosan-CAS No. 3380-34-5). A list of the studies being submitted is presented below. More specific information related to this product may be found in the cover letter and attachments accompanying this transmittal document.
**Note:** These studies are the property of Ciba Specialty Chemicals Corporation and are to be used only to support the Safety and Efficacy of triclosan in FDA regulated products. Use by any other entity (other than FDA )is explicitly prohibited without the written permission of Ciba Specialty Chemicals Corporation.

## 3. TRANSMITTAL DATE: August 26th, 2003

## 4. LIST OF SUBMITTED STUDIES

| *OTC. Vol. No.* | *Study Title* |
|---|---|
| 122 | Schroeder, R.E., et al. *A Segment II Teratology Study in Rabbits with Igacare MP (C-P Sample No. 38328)*. Bio/dynamics, Inc. Project No. 91-3666. Colgate-Palmolive Study No. 91-006. April 16, 1992. |
| 123 | Schroeder, R.E., et al. *A Range-Finding Study to Evaluate the Toxicity of Irgacare MP (C-P Sample No. 38328) in the Pregnant Rat*. Bio/dynamics, Inc. Project No. 91-013. Colgate-Palmolive Study No. 91-3654. May 6, 1992. |
| 124 | Schroeder, R.E., et al. *A Segment II Teratology Study in Rats with Irgacare MP (C-P Sample No. 38328)*. Bio/dynamics, Inc. Project No. 91-3665. Colgate-Palmolive Study No. 91-005. April 16, 1992. |
| 125 | Hoberman, A.M., et al. *Dosage-Range Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of C-P* |

*Sample No. 38328 Administered Orally Via the Diet to Crl:CD®-1(ICR)BR Presumed Pregnant Mice*. Argus Research Laboratories, Inc. Protocol Number 403-010P. July 22, 1992.

126 Hoberman, A.M., et al. *Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of C-P Sample No. 38328 Administered Orally Via the Diet to Crl:CD®-1(ICR)BR Presumed Pregnant Mice*. Argus Research Laboratories, Inc. Protocol Number 403-010. October 22, 1992.

127 Denning, H.J., Sliwa, S. and Wilson, G.A. *Triclosan: Effects on Pregnancy and Post-Natal Development in Rats: Volume 1.* Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Document No. D92/105. December 1992.

128 Denning, H.J., Sliwa, S. and Wilson, G.A. *Triclosan: Effects on Pregnancy and Post-Natal Development in Rats: Volume 2: Appendices 1-17.* Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Document No. D92/105. December 1992.

129 Wnorowski, G. *Acute Oral Toxicity Limit Test for Triclosan (Irgasan® DP300) Lot No. 5.2.0211.0.* Product Safety Labs. Study No. 2800. March 11, 1994.

130 Wnorowski, G. *Dermal Sensitization Test - Buehler Method for Triclosan (Irgasan® DP 300, Lot No. 5.2.0211.0*. Product Safety Labs. Study No. 2635. April 4, 1994.

131 Schmid, H., Dotti, B., Keller, B., et. Al. *13-Week Oral Toxicity (Feeding) Study with FAT 80'023/R (Triclosan) in the Hamste: Part 1.* RCC Project Number 356490. October 20, 1994.

132 Schmid, H., Dotti, B., Keller, B., et. Al. *13-Week Oral Toxicity (Feeding) Study with FAT 80'023/R (Triclosan) in the Hamste: Part 2.* RCC Project Number 356490. October 20, 1994.

133 Schmid, H., Dotti, B., Keller, B., et. Al. *13-Week Oral Toxicity (Feeding) Study with FAT 80'023/R (Triclosan) in the Hamste: Part 3.* RCC Project Number 356490. October 20, 1994.

134 Van Dijk, A. *$^{14}$C-Triclosan: Absorption, Distribution, Metabolism and Elimination After Single/Repeated Oral and Intravenous Administration to Hamsters.* RCC Project 351707. November 11, 1994.

135 Thomas, Rer. Nat., H. *The effect of FAT 80'023/R (triclosan) and the model inducers: phenobarbitone, 3-methylcholanthrene, pregnenolone-16alpha-carbonitrile and nafenopin on selected biochemical and morphological liver parameters in the Syrian*

*hamster.* Ciba-Geigy Limited. Laboratory Reprot No. CB 93/40. September 16, 1994.

136 Persohn, E. *FAT 80'023/R (triclosan): assessment of replicative DNA synthesis in the course of a 13-week oral toxicity study in the hamster.* RCC Project 356490. Ciba Laboratory Report No. 93/47. September 19, 1994.

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138 Van Dijk, A. *AMMENDMENT: $^{14}$C-Triclosan: Absorption, Distribution, Metabolism and Elimination After Single/Repeated Oral and Intravenous Administration to Hamsters.* RCC Project 351707. February 14, 1995.

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142 Molitor, E. and Persohn, E. *The effects of FAT 80'023/Q (Irgasan DP300) on selected biochemical liver parameters following dietary administration to male rats.* Ciba-Geigy Limited, Switzerland. August 2, 1993.

143 Sagelsdorff, P. and Buser, G. *Investgation of the binding of Irgasan DP300 to human, hamster and mouse plasma proteins in vitro.* Ciba-Geigy, Switzerland Report No. CB 95/07. July 19, 1995.

144 Van Dijk, A. $^{14}$C-Triclosan: Absorption, distribution and excretion (ADE) after single oral and repeated oral administration to male rats. RCC Umweltchemie AG, Itingen, Switzerland. RCC Project 341998. Sponsored by Ciba-Geigy AG, Grenzach-Wyhlen, Germany. July 17, 1996.

145 Henderson, L.M., Ransome, S.J., Brabbs, C.E., Tinner, A.J., Davies, S.E., and Lloyed, A. An assessment of the mutagenic potential of triclosan using the mouse lymphoma TK locus assay. Huntingdon Research Centre Ltd., Cambridgeshire, England. HRC Report Number ULR 216/88644. Sponsored by Unilever

Research Laboratory, Bedfordshire, England. September 15, 1988.

146 Frankos, V.H., Goodman, D.G., Lake, B.G., Rodricks, J.V., and Ward, J.M. Implications for human health of the triclosan animal bioassay data. ENVIRON International Corporation, Alrington, Virgina, USA. December, 2000. Sponsored by Colgate-Palmolive Company, Piscataway, New Jersey, USA.

147 Beiswanger, B.B., and Tuohy, M.A. *Analysis of Blood Plasma Samples for Free Triclosan, Triclosan-Glucuronide, Triclosan Sulfate and Total Triclosan From Subjects Using a Triclosan Dentifrice or a Dentifrice, Bar Soap and Deodorant*. Indiana University School of Dentistry, Oral Health Research Institute Study No. 89-A-111. October 17, 1990.

148 Schroeder, R.E., et al. *A Range-Finding Study to Evaluate the Toxicity of Irgacare MP (C-P Sample No. 38328) in the Pregnant Rabbit*. Bio/dynamics, Inc. Project No. 91-014. Colgate-Palmolive Study No. 91-3655. May 6, 1992.

**COMPANY OFFICIAL:** **Carl D. D'Ruiz, MPH** _____
*Signature*

**COMPANY NAME:** **Ciba Specialty Chemicals Corporation**

**COMPANY CONTACT:** **Carl D. D'Ruiz, MPH** **(336) 801-2493**

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, ...).

EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

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

# REPORT ON TRICLOSAN ANTIMICROBIAL RESISTANCE:

**Report prepared by K.Jones (rapporteur), J.Fink-Gremmels, T.Hardy, R.Hay, W.Klein, A.Knaap, J.Vives-Rego and .I.White,**

# REPORT

**TABLE OF CONTENTS:**

# 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, ...).

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**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.*

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