



26 August 2003

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

Via Next Day Courier

**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

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., <u>Selected Portions of the Report of the Expert Panel on the Safety of Triclosan in Toothpaste and Oral Rinse Products</u> . Environ Corporation Expert Panel Report. December 15, 1992.
102	12 September 1994	Goodman, D.G. <u>Pathology Working Group Report on Triclosan Chronic Toxicity/Carcinogenicity Study in Sprague-Dawley Rats</u> . 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. <u>Ames Metabolic Activation Test to Address the Potential Mutagenic Effect of Triclosan</u> . 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. <u>Mouse Micronucleous Test on Triclosan</u> . 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., <u>An Assessment of the Mutagenic Potential of Triclosan Using the Mouse Lymphoma TK Locus Assay</u> . 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. <u>Triclosan: Assessment of Genotoxicity in an Unscheduled DNA Synthesis Assay Using Adult Rat Hepatocyte Primary Cultures</u> . Inveresk Research International Limited. Project No. 738388. Report No. 4667. November 2, 1988.
107	12 September 1994	Heidemann, H.G. <u>Chromosome Aberration Assay in Chinese Hamster V79 Cells In Vitro with FAT 80'023/Q (Triclosan)</u> . Cytotest Cell Research GmbH & Co. KG. Project No. 179100. December 17, 1990.
108	12 September 1994	Völkner, W. <u>Chromosome Aberration Assay in Bone Marrow Cells of the Rat with FAT80'023/Q (Triclosan)</u> . Cytotest Cell Research GmbH & Co. KG. Project No. 218305. April 23, 1991.
109	12 September 1994	SanSebastian, J.R., et al. <u>Rat Hepatocyte Primary Culture/DNA Repair Test on 39317</u> . Pharmakon USA. Study No. PH 311-CP-001-93. June 24, 1993.
110	12 September 1994	Stankowski, L.F., et al. <u>Ames/Salmonella Plate Incorporation Assay on Test Article 39316 (CC# 14663-09)</u> . Pharmakon USA. Study No. PH 301-CP-001-93. Dec. 2, 1993.
111	12 September 1994	Ciba-Geigy. <u>Summary of Current Available Safety Data on Triclosan</u> . Triclosan Industry Alliance. August 15, 1994.

112	12 September 1994	Goodman, D.G. <i>Pathology Working Group Report on Triclosan 90-Day Subchronic Toxicity Study in Sprague-Dawley Rats</i> . 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. <i>Analysis of Metaphase Chromosomes Obtained from CHO Cells Cultured In Vitro and Treated with Triclosan</i> . Huntington Research Centre Ltd., ULR 214/88731. Unilever Test No. KC 880171. August 11, 1988.
114	12 September 1994	Trutter, J.A. <i>13-Week Subchronic Oral Toxicity Study of Triclosan in CD-1® Mice</i> . Hazleton Washington, Inc. Lab. Project I.D. No. 483-287. January 28, 1993.
115	12 September 1994	Trutter, J.A. <i>13-Week Subchronic Oral Toxicity Study of Triclosan in CD-1® Mice (Volume 2)</i> . Hazleton Washington, Inc. Lab. Project I.D. No. 483-287. January 28, 1993.
116	12 September 1994	Trimmer, G.W. <i>90-Day Subchronic Dermal Toxicity Study in the Rat with Satellite Group with Irgasan DP 300 (MRD-92-399)</i> . 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. <i>FAT 80'023/S (Triclosan) Potential Tumorigenic and Chronic Toxicity Effects in Prolonged Dietary Administration to Hamsters</i> . 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, <i>14-Day Repeated Dose Dermal Study of Triclosan in Rats</i> , CHV 6718-102, Corning Hazelton, Inc., April 28, 1997
119	13 September 2001	Burns, J.M., et. al, <i>14-Day Repeated Dose Dermal Study of Triclosan in Mice</i> , CHV 6718-101, Corning Hazelton, Inc., April 28, 1997
120	13 September 2001	Burns, J.M., et. al, <i>14-Day Repeated Dose Dermal Study of Triclosan in CD-1 Mice</i> , 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. <i>A Segment II Teratology Study in Rabbits with Irgacare MP (C-P Sample No. 38328)</i> . 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. <i>A Range-Finding Study to Evaluate the Toxicity of Irgacare MP (C-P Sample No. 38328) in the Pregnant Rat</i> . 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. <i>A Segment II Teratology Study in Rats with Irgacare MP (C-P Sample No. 38328)</i> . 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. <i>Dosage-Range Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of C-P Sample No. 38328 Administered Orally Via the Diet to CrI:CD@-1(ICR)BR Presumed Pregnant Mice</i> . Argus Research Laboratories, Inc. Protocol Number 403-010P. July 22, 1992.
126	27 August 2003	Hoberman, A.M., et al. <i>Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of C-P Sample No. 38328 Administered Orally Via the Diet to CrI:CD@-1(ICR)BR Presumed Pregnant Mice</i> . Argus Research Laboratories, Inc. Protocol Number 403-010. October 22, 1992.
127	27 August 2003	Denning, H.J., Sliwa, S. and Wilson, G.A. <i>Triclosan: Effects on Pregnancy and Post-Natal Development in Rats: Volume 1</i> . 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. <i>Triclosan: Effects on Pregnancy and Post-Natal Development in Rats: Volume 2: Appendices 1-17</i> . Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Document No. D92/105. December 1992.
129	27 August 2003	Wnorowski, G. <i>Acute Oral Toxicity Limit Test for Triclosan (Irgasan® DP300) Lot No. 5.2.0211.0</i> . Product Safety Labs. Study No. 2800. March 11, 1994.
130	27 August 2003	Wnorowski, G. <i>Dermal Sensitization Test - Buehler Method for Triclosan (Irgasan® DP 300, Lot No. 5.2.0211.0</i> . Product Safety Labs. Study No. 2635. April 4, 1994.
131	27 August 2003	Schmid, H., Dotti, B., Keller, B., et. Al. <i>13-Week Oral Toxicity (Feeding) Study with FAT 80'023/R (Triclosan) in the Hamste: Part 1</i> . RCC Project Number 356490. October 20, 1994.
132	27 August 2003	Schmid, H., Dotti, B., Keller, B., et. Al. <i>13-Week Oral Toxicity (Feeding) Study with FAT 80'023/R (Triclosan) in the Hamste: Part 2</i> . RCC Project Number 356490. October 20, 1994.
133	27 August 2003	Schmid, H., Dotti, B., Keller, B., et. Al. <i>13-Week Oral Toxicity (Feeding) Study with FAT 80'023/R (Triclosan) in the Hamste: Part 3</i> . RCC Project Number 356490. October 20, 1994.
134	27 August 2003	Van Dijk, A. <i>¹⁴C-Triclosan: Absorption, Distribution, Metabolism and Elimination After Single/Repeated Oral and Intravenous Administration to Hamsters</i> . RCC Project 351707. November 11, 1994.
135	27 August 2003	Thomas, Rer. Nat., H. <i>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</i> . Ciba-Geigy Limited. Laboratory Reptot No. CB 93/40. September 16, 1994.
136	27 August 2003	Persohn, E. <i>FAT 80'023/R (triclosan): assessment of replicative DNA synthesis in the course of a 13-week oral toxicity study in the hamster</i> . RCC Project 356490. Ciba Laboratory Report No. 93/47. September 19, 1994.

137	27 August 2003	Van Dijk, A. <u><i>¹⁴C-Triclosan: Absorption, Distribution, Metabolism and Elimination After Single/Repeated Oral and Intravenous Administration to Mice.</i></u> RCC Project 337781. March 1, 1995.
138	27 August 2003	Van Dijk, A. <u><i>AMMENDMENT: ¹⁴C-Triclosan: Absorption, Distribution, Metabolism and Elimination After Single/Repeated Oral and Intravenous Administration to Hamsters.</i></u> RCC Project 351707. February 14, 1995.
139	27 August 2003	Duchosal, F. and Thevenaz, Ph. <u><i>4-Hour, Acute Inhalation Toxicity Study with FAT 80'023/Q.</i></u> RCC Project Number 254597. June, 1990.
140	27 August 2003	Eldridge, S. <u><i>Cell proliferation in rodent liver.</i></u> Pathology Associates, Inc. January, 13, 1993.
141	27 August 2003	Molitor, E., Persohn, E., and Thomas, H. <u><i>The effect of FAT 80'023/Q (Irgasan DP300) on selected biochemical liver parameters following subchronic dietary administration to male and female mice.</i></u> Ciba-Geigy Limited, Switzerland, Report CB 91/18. May 22 1992.
142	27 August 2003	Molitor, E. and Persohn, E. <u><i>The effects of FAT 80'023/Q (Irgasan DP300) on selected biochemical liver parameters following dietary administration to male rats.</i></u> Ciba-Geigy Limited, Switzerland. August 2, 1993.
143	27 August 2003	Sagelsdorff, P. and Buser, G. <u><i>Investigation of the binding of Irgasan DP300 to human, hamster and mouse plasma proteins in vitro.</i></u> Ciba-Geigy, Switzerland Report No. CB 95/07. July 19, 1995.
144	27 August 2003	Van Dijk, A. <u><i>¹⁴C-Triclosan: Absorption, distribution and excretion (ADE) after single oral and repeated oral administration to male rats.</i></u> 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. <u><i>An assessment of the mutagenic potential of triclosan using the mouse lymphoma TK locus assay.</i></u> 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	Study skipped
147	27 August 2003	Beiswanger, B.B., and Tuohy, M.A. <u><i>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.</i></u> 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. <u><i>A Range-Finding Study to Evaluate the Toxicity of Irgacare MP (C-P Sample No. 38328) in the Pregnant Rabbit.</i></u> 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., <u>Antimicrobial Spectrum of Triclosan, a Broad Spectrum Antimicrobial for Topical Application</u> (1974); Zbl. Bakt. Hyg., I Abt. Orig. A 226, 376-389.
19 June 1995	Marsh P.D., <u>Dentifrices Containing New Agents for the Control of Plaque and Gingivitis: Microbiological Aspects</u> , 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., <u>Influence of Two Handwashing Frequencies on Reduction in Colonizing Flora with Three Handwashing Products used by Health Care Personnel</u> , Am. J. Infect. Control (1989); 17:83-8.
19 June 1995	Bartzokas C.A., Corkill J.E, Makin T., <u>Evaluation of the Skin Disinfecting Activity and Cumulative Effect of Chlorhexidine and Triclosan Handwash Preparations on Hands Artificially Contaminated with <i>Serratia Marcescens</i></u> , Infect. Control (1987); 8: 163-7.
19 June 1995	Butz A.M., Laughon B.E., Gullette D.L., Larson E.L., <u>Alcohol Impregnated Wipes as an Alternative in Hand Hygiene</u> , 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., <u>Control and Eradication of Methicillin-Resistant <i>Staphylococcus aureus</i> on a Surgical Unit</u> , The New England Journal of Medicine (1984); 311: 1422-25.
19 June 1995	Webster J., <u>Handwashing in a Neonatal Intensive Care Nursery: Product Acceptability and Effectiveness of Chlorhexidine 4% w/v and Triclosan 1% w/v</u> , J. Hosp. Infect. (1992); 21: 137-41.
19 June 1995	Webster J., Faoagali J., Cartwright D., <u>Elimination of Methicillin-Resistant <i>Staphylococcus</i> from a Neonatal Intensive Care Unit after Washing with Triclosan</u> , 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., <u>Methicillin-Resistant <i>Staphylococcus aureus</i>; the Role of Antisepsis in the Control of an Outbreak</u> , J. Hosp. Infect. (1987); 10: 255-9.
19 June 1995	Brady L.M., Thompson M., Palmer M.A., Harkness J.L., <u>Successful Control of Endemic MRSA in a Cardiothoracic Surgical Unit</u> , Med. J. Aust. (1990); 152: 240-5.
19 June 1995	Russell A.D., <u>Bacterial Resistance to Antiseptics and Disinfectants</u> , Journal of Hospital Infection (1986); 7: 213-25.
19 June 1995	Masanori S., Shimizu K., Noguchi N., Kono M., <u>Triclosan-Resistance <i>Staphylococcus aureus</i></u> The Lancet (1993); 341: 756.
19 June 1995	Uhl S., Reply to <u>Triclosan-Resistance <i>Staphylococcus aureus</i></u> The Lancet (1993); 342.
19 June 1995	Cox A.R., <u>Efficacy of the Antimicrobial Agent Triclosan in Topical Deodorant Products: Recent Developments In-vivo</u> , J. Soc. Cosmet. Chem. (1987); 38: 223-31.
19 June 1995	Volpe A.R., Petrone M.E., DeVizio W., Davies R.M., <u>A Review of Plaque, Gingivitis, Calculus and Caries Clinical Efficacy Studies with a Dentifrice Containing Triclosan and PVM/MA Copolymer</u> , 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	<u>In-vitro Efficacy</u> : 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	<u>In-vivo Efficacy</u> : Efficacy Evaluation of Triclosan Handwashing Products for Use in the Health Care Environment using modified ASTM method E1174, Hill Top Biolabs, Miami, 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	<i>In-vitro</i> 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	<i>In-vivo</i> Efficacy: Efficacy Evaluation of Triclosan Health Care Personnel Handwash Products, Hill Top Research, Inc. (Study No. 00-105877-11, Miami, 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

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