



**Ciba**

11 February 2002

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
Department of Health and Human Resources  
Room 1-23  
12420 Parklawn Drive  
Rockville, MD 20857

**Via Next Day Courier**  
**Return Receipt Requested**

3533 02 FEB 12 2:02

**Subject: Citizen Petition: OTC Docket 75N-183H (triclosan)**

Ciba Specialty Chemicals Corporation ("Ciba"), Home and Personal Care Segment submits this petition under 21 CFR § 10.30 requesting the Commissioner of Food and Drugs to re-open the administrative record associated with the OTC Tentative Final Monograph for Health-Care Antiseptic Drug Products as proposed under Subpart E of 21 CFR Part 333 (59 FR 31402 and 59 FR 58799) to allow for the submission and evaluation of additional efficacy and safety data, contained herein, supporting the Category I efficacy and safety status of triclosan at concentrations up to 1 percent.

Ciba submitted specific comments on this rulemaking (Docket No. 75N-183H) on June 19, 1995 and December 14, 1995. Ciba and the Triclosan Industry Alliance also submitted a Citizen's Petition on September 13, 2001 which supported the Category I safety status of triclosan for long-term use. In that submission, Ciba also notified the Agency that additional new data supporting the Category I efficacy and safety status of triclosan at concentrations up to 1 percent would be submitted in a subsequent petition. A discussion of the action requested under this petition is presented below.

**Action Requested**

Under this Citizen's Petition, Ciba formally requests that FDA:

- Re-open the administrative record to allow for the submission and evaluation of additional efficacy and safety data (contained herein) supporting the Category I safety and use status of triclosan at concentrations up to 1 percent;
- Include the efficacy and safety data contained herein in the administrative record supporting the Category IE and IS status of triclosan; and
- Utilize the data referenced in this petition 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 products) and the planned Monograph for topical antimicrobial food handler, consumer hand, and consumer body products.

A discussion of efficacy and safety data being submitted is presented below.

75N-183H

4090 Premier Drive  
P.O. Box 2444  
High Point, NC 27261-2444

Tel. 888 396 2422

CP12

## 1. Efficacy Data

### Triclosan is Efficacious and Should be Classified as a Category I Ingredient

Ciba believes that sufficient data exist demonstrating triclosan's efficacy. The efficacy information presented in this document contains new *in vitro* and *in vivo* data that substantially augments the data set previously submitted on triclosan's efficacy by Ciba (and others) in December 1995 (Ciba comments to OTC Docket 75N-183H (triclosan), December 14, 1995) and fully supports the use of triclosan as a Category I ingredient for the various skin antiseptic applications described in the TFM.

In general, the efficacy data for triclosan consists of the following:

*In-vitro* efficacy data (APPENDIX A) - values for formulated triclosan using a time-kill (suspension) method generated on nineteen microorganism species, including yeast;

*In-vivo* efficacy (APPENDICES B, C) - data for formulated triclosan; as well as a placebo formulation demonstrating the significant efficacy contribution of triclosan.

A detailed discussion of each efficacy issue is presented below.

#### (i) *In-vitro* Efficacy

Following the TFM proposed testing guidelines, the MIC values of triclosan alone (neat) were determined against specific Gram-positive and Gram-negative species of bacteria (plus a yeast) as listed under 330.470, section (a)(1)(ii) page 31444 in the TFM. Where indicated in the TFM, specific ATCC strains were used and where unspecified, a strain was selected at random. In a departure from TFM recommendations, the latest edition (i.e., 3rd vs. 2nd) of the National Committee for Clinical Laboratory Standards method was used (Ciba comments to OTC Docket 75N-183H (triclosan), December 14, 1995).

In general, the tests indicated that triclosan was bacteriostatic (at concentrations as low as 0.125 ppm) against all of the Gram-positive species and twelve of the fourteen Gram-negative species tested.

Based on the MIC data as a whole, the bacteriostatic activity of triclosan was found to be broad spectrum (Ciba comments to OTC Docket 75N-183H (triclosan), December 14, 1995).

The TFM suggested that time-kill studies be conducted to measure the *in-vitro* bactericidal activity of formulated active ingredients. Ciba has previously submitted *in vitro* time-kill data to verify antimicrobial activity for triclosan when formulated in aqueous based prototype liquid skin cleansers. The formulations contained anionic surfactant plus other ingredients typically found in hand wash products (Ciba comments to OTC Docket 75N-183H (triclosan), December 14, 1995).

In this document, Ciba is submitting additional time-kill test data on formulated triclosan using a "suspension" method considered as fairly standard in the United States and Europe. This entailed using different concentrations of triclosan in an aqueous surfactant liquid formulation (typical of hand wash products). Bactericidal activity of the active formulation was determined against a roster of Gram-positive and Gram-negative species at 15 second, 30 second, and one-minute

contact periods. Two levels of triclosan were tested, 0.3 and 0.6%, respectively. The specifics of the test protocol and test data are attached (Appendix A).

It should be noted that these studies originally contained confidential information in addition to the data on triclosan, however for this submission, those sections of the reports not related to triclosan have been redacted. Study Number L00-D047 presents the results of a formulation containing 0.3% triclosan and is identified in the report as test material 3372-151. Study Number L00-D033 presents the results of a formulation containing 0.6% triclosan and is identified in the report as test material 3372-123.

The time-kill results demonstrated significant antimicrobial activity from formulated triclosan relative to specific test organisms and contact time.

(ii) In-vivo Efficacy

The TFM recommended a modification of ASTM method E1174 for the testing of antiseptic handwashes or health-care personnel handwashes. The reports in Appendices B and C summarize studies conducted by an independent testing laboratory on proprietary formulations containing triclosan, at 0.3 and 0.6%, a reference control (4% chlorhexidine), as well as a placebo (0%) formulation. The tests follow the current ASTM method E1174 (i.e., E1174-00 ASTM methodology) and utilize a standard 4% chlorhexidine gluconate (Hibiclens®) handwash formulation as a control. The material identified as HTR Code A (Lot Code 3434-9) in HTR Study 00-105877-11 contains 0.3% triclosan, and the material identified as HTR Code B (Lot Code 3434-10) contains 0.6% triclosan.

The results of these tests indicate a significant antibacterial effect from the triclosan formulations in elimination of the test organism (*Serratia marcescens*) from skin. The placebo formulation (0% triclosan, Appendix C) is not effective at eliminating the test organisms from the skin following repeated washes. At 0.3 and 0.6% concentrations, the triclosan formulations are superior overall to the 4% chlorhexidine in efficacy and therefore supportive of inclusion in the monograph as a category IE ingredient for application in a healthcare environment.

This data is representative and consistent with test results from other studies using similar protocols. Information of this type was presented in our previous comments to this TFM (Ciba letter to Docket No. 75N-183H, June 16, 1995) and appear in a December 15, 1995 submission by the SDA/CTFA to the FDA.

Clearly, the result of these various efficacy tests and studies indicate that triclosan is efficacious from both an *in vivo* and *in vitro* perspective and that triclosan warrants inclusion as a category I ingredient for efficacy for healthcare uses under the Final monograph for healthcare antiseptic drug products under the new Subpart E of 21 CFR Part 333 (59 FR 31402 and 59 FR 58799).

## 2. Safety Data

As stated in its Citizen Petition of September 9, 2001, Ciba believes that the available data are sufficient to support the safety of both short- and long-term uses of triclosan in topical applications containing up to 1 percent active ingredient. In order to further support the Category I Safety status of triclosan, Ciba formally requests that FDA include in the Administrative Record the results of a new Human Dermal Pharmacokinetics (PK) Study which demonstrates that triclosan is safe for use at concentrations up to 1 percent.

Recent *in vitro* data indicate that triclosan can penetrate through human skin and is metabolized locally by Phase II conjugation (Moss, et al. Food Chemical Toxicology 38 (2000), p. 361). These studies also suggest that dermal absorption of triclosan in humans would be approximately one-third that observed *in vivo* and *in vitro* for rat or roughly 6-10% of an applied dose. These data are consistent with previous estimates of dermal absorption of triclosan through human skin as approximately 7-10% of an applied dose (Expert Panel Review, 1994). To confirm the dermal pharmacokinetic profile of triclosan following repeat use of a hand wash formulation, a pilot study was conducted to assess the absorption, elimination, and steady state levels of triclosan in humans.

The Human Dermal PK Study report is provided in Appendix D. A discussion of the study is presented below.

(i) Human Dermal PK Study

The objective of the study was to confirm the steady state and elimination pharmacokinetics of triclosan in adult humans after repeated dermal exposure to a hand wash containing 1% triclosan (test material).

Seven adult male and female human volunteers were selected to participate in the 30 day study. For the first 20 study days (Days 1-20), each subject washed their hands with the test material 6 times per day approximately every 2 hours. The volunteers returned to the clinical site for blood sampling (single sample taken prior to first hand washing) on study days 1, 5, 10, and 15. On study day 20, volunteers were sequestered at the test site for 12 hours in order to evaluate the steady state kinetic profile of the dermal absorption of triclosan. During the sequestration period, hands were washed every two hours and blood samples were taken prior to the first hand washing and prior to subsequent washings (0), at 0.5 and 1 hour after the first hand washing and prior to subsequent hand washings at 2, 4, and 6 hours. The final kinetic blood sample was obtained 12 hours after hand washing was initiated. After the sequestration period, volunteers discontinued use of the test material and returned to the clinical site on Days 21, 23, and 30 for additional blood samples to assess the elimination kinetics of triclosan.

The level of free and total (free + conjugated) triclosan was measured in plasma obtained from volunteers during the experiment. The sampling times were chosen to capture the absorption, steady state, and elimination pharmacokinetic profiles of triclosan, and were based on results obtained from previous clinical experiments. The baseline levels of free and total triclosan were low indicating that most of the volunteers refrained from using triclosan-containing products prior to the start of the experiment. Steady state levels of free and total triclosan after the start of hand washing were reached by Day 10. The maximum free and total triclosan levels during the experiment for any volunteer were 69.9 and 229 ng/ml, respectively. After exposure stopped on Day 20, free and total triclosan levels returned to baseline levels by Day 23 and 30, respectively. Using a one compartment model with first order elimination kinetics, the average elimination half lives for men, women, and men + women were  $1.53 \pm 0.33$ ,  $1.14 \pm 0.71$ , and  $1.37 \pm 0.53$  days, respectively.

Based on these data, percutaneous absorption of triclosan from the repeated use of a hand wash formulation containing 1% triclosan is limited, resulting in low levels of free and total triclosan in the systemic circulation. By comparison, gastrointestinal absorption of triclosan is almost complete. Studies with oral ingestions of triclosan up to 11.25 mg demonstrated peak plasma

levels of triclosan of approximately 700 ng/ml. Therefore, it would be expected that exposure to triclosan from the use of a hand wash formulation containing 1% triclosan would result in significantly lower peak plasma levels than from oral exposure to similar amounts of triclosan. Lastly, consistent with gastrointestinal absorption, triclosan is rapidly eliminated from the body following dermal absorption.

#### **Environmental impact**

According to 21 CFR 25.31(c), this petition qualifies for a categorical exclusion from the requirement for submission of an environmental assessment.

#### **Economic impact**

According to 21 CFR 10.30(b), information on economic impact is to be submitted only when requested by the Commissioner following review of the petition.

#### **Certification**

The undersigned certifies that, to the best of his/her knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data known to the petitioner which are unfavorable to the petition.

#### **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. The favorable safety profile of triclosan has been well established in numerous laboratory and clinical studies and through extensive human experience.

Ciba believes that triclosan is safe (for both short- and long-term use) and efficacious at concentrations up to 1 percent and should be classified as a Category IE and IS active ingredient for both short- and long-term use under FDA's Monograph for antimicrobial health-care and consumer/food-handler products.

We would once again like to thank the Agency for evaluating the enclosed data under OTC Docket 75N-183H and welcome the opportunity to work with the FDA to help classify triclosan as a Category I active ingredient under this rulemaking. Attached please find a copy of references cited in this document. Please contact the undersigned at (336) 801-2493 if there are any further questions or comments regarding this petition.

Sincerely,



Carl David D'Ruiz, MPH  
Head, Product Stewardship & Regulatory Affairs  
Home and Personal Care Segment

**Attachments**

**Desk copy:**

Charles J. Ganley, MD  
Dr. Robert Osterberg  
Dr. Norman See  
Debbie Lumpkins  
Dr. Jonathan Wilkin  
~~OTC Docket No. 78N-0038~~

**Cc:**

K. Hostetler  
C. Ehrenberger  
M. Bernheim  
W. Salminen