



**Ciba**

September 29, 2004

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

**Re: Safety and Efficacy Data in Support of Additional OTC Antigingivitis/  
Antiplaque Ingredient: Triclosan [Docket No. 1981N-0033P]**

Ciba Specialty Chemicals Corporation ("Ciba"), Business Line Home and Personal Care is pleased to submit the information contained herein in response to FDA's call for safety and efficacy data for triclosan as an antigingivitis/antiplaque ingredient in dental pastes and oral rinses at concentrations of 0.3 percent maximum.

As stated in the Federal Register Notice of July 6, 2004 (69 FR 40640), FDA has reviewed the Time and Extent Application (TEA) submitted by Ciba for triclosan and has determined that the condition is eligible for consideration in the OTC drug monograph system. Ciba believes that sufficient data exists to support the generally regarded as safe and effective (GRAS/E) status of triclosan as an antigingivitis/antiplaque ingredient for OTC use. Below is a summary of this data.

### Safety and Efficacy Data

A variety of safety and efficacy data exists that supports the safety and efficacy of triclosan in antigingivitis/antiplaque products. Below is a summary of such existing data. This data is being submitted in support of the listing of triclosan as an active ingredient under this monograph and also serves to support the determination of generally regarded as safe and effective (GRASE) under the FDA TEA and OTC drug review process.

#### **1. SAFETY DATA**

The safety of triclosan for toothpaste and mouth rinse OTC applications has been clearly demonstrated by an extensive amount of pre-clinical and clinical safety testing. Selected studies and Expert Panel summaries were submitted by Ciba to OTC docket number 81N-033P on November 1, 2003. A summary of the studies submitted is presented in Appendix 1. As seen in Appendix 1, there is quite an extensive amount of pre-clinical and clinical data that demonstrates the safety of triclosan in oral applications. Moreover, the long history of safe use of triclosan-in human oral and dermal products (almost 40 years) clearly demonstrates that triclosan is safe for OTC oral applications. Table 1 provides a list of the types of safety data available for triclosan. Also included below is a general discussion of some of the more relevant safety issues associated with triclosan use in OTC antigingivitis/antiplaque products.

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**Table 1. Types of Safety Data Submitted for Triclosan**

<b>Pre-Clinical Studies</b>
Acute toxicity in multiple species
Eye and skin irritation
Skin sensitization
Subchronic toxicity in multiple species
Chronic toxicity and oncogenicity in multiple species
Reproductive and developmental toxicity in multiple species
<i>In Vitro</i> and <i>In Vivo</i> genotoxicity in many different assays
Absorption, distribution, metabolism, and elimination (ADME) studies in multiple species
<b>Clinical Studies</b>
Absorption, distribution, metabolism, and elimination (ADME) studies
Pharmacological tolerance
Skin sensitization

In addition to these studies, various other studies have been published which support triclosan's safety. A listing of these studies is presented in Appendix 2. Copies of these studies are included with this transmittal.

#### **Incidence And Risk Of Adverse Reactions And Significant Side Effects**

Triclosan-containing toothpastes/mouth rinses have been safely used in the U.S. and other parts of the world for over 14 years (according to Sreenivasan and Gafar, 2002, TCS has been used in dental products globally since 1989). Ciba is unaware of any adverse effects caused by triclosan in the various toothpaste/mouth rinse products. A search of Medwatch (<http://www.fda.gov/medwatch/safety.htm>) did not uncover any safety alerts for any FDA approved OTC products containing triclosan as antigingivitis/antiplaque ingredient in the U.S. during the years 1997 – 2003. It is important to note that FDA approved an oral care product containing triclosan on July 11, 1997. Furthermore, our own research into global products that utilize triclosan in oral/dental products indicates a similar trend in lack of reported or publicly documented adverse effects.

#### **Margins Of Safety Under Conditions Of Normal Use**

FDA has reviewed the safety of triclosan in dental paste with antigingivitis/antiplaque claims during the review of NDA number 020231 (see the attached FDA CDER review for NDA No. 020231). Under this application, FDA concluded that the margin of safety was sufficient even under conditions of widespread OTC availability in multiple types of products (e.g., toothpaste, soap, deodorant, etc.).

### **Potential For Inducing Untoward Effects On The Oral Tissues**

Triclosan does not induce untoward effects on oral tissues. On the contrary, triclosan is an anti-inflammatory agent that can decrease oral irritation and ulceration caused by other toothpaste/mouth rinse additives and/or health conditions. Numerous articles exist in the public literature (Eley, 1999; Worthington et al., 1993), which support triclosan's safety in oral tissues.

### **Changes In The Balance Of The Oral Microflora Under Conditions Of Expected OTC Use**

Triclosan does not adversely alter the balance of the oral microflora after long-term repeated use of triclosan-containing toothpastes/mouth rinses. Several articles exist in the public literature (Eley, 1999; Fine, 1998; Sreenivasan and Gaffar, 2002; Stephen, 1990; Zambon, 1995) that support this assessment.

### **Active Ingredient Ingestion**

Many different types of subchronic and chronic studies have been conducted with triclosan using both oral gavage and dietary admixture administration. During the review of NDA No. 020231, FDA concluded that an adequate margin of safety existed between the systemic dose received after swallowing triclosan-containing toothpaste and the effect levels in animal studies (public file of FDA CDER review for NDA No. 020231).

Triclosan has a long history of safe use in many different types of orally- and topically-applied products. Despite the plethora of triclosan-containing products, only a few reports of skin sensitization have been attributed to triclosan. Triclosan has also been tested in various skin sensitization studies, the most recent being a guinea pig study using the Buehler method. Triclosan did not cause sensitization in any of the guinea pigs during the challenge phase.

### **Triclosan: Benefits and Safety**

Triclosan effectively slows or stops the growth of bacteria but it is not an antibiotic. It is used in small amounts in skin and oral care consumer products like soaps, deodorants and toothpastes. This helps to prevent the risk of infections, controls body malodors, and can prevent dental diseases. An extensive database and the use over more than 35 years without adverse effects confirm that Triclosan is effective and safe for humans and the environment.

Multiple studies on the behavior of Triclosan in the human body show that Triclosan, when absorbed through the skin or orally, is very rapidly eliminated from the body within days, is not bioaccumulative, and has no adverse impact on human health. It has been shown that Triclosan has no mutagenic or teratogenic potential and does not affect reproduction.

## Antimicrobial Resistance

Ciba has been monitoring this issue since the mid-1990's. Both Ciba and various independent researchers (as well as numerous government authorities) agree that no evidence of antimicrobial resistance stemming from the use of triclosan occurs in the natural environment. Below is a list of major milestones and studies supporting this finding:

- 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 also 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" ...moreover, "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."

- Several other more recent studies and comprehensive surveys (Braoudaki, M., et al., 2004; Cole, EC. et al. 2003; and Russell, AD 2004), have indicated that there is no association between triclosan usage and antibiotic resistance. Copies of these studies are included in this submission.

## **2. EFFICACY DATA**

The efficacy of triclosan-containing toothpaste and mouth rinse to reduce both plaque and gingivitis in long-term clinical trials has been well documented. Moreover, FDA has also approved such products under formulation-specific NDAs. The overall conclusion of these studies is that triclosan clearly reduces plaque and gingivitis when properly formulated in a toothpaste or mouth rinse.

Review of the public literature indicates that significant reductions of dental plaque and/or gingivitis have been documented for toothpaste and mouth rinses utilizing triclosan alone and in the following combinations:

Triclosan and Sodium Fluoride  
Triclosan and Zinc Citrate  
Triclosan and Pyrophosphate

Triclosan and PVM/MA Copolymer  
Triclosan, Gantrez® copolymer and Sodium Fluoride  
Triclosan and polydimethylsiloxane (silicone oil)  
Triclosan and essential oils

Numerous clinical studies have been conducted to provide an assessment of the effectiveness of dentifrice and rinse formulations containing triclosan and these ingredients for the control of supragingival dental plaque and gingivitis. The results of many of these clinical studies indicate that toothpastes and rinses containing triclosan provide a statistically significant and clinically relevant level of efficacy for the control of supragingival plaque and gingivitis. Such studies also provide an overview of triclosan's mode of efficacy. A list of over 50 such studies are presented in Appendix 3. Copies of these studies are included in this submittal for FDA's review.

Ciba studies related to the efficacy of triclosan (IRGACARE® MP) in toothpaste also indicate that triclosan at concentrations of 0.3% significantly reduces the growth of oral bacteria and plaque. Summaries of the results obtained from these studies are presented in Appendix 4.

### 3. CONCLUSION

It is our belief that the myriad of publicly available studies related to triclosan's safety and efficacy in the area of oral health care should satisfy FDA's GRASE/E data requirements. However, should any further studies be required to support the Category I status of triclosan under this monograph, Ciba formally requests that a Category III status be assigned until the relevant study protocols are reviewed and the studies are completed.

Ciba thanks the FDA for the opportunity to submit additional data related to triclosan's safety and efficacy and hopes that it can work together with the Agency to include triclosan as an active ingredient under this Monograph. Any further questions can be addressed by the undersigned at (336) 801-2493 or [carl.druiz@cibasc.com](mailto:carl.druiz@cibasc.com).

Sincerely,



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Attachments