

Ciba



October 1, 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]
Federal Register Notice of July 6, 2004 (69 FR 40640)**

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.

In follow-up to Ciba's comments filed on September 29th, attached is an additional clinical study conducted in China demonstrating triclosan's efficacy against gingivitis.

As stated in the Time and Extent Application (TEA) filed on November 23, 2003, Ciba estimates that triclosan is currently used in 61 countries worldwide for oral care applications involving antiplaque/antigingivitis claims. Approximately 23 percent of these countries have been using triclosan in oral care applications for over five years or more. Furthermore, the FDA approved triclosan on July 11, 1997 as an antigingivitis/antiplaque ingredient in an OTC drug (NDA No. 020231).

According to Ciba's estimates, approximately 3.5 billion units of dental paste and oral rinses containing triclosan (making anti-plaque and anti-gingivitis claims) in oral care applications have been consumed in 13 selected countries during the past six years. In the US alone, approximately 644 million units have been sold during this same timeframe for OTC use. These numbers represent human exposures in the tens to hundreds of millions. This does not include the remaining 48 countries that have had similar type sales during the past three to four years.

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,

81N-033P

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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 GRASE status. Any further questions can be addressed by the undersigned at (336) 801-2493 or carl.druiz@cibasc.com.

Sincerely,

A handwritten signature in black ink, appearing to read 'Carl D'Ruiz', written in a cursive style.

Carl D'Ruiz, MPH
Director, Regulatory Affairs
Ciba Specialty Chemicals Corporation
Business Line Home and Personal Care

Attachments

Publication

<http://www.crestdental.com.cn/profession/publication/pub1-03.htm>

Reduction of Gingivitis in a Chinese Population
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摘 要

流行病学资料表明：在中国人口中，牙龈炎是一个非常常见的疾病。但人们对使用抗菌牙膏的预防性优点还不太了解。此次研究的目的在于评价一个包含 triclosan 的牙膏（佳洁士多合一牙膏）与一个氟化钠牙膏（中国佳洁士牙膏），在防止牙龈炎上的有效性。这是一次在中国北京进行的随机、双盲式平行组研究。被挑选出来的受试者，每天两次使用一支氟化钠牙膏刷牙，持续两个月。在刷牙适应期之后，使用两种不同的指标：Bleeding Index(BI) 和 Loe-Silness Gingival Index(GI)，受试者接受牙龈炎检查。在基线处，351 个受试者接受了一次洁治并被随机分组。在为期 3 个月的治疗小组之间，无论使用 BI 还是 GI ($p>0.05$) 指标，牙龈炎均不存在显著的差别。与之相反，在为期 6 个月的治疗小组之间 ($p<0.05$)，无论使用哪一种指标测量，均存在显著的差别。疗效的差异与基线的牙龈炎指标越高，所观察到的治疗效果越显著。经过 6 个月的实验，使用测试牙膏比使用氟化钠牙膏能显著降低 BI 和 GI 平均值。

(这一研究由 The Procter & Gamble 赞助)

OBJECTIVE

The purpose of this study was to 1) evaluate the anti-gingivitis efficacy of Crest Many-In-One (triclosan) dentifrice relative to China Crest (NaF) dentifrice and 2) to gain further insight into the oral health status of the Chinese population.

TREATMENT GROUPS

Crest Many-In-One containing 0.28% triclosan, 0.321% sodium fluoride and 3.3% pyrophosphate.

BACKGROUND

Previous Many-In-One studies demonstrated 1) a statistically significant anti-plaque benefit when compared to China Crest and 2) Demonstrated a statistically significant anti-calculus benefit when compared to China Crest.

STUDY DESIGNS

- Randomized, double-blind, parallel-group
- 8 month
- 2 month brushing acclimation
- 6 month test period
- 374 entered the acclimation

- qualifying with a BI score of at least 1.9
- 351 were randomized to product at baseline
- based on baseline BI score and gender
- after receiving a prophylaxis
- 3 month and 6 month efficacy evaluations
- subjects completed the study

MEASUREMENT

Bleeding Index (BI)

MF/DL sweep (2 sites/tooth)56 total sites

Score	Criteria
0	Normal appearance, healthy gingiva
1	Color changes related to inflammation but no bleeding
2	Slight bleeding that remained at the point of bleeding
3	Bleeding extending from the point of sampling and flowing around the gingival margin.
4	Profuse bleeding that overflowed the gingival margin.
5	Spontaneous bleeding (without provocation).
9	A non-gradable or missing site.

*Mazza et al., 1981

STUDY DEMOGRAPHICS

	China Crest (C=177)	Many-In-One (n=174)	Total (n=351)
Female	124(70%)	121(70%)	245
Male	53(30%)	53(30%)	106
Total	177	174	351
Age	33.93 (19-60)	34.02 (18-63)	33.88 (18-63)

STATISTICAL METHODS

- Treatment effect for BI was determined using the analysis of covariance (ANCOVA) method at a one-sided, 5% significance level.
- Baseline BI scores were used as the covariate.
- A significant treatment to baseline interaction was observed, therefore the interaction term was kept in the model to determine treatment difference at various baseline scores.

RESULTS

Adjusted Means and Treatment Difference at Various Baseline BI Scores for Month 6

Baseline Score	Many-In-One	China Crest	Treatment Difference	P-Value (one-sided)
2.259	1.679	1.802	0.123	0.0003
2.115	1.617	1.706	0.089	0.0006
1.911	1.529	1.571	0.041	0.029
1.696	1.438	1.427	-0.010	0.358

CONCLUSIONS

- There were statistically significant reductions ($p < 0.05$) in gingivitis in favor of Many-In-One when compared to China Crest over 6 months.
- The magnitude of the treatment benefit for the triclosan dentifrice increases with increasing baseline disease severity.

(This research is sponsored by The Procter & Gamble)