PHARMACOKINETICS OF TRICLOSAN IN RATS FOLLOWING A SINGLE ORAL ADMINISTRATION

Laboratory: Colgate-Palmolive Co.

Report Date: March, 1987-March, 1990

Study Design

Two pharmacokinetic studies were reported.

[1] In this study, 2 male Sprague-Dawley rats were given a 33% slurry of silicate toothpaste in water containing a 0.066% concentration Triclosan. Three rats received a 0.066% Triclosan aqueous solution containing 0.66% SLS. All five animals received 5 mg Triclosan/kg body weight via oral gavage in a single administration of silicate toothpaste in water.

[2] In this study, 2 male Sprague-Dawley rats were given 5 mg/kg ^{14}C labelled Triclosan in a 0.66% SLS aqueous solution via oral gavage in a single administration. The concentration of labelled Triclosan in the aqueous solution was 0.066%.

In both studies, the volume of dose was adjusted to the animal's body weight. The rats were housed individually in polycarbonate metabolism cages and were given one week prior to treatment to acclimate. Food was withheld 16 hours prior to and 4 hours following treatment, otherwise food and water were given ad libitum. All rats were killed (with CO_2) 72 hours after treatment.

Although the formulation tested was different, the method of collection of samples was the same for both studies. Blood, urine, fecal, organ, tissue and carcass samples were collected. Approximately 300 mg blood samples were collected via the tail vein at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 24, 48, and 72 hours after dosing. In the non-labelled study, the plasma was analyzed by GC for levels of Triclosan glucuronide and Triclosan sulfate. In the labelled study, the plasma was analyzed to determine concentrations of radiolabelled Triclosan, Triclosan sulfate and Triclosan glucuronide.

Reported Results

[1] Triclosan was absorbed quickly into the blood of the rats receiving nonlabelled Triclosan (either in toothpaste slurry or aqueous solution). The levels of Triclosan sulfate and Triclosan glucuronide were much higher than that of free Triclosan, demonstrating rapid metabolism to the sulfate and glucuronide conjugates.

Within 6 hours after dosing, peak plasma concentrations for Triclosan sulfate and Triclosan glucuronide were observed. The authors believe that this suggests a possible entero- hepatic recirculation in rats. Although the concentrations of sulfate and glucuronide were about equal within 6 hours of dosing, after 6 hours the concentration of sulfate increased to approximately twice the level of glucuronide.

Plasma concentrations of sulfate and glucuronide were higher in the rats given toothpaste slurry versus the aqueous solution within the first hour after treatment. However, the area under curve (AUC) analysis for the toothpaste slurry group was 58% of that demonstrated by the aqueous solution group. The plasma elimination half lives in the rats given Triclosan aqueous solution were 11.5 hours for Triclosan, 9.13 hours for Triclosan glucuronide and 9.72 hours for Triclosan sulfate. In rats given Triclosan in toothpaste slurry, the plasma elimination half lives were 65 hours for Triclosan, 10.5 hours for Triclosan glucuronide and 13.8 hours for Triclosan sulfate.

Mean urinary excretion (expressed as % of dose) in animals given Triclosan aqueous solution were 0.94 for Triclosan, 0.119 Triclosan glucuronide and 0.211 Triclosan sulfate. In animals given the toothpaste slurry, mean urinary excretions (as % of dose) were 0.126, 0.054 and 0.065 for Triclosan, Triclosan glucuronide and Triclosan sulfate, respectively. However, 57.30% and 62.32% of the dose was eliminated in the feces during the study period for the Triclosan aqueous solution and the Triclosan dentifrice groups, respectively. The values of 57.30% and 62.32% represent total Triclosan-- Triclosan, Triclosan sulfate and Triclosan glucuronide--as a percentage of the dose. Free Triclosan was the predominate form of fecal elimination. The GC method used to analyze the rat carcasses showed that only 1.06% and 2.79% of the dose remained in the rat carcasses at 72 hours after dosing for the Triclosan dentifrice and Triclosan solution groups respectively.

[2] The results demonstrate that ^{14}C-Triclosan was also absorbed quickly into the blood. Free Triclosan was below detection (50 ppb) for the entire study period suggesting that the Triclosan was rapidly metabolized. As with the previous group, two peak plasma concentrations of Triclosan glucuronide and Triclosan sulfate were observed suggesting entero-hepatic recirculation. The elimination half-life of ^{14}C for the plasma was 14.7 hours and 15.2 hours for rat one (#H1) and rat two(#H2), respectively. Of the two rats given labelled Triclosan, rat one (#H1) excreted 6.4% of the dose in his urine and rat 2 (#H2) excreted 5.3% of the total dose. Rat 1 eliminated 80.29% of the dose as fecal material while rat 2 eliminated 87.10%. Only 1% percent of the radioisotope dose remained in the rat tissues, organs and carcass at 72 hours after dosing. The ^{14}C concentrations were highest in the pituitary gland, large intestine, gingiva, liver and kidneys. The lowest concentration was in brain tissue. Total recoveries were found to be 87.7 and 93.4% of the dose.

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DETERMINATION OF FAT 80 023 (IRGASAN DP 300) IN BLOOD AND TISSUE SAMPLES TAKEN DURING A TWO-YEAR CHRONIC ORAL TOXICITY/ONCOGENICITY STUDY IN ALBINO RATS

Laboratory: CIBA GEIGY

Report Date: April 30, 1986

Study Design

This report provided the analytical component of the two year oral toxicity/carcinogenicity study in rats. In this study, Triclosan was administered to male and female Sprague-Dawley rats in the diet at concentrations of 0, 300, 1000, 3000 ppm for 13, 26, 52, 78 and 104 weeks. An additional group of rats was fed a concentration of 6000 ppm for 52 weeks. Blood, liver and kidney were analyzed for Triclosan and metabolites at each of the sacrifice intervals.

Reported Results

Blood: The amount of Triclosan in blood was proportional to the dose in the diet. Practically all of the Triclosan was in the conjugated form, with the sulfate as the predominant form. Females tended to have higher levels with increasing dosing time. Results from the analyses are indicated below:

	DOSE(PPM)			
Time	300	1000	3000	6000
13	17/19	50/45	103/96	-
26	17/17	58/42	137/83	-
52	18/14	44/34	107/75	169/134
78	21/10	59/34	118/79	-
104	17/7	26/27	86/54	-

* Results are total Triclosan(PPM,female/male);
Time is treatment duration in weeks.

Kidney: The amount of Triclosan in kidney was generally proportional to administered dose. The sulfate conjugate was the main form observed. The levels in kidney tended to increase over time. No sex differences were noted.

Liver: Triclosan content of liver was proportional to administered dose with free material the predominant form in both sexes.

GP 41 353 STUDY OF PHARMACOKINETICS AND METABOLISM IN MOUSE, RAT, RABBIT, AND DOG

Laboratory: CIBA-GEIGY, Ltd./CIBA-GEIGY

Report Date: December 1, 1972

Study Design

Tritiated or ^{14}C-labelled Triclosan was administered orally or intravenously to mice, rats, rabbits and dogs in order to study the absorption, distribution, metabolism and excretion of the compound.

Male mice (20 ± 1 g) were dosed intravenously with 10 mg/kg of radiolabelled Triclosan and the total radioactivity was determined in 19 organs and tissues of two mice each at 1, 5, 30 and 120 minutes after dosing.

Male and female Wistar WU and SIV-50 rats (200-250 g) were also used in this study. Blood samples were taken by cardiac puncture from groups of 4-5 rats at various time intervals up to 24 hours after oral or intravenous dosing of 5 mg/kg. Excretion of Triclosan in urine and feces was monitored at 24 hour intervals for 3-7 days in groups of 4-5 rats dosed orally with 0.4 or 5 mg/kg of radiolabelled Triclosan. Concentrations of total radioactivity in the organs, gastrointestinal contents and carcasses were determined in rats at various time intervals up to 24 hours after oral or intravenous dosing of 5 mg/kg. For these experiments, two orally dosed rats and four intravenously dosed rats were sacrificed at each time point. To examine elimination in bile, 3 rats were dosed intraduodenally and 5 rats were dosed orally with 5 mg/kg. Bile samples were then taken at 2 hour intervals over a 10 hour period. Total radioactivity and the identity of metabolites were determined in these samples.

Male, mixed-bred rabbits (3 animals per dose, 2-3 kg each) were administered single doses of 5 and 50 mg/kg by stomach tube. Total radioactivity was determined in 24 hour samples of urine and feces over a 72 hour period.

Two male beagle dogs (10 and 14 kg) were administered a single intravenous dose of 5 mg/kg, and 14 days later a single 5 mg/kg oral dose. Following each dosing, total radioactivity in blood was monitored over a 48 hour period. Additionally, total radioactivity and the identity of metabolites were identified in 24 hour samples of urine and feces collected over a 5 day period after dosing.

Reported Results

Absorption

Triclosan was well absorbed following oral administration in rats (≥ 70%), rabbits (≥ 70%), and dogs (50-65%).

Blood Concentrations and Enterohepatic Circulation

In rats administered 5 mg/kg of Triclosan intravenously, blood levels were 5.4 μ g/ml after 10 minutes and 6.0 μ g/ml after 30 minutes. The increase in blood concentration was attributed to the rapid formation of very polar metabolites with a decreased volume of distribution. The relatively slow decline in blood concentrations, also observed in mice and dogs, is likely attributable to a marked enterohepatic circulation. Indeed, high levels of radioactivity were observed in the bile of mice. The blood concentration curve was similar in dogs, with maximum blood levels following intravenous administration of 5 mg/kg of Triclosan reported as 5.9 and 9.4 μ g/ml in the two dogs tested.

Organ Concentrations

In rats, following oral administration of 5 mg/kg of Triclosan, maximum levels of approximately 5 μ g/g were measured in the liver and kidneys 2 hours after dosing. Although organ concentrations declined slowly, all organ concentrations determined after 24 hours were less than 0.6 μ g/g. One hour following intravenous administration of 5 mg/kg of Triclosan in rats, the highest concentrations were observed in the liver (6.0 μ g/g), the lungs (5.5 μ g/g), and the brown fat (6.9 μ g/g). Except for the lungs, the concentrations at one hour after the intravenous dose were on the same order as those two hours after oral dosing. In mice, comparatively high concentrations of Triclosan were present in the lungs (40.6 μ g/g), liver (43.8 μ g/g), adrenals (105.7 μ g/g), brain (16.9 μ g/g), brown fat (24.4 μ g/g), kidneys (38.0 μ g/g) and thyroid (48.3 μ g/g) one minute after intravenous dosing. At 30 minutes after dosing, only the liver (26 μ g/g) and kidney (32 μ g/g) concentrations were still relatively high.

Metabolism and Excretion

In rats, up to 91% of the administered dose of Triclosan was excreted in the feces, while 3-17% was excreted in the urine (metabolites not identified). Approximately 65% of the Triclosan dose was excreted in the bile. Of the radioactivity in the bile, 30% was unchanged Triclosan, approximately 30% was unconjugated more polar metabolites, and 20-30% was the glucuronide of Triclosan. In rabbits, 60-75% of the administered dose was excreted in the urine. In dogs, where metabolism differs according the route of administration, approximately 70% of the administered dose was excreted in the feces. After intravenous administration, 60% of the radioactivity in the feces was unchanged Triclosan, whereas, after oral administration, 85-90% is unchanged Triclosan. In dogs, 16% of the dose was recovered in urine following intravenous administration (approximately 50% unchanged and 15-20% glucuronides, mostly of more polar metabolites), whereas, only about 8.5% is recovered in urine following oral administration (approximately 30% unchanged, 30-40% Triclosan glucuronide, and remaining glucuronides of more polar metabolites). In rats and rabbits, most of the excretion occurs within the first two days, whereas, in dogs, elimination continued for at least five days.

REPRODUCTION AND TERATOLOGY STUDIES

The developmental toxicity studies conducted earlier by Ciba-Geigy in the 1960s and 1970s were considered inadequate based on currently accepted protocols and GLP requirements, so the following studies were conducted by the Sponsor and are reviewed here:

Study Title	Date	GLP Status
A Segment II Teratology Study in Mice;	October 1992	GLP Study
A Segment II Teratology Study in Rats;	January 1992	GLP Study
A Segment II Teratology Study in Rabbits;	January 1992	GLP Study
Two Generation Reproduction Study of Triclosan in Rats;	March 1988	GLP Study

A SEGMENT II TERATOLOGY STUDY IN MICE

Laboratory: Argus Research Laboratories, Incorporated

Report Date: October 22, 1992

Study Design

Irgacare MP was administered by diet to presumed pregnant CD-1 mice (24/group) at targeted dose levels of 0, 10, 25, 75 and 350 mg/kg/day from days 6-15 of gestation. Animals were observed twice daily for mortality/morbidity and obvious signs of pharmacologic or toxicologic effects. Each female was given a physical examination on days 0, 6-15 and 18 of gestation. Females were weighed on days 0, 6, 8, 10, 12, 14, 16 and 18 of gestation, and food intake data were recorded for days 0-6, 6-11, 11-16 and 16-18 of gestation. All surviving females were killed on day 18 of gestation and given a gross necropsy examination. Gravid uterus, uterine contents, brain and liver were weighed. Numbers of corpora lutea, implantation sites, live and dead fetuses, and resorptions were recorded. Fetuses were evaluated for external malformations/variations, sexed and weighed. Subsequently, one-half of the fetuses from each litter were processed for visceral evaluation and the remaining fetuses were processed by staining with Alizarin Red S and evaluated for skeletal malformations or ossification variations.

Reported Results

All animals survived the duration of treatment and to scheduled necropsy. Pregnancy rates and the number of litters on day 18 of gestation were comparable between control and treatment groups. Clinical observations, food intake, terminal body weight and brain weights were unaffected by treatment. At necropsy there was an increase in the incidence of tan spots (fat deposition)in the livers of dams in the 350 mg/kg group. Absolute liver weight and liver/body weight and liver/brain weight ratios were increased in the 75 and 350 mg/kg groups. Maternal body weight in the 350 mg/kg group was increased, but is considered a consequence of the increased liver weight. There were no aborted pregnancies. Five dams delivered prematurely, but these are considered incidental, since the incidence was not dose related. Numbers of corpora lutea, implant sites, live and dead fetuses, resorptions and fetal sex ratios were comparable for all groups. Fetal body weights were reduced for the 75 and 350 mg/kg groups. For these same two groups, there was an increase in the incidence of irregular skull ossification and delayed ossification of forepaw and hindpaw phalanges. The NOAEL was 25 mg/kg/day for both maternal and fetal effects. Fetal effects are a consequence of maternal toxicity and not a true fetotoxic effect.

A SEGMENT II TERATOLOGY STUDY IN RATS

Laboratory: Bio/dynamics Inc.

Report Date: January 1992

Study Design

Irgacare MP was administered orally via gastric intubation to mated female rats (24/group) at dose levels of 0, 15, 50 and 150 mg/kg/day from days 6-15 of gestation. Animals were observed twice daily for mortality/morbidity and for obvious pharmacologic and/or toxicologic effects. Each female was given a detailed physical examination on days 0, 6, 8, 10, 12, 14, 16, 18 and 20 of gestation and food consumption data were recorded for days 0-6, 6-11, 11-16 and 16-20 of gestation. All surviving females were sacrificed by CO_2 inhalation on day 20 of gestation and given a gross postmortem evaluation. At necropsy, liver weights were recorded and the uteri were removed, weighed intact, and evaluated for the number of live, dead, and resorbed fetuses, and the number of implantation sites. The ovaries were also dissected and the number of corpora lutea recorded. Fetuses recovered at this time were evaluated for external malformations/variations, sexed, and weighed. Subsequently, one-half of the fetuses in each litter were processed for visceral evaluation (microdissection procedure) and the remaining fetuses were processed for staining of the ossified structures with Alizarin Red S and evaluated for skeletal malformations and/or ossification variations.

Reported Results

No treatment-related mortality was observed. Pregnancy rates and the number of litters recovered on day 20 of gestation were comparable between the control and treatment groups. At the 150 mg/kg/day dose level, a slight, although statistically significant, decrease in food consumption was seen over the 6-11 day gestational period. This reduction appeared to be transient and not biologically significant, however, it was the only suggestion of a maternal toxic effect. The only developmental toxicity seen at this high-dose level was increased fetal and litter incidences of delayed ossification involving the cranium, vertebrae, sternebrae, metacarpals and pelvic girdle. Fetal effects are a consequence of maternal toxicity and not a true fetotoxic effect.

SEGMENT II TERATOLOGY STUDY IN RABBITS

Laboratory: Bio/dynamics Inc.

Report Date: January 1992

Study Design

Irgacare MP was administered orally via gastric intubation to mated female rabbits (18-19/group) at dose levels of 0, 15, 50, and 150 mg/kg/day from days 6-18 of gestation. Animals were observed twice daily for mortality/morbidity and for obvious pharmacologic and/or toxicologic effects, and each female was given a detailed physical examination on days 0, 6-19 (daily), 24, and 30 of gestation. Food consumption data were recorded for days 1, 3, 5, 6-19 (daily), 24, and 29 of gestation. All surviving females were sacrificed by sodium pentobarbital injection on day 30 of gestation and given a gross postmortem evaluation. At necropsy, liver weights were recorded and the uteri were removed, weighed intact, and evaluated for the number of live, dead and resorbed fetuses, and the number of implantation sites. The ovaries were also dissected free and the number of corpora lutea recorded. Fetuses recovered at this time were evaluated for external malformations or variations, weighed, and the gender was determined. Subsequently, all fetuses were evaluated for visceral irregularities (microdissection procedure) and then processed for staining of the skeletal structures with Alizarin Red S and evaluated for skeletal malformations and/or ossification variations.

Reported Results

No treatment-related mortality was observed. Pregnancy rates and the number of litters recovered on day 30 of gestation were similar between control and treatment groups. Maternal toxicity was evident only at the 150 mg/kg/day dose level. This was evidenced by lower gestational weights during the treatment period (eg: day 16: 3.5 kg vs control: 3.8 kg), reduced weight gain over the 6-19 day gestational interval (75 g vs control: 219 g), and reduced food consumption over the treatment period (eg: day 15-16: 39 g vs control: 58 g). There was no treatment-related increase in external, visceral, or skeletal malformations in fetuses recovered from females treated with Irgacare MP at all dose levels. No developmental toxicity was observed up to a dose of 150 mg/kg/day to the dams. Thus, the NOEL for maternal toxicity with Irgacare MP in the rabbit was 50 mg/kg/day, and the NOEL for developmental toxicity was 150 mg/kg/day.

TWO GENERATION REPRODUCTION STUDY OF FAT 80'023 (TRICLOSAN) IN RATS

Laboratory: Hazleton Laboratories America/CIBA-GEIGY

Report Date: March 18, 1988

Study Design

Two hundred Crl:CD(SD)Br rats (100 males and 100 females) were assigned to F0 groups by a computerized randomization process. The animals were acclimated to laboratory conditions for 16 days prior to compound administration. Groups of 25 males and 25 females of the F0 generation was fed daily diets which contained FAT 80'023 in concentrations of either 0, 300, 1000 or 3000 ppm. These doses correspond to a daily dose of Triclosan of approximately 0, 15, 50 and 150 mg/kg/day. All F0 animals were approximately 6 weeks old at the commencement of the study and were approximately 17 weeks old at the start of breeding. Thirty F1 rats per sex per group were selected for breeding to produce the F2 generation; these animals were maintained on Triclosan at the same exposure level that their respective parents had received. The growth phase for F1 animals ranged from approximately 12-14 weeks during which time they received the respective group diets containing Triclosan. All F2 pups were sacrificed after weaning.

All animals were observed twice daily for mortality and morbidity. Body weights were recorded weekly for all animals during treatment. In addition, body weights were taken at sacrifice for males and for those females that were not confirmed as being mated, or failed to produce a litter by presumed day 26 of gestation, or had discontinued lactating due to death or weaning of a litter. All pregnant females were weighed on days 0, 7, 14 and 20 of gestation and post-partum days 0, 4, 7, 14 and 21. Food consumption of both males and females was measured weekly during the premating phases. Food consumption was also measured on days 7, 14 and 20 of gestation for the pregnant females and days 4, 7, 14 and 21 of lactation. Following mating, weekly recording of food consumption was resumed for the males, nonpregnant females and females not confirmed pregnant, and post-lactating females. No food consumption data were collected during the mating period.

Adult rats of both generations (F0,F1) were paired for mating after at least 10 weeks of treatment with Triclosan containing diets. The appearance of a vaginal plug or the presence of sperm was considered day 0 of gestation. On lactation days 0, 4, 7, 14 and 21, the number of live and dead pups of each sex per litter, body weight of each live pup, and clinical observations on the live pups were recorded. On lactation day 4, all litters were culled to 8 pups of equal sex

distribution whenever possible. The culled pups were then sacrificed. Dead pups were examined for cause of death. Both culled pups and the dead pups were examined grossly for cervical, thoracic or abdominal visceral abnormalities. Each litter was weaned on lactation day 21.

After all litters were weaned, one male and one female pup were randomly selected to form the F1 generation. For litters without sufficient male or female pups, weanlings were randomly selected from the available pups to provide the 30 males and 30 females needed for each test group in the F1 generation. All remaining weanlings were sacrificed and subjected to gross examination of cervical, thoracic and abdominal viscera.

For the F2 generation, weekly food consumption of the respective group diets containing Triclosan, body weights and clinical observations were recorded following weaning. These animals were sacrificed at approximately 10-11 weeks of age and the cervical, thoracic and abdominal viscera were examined for abnormalities.

Following delivery of the F1 pups, the F0 males were sacrificed. Following weaning of the F1 pups, the F0 dams were sacrificed and subjected to gross necropsy. Tissues of various organs were preserved for possible future histopathological examination. Prior to fixation, uterine examination was done on each female. Each uterus was examined for signs of implantation and resorption, and the presence of dead or normally developing fetuses; the ovaries were examined for corpora lutea. A similar examination was done on the F1 parental animals, except only the number of implantation sites was recorded for the F1 females at necropsy.

Reported Results

No treatment-related deaths were reported in animals of either generation. Clinical and cageside observations of the F0 and F1 parental groups during growth, gestation and lactation did not indicate a compound-related effect. During the F0 growth phase, mean body weights were occasionally significantly above control values for the mid dose (1000 ppm). Given the lack of a dose-response relationship, this finding was not considered to be treatment-related. For the F1 males, mean body weights were lower than controls in the high-dose group (3000 ppm) during their growth phase (weeks 0-12) and for the low-dose females (1000 ppm) during weeks 4-8 and 11. Food consumption, however,was similar between groups. During gestation, the F0 female mean body weights and food consumption levels differed significantly, but a dose-response relationship was not observed. During gestation, body weights for the F1 parents were lower than controls at all intervals for the high-dose group, and for the low- and mid-dose groups on day 20 only. Significant decreases in body weight gain were noted for all treatment groups during different periods of gestation, but a dose-response relationship was not observed. During lactation, the mean body weights of the F0 dams were less than controls in the high-dose group (3000 ppm) on day 7, but the mean body weight

gains were similar to the corresponding control weight gains. No clear dose-response effects were observed during lactation for the F1 dams as well. Thus, there was no clear evidence of treatment-related toxicity observed in the F0 animals during any phase of treatment. A slight increase in minor effects on the livers of the F0 males (mainly discoloration) from the high-dose group (3000 ppm) was noted but lacked statistical significance. Dilated renal pelvis(es) were noted in 3, 1, 4 and 5 males and in 4, 1, 4 and 6 of the females in the control, low-, mid- and high-dose F1 groups respectively. These effects were not evident in the F1 adult sacrifice or the F2 pup necropsies.

There were no apparent effects on reproductive performance for the F0 females. Estrus cycles were unaffected by treatment; mean duration of gestation was similar among the groups. The gestation index was 100% for all groups. The percent pregnant did not statistically differ from controls for either generation. The male and female fertility indices were similar among groups as well.

The F1 viability index (survival for days 0-4) was similar for all treatment groups except for the high-dose group (3000 ppm). The viability index for controls was 90, for the low-dose group 94, the mid-dose group 96, and the high-dose group 82. Statistical significance was not noted. The weaning index (survival for days 4-21) was also comparable among all groups. Mean body weights of the F1 pups from the high-dose group were significantly lower than controls at days 14 and 21.

Reproductive performance was unaffected by treatment of the F1 parent animals. Fertility indices did not indicate a dose-response effect. Pregnancy rates, estrus cycles and gestation duration were similar among the groups.

For the F2 pups, the viability index (survival day 0-4) was 87%, 97%, 90% and 84% for control, low-, mid- and high-dose groups respectively; weaning indices (survival from day 4-21) were 93%, 99%, 99% and 86%, for the same groups, respectively. Although the mean body weights of the high-dose group were significantly below the controls at birth, subsequent weighings were either above or similar to controls. Upon necropsy, the most common finding among the F2 pups was dilated renal pelvis(es). They occurred in 9, 10, 15 and 8 pups from the control, low-, mid- and high-dose groups respectively.

The no-effect level for reproductive performance of the adults is 3000 ppm (approximately 150 mg/kg/day) based on this dietary study. Evidence of effects on neonates was seen at the highest dose (3000 ppm) as indicated by statistically significantly reduced pup weight on postnatal days 14 and 21, and survival of the F1 and possibly the F2 pups. The highest no-adverse-effect level (NOAEL) for the offspring was 1000 ppm (approximately 50 mg/kg/day).

GENETIC TOXICITY STUDIES

There were 15 genetic toxicity studies conducted from 1973-1980 that are provided in the DMF, and they are listed below:

Title	Date	GLP Status
Genetic Activity of Irgasan DP300 in the MP-1 Strain of S. Cerevisiae	6/22/78	Pre-GLP
Mutagenicity Test on Saccharomyces Cerevisiae MP-1 in Vitro With FAT 80023/A	11/27/78	Pre-GLP
Salmonella/Mammalian-Microsome Mutagenicity Test With FAT 80023/A	3/1/78	Pre-GLP
Mutagenic Effects of "Irgasan" on Drosophila Melanogaster	1/79	Pre-GLP
Intrasanguine Host-Mediated Assay With Salmonella Typhimurium With FAT 80023/A	3/27/79	Pre-GLP
Point Mutation With Mouse Lymphoma Cells. I. In vitro-Test/II. Host Mediated Assay With FAT 80023/A	3/27/79	Pre-GLP
Chromosome Studies in Male Germinal Epithelium FAT 80023/A; Mouse	2/21/79	Pre-GLP
The Effect of Irgasan DP300 in the "Mammalian Spot Test", An In Vivo Method for the Detection of Genetic Alterations in Somatic Cells of Mice	6/22/78	Pre-GLP
Use of the Mouse Spot Test to Investigate the Mutagenic Potential of Triclosan (Irgasan DP300)	1980	Pre-GLP
Chromosome Studies on Somatic Cells-GP 41 353 (Triclosan) Chinese Hamster	4/16/73	Pre-GLP
Chromosome Studies in Somatic Cells Long-Term Study With FAT 80023/A Chinese Hamster	2/15/79	Pre-GLP
Nucleus Anomaly Test on Somatic Interphase Nuclei GP 41 353 (Triclosan) Chinses Hamster	5/31/74	Pre-GLP

The studies provided sufficient data to adequately assess most of the parameters required. Based on these studies, triclosan is not considered mutagenic, however, some of the studies were Pre-GLP and not conducted in accordance with currently accepted protocols and procedures. Therefore, the Sponsor was requested to conduct the two studies reviewed on the next page. They were conducted according to GLP requirements at Pharmakon Research International Company, Waverly, PA, and reported in June 1993. There are also several genetic toxicity studies reviewed in the DMF Amendment on page 53-56 of this review.

RAT HEPATOCYTE PRIMARY CULTURE/DNA REPAIR TEST WITH TRICLOSAN
(Pharmakon Study #PH 311-CP-001-93)

STUDY DESIGN

The potential of triclosan to induce unscheduled DNA synthesis was evaluated in primary culture of adult rat hepatocytes as measured by silver grain counts in photographic emulsion. Concentrations of triclosan of 0.6-80 ug/ml were tested with toxicity observed at concentrations >5 ug/ml. Positive controls demonstrated the sensitivity of the test system as expected. No evidence of unscheduled DNA synthesis was seen at any concentration of triclosan.

SPONSOR'S CONCLUSION

Triclosan does not induce unscheduled DNA synthesis in cultured primary rat hepatocytes, when tested at concentrations extending into the toxic range.

This Reviewer's Comment

AGREE: Unscheduled DNA synthesis was not induced by triclosan.

AMES/SALMONELLA PLATE INCORPORATION ASSAY WITH TRICLOSAN
(Pharmakon Study #PH 301-CP-001-93)

STUDY DESIGN

The mutagenic potential of triclosan was evaluated in five tester strains of Salmonella typhimurium (TA 1535, TA 1537, TA 1538, TA 98 and TA100) in the presence and absence of an exogenous metabolic activation system (S9). Triclosan was toxic to the tester strains at higher dose levels, so 0.05-5.0 ug/plate with S9 and 0.0017-1.167 ug/plate without S9 were chosen as the top dose level in the mutation tests. Positive control mutability checks revealed expected responses. No increases in revertant colonies of any of the five tester strains were observed following treatment with triclosan at any dose level, either in the presence or absence of metabolic activation with S9 mix.

SPONSOR'S CONCLUSION

No evidence of mutagenic potential of triclosan was obtained in this bacterial test system at the dose levels used.

This Reviewer's Comment

AGREE. There is no evidence of mutagenic activity by triclosan in this assay.

CARCINOGENICITY STUDIES

TRICLOSAN, 2-YEAR ORAL ADMINISTRATION TO RATS

STUDY DESIGN

The study protocol was reviewed by the Division of Anti-Infective Drugs prior to initiation of the study and contained all of the parameters that are normally included in a carcinogenicity study.

Triclosan was administered to male and female Sprague-Dawley rats (740 total) in the diet at concentrations of 0, 300, 1000, and 3000 ppm for 13, 26, 52, 78 and 104 weeks. An additional group of rats was fed a concentration of 6000 ppm for 52 weeks. The average daily intake of triclosan on a body weight basis was approximately 0, 16, 52, 168, and 418 mg/kg/day for males, and 0, 20, 67, 218, and 532 mg/kg/day for females.

Parameters observed included survival, clinical signs, ophthalmic and physical exams, body weight, food intake, hematology, clinical chemistry, urinalysis, gross and histopathology.

REPORTED RESULTS

Survival was not affected by treatment. Treatment-related effects that were observed at 3000 and 6000 ppm included reduced body weight and food intake; decreased serum protein, glucose, triglyceride levels, and RBC count; and increased clotting times. Both high dose group animals exhibited centrilobular hepatocytes that were enlarged and contained cytoplasmic inclusions. There was no evidence of carcinogenicity. The NOAEL was considered to be 1000 ppm in the diet or 52-67 mg/kg/day.

BACKGROUND

This study has had multiple in-depth reviews and was referred to the CDER Carcinogenicity Assessment Committee (CAC) for evaluation. The CAC did a thorough review of the study including pathology and statistical evaluation of survival and tumor incidence data.

CONCLUSION OF THE CARCINOGENICITY ASSESSMENT COMMITTEE

The rat carcinogenicity study was not optimally designed nor optimally conducted according to currently accepted protocols and procedures. However, it provides some information to assess systemic carcinogenicity. The study was designed according to the existing OECD guidelines at the time, and was reviewed by CDER prior to initiation of the study.

1. Survival - Overall survival was less then 50%, but since at least 25 animals/sex from each group survived to terminal sacrifice, sufficient data was available to assess lifetime carcinogenicity. This was true since many of the animals were sacrificed moribund during the last month of the study.

2. Dose Level - The MTD was not achieved based on the preliminary 90-day study. However, the committee concluded that for the majority of the study, animals received at least half of the MTD. Since triclosan was administered in the diet at a constant 3000 ppm in the high dose group, intake dropped from 400 mg/kg/day to 114 mg/kg/day over the life of the study.

3. Carcinogenicity - There was no evidence that triclosan was carcinogenic.

This Reviewer's Comment

AGREE: The adequacy of this study is marginal at best, but the study does provide some information for the assessment of oral carcinogenicity. The dose level was lower than the determined MTD and triclosan intake was less than expected for much of the study. However, triclosan intake was at least half of the MTD for most of the study. Survival was also less than expected with less than 50% survival in all groups at 104 weeks. However, there were at least 25 animals/sex/group that survived to 104 weeks, with many moribund sacrifices occurring during the last month of the study. The Sponsor conducted a very aggressive moribund sacrifice program as they didn't want to loose tissues to autolysis during the last few weeks of the study.

This study is inadequate to assess systemic carcinogenicity by itself. Therefore, another oral carcinogenicity study in a species other than the rat is required to be conducted according to currently accepted protocol and GLP requirements to satisfy the requirement for assessment of carcinogenicity.

AMENDMENT TO DMF 916

CIBA-Geigy Corporation, the Sponsor of the triclosan DMF filed an amendment in September of 1994 to update the nonclinical pharmacology and toxicology database for triclosan. Since this NDA is supported by the DMF, Colgate submitted the same information as an amendment to the NDA on October 27, 1994.

The following 32 studies were submitted.

DMF Vol. No.	Study Title
101	Borzelleca, J. F., Frankos, V. H., Johnson, E. M., Jordan, W., Squire, R. A., and Weil, C. Report of the Expert Panel on the Safety of Triclosan in Toothpaste and Oral Rinse Products. Environ Corporation Expert Panel Report. December 15, 1992.
102	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.
103	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 U. School of Dentistry, Oral Health Research Institute Study #89-A-111. October 17, 1990.
104	Purchase, R. et al. The Free and Conjugated Triclosan Concentrations, Clinical Chemical Analysis and Haematology of Blood Samples from a Human Volunteer Study. The British Industrial Biological Research Association Project No. 3.0720 (Protocol 3). Report No. 720/3/88. April 1988.
105	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.
106	Safford, B. A Critical Assessment of the 65-Week In-Use Human Trial with Toothpaste Containing 0.2% Triclosan. Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Document D91/007. January
107	Barnes, E. Mentadent P Toothpaste: Triclosan Toothpaste Study in Man, Haematological and Biochemical Data. Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Document No. D91/053. July 1991.

DMF Vol. No.	Study Title
108	Barnes, E. Mentadent P Toothpaste: Triclosan Toothpaste Study in Man, Haematological and Biochemical Data: Appendices 1 to 4. Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Document No. D91/053. July 1991.
109	Barnes, E. Mentadent P Toothpaste: Background Study in Man, Haematological and Biochemical Data. Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Document No. D91/052. July 1991.
110	Barnes, E. Mentadent P Toothpaste: Background Study in Man, Haematological and Biochemical Data: Appendices 1-5. Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Document No. D91/052. July 1991.
111	Jones, E. and Wilson, L. Ames Metabolic Activation Test to Address the Potential Mutagenic Effect of Triclosan. Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Study No. KA 880169. September 9, 1988.
112	Henderson, L. M., Produlock, R. J., Haynes, P. and Meaking, K. Mouse Micronucleus Test on Triclosan. Environmental Safety Laboratory, Unilever Research Lab., Colworth House. Study No. KC 880168. August 12, 1988.
113	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.
114	Riach, C. G., McBride, D. and 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.
115	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.
116	Volkner, W. Chromosome Aberration Assay in Bone Marrow Cells of the Rat with FAT 80'023/Q (Triclosan). Cytotest Cell Research GmbH & Co. KG. Project No. 218305. April 23, 1991.

DMF Vol. No.	Study Title
117	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. 91-3655. Colgate-Palmolive Study No. 91-014. May 6, 1992.
118	Schroeder, R. E., et al. A Segment II Teratology Study with Irgacare MP (C-P Sample No. 38328). Bio/dynamics, Inc. Project No. 91-3666. Colgate-Palmolive Study No. 91-006. April 16, 1992.
119	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. 91-3654. Colgate-Palmolive Study No. 91-013. May 6, 1992.
120	Schroeder, R. E., et al. A Segment II Teratology Study with Irgacare MP (C-P Sample No. 38328). Bio/dynamics, Inc. Project No. 91-3665. Colgate-Palmolive Study No. 91-005. April 16, 1992.
121	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.
122	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.
123	Denning, H. J., Sliwa, S., and Willson, 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.
124	Denning, H. J., Sliwa, S., and Willson, 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.
125	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.
126	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. December 2, 1993.

DMF Vol. No.	Study Title
127	Ciba-Geigy. Summary of Current Available Safety Data on Triclosan. Triclosan Industry Alliance. August 15, 1994.
128	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.
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® DP300) Lot No. 5.2.0211.0. Product Safety Labs. Study No. 2635. April 4, 1994.
131	Trimmer, G. W. Fourteen-Day Dermal Rangefinding Study in the Rat with Irgasan® DP300 (MRD-92-399). Exxon Biomedical Sciences, Inc. Lab. Project I. D. 139910A. September 3, 1993.
132	Trimmer, G. W. Ninety-Day Subchronic Dermal Toxicity Study in the Rat with Satellite Group with Irgasan® DP300 (MRD-92-399). Exxon Biomedical Sciences, Inc. Lab. Project I. D. 139910B. July 14, 1994.

Of the 32 studies submitted, 8 volumes (Volumes 101, 102, 118, 120, 122, 125, 126 and 128) had previously been submitted to the NDA and are addressed earlier in this review. Another 7 volumes (Volumes 103, 104, 106, 107, 108, 109 and 110) are reports of clinical trials and therefore are not reviewed here. The remaining 17 volumes (Volumes 105, 111, 112, 113, 114, 115, 116, 117, 119, 121, 123, 124, 127, 129, 130, 131 and 132) are nonclinical toxicology studies and are reviewed here.

Volume 105: CHROMOSOMAL ABERRATIONS, IN VITRO TEST IN CHO CELLS.

STUDY DESIGN

Triclosan was tested in vitro for chromosomal aberrations in a mammalian cell line derived from Chinese hamster ovary tissue. They were incubated with the test compound both with and without metabolic activation with rat S-9 mix. The top dose of 1 ug/ml was used in the absence of S-9 and 38 ug/ml with S-9. Positive control compounds caused expected increases in chromosomal aberrations. Triclosan did not cause a significant increase in chromosomal aberrations at any dose level in either the presence or absence of metabolic activation with S-9 mix.

SPONSOR'S CONCLUSION:

Triclosan has shown no evidence of clastogenic activity in this in vitro cytogenetic assay.

This Reviewer's Comment:

AGREE. There is no evidence of clastogenic activity by triclosan in this assay.

Volume 111: AMES TEST WITH TRICLOSAN

STUDY DESIGN

The tester strains used were TA 1535, TA 1537, TA 98 and TA 100. Triclosan was toxic to the tester strains at higher dose levels, so 1.5 ug/plate was chosen as the top dose level in the mutation tests. Positive control mutability checks revealed expected responses. No increases in revertant colonies of any of the four tester strains were observed following treatment with triclosan at any dose level, either in the presence or absence of metabolic activation with S-9 mix.

SPONSOR'S CONCLUSION

No evidence of mutagenic potential of triclosan was obtained in this bacterial test system at the dose levels used.

This Reviewer's Comment

AGREE. There is no evidence of mutagenic activity by triclosan in this assay.

Volume 112: MOUSE MICRONUCLEUS TEST

STUDY DESIGN

The effect of triclosan on the incidence of micronucleated polychromatic erythrocytes in mice was assessed by a single dose of 5000 mg/kg body weight administered orally by gavage. No toxicity was observed. A negative control group was used, and the positive control material, mitomycin C, produced increases in the frequency of micronucleated polychromatic erythrocytes and decreases in the ratio of polychromatic to normochromatic erythrocytes. At all sampling times (24, 48, and 72 h after dosing), mice treated with triclosan showed no significant increase in the frequency of micronucleated polychromatic erythrocytes or significant decreases in the ratio of polychromatic to normochromatic erythrocytes.

SPONSOR'S CONCLUSION

Triclosan showed no evidence of clastogenic potential when administered orally in this in vivo test procedure.

This Reviewer's Comment

AGREE. There was no evidence of clastogenic activity by triclosan in this assay.

Volume 113: MOUSE LYMPHOMA ASSAY

STUDY DESIGN

Triclosan was tested for mutagenic potential in an in vitro mammalian cell mutation assay in a subline of mouse lymphoma L5178Y cells at the thymidine kinase locus. Cells were treated with triclosan at 20 ug/ml in the absence of S-9 and 15 ug/ml in the presence of S-9 mix. Treatment with triclosan failed to induce increases in mutant frequency in any of the tests, either in the absence or presence of S-9 mix.

SPONSOR'S CONCLUSION

Triclosan does not demonstrate mutagenic potential in this in vitro test system.

This Reviewer's Comment

Agree. There was no evidence of mutagenic activity by triclosan in this assay.

Volume 114: UNSCHEDULED DNA SYNTHESIS IN RAT HEPATOCYTE CULTURES

STUDY DESIGN

Triclosan was tested for its ability to induce unscheduled DNA synthesis in primary cultures of adult rat hepatocytes as measured by silver grain counts in photographic emulsion. Concentrations of triclosan of 0.6-80 ug/ml were tested with toxicity observed at concentrations >5 ug/ml. Positive controls demonstrated the sensitivity of the test system as expected. No evidence of unscheduled DNA synthesis was seen at any concentration of triclosan.

SPONSOR'S CONCLUSION

Triclosan does not induce unscheduled DNA synthesis in cultured primary rat hepatocytes, when tested at concentrations extending into the toxic range.

This Reviewer's Comment

AGREE: There was no evidence of unscheduled DNA synthesis induced by triclosan.

Volume 115: CHROMOSOME ABERRATIONS IN CHINESE HAMSTER V79 CELLS

STUDY DESIGN

Triclosan was assessed for its potential to induce structural chromosome aberrations in V79 cells of the Chinese hamster in vitro. The doses of triclosan used were 0.1-3.0 ug/ml, in the presence and absence of S-9 and at intervals of 7 h, 18 h, and 28 h after treatment. Positive controls showed distinct increases in cells with structural chromosome aberrations. There were increases in cells with structural chromosomal aberrations after treatment with triclosan at the intervals of 18 and 28 h at levels below the cytotoxic levels, with and without S-9 mix.

SPONSOR'S CONCLUSION

In this study the triclosan induced structural chromosome aberrations in the V79 Chinese hamster cell line.

This Reviewer's Comment

RESULTS ARE QUESTIONABLE: The incidence of chromosomal aberrations was increased in the triclosan groups in this assay. These results are equivocal and of questionable importance since some toxicity was seen and triclosan has been studied in numerous other chromosomal aberration studies without positive effect.

Volume 116:CHROMOSOMAL ABERRATIONS IN RAT BONE MARROW

STUDY DESIGN

Triclosan was administered orally at 4000 mg/kg in 10 ml/kg to 10 animals (5M & 5F)/group. Bone marrow cells were collected for chromosome aberration analysis at 6 h, 24 h and 48 h after a single administration of triclosan. For each animal, 50 metaphase cells were scored for gaps, breaks, fragments, deletions, exchanges and chromosomal disintegrations. The positive control showed an increase of induced aberration frequency. The chromosomal aberration frequency was not significantly increased by triclosan treatment.

SPONSOR'S CONCLUSION

Triclosan is considered to be non-clastogenic in this chromosome aberration assay in vivo.

This Reviewer's Comment

AGREE. Triclosan did not increase the incidence of chromosomal aberrations in rat bone marrow cells and is not considered clastogenic in this assay.

Volume 117: RANGE-FINDING TOXICITY STUDY IN PREGNANT RABBITS

STUDY DESIGN

This range-finding study was conducted to provide preliminary information to aid in setting dose levels for the Segment II teratology study. Dose levels of 0, 5, 10, 25, 50 and 75 mg/kg/day were administered to 5 presumed pregnant NZW female rabbits/group during presumed gestation days 6-18. No maternal effects were seen at dose levels of 5, 10, 25 and 50 mg/kg/day, nor were fetal effects seen at 75 mg/kg/day. Maternal toxicity was observed at 75 mg/kg/day as exhibited by weight loss and reduced food intake.

SPONSOR'S CONCLUSION

Dose levels of 0, 15, 50 and 150 mg/kg/day were selected for the Segment II teratology study in rabbits.

This Reviewer's Comment

AGREE. These levels were acceptable for the study, but maternal toxicity was expected at the highest dose level.

Volume 119: RANGE-FINDING TOXICITY STUDY IN PREGNANT RATS

STUDY DESIGN

This range-finding study was conducted to provide preliminary information to aid in setting dose levels for the Segment II teratology study. Dose levels of 0, 5, 10, 25, 50 and 75 mg/kg/day were administered to 5 presumed pregnant CD female rats/group during presumed gestation days 6-15. No maternal or fetal effects were seen at dose levels of 5, 10, 25 and 50 mg/kg/day. Body weight loss was observed at 75 mg/kg/day in one female. The other 4 females in the group were similar to control. Mean fetal weights were also reduced at the highest dose level.

SPONSOR'S CONCLUSION

Dose levels of 0, 15, 50 and 150 mg/kg/day were selected for the Segment II teratology study in rats.

This Reviewer's Comment

AGREE. These levels were acceptable for the study, but maternal toxicity was expected at the highest dose level.

Volume 121: RANGE-FINDING TOXICITY STUDY IN PREGNANT MICE

STUDY DESIGN

This range-finding study was conducted to provide preliminary information to aid in setting dose levels for the Segment II teratology study. Dose levels of 0, 5, 10, 20, 40, 80 and 160 mg/kg/day were administered to 5 presumed pregnant CD female rats/group during presumed gestation days 6-15. No maternal or fetal effects were seen at dose levels of 5, 10, 20 and 40 mg/kg/day. Maternal body weight reduction was observed at 80 and 160 mg/kg/day. Mean fetal weights were reduced at the dose levels of 40, 80, and 160 mg/kg/day. Resorptions were increased in the 160 mg/kg/day group.

SPONSOR'S CONCLUSION

Dose levels of 0, 10, 25, 75 and 350 mg/kg/day were selected for the Segment II teratology study in rats.

This Reviewer's Comment

AGREE. These levels were acceptable for the study, but maternal toxicity was expected at the highest dose level.

Volume 123 and 124(Two Volume Report):
PREGNANCY AND POST-NATAL DEVELOPMENT IN RATS

STUDY DESIGN

Triclosan was administered by gavage in corn oil to groups of 30 female Wistar rats at levels of 0, 30, 100 and 300 mg/kg/day on days 6-15 of presumed pregnancy. Day 21 of pregnancy, 25 females per group were sacrificed and uterine contents examined by Caesarean section. Corpora lutea, resorptions, live and dead fetuses were counted. Fetuses were examined for skeletal and soft tissue anomalies. The additional 5 females per group were allowed to go to natural birth and nurse the offspring to weaning. Dams and offspring were killed and examined at weaning, 21 days post-partum. In the 300 mg/kg group maternal toxicity was exhibited as reduced weight gain and food intake and increased water intake. There was no increase in the number of resorptions or fetuses with skeletal or soft tissue variations or abnormalities. In the post-partum phase, there were no maternal or fetal effects that were attributable to triclosan.

SPONSOR'S CONCLUSION

Despite slight maternal toxicity after repeated administration of 300 mg/kg/day triclosan by gavage, there were no fetal or post-partum effects which could be attributable to maternal treatment with triclosan during the period of organogenesis (days 6-15 of pregnancy).

This Reviewer's Comment

AGREE: There were no treatment related fetal effects at the highest level of 300 mg/kg/day, however, maternal effects were observed and included reduced weight gain and food intake, and increased water intake.

Volume 129: ACUTE ORAL TOXICITY OF TRICLOSAN IN RATS

STUDY DESIGN

Triclosan was administered by gavage in a single dose at the level of 5000 mg/kg to 5 Sprague-Dawley rats/sex. Animals were observed for survival and signs of toxicity for 14 days after which they were killed and necropsies performed. One female died on day 3 and all animals exhibited toxic signs including diarrhea, soft feces, ano-genital staining, hunched posture, lethargy, abdominal distention, piloerection, ocular discharge and/or irregular respiration. Surviving animals recovered by day 7 and gained weight over the 14 day observation period. Gross necropsy of the one death revealed discoloration of lungs and GI tract, with gross findings at term being unremarkable

SPONSOR'S CONCLUSION

The single dose toxicity of triclosan is greater than 5000 mg/kg in this study.

This Reviewer's Comment - AGREE.

Volume 130: DERMAL SENSITIZATION TEST - BUEHLER METHOD

STUDY DESIGN

This test was conducted in guinea pigs using the Buehler Method to determine the potential for triclosan to produce dermal sensitization. Triclosan and the positive control material (DNCB) were applied to groups of 10 healthy animals during an induction period of 3 weeks. Two naive animals served as negative control animals and were treated with triclosan and DNCB only in the challenge phase. Twelve days after the last induction dose, the respective groups received either challenge doses of DNCB or triclosan. The animals were scored for irritation at 24 and 48 hours after each induction or challenge dose. Test sites showed varying degrees of erythema during the induction phase as expected. Irritation was so severe during the induction phase that the solution of triclosan had to be reduced in concentration from the initial 25% to 2% for the last week of the induction period. Following the challenge dose, no irritation was seen in naive (negative control) sites, and DNCB sites exhibited irritation as expected. Some triclosan sites showed erythema following the challenge application, but erythema was not severe enough to be considered a sensitization response.

SPONSOR'S CONCLUSION

Triclosan is not considered to be a contact sensitizer in this study.

This Reviewer's Comment - AGREE.

Volume 131: 14-DAY DERMAL RANGEFINDING STUDY IN THE RAT

Volume 132: 90-DAY DERMAL TOXICITY STUDY IN THE RAT

STUDY DESIGN

The rangefinding study was conducted to aid in setting levels for the 90-day study. Groups of 2 male and 2 female Sprague-Dawley rats received Triclosan at dosages of 0, 10, 25, 50, 100 or 200 mg/kg/day through topical application for 14 consecutive days. Parameters observed were survival, toxic signs, body weight, food intake, dermal responses and gross necropsy. The only two animal deaths were attributed to the wrapping procedure. Decreased body weight gains and food intake were seen in the 100 and 200 mg/kg/day group males. In these same groups, dermal irritation was significant in both males and females. Based on these results, levels of 0, 10, 40 and 80 mg/kg/day were selected for the subsequent 90-day study.

In the 90-day study, groups of 10 male and 10 female Sprague-Dawley rats received daily topical doses of 0, 10, 40 or 80 mg/kg/day. There was also a fifth group dosed at the highest level and assigned as a 28-day recovery group retained after cessation of treatment. Parameters observed were survival, dermal responses, toxic signs, body weight, food intake, ophthalmology, hematology, clinical chemistry, urinalysis, gross necropsy and histopathology. Five animals died prior to scheduled termination and were considered incidental. Erythema and edema (with desquamation, exfoliation, and/or eschar) were seen in all test groups and generally increased in frequency and severity as the test levels increased, and was not seen in the control group. Increased dermal fibrosis was observed in the recovery group. No effects on body weight or food intake were seen in this 90-day study as were seen in the rangefinding study. There was a higher incidence of occult blood in the urine of a few high dose animals (topically treated), but this was not accompanied by any observed hematology or clinical chemistry effects.

SPONSOR'S CONCLUSION

There were no definitive systemic treatment related effects attributable to dermal application of triclosan. Dermal responses of erythema and edema were observed in all triclosan treated groups with dermal fibrosis increased in recovery animals. Excluding dermal effects, the NOAEL was 80 mg/kg/day.

This Reviewer's Comment

AGREE: There was no definitive evidence of systemic toxicity at dermal dose levels up to 80 mg/kg/day for 90 days.

SUMMARY AND EVALUATION

Introduction

The subject of this NDA is a dentifrice containing 0.24% fluoride (as sodium fluoride) and 0.3% triclosan. It is similar to products that have been marketed in Italy since 1985 and numerous other countries since 1990. The subject dentifrice has been marketed in some 30 countries by the Sponsor since 1992. Currently, there are over 40 countries where similar dentifrice materials containing fluoride and triclosan are marketed. Fluoride is present in most toothpastes sold worldwide and in many mouthwash materials. Triclosan is present in dozens of consumer products in this country and many have been approved and marketed worldwide for over 30 years.

FLUORIDE

The use of sodium fluoride in dentifrice materials is documented in the OTC monograph on anticaries drug products for human use; Fed. Reg. 50 (189) 39854-39873, September 30, 1985. In this monograph sodium fluoride is considered safe and effective for use as an anticaries agent when marketed in packages containing no more than a total of 260 mg of fluoride. The proposed formulation for the product in this NDA would contain 300 mg of sodium fluoride (136 mg fluoride) and 375 mg of triclosan in a 4.4 oz tube of the subject dentifrice. High fluoride dentifrice products have subsequently been approved by FDA that allow up to 1500 ppm of fluoride.

TRICLOSAN

Pharmacokinetics

The pharmacokinetic profile of triclosan has been investigated in a number of species including monkey, dog, rabbit, rat and mouse. Triclosan is readily absorbed following oral ingestion, with peak plasma concentration reached in 2-10 hours. In the rat peak plasma levels were reached 2 hours after a single oral dose of up to 300 mg/kg. Absorbed triclosan is rapidly metabolized with predominant metabolites being in the form of glucuronide and sulfate conjugates. The major route of triclosan excretion in monkeys, rabbits and guinea pigs is renal with the glucuronide metabolite being the main form found in the urine. In rats and dogs, fecal excretion is the main route of elimination. In the rat there is a significant enterohepatic circulation following oral ingestion of triclosan, however, this does not seem to be true for monkeys or man.

Pertinent pharmacokinetic parameters for triclosan in several species are summarized in the following table:

Species	Route	t(max) (hour)	t(1/2) (hour)	Urine (% dose)	Feces (% dose)
Rat	Oral	0.5-3	6-65	0.2-17	57-91
	Dermal	6	14-50	1-28	22-89
	I.V.	0.5	9	9	18
	Intra-vaginal	2-4	---	14	26
	I.P.	---	18	8	80
Rabbit	Oral	---	---	60-74	16-22
	Dermal	---	15	1-53	>1-38
Guinea Pig	I.P.	---	13	62	14
Dog	Oral	2-8	---	8-12	68-71
	I.V.	1-2	---	13-18	67-70
Monkey	Oral	12-24	---	58	25

Single Dose Toxicity

Triclosan shows relatively low toxicity following single dose oral administration to laboratory animals. Toxic oral doses of triclosan have been reported as 2.5 to >5 g/kg for the mouse, rat and dog. Lethargy, piloerection, hypothermia, sedation and dyspnea were toxic signs observed. Severe gastrointestinal tract irritation is the primary effect seen in rats at necropsy. By other routes of administration, some toxicity was observed. In mice and rats, toxic doses were: IV, 19-42 mg/kg and IP, 132-184 mg/kg. No dermal toxicity was seen in the rabbit at doses up to 6000 mg/kg. Lethal concentration in air for a 4 hour inhalation exposure in rats was 436 mg/m^2. Triclosan is a moderate, transient eye irritant and moderate dermal irritant in rabbits. Triclosan does not induce photo irritation, photo sensitization or dermal sensitization in mice or guinea pigs.

Multiple Dose Toxicity

Triclosan has been exhaustively evaluated in numerous multiple dose toxicity studies in most of the common laboratory species. In 90-day studies, triclosan was administered to mice, rat, rabbit, dog and baboon by gavage, capsule or diet.

In mice, the dose of 150 mg/kg/day caused increased liver weights and an increased incidence of hepatocyte hypertrophy and focal necrosis. There was a wide range between doses, and the next lower dose level of 7 mg/kg/day was considered the NOAEL.

In rats several 90 day studies were conducted. The NOAEL was found to be in the range of 50-100 mg/kg/day. At higher doses, body weight and food intake were reduced with lethargy and sedation observed and microscopically, increased incidence of hypertrophy of centrilobular hepatocytes with cytoplasmic inclusions.

Two 90-day studies were conducted in rabbits with doses ranging from 3.0 to 150 mg/kg/day in a gavage study, and 12.5 to 125 mg/kg/day in the second study wherein triclosan was administered by diet. In the gavage study, 4 of 6 rabbits died in the highest dose group. A NOAEL of 3 mg/kg/day was established when triclosan was administered by gavage. Toxic effects included decreased body weight and food intake with pathology showing edema and necrosis in the lung. In the dietary study, there were no toxic effects on body weight, food intake, gross necropsy or histopathology. The NOAEL was 125 mg/kg/day when triclosan was administered by diet.

Two 90-day studies were conducted in dogs with doses of 25-200 mg/kg/day by capsule and 5-25 mg/kg/day by diet. No toxic effects were seen in the dietary study since the dose levels were so low. In the capsule study, 4 of 6 animals died in the 200 mg/kg/day group, and 2 of 6 animals died in the 100 mg/kg/day group. Emesis and diarrhea were prevalent in both of these groups, as were clinical chemistry findings that included: increased serum alkaline phosphatase, SGOT, SGPT, erythrocyte sedimentation rate and reticulocytes.

Body weight and food intake were decreased in all treatment groups, and liver, pancreas, kidney and adrenal weights were increased. Histologically, effects were seen in all treatment groups and were confined to the liver, and included centrilobular hepatocyte hypertrophy. A NOAEL was not established in this study since effects were seen at the lowest dose level of 25 mg/kg/day.

In baboons, studies were conducted for 4, 13, 26 and 52 weeks, with dose levels ranging from 1 to 300 mg/kg/day. No deaths occurred and body weight and food intake were not affected. Clinical chemistry, hematology, organ weights, gross necropsy and histopathology were not affected. The primary clinical finding was diarrhea with abdominal pain in the 300 mg/kg/day group and intermittent diarrhea in the 100 mg/kg/day group. The NOAEL was found to be 30 mg/kg/day in baboons following 52 weeks of treatment.

Triclosan was administered to male and female Sprague-Dawley rats for 104 weeks at dietary levels equivalent to approximately 0, 20, 60 and 190 mg/kg/day. An additional group received approximately 475 mg/kg/day for 52 weeks. Survival was comparable in control and triclosan-treated groups. Chronic toxicity was observed in the two highest dose groups and was exhibited in both males and females. Treated-related effects attributable to the administration of triclosan in the groups receiving 190 and 475 mg/kg/day include: reduced body weight and food intake, decreased serum protein, glucose, triglyceride and RBC count, and increased clotting times. Animals in these two highest dose groups also exhibited hypertrophy of centrilobular hepatocytes with cytoplasmic inclusions. The NOAEL was 60 mg/kg/day.

Reproduction and Developmental Toxicity

Segment II developmental toxicity studies were conducted in CD-1 mice, Spraque-Dawley rats and NZW rabbits, using currently accepted protocols and procedures, and according to GLP requirements. Triclosan is not teratogenic in the studies.

In the mouse study, the oral NOAEL for both maternal and fetal effects was 25 mg/kg/day following administration during days 6-15, at dose levels of 0, 10, 25, 75 and 350 mg/kg/day. At the higher levels of 75 and 350 mg/kg/day, maternal body weight and liver weight, including ratios were increased. The increase in body weight was considered a consequence of the increased liver weight. For these same two higher dose groups, fetal body weights were reduced and the incidence of irregular or delayed ossification was increased for fetal skull and phalanges. This reviewer considers these fetal effects a result of maternal toxicity and not a true fetotoxic effect.

The only maternal effect seen in the rat following oral administration of triclosan at the dose levels of 0, 15, 50 and 150 mg/kg/day was reduced food intake during the early treatment period at the highest dose level. In the same group, the incidence of delayed ossification was increased for fetal cranium, vertebrae, sternebrae, metacarpals and pelvic girdle. The oral NOAEL was 50 mg/kg/day for both maternal and fetal effects.

Triclosan was orally administered at the levels of 0, 15, 50 and 150 mg/kg/day in the rabbit study. Maternal effects included reduced body weights and body weight gain, and reduced food intake at the highest dose level. There were no fetal effects seen at the highest dose level. The oral NOAEL in rabbits was 50 mg/kg/day for maternal effects, and 150 mg/kg/day for fetal effects.

A two generation reproduction study was conducted in rats at dietary levels equivalent to 0, 15, 50 and 150 mg/kg/day. There were no treatment related effects seen in adult male or female rats of either generation. At the highest dose level, pup body weight and survival of both F1 and F2 offspring were reduced. The highest NOAEL for reproductive performance of both male and female rats if two generations is 150 mg/kg/day. The highest NOAEL for effects on offspring is 50 mg/kg/day.

Genetic Toxicity

The mutagenic potential of triclosan was evaluated in a variety of in vitro and in vivo assays. These included: recombination in S. Cerevisiae, reverse mutation in Salmonella, recessive lethal in Drosophila, host-mediated in Salmonella, point mutation in mouse lymphoma, dominant lethal in mouse, mammalian spot tests, chromosome studies in mouse germinal epithelium and Chinese hamster ovary, and anomaly test in Chinese hamster somatic nuclei. The incidence of structural chromosomal aberrations in Chinese Hamster V79 cells was increased in the triclosan groups in one assay. These results are equivocal and of questionable importance since some cytotoxicity was seen, and triclosan has been studied in numerous other chromosomal aberration studies, including V79 cells, without positive effect. Therefore, triclosan is not considered mutagenic or genotoxic at levels below the outright toxic levels.

Carcinogenicity

Triclosan was evaluated in a carcinogenicity study in Sprague-Dawley rats at dietary levels equivalent to approximately 0, 20, 60 and 190 mg/kg/day for 104 weeks. Survival was not affected by triclosan treatment, however, survival was less than 50% for all groups even controls. Since at least 25 animals/sex/group survived to termination with many animals from all groups being sacrificed in a moribund condition during the last month of the study, sufficient data was available to assess lifetime carcinogenicity. The MTD was not achieved based on the 90-day rangefinding study, but triclosan intake was more than half the MTD for most of the study which provided adequate exposure. Signs of toxicity were exhibited as reduced body weight and food intake; decreased serum protein, glucose, triglyceride levels, and RBC count; increased clotting times, and histologically the increased incidence of hypertrophy of centrilobular hepatocytes with cytoplasmic inclusions. The NOAEL was 60 mg/kg/day. There was no evidence of carcinogenicity.

By itself, this study is inadequate to meet the NDA requirement for assessment of systemic carcinogenicity. Therefore, another oral carcinogenicity study in a species other than the rat is required to be conducted according to a currently accepted protocol and GLP requirements. The Sponsor has agreed to conduct a Phase IV mouse carcinogenicity study, which is currently underway.

Special Studies

Two studies were conducted in rats with the dentifrice material that is the subject of this NDA. At terminal sacrifice in these two studies, plasma concentrations of triclosan and/or the sulfate and glucuronide metabolites were also determined.

In a 28-day oral mucosal irritation study, 1 g/kg of the dentifrice material was applied to the abraded and intact oral mucosa once daily for 28 days, with one group continuing on for a 7 day recovery period. Interim sacrifices were conducted on days 2, 5, 14, 28 and 35 days after initiation of treatment. The positive control material (5% sodium lauryl sulfate) and the negative control produced expected results. All animals survived to scheduled termination. Irritation caused from the abrasion technique was healed in most animals by days 7-14. There were no macroscopic or microscopic effects which were related to application of the dentifrice material. The dentifrice material is not considered an oral mucosal irritant. Mean plasma concentrations of triclosan following 28 days of treatment were 630-1120 ng/ml plasma for males and 1500-2100 ng/ml plasma for females, using gas chromatography.

A 13-week study was conducted in rats wherein the dentifrice material was administered by gavage once daily at the levels of 0.40, 1.28 and 4.00 g/kg/day to deliver levels of triclosan of 1.2, 3.84 or 12 mg/kg/day. An interim sacrifice after 45 days of treatment was scheduled with all surviving animals sacrificed at the end of the 13-week treatment period. At termination, plasma samples were analyzed by gas chromatography for triclosan and its glucuronide and sulfate conjugates. For toxic effects, the highest dose level of the dentifrice of 4.00 g/kg/day was considered a no effect level with no treatment related effects being seen. At terminal sacrifice, mean total plasma concentration of triclosan was in the range of 6-11 ppm. Plasma sulfate conjugate concentrations were approximately 3 times the plasma glucuronide conjugate concentrations.

RECOMMENDATION:

It is recommended by this reviewer that NDA 20-231 be approved pending submission by the Sponsor of satisfactory labeling and a satisfactory progress report for the Phase IV mouse carcinogenicity study currently in progress.

The progress report should contain the following as a minimum:

1. A copy of the Final Protocol with Amendments (if any), signed by both the Study Director and Study Monitor.

2. A brief letter report, signed by the Study Director, describing current status of the study, including:
   a. Number of animals/group initiated
   b. Number of animals/group surviving quarterly
   c. Initial and quarterly group mean body weights
   d. Study schedule with in-life starting and termination dates

CONCLUSION:

The submission is approvable when the Sponsor provides satisfactory labeling and a satisfactory progress report for the Phase IV mouse carcinogenicity study currently being conducted. Comments to the Sponsor follow on the next page.

David E Bailey
DAVID E. BAILEY, Ph.D.
January 18, 1995
DATE

Norman C. Jones
1/19/95
Acting Sup. Pharmacologist

cc:ORIGINAL, NDA 20-231
HFD-160
HFD-160/Pharm/DBailey 1-18-95
HFD-160/CSO/SWilliams
HFD-160/MO/FHyman

RECOMMENDATION:

It is recommended by this reviewer that NDA 20-231 be approved pending submission by the Sponsor of satisfactory labeling and a satisfactory progress report for the Phase IV

The progress report should contain the following as a minimum:

CONCLUSION:

The submission is approvable when the Sponsor provides satisfactory labeling and a satisfactory progress report for the Phase IV study currently being conducted. Comments to the Sponsor follow on the next page.

David E Bailey
DAVID E. BAILEY, Ph.D.

January 18, 1995
DATE

Norman C. Lee
1/19/95
Acting Sup. Pharmacologist

cc:ORIGINAL, NDA 20-231
HFD-160
HFD-160/Pharm/DBailey 1-18-95
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HFD-160/MO/FHyman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20231

STATISTICAL REVIEW(S)

JAN 3 1996

STATISTICAL REVIEW AND EVALUATION

Blay 540 Pm.

NDA: 20-231 (Amendment)

Drug Class: 4S

Applicant: Colgate-Palmolive

Name of Drug: Triclosan .3%, Sodium Fluoride USP .24% Dentifrice

Indication: Reduction and prevention of gingivitis, supragingival plaque, and caries

Documents Reviewed: NDA supplemental volumes 8.1 - 8.6, dated July 31, 1995.

Medical Input: Fred Hyman, D.D.S., HFD 550

Statistical Reviewer: Michael Welch, Ph.D., HFD 720

1.0 Background

The Colgate triclosan dentifrice is an antimicrobial, fluoride-containing toothpaste indicated for over-the-counter use as an aid in the prevention of plaque, gingivitis, dental caries, and tartar. In the initial NDA submissions, dated 12/29/92 and 9/10/93, the sponsor submitted the results of five, independent, placebo-controlled trials to demonstrate the safety and efficacy of the triclosan dentifrice to reduce progression of supragingival plaque and gingivitis. Two of those trials (study 90-TRI-0005 in Florida and study 90-TRI-0006 in New York) used the to-be-marketed product formulation and were considered pivotal studies. To support the anticaries indication, the sponsor documented the results from two, anticaries trials in adult populations (study 1988-5A in California and study 1988-6A in Israel) and provided safety results from a children's trial (study 0004.90) that was being completed in Manchester, England.

The statistical review and evaluation of the original NDA was dated 8/24/94 and concluded that the sponsor had demonstrated effectiveness of the triclosan dentifrice to reduce supragingival plaque and gingivitis. However, the Dental Officer's principal conclusion was that the submission did not provide sufficient rationale for the anti-plaque claim, and that the magnitude of the plaque reduction demonstrated by the pivotal studies was not clinically significant. Other clinical issues questioned the validity of the conducted trials to support an OTC indication and questioned the possibly active effects of the copolymer ingredient, a retentivity agent which enhances delivery of the triclosan.

Regarding the anticaries trials, both statistical and clinical reviews concluded that these studies were not well designed, and that the efficacy results may be inconclusive due to possible consequences of unplanned analyses. It was recommended that the sponsor provide the complete study reports and data from all the anticaries trials for additional review. A not-approvable (NA) letter, dated 1/25/95, addressed these and other issues, and the current NDA amendment is in response to the NA letter.

2.0 Reviewer's Summary of NA Letter Issues and Sponsor's Reply

Part One of the letter addresses three[1] main clinical/statistical issues as the basis for non-approvability:

1. The plaque and gingivitis studies were conducted only on adults who received a professional prophylaxis at baseline. Consequently the trials were not deemed adequate to support an OTC indication.

2. The efficacy results from anti-caries studies in adults were based on unplanned interim analyses. No efficacy analysis was submitted for the childrens' study in England.

3. The two pivotal studies showed modest gains in plaque reduction while the non-pivotal New Jersey study (90-TR-0004) showed much larger gains. As the copolymer was present in the placebo for the pivotal studies but not for the other study, the data suggested that the copolymer may be an active drug ingredient. Other, numerous formula variations were noted across studies.

In reply to item 1., the sponsor maintains that the submitted information is sufficient to support OTC use of the product for the proposed indication. They indicate that the prophylaxis was appropriate for the claim and, moreover, efficacy was demonstrated for individuals without an initial baseline prophylaxis in two foreign marketing studies. The sponsor also states that the Manchester study in children shows the safety of the product for that population. Refer to the Dental Officer's review for a detailed discussion of this issue.

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[1] A fourth NA item indicated the anti-tartar claim was based on studies which did not use the to-be-marketed formulation. However this claim is considered a cosmetic one by the agency.

In response to the anti-caries issue, the sponsor's reply states that the trials were conducted for submission to the American Dental Association and not intended as NDA pivotal studies to support the anti-caries claim and that the California study was continued into a fourth year to further evaluate safety. Moreover, they maintain that effectiveness was adequately demonstrated through laboratory profile testing according to the agency's final monograph for anti-caries products. The Division of Over-the-Counter Drugs, however, still needs to decide if the monograph guidelines can apply to fluoride products in combination with triclosan. Regardless of the sponsor's intent, they did submit the end-of-study reports (for all studies) and the efficacy data on computer disk (for the California and Manchester studies), as requested. Efficacy results based on these data are presented in Section 3.0 of this review.

Regarding the activity of the copolymer (item 3.) the sponsor has advised that the absolute magnitudes of the plaque reductions are not comparable across trials. However, an inter-study comparison of anti-plaque results is feasible, and a reviewer's analysis is presented in Section 4.0. The sponsor maintains that the copolymer is inactive and cites several small studies. The Dental Officer's reviewer discusses these studies in detail and concludes that the additional evidence cited is insufficient to support the sponsor's claim. The sponsor is, however, willing to conduct a phase 4 study to further test the activity of the copolymer ingredient.

Part Two of the NA letter lists other clinical and statistical comments. In this section of the letter, the sponsor was asked to address the clinical significance of the plaque reductions observed for the pivotal studies. The Dental Officer has concluded that the sponsor has not submitted any new substantive evidence to support the anti-plaque claim and recommends that the claim not be included in the product label. Several criticisms from the statistical review of the NDA were also indicated in Part Two of the letter. The sponsor concurred with each comment and their reply to these statistical comments was satisfactory.

New Issue. The Dental Officer has recently questioned the sponsor's anti-gingivitis claim to be relevant for an OTC indication. The concern is that the sponsor had recruited study individuals who apparently exhibited high average baseline scores and thus may have had advanced levels of gingivitis; such study individuals may therefore represent a very small part (less than 10%) of the OTC consumer population. This concern could be somewhat lessened if the sponsor's data were to show that the anti-gingivitis efficacy of the product were equally demonstrated for those subjects with low baseline scores. This issue is explored in Section 5.0.

3.0 Anti-Caries Studies

California and Israel Studies

In the original NDA, the sponsor submitted the 26 month results from two, independent, randomized, double-blind, parallel group studies in adults conducted in California (Study 1988-5A) and Israel (Study 1988-6A). These studies were designed for a three year duration and had a primary objective of demonstrating that the triclosan agent did not undermine the anticaries efficacy of sodium fluoride. The sponsor's NDA amendment includes the study report, efficacy data (on disk), and laboratory safety report for the completed, 48 month California study; and the study report for the completed, 36 month Israel study.

Although each study included a positive control dentifrice consisting of sodium fluoride in a silica base and a test dentifrice containing 0.3% triclosan and 2.0% copolymer, the medical division deemed the Israel study unacceptable for support of the anti-caries indication, since the level of fluoride in the test dentifrice (1500 ppm) was much higher than that for the NDA formulation (1100 ppm). The Israel study results are, however, included here for completeness.[2]

Patients recruited for the California and Israel studies were adults in good general health with moderate levels of caries and/or gingival recession. Patient examinations were conducted at baseline, 18, 26, and 36 months for the Israel study and at baseline, 26, 36 and 48 months for the California study to measure coronal caries incidence for DMFT (decayed, missing, or filled teeth, also denoted as DFT) and DMFS (decayed, missing, or filled surfaces, also denoted as DFS). The sponsor analyzed average change from baseline in DFT and DFS as primary efficacy variables.

Manchester Study

Study # 0004.90 was a single center, double blind, randomized, parallel group, 30 month trial in 4060 children, ranging in age from 11 to 13 years. The children were recruited from over 45 secondary schools in the Manchester area and had prior caries experience. Treatment arms consisted of the 0.3% triclosan/2.0% copolymer test dentifrice and a 0.24% NaF/Silica dentifrice, both with 1100 ppm fluoride. Two dental examiners were used to measure incidence of DFS and DFT at baseline, 15 months, and 30 months; each

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[2] A third, active control study arm was included in each of the adult anti-caries trials: for the California study, this arm used a 1500 ppm sodium fluoride dentifrice while the Israel study's third arm used 1100 ppm. The results for these arms were provided in the sponsor's amendment but are not directly relevant to this NDA.

subject was evaluated by the same examiner. The sponsor's original NDA submission for this study included only the protocol and safety report; the amendment to the NDA includes the complete study report and the efficacy data on disk.

3.1 Reviewer's Summary of Anti-Caries Efficacy and Safety Results

For all the anti-caries studies, it should be noted that the statistical criteria for efficacy were defined in the study reports and were not the same criteria as specified in the protocols. The protocols indicate a statistical procedure such as ANOVA for comparison of treatment group averages in incremental DFS and DFT, and the studies were powered accordingly. The study reports, however, refer to the 1988 *Report of workshop aimed at defining guidelines for caries clinical trials: superiority and equivalency claims for anticaries dentifrices*[3], published by the Council on Dental Therapeutics of the American Dental Association, and cite the ADA's recommendation that equivalency be demonstrated by showing that the upper and lower limits of a 90% confidence interval about the true *ratio* of treatment group means is within 10% of unity.

While the Manchester study report adopted this approach, the report for the California (and Israel) studies *relaxed* the equivalency assumption and proceeded to demonstrate only that the test product was no worse than the positive control, that is, only the upper limit of the 90% confidence interval about μ_t/μ_c did not exceed 1.10. Note that for values less than 1.0, this ratio indicates the test product is more effective in caries reduction than the active control. Both study reports utilized Fieller's procedure to calculate confidence intervals for μ_t/μ_c, following methods in Wallenstein, S., Fleiss, J.L. and Chilton, N.W. (1982) "*Confidence Intervals for Percentage Reduction in Caries Increments*," J. Dent. Res., 61, 828-830.

The efficacy results for all studies are summarized in Table 3.1. All incremental scores represent change from baseline. For the California study, the 18 and 26 month results are different than those reported in the original NDA submission due to additional subjects completing the study. It should be noted that the new 26 month results do not satisfy the equivalency criteria set forth by the sponsor, as the upper limit of the 90% confidence interval for μ_t/μ_c exceed the 110% value for both DFS and DFT; whereas in the original submission, the upper limits for the 26 month DFS ratio, for example, was 108%, based on sample sizes of 717 and 702 for test and control groups, respectively.) The new results also indicate there is no apparent time trend in efficacy results across the four year period of study. Note, however, that *only* the 36 month ratios appear to satisfy the

[3] It is likely this publication was not available at the time the study protocols were developed.

TABLE 3.1
COLGATE TRICLOSAN ANTICARIES STUDIES
INCREMENTAL DFT AND DFS[1] FOR ALL EXAMINATIONS

Parameter	NaF/Silica[2] Triclosan/Copolymer		NaF/Silica[2] (Control)		Ratio of Observed Means[3] (expressed as % of control)	90% Confidence Interval for Ratio of True Means[4]	
	N	Mean (Std Dev)	N	Mean (Std Dev)		LOWER	UPPER
California Study (1988-5A)							
18 MO DFS	828	1.20 (1.81)	804	1.21 (1.89)	99.2	87.5	112.5
18 MO DFT	828	0.43 (0.93)	804	0.44 (0.89)	97.7	82.2	116.0
26 MO DFS	770	1.69 (2.43)	760	1.65 (2.43)	102.4	90.6	115.9
26 MO DFT	770	0.53 (0.98)	760	0.54 (0.99)	98.1	84.0	114.7
36 MO DFS	786	2.07 (2.80)	756	2.16 (3.02)	95.8	85.4	107.7
36 MO DFT	786	0.63 (1.12)	756	0.68 (1.21)	92.6	79.7	107.7
48 MO DFS	731	2.58 (3.23)	697	2.54 (3.05)	101.6	91.2	113.1
48 MO DFT	731	0.79 (1.32)	697	0.80 (1.30)	98.8	85.5	114.1
Israel Study (1988-6A)							
18 MO DFS	666	1.37 (1.81)	625	1.45 (1.92)	94.5	83.7	106.8
18 MO DFT	666	0.50 (0.95)	625	0.57 (0.99)	87.7	74.1	103.7
26 MO DFS	578	3.72 (3.96)	544	3.84 (3.99)	96.9	87.3	107.5
26 MO DFT	578	0.90 (1.29)	544	0.95 (1.33)	94.7	82.4	109.0
36 MO DFS	657	5.21 (4.84)	639	5.23 (4.91)	99.6	91.4	108.5
36 MO DFT	657	1.30 (1.72)	639	1.39 (2.10)	93.5	82.2	106.7
Manchester Childrens Study							
15 MO DFS	1823	2.11 (2.88)	1842	2.21 (2.93)	95.5	88.7	102.7
15 MO DFT	1823	1.37 (1.68)	1842	1.43 (1.82)	95.8	89.5	102.6
30 MO DFS	1717	4.57 (4.51)	1745	4.62 (4.70)	98.9	93.5	104.6
30 MO DFT	1717	2.76 (2.42)	1745	2.81 (2.54)	98.2	93.4	103.3

NOTES:

1. Incremental Decayed or Filled Teeth and Decayed or Filled Surfaces are changes from baseline.
2. The California and Manchester studies utilized 1100 ppm F in the triclosan and control dentifrices. The Israel study used 1500 ppm F. (Sponsor's third study arms for adult studies not shown.)
3. The ratio is computed as $(\bar{x}_t / \bar{x}_c)*100$ where t denotes the test group, and c denotes control.
4. The upper bound of the 90% two-sided confidence interval denotes a 95% one-sided confidence interval for evaluating if the test product is "as least as good as" the control. The sponsor set an upper bound of 110% according to ADA criteria: upper limits exceeding 110% do not support the (alternative) hypothesis that the new treatment is as effective as the control in caries prevention. Confidence intervals are not adjusted for multiple comparisons.

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sponsor's equivalency criteria. As the original protocol defined a 36 month trial, the sponsor claims efficacy has been demonstrated based on only those results.

For the Israel study, the 18 and 26 month results are the same as originally reported, and the 36 month results are newly submitted. For the Manchester study, it can be noted from the table that the confidence intervals are about half the size of those for the other studies and the equivalence criteria are easily met. Other factors being equal, this is a result of the much larger sample size for that study. For all studies and time points, the treatment groups were well balanced with respect to baseline DFS and DFT as no statistical differences in mean baseline scores are indicated.

If the California study were to be considered pivotal for the anti-caries claim, then the sponsor's analyses would have several shortcomings. For example the study report does not address any subset analysis by demographic factor, and no intent-to-treat (ITT) analysis was submitted. The sponsor did provide efficacy data on disk, but the data did not include demographic variables, so a reviewer's subset analysis was not possible. An ITT analysis could be accomplished, however, and the results of this analysis are shown in Table 3.2 for the 36 month and 48 month DFS and DFT results.

TABLE 3.2
CALIFORNIA ANTICARIES STUDY
REVIEWER'S INTENT TO TREAT ANALYSIS

Parameter	NaF/Silica Triclosan/Copolymer			NaF/Silica (Control)			Ratio of Observed Means (expressed as % of control)	90% Confidence Interval for Ratio of True Means	
	N	Mean	(Std Dev)	N	Mean	(Std Dev)		LOWER	UPPER
36 MO DFS	840	2.07	(2.83)	823	2.17	(3.01)	95.4	85.4	106.7
36 MO DFT	840	0.64	(1.14)	823	0.69	(1.22)	92.7	80.3	106.9
48 MO DFS	840	2.50	(3.22)	823	2.64	(3.36)	94.7	85.4	105.1
48 MO DFT	840	0.77	(1.30)	823	0.84	(1.34)	92.4	80.9	105.6

NOTES: 1. See Tables 3.1 notes for definitions.
2. Missing observations assigned previous non-missing scores.

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In Table 3.2, subjects with missing values for the 36 month exam were assigned their score from the previous year provided that it was not also missing; then, subjects with missing 48 month values were assigned their 36 month score provided that score remained non-missing. The total numbers of subjects who were evaluated for at least one

exam were 855 and 864 for the control and treatment groups, respectively, hence the ITT analysis does not capture the relatively few subjects who had missing scores for both 26 and 36 month exams. The analysis assumes then that no additional caries occurred for those subjects who were not evaluated. In fact, the mode (and median) of the treatment group distributions of month-to-month change is zero, so the imputation seems to be reasonable, although it clearly works in favor of the sponsor's claim.

It may be more important, however, to recognize that the comparisons of these incremental scores are sensitive to extreme values. For example, Figure 3.1 shows the 36 month DFS increment box and whisker plots for both treatment groups.[4]

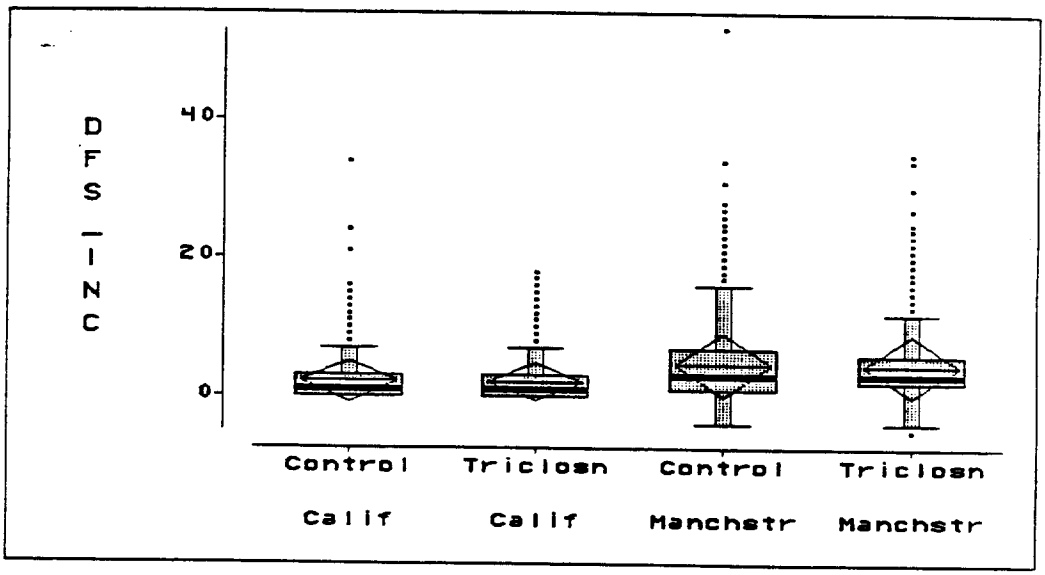

FIGURE 3.1
DFS Increments - California Study at 36 Months and Manchester Study at 30 Months
Colgate Triclosan Anticaries Studies - NDA 20231

The value DFS = 34 for the California control group appears to represent an unusual result, although likely a real event; however, since it occurs in the control group, it has the effect of lowering the ratio. If this value were removed from the 36 month analysis (the 48 month DFS increment is missing for this subject), the upper limits of the confidence intervals would increase to 109% for the evaluable patient data set and 108% for the ITT

[4] In these and all such box plots shown in this review, the heavy horizontal line denotes the sample median of the distribution; the bottom and top of the "box" denote the 1st and 3rd quartiles (25th and 75th percentiles): the diamond shape in the box denotes a 95% confidence interval for the mean whose estimate is shown by the thin horizontal line: the ends of the "whiskers," denoted by the serifs, indicate the largest (or smallest) sample value that does not lie more than 2 times the interquartile range (3rd minus 1st quartile) from the median: thus the values beyond the serifs may denote extreme values.

results. The additional omission of the second largest control group value (DFS = 24) increases the ratios over 110%. One may question the appropriateness of the sponsor's statistical approach in view of these highly skewed distributions and resulting sensitivity to extreme values. For the California study, the 3rd quartile for both treatment groups is less than 3 with most outcomes resulting in either 0, 1, or 2. A similar situation occurs for the Manchester study; however, the possible outlier (DFS increment = 53) only slightly increases the confidence interval upper bound, and the value has little influence on the outcome as a result of the study's larger sample size. (Note from Figure 3.1 that negative outcomes for DFS (and DFT) increments are indicated for the Manchester study; the California study has non-negative outcomes, but there are values at 36 months, for example, that are 1 to 5 units *less* than scores at 26 months. Thus the scoring procedures are clearly not consistent between the two studies.)

(*Note:* With regard to all these results, the significance level for judging the confidence intervals should be adjusted to account for comparison of multiple endpoints (DFS and DFT) as well as the multiple time points. This would have the effect of widening the intervals. The resulting confidence intervals for evaluable subjects would exceed the 110% criteria for all comparisons.)

California Study Safety Report

The sponsor's safety report indicates that the primary objective of the California study (though acknowledging it was not specifically stated in the protocol) was to evaluate the long-term safety of the triclosan dentifrice relative to the active controls. The sponsor indicates that the reported incidences of dentifrice-related adverse event rates were 5.2%, 3.5%, and 3.4% for the triclosan, NaF 1100, and NaF 1500 groups, respectively, but that no single adverse event was reported by more than 1% of the subjects; the most reported event was numbing or burning of the oral cavity for the triclosan group (10 incidences). In comparing the triclosan and NaF 100 groups, the sponsor's report states that 51 subjects in the triclosan group reported 58 events associated with the oral cavity and 30 subjects in the NaF 1100 group reported 31 events. Based on about 1000 subjects per group, the resulting rates (5.1% and 3.0%) are statistically different ($p = .017$). It should be noted that 17 of the 58 incidences reported by those in the triclosan group were associated with either "irritation/lesion" or "numbing/burning," while only 2 incidences were reported by control group subjects for these categories.

The sponsor laboratory analysis report states that no treatment-related changes were indicated in any of the hematology, clinical chemistry, or urinalysis variables that were assessed. This analysis did not include subset evaluations for any demographic factor, although the numbers of subjects by age and sex were tabulated by treatment group. The

sponsor's overall conclusion is that none of the study dentifrices had any adverse effect on standard measures of laboratory safety and that there were no adverse reactions that could be associated with the use of any of the study dentifrices.

It should be noted that the numbers of subjects reported as having completed the safety examinations do not coincide with the numbers reported for the efficacy study. For example, 786 and 756 subjects in the test and NaF 1100 control arms, respectively, received 36 month efficacy evaluations; for the 36 month safety assessment these numbers are 798 and 761. The sponsor's reports do not appear to address the reason for these differences.

Manchester Efficacy Analysis

The statistical analysis of the Manchester study was much more thorough than that presented for the California study, but it was still exploratory in nature. The study report included efficacy analyses by both gender and examiner. In general, no statistical differences between treatment groups were indicated for any of the subset analyses. The sponsor also provided a report on inter-examiner and intra-examiner reliability exercises that were conducted as part of the study; in general, examiner consistency was satisfactory. However, a reviewer's analysis of the end-of-study DFS and DFT increments by examiner is given in Table 3.3; note that only those results for examiner A satisfy the equivalency criteria (baseline values are similar between the two examiners). While the differences in ratio estimates between examiners are not statistically significant, the differences in examiner average scores, within treatment group, are significant and likely indicate a real difference.

The sponsor's report did not include a an ITT efficacy analysis, with imputation for missing observations at end-of-study; however, considering that patient losses (about 15%) were treatment unrelated, such an analysis would likely be uninformative. The safety report for this study was included in the original NDA, and the reader is referred to the Dental Officer's review.

TABLE 3.3 MANCHESTER ANTICARIES STUDY REVIEWER'S ANALYSIS BY EXAMINER							
Parameter	NaF/Silica Triclosan/Copolymer		NaF/Silica (Control)		Ratio of Observed Means (expressed as % of control)	90% Confidence Interval for Ratio of True Means	
	N	Mean (Std Dev)	N	Mean (Std Dev)		LOWER	UPPER
Examiner A							
30 MO DFS	893	4.79 (4.48)	893	4.98 (4.61)	96.3	89.5	103.5
30 MO DFT	893	2.90 (2.42)	893	3.06 (2.58)	95.0	89.0	101.4
Examiner B							
30 MO DFS	824	4.33 (4.54)	852	4.26 (4.75)	101.7	93.2	110.9
30 MO DFT	824	2.60 (2.42)	852	2.55 (2.48)	101.7	94.2	109.8
NOTES: See Table 3.1 notes for definitions.							NDA 20231

Reviewer's Conclusion

Although the California and Manchester studies would probably not suffice as pivotal studies to support an anticaries claim, mainly due to the exploratory interpretation of results (thus the lack of clearly defined confirmatory analysis criteria) and the incompleteness of the sponsor's efficacy and safety analyses, the studies most likely are supportive of the triclosan dentifrice as not inhibiting the anti-caries effect of the fluoride. Although the final efficacy results can easily be assessed as failing the ADA's criteria, all ratios are less than unity, and it is likely that the product would be no more than 15% worse in caries reduction than the control. Moreover, there appears to be no reason for concern regarding the sponsor's unplanned, interim analysis in the original submission. The safety analysis, however, indicates that irritiation and/or numbing of the oral cavity occurred more often with those using the triclosan dentifrice. In conclusion, it is recommended that these study results be used as supportive but not sole evidence regarding the sponsor's anticaries claim.

4.0 Copolymer Effects

In this section, the anti-plaque and anti-gingivitis effects are briefly compared across the three U.S. studies. The reader should keep in mind that any such inter-study comparisons are only exploratory in nature, and it is impossible to ascertain the precise nature of any differences indicated. While the sponsor maintains that the copolymer does not

contribute to an anti-plaque effect, they have agreed to conduct a phase 4 study to further assess any contribution the copolymer may have in enhancing effects of the triclosan.

Table 4.1 presents the reviewer's summary of the results from all the U.S. studies for the plaque and gingivitis indices and severity scores. The reader should refer to the original statistical review for complete discussion of trial design for the New York and Florida studies and analyses of those trials' results. The New Jersey study, though not a pivotal study, was designed with a nearly identical protocol; results from that study were not included in the original review. All 3-month results and all severity scores are secondary endpoints; they are included in Table 4.1 for completeness but are not explicitly addressed in this review.

In the original NDA submission, the sponsor cited the *percent difference in treatment group averages at end-of-study* as the indication of efficacy, whereas their claims of statistical significance (p values) were based on differences in group averages *adjusted for baseline disease scores.* (In all studies, subjects received a supragingival prophylaxis after measurement of baseline plaque and gingival scores.) The treatment groups were well balanced with respect to baseline measurement, and, as it turned out, the unadjusted averages shown in Table 4.1, suffice to demonstrate statistical significance between treatment group outcomes[5]. The table also includes the reviewer's 95% confidence intervals about the true end-of study percent differences; these were computed utilizing Fieller's confidence interval approach (*op. cit.*).

The treatment group percent differences for the New Jersey plaque scores at 3 and 6 months (20% and 32%) appear to be much larger than those for either the New York study (4% and 17%) or the Florida study (7% and 12%). This was the basis for the division's speculation that the copolymer (present in the pivotal study formulations for both test and control but absent in the New Jersey study formulation for the control) could indicate an active effect on plaque buildup.

One should note from Table 4.1, however, that the New Jersey study baseline values for both plaque and gingivitis scores are much lower than those for either of the other two studies, and this difference (as well as any other known differences) should be accounted for when comparing study outcomes. While the baseline disease levels are dissimilar, the studies do not exhibit differences in age and sex distributions. The baseline differences are best illustrated in the box and whisker plots shown in Figures 4.1 and 4.2. These figures also include the end of study scores.

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[5] For the six month comparison the p values are less than .0001 for both adjusted and unadjusted average comparison.

TABLE 4.1
COLGATE TRICLOSAN PLAQUE AND GINGIVITIS STUDIES
REVIEWER'S SUMMARY OF EFFICACY RESULTS

		PLACEBO			TRICLOSAN						
STUDY	ENDPOINT	N	MEAN	SD	N	MEAN	SD	T_DIFF	P_VAL	PCT_DIFF	95% CI
FL	PI_BASE	150	2.43	0.34	150	2.45	0.38	-0.47	.637	-0.81	-4.3 - 2.5
FL	PI_3MOS	150	1.77	0.42	150	1.65	0.43	2.44	.015	6.70	1.3 - 11.8
FL	PI_6MOS	149	1.68	0.45	145	1.48	0.49	3.67	.000	11.90	5.7 - 17.8
NY	PI_BASE	155	2.45	0.50	155	2.45	0.49	-0.03	.974	-0.07	-4.7 - 4.3
NY	PI_3MOS	155	1.59	0.51	155	1.53	0.57	1.11	.268	4.24	-3.4 - 11.4
NY	PI_6MOS	152	1.97	0.53	154	1.63	0.58	5.29	.000	17.00	11.0 - 22.7
NJ	PI_BASE	64	1.75	0.36	60	1.77	0.34	-0.29	.770	-1.04	-8.3 - 5.7
NJ	PI_3MOS	64	1.67	0.51	60	1.33	0.39	4.10	.000	20.08	11.2 - 28.0
NJ	PI_6MOS	63	1.63	0.39	58	1.11	0.34	7.80	.000	32.22	25.2 - 38.8
FL	GI_BASE	150	1.30	0.16	150	1.29	0.18	0.31	.757	0.47	-2.6 - 3.4
FL	GI_3MOS	150	1.13	0.18	150	0.95	0.20	8.60	.000	16.50	12.9 - 20.0
FL	GI_6MOS	149	1.17	0.15	145	0.94	0.13	13.81	.000	19.27	16.8 - 21.7
NY	GI_BASE	155	1.43	0.22	155	1.41	0.22	0.77	.440	1.35	-2.1 - 4.7
NY	GI_3MOS	155	1.19	0.28	155	1.00	0.28	5.94	.000	15.92	10.9 - 20.7
NY	GI_6MOS	152	1.14	0.25	154	0.81	0.23	11.93	.000	29.03	24.9 - 33.0
NJ	GI_BASE	64	1.16	0.18	60	1.17	0.19	-0.41	.685	-1.16	-7.0 - 4.4
NJ	GI_3MOS	64	1.52	0.36	60	1.29	0.26	4.08	.000	15.15	8.3 - 21.4
NJ	GI_6MOS	63	1.19	0.27	58	0.87	0.21	7.17	.000	26.48	20.2 - 32.3
FL	PS_BASE	150	0.24	0.14	150	0.25	0.14	-0.60	.547	-4.02	-18.2 - 8.5
FL	PS_3MOS	150	0.11	0.10	150	0.09	0.08	2.14	.033	20.25	1.9 - 35.4
FL	PS_6MOS	149	0.11	0.10	145	0.09	0.09	1.95	.051	18.69	-0.0 - 34.2
NY	PS_BASE	155	0.35	0.14	155	0.34	0.13	0.58	.562	2.58	-6.4 - 10.8
NY	PS_3MOS	155	0.22	0.12	155	0.19	0.12	1.94	.053	12.47	-0.1 - 23.7
NY	PS_6MOS	152	0.21	0.12	154	0.17	0.11	2.98	.003	18.59	6.8 - 29.1
NJ	PS_BASE	64	0.19	0.13	60	0.21	0.13	-0.57	.571	-7.07	-36.0 - 15.6
NJ	PS_3MOS	64	0.21	0.17	60	0.10	0.10	4.14	.000	50.43	31.8 - 65.0
NJ	PS_6MOS	63	0.19	0.12	58	0.05	0.06	8.37	.000	75.70	66.0 - 84.2
FL	GS_BASE	150	0.30	0.16	150	0.29	0.18	0.21	.832	1.37	-12.1 - 13.4
FL	GS_3MOS	150	0.16	0.15	150	0.07	0.11	6.07	.000	55.50	41.9 - 67.2
FL	GS_6MOS	149	0.18	0.14	145	0.05	0.06	10.46	.000	73.33	66.1 - 79.8
NY	GS_BASE	155	0.45	0.19	155	0.43	0.19	0.71	.476	3.51	-6.4 - 12.6
NY	GS_3MOS	155	0.32	0.15	155	0.24	0.15	4.85	.000	25.37	15.9 - 34.1
NY	GS_6MOS	152	0.28	0.13	154	0.15	0.10	9.60	.000	47.60	40.1 - 54.5
NJ	GS_BASE	64	0.24	0.14	60	0.26	0.16	-0.98	.326	-11.00	-36.6 - 10.1
NJ	GS_3MOS	64	0.55	0.21	60	0.37	0.19	4.78	.000	31.90	20.2 - 42.4
NJ	GS_6MOS	63	0.28	0.20	58	0.12	0.08	5.75	.000	57.93	45.9 - 67.2

NOTES:

1. PI and GI denote the plaque and gingival indices measured at baseline, 3 or 6 months. PS and GS denote the severity indices. Primary endpoints are PI and GI at 6 months.
2. The unit of analysis is the average within-subject index. MEAN and SD denote the (unadjusted) averages and standard deviations of these subject scores.
3. T_DIFF is the t statistic for testing equality of true (unadjusted) treatment group means.
4. P_VAL is the p-value for T_DIFF.
5. PCT_DIFF is computed as 100 * (PLACEBO MEAN - TRICLOSAN MEAN) / PLACEBO MEAN.
6. The 95% confidence intervals for PCT_DIFF were computed using Fieller's method.

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One may question if the New Jersey study subjects with higher baseline scores responded similarly to New York or Florida subjects with lower baseline scores. If there is similarity in study efficacy for these subgroups, then the data might not be supportive of a copolymer effect. Consider then partitioning each study's data in a low and high baseline subsets, separately for the plaque and gingivitis indices, based on each group's median baseline value shown Figures 4.1 and 4.2. and then recomputing the statistics of Table 4.1. These results are shown in Table 4.2. Figures 4.3 and 4.4 show the box plots for the study subsets and indicate similarity in baseline scores.

Judging from the percent difference column in Table 4.2, it appears that the six month gingival scores are fairly consistent across subsets for all studies, while the plaque scores are similar across subsets for only the New Jersey study. (The apparent interaction exhibited by the Florida study results is consistent with the age-treatment interaction addressed in the analysis of the original review.) Although the six month anti-plaque and anti-gingivitis effects appear stronger for those with *lower* baseline scores, it should be kept in mind that the *absolute* differences in end-of-study averages may be the same. For example, the New Jersey study six month plaque percent different results show 36.8% and 30.1% for the low and high subsets, respectively, whereas the absolute differences in treatment group averages are about 0.53 for both subsets.

Pairwise comparisons of the group percent differences indicate that the New Jersey outcomes are consistent with results from both the New York and Florida studies. For example, the group percent differences in plaque scores at six months between New Jersey and New York are 30.1% and 21.8% (Table 4.2) with standard errors[6] of 4.42 and 4.03, respectively, hence the difference in percentages is not statistically different from zero ($p = .17$). The p values for all such pairwise comparisons are given in Table 4.3.

The more extreme differences are indicated for the New Jersey - Florida comparison for plaque scores and the New York - Florida comparison for gingivitis scores. However, even these contrasts can be considered only marginally significant in view of the multiple comparisons. *Thus, the results from these comparisons would not support the conclusion that the mean plaque reduction for the New Jersey study was substantially greater than the plaque reductions for the two pivotal studies*

[6] The standard error of the percent difference was estimated by dividing the length of the Fieller's confidence interval by $2*1.96 = 3.92$.

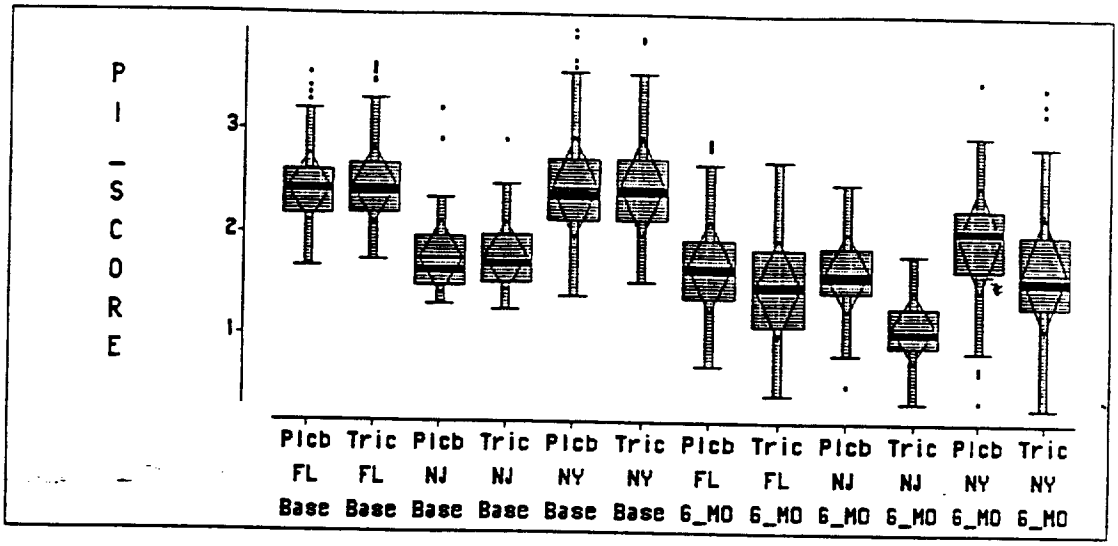

FIGURE 4.1
Plaque Index Scores at Baseline and at Six Months
All U.S. Studies - NDA 20231

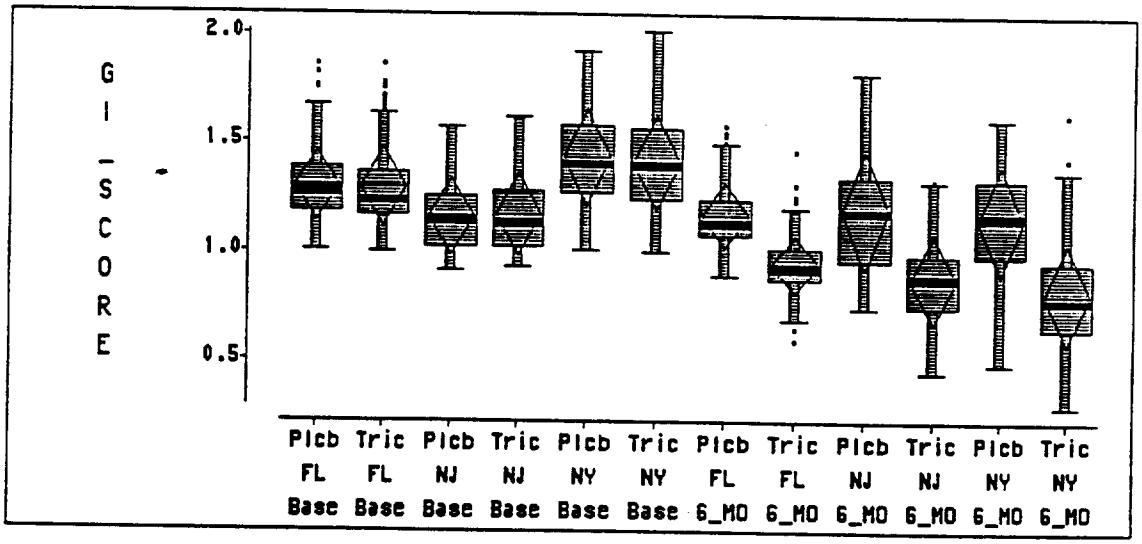

FIGURE 4.2
Gingival Index Scores at Baseline and at Six Months
All U.S. Studies - NDA 20231

TABLE 4.2
COLGATE TRICLOSAN PLAQUE AND GINGIVITIS STUDIES
REVIEWER'S SUMMARY OF EFFICACY RESULTS

STUDY	ENDPOINT	PLACEBO N	PLACEBO MEAN	PLACEBO SD	TRICLOSAN N	TRICLOSAN MEAN	TRICLOSAN SD	T_DIFF	P_VAL	PCT_DIFF	95% CI
FL_LO	PI_BASE	73	2.16	0.17	77	2.16	0.17	-0.21	.836	-0.26	-2.8 - 2.2
FL_HI	PI_BASE	77	2.69	0.26	73	2.76	0.30	-1.41	.161	-2.38	-5.8 - 0.9
FL_LO	PI_3MOS	73	1.52	0.29	77	1.45	0.36	1.31	.191	4.68	-2.3 - 11.3
FL_HI	PI_3MOS	77	2.01	0.37	73	1.87	0.38	2.30	.023	7.06	1.1 - 12.7
FL_LO	PI_6MOS	73	1.46	0.32	74	1.24	0.43	3.43	.001	14.75	6.5 - 22.5
FL_HI	PI_6MOS	76	1.89	0.45	71	1.73	0.42	2.31	.022	8.77	1.4 - 15.6
NY_LO	PI_BASE	79	2.07	0.25	76	2.07	0.23	-0.04	.970	-0.07	-3.8 - 3.5
NY_HI	PI_BASE	76	2.85	0.37	79	2.82	0.37	0.45	.650	0.96	-3.2 - 5.0
NY_LO	PI_3MOS	79	1.33	0.37	76	1.30	0.48	0.55	.583	2.83	-7.6 - 12.5
NY_HI	PI_3MOS	76	1.86	0.50	79	1.75	0.56	1.38	.171	6.25	-2.7 - 14.6
NY_LO	PI_6MOS	77	1.80	0.46	76	1.41	0.52	4.96	.000	21.84	13.7 - 29.5
NY_HI	PI_6MOS	75	2.14	0.55	78	1.85	0.54	3.24	.001	13.35	5.5 - 20.6
NJ_LO	PI_BASE	34	1.50	0.07	29	1.50	0.09	0.19	.852	0.25	-2.5 - 2.9
NJ_HI	PI_BASE	30	2.03	0.34	31	2.02	0.29	0.13	.900	0.50	-7.6 - 7.9
NJ_LO	PI_3MOS	34	1.48	0.45	29	1.15	0.32	3.30	.002	22.27	10.2 - 32.7
NJ_HI	PI_3MOS	30	1.69	0.50	31	1.51	0.37	3.39	.001	20.07	9.1 - 29.6
NJ_LO	PI_6MOS	33	1.49	0.30	27	0.94	0.31	6.94	.000	36.79	27.6 - 45.5
NJ_HI	PI_6MOS	30	1.78	0.43	31	1.25	0.31	5.59	.000	30.08	20.9 - 38.2
FL_LO	GI_BASE	72	1.17	0.06	85	1.17	0.06	0.35	.726	0.28	-1.3 - 1.8
FL_HI	GI_BASE	78	1.41	0.14	65	1.45	0.16	-1.56	.120	-2.73	-6.3 - 0.7
FL_LO	GI_3MOS	72	1.06	0.14	85	0.87	0.16	7.94	.000	17.80	13.7 - 21.7
FL_HI	GI_3MOS	78	1.20	0.18	65	1.05	0.21	4.84	.000	12.99	7.8 - 18.0
FL_LO	GI_6MOS	72	1.10	0.09	82	0.89	0.11	12.92	.000	19.32	16.6 - 21.9
FL_HI	GI_6MOS	77	1.23	0.16	63	1.01	0.13	8.65	.000	17.66	14.0 - 21.2
NY_LO	GI_BASE	79	1.25	0.12	84	1.25	0.10	-0.02	.984	-0.03	-2.8 - 2.7
NY_HI	GI_BASE	76	1.62	0.14	71	1.60	0.15	0.71	.480	1.03	-1.9 - 3.9
NY_LO	GI_3MOS	79	1.09	0.26	84	0.93	0.25	3.92	.000	14.55	7.6 - 21.1
NY_HI	GI_3MOS	76	1.29	0.25	71	1.08	0.30	4.67	.000	16.33	9.7 - 22.6
NY_LO	GI_6MOS	77	1.04	0.25	84	0.75	0.20	8.10	.000	28.00	22.1 - 33.6
NY_HI	GI_6MOS	75	1.26	0.20	70	0.89	0.25	9.80	.000	28.98	23.6 - 34.1
NJ_LO	GI_BASE	32	1.02	0.07	32	1.03	0.06	-0.75	.457	-1.23	-4.5 - 2.0
NJ_HI	GI_BASE	32	1.30	0.13	28	1.33	0.16	-0.91	.364	-2.66	-8.6 - 3.0
NJ_LO	GI_3MOS	32	1.46	0.38	32	1.26	0.25	2.49	.016	13.63	3.1 - 22.7
NJ_HI	GI_3MOS	32	1.58	0.34	28	1.32	0.26	3.26	.002	16.31	7.0 - 24.6
NJ_LO	GI_6MOS	32	1.11	0.21	32	0.82	0.15	6.39	.000	26.25	19.2 - 32.7
NJ_HI	GI_6MOS	31	1.27	0.30	26	0.95	0.24	4.47	.000	25.78	15.6 - 34.9

NOTES:

1. PI and GI denote the plaque and gingival indices measured at baseline, 3 months or 6 months HI and LO denote subsets separated by the medians of the group baseline scores (see Fig. 4.1)
2. The unit of analysis is the average within-subject index. MEAN and SD denote the (unadjusted) averages and standard deviations of these subject scores.
3. T_DIFF is the t statistic for testing equality of true (unadjusted) treatment group means.
4. P_VAL is the p-value for T_DIFF.
5. PCT_DIFF is computed as 100 * (PLACEBO MEAN - TRICLOSAN MEAN) / PLACEBO MEAN.
6. The 95% confidence intervals for PCT_DIFF were computed using Fieller's method.

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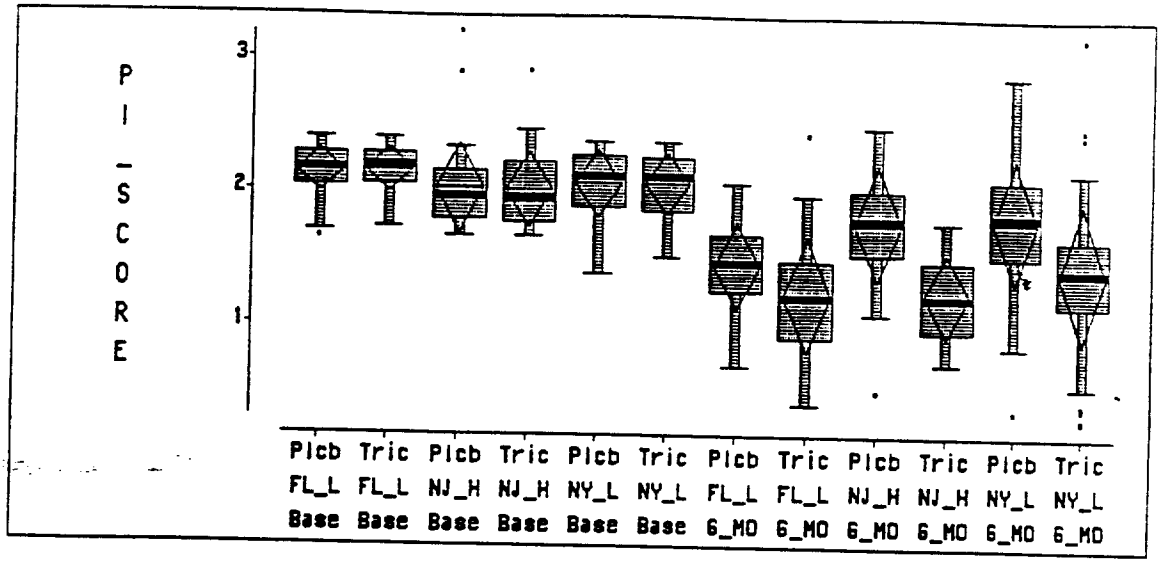

FIGURE 4.3
Plaque Index Scores at Baseline and at Six Months
High/Low (H/L) Baseline Subsets of U.S. Studies - NDA 20231

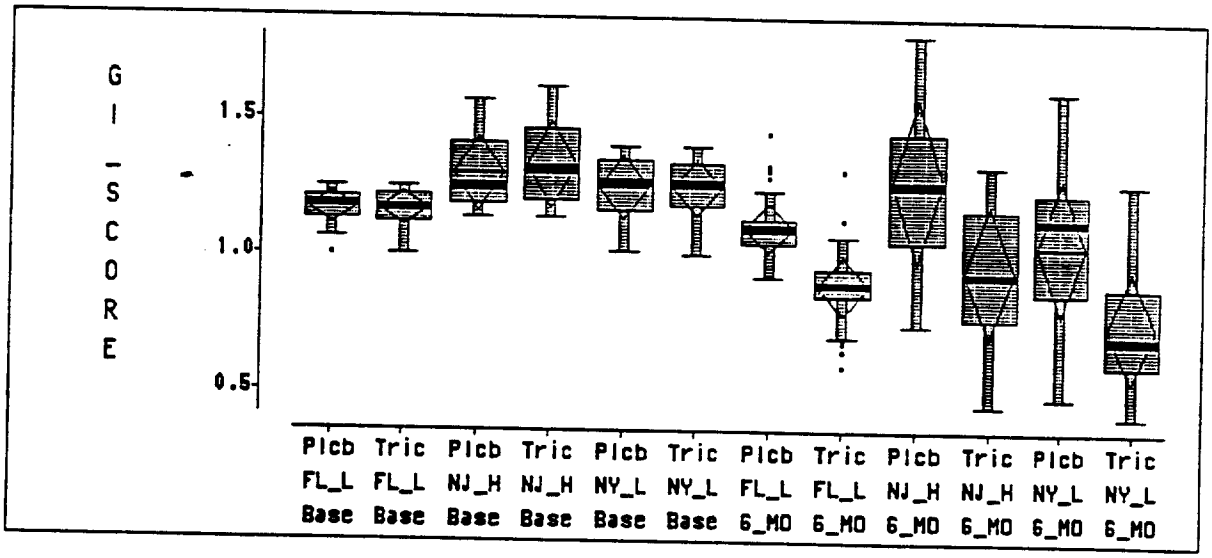

FIGURE 4.4
Gingival Index Scores at Baseline and at Six Months
High/Low (H/L) Baseline Subsets of U.S. Studies - NDA 20231

TABLE 4.3 Comparisons of Treatment Group Percent Differences p values for pairwise t-tests			
	New Jersey	New York	Florida
New Jersey		.17 (P)	.01 (P)
New York	.70 (G)		.22 (P)
Florida	.20 (G)	.01 (G)	
Note: P and G refer to the plaque and gingivitis endpoints.			

It should be noted that one can, and perhaps should, compute group percent differences and standard errors based on averages that are adjusted though analysis of covariance using the baseline covariate. However, due to the balance of baseline values across treatment groups within study and within the study subsets examined here, the adjustment procedure would give substantially the same estimates and conclusions as drawn here.

Reviewer's Conclusion

Comparison of plaque and gingivitis scores across studies using subjects with comparable baseline scores does not indicate that the New Jersey study results are inconsistent with those of the pivotal studies. However, this does not rule out the existence of an active copolymer effect as the analysis was exploratory and based on fairly small samples. Since there is a clinical basis for the copolymer to act as an active ingredient (see the Dental Officer's review) the phase 4 study would be warranted.

5.0 Anti-Gingivitis Effects

As the triclosan dentifrice is indicated for OTC use, the study subjects of the plaque and gingivitis trials should be representative of the consumer population. The Dental Officer has expressed concern that the sponsor recruited study individuals who exhibited high baseline scores that may be inconsistent with those expected of potential users. It was asked if the product's anti-gingivitis effect was largely contributable to subjects who had high baseline values. This section addresses this concern.

The results in Table 4.2 support the observation that the treatment group percent differences for the six month gingivitis endpoint are comparable at low and high levels of baseline gingivitis for all three studies. Although the New York and Florida trials

recruited individuals with high gingival (and plaque) scores, the anti-gingivitis effect for these individuals does not appear to be stronger than for those with the lower scores. In fact, it is important to note the results of the New Jersey study in this respect, since the baseline scores for that study are much lower that those for either of the pivotal studies.

Figure 5.1 perhaps better illustrates the consistency of the anti-gingivitis effect over baseline. Each graph shows scatterplots of the three or six month scores versus the baseline score, with different plot symbols representing treatment group. A simple linear regression line is shown for each group. The near parallelism of the two regression lines indicates that the treatment effect is consistent throughout the range of the baseline variable. Figure 5.2 shows the same results for the plaque indices. While a consistent anti-plaque effect is not illustrated until end-of-study, the evidence for a consistent anti-gingivitis effect is evident in both the three and six month results.

Reviewer's Conclusion

The sponsor's studies do not indicate that the anti-gingivitis effect is attributable to subjects with high levels of disease as measure by the gingival index at baseline. Efficacy is indicated for all study individuals throughout the range of baseline measurements.

APPEARS THIS WAY
ON ORIGINAL

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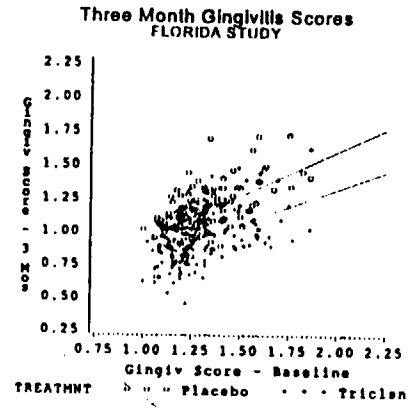

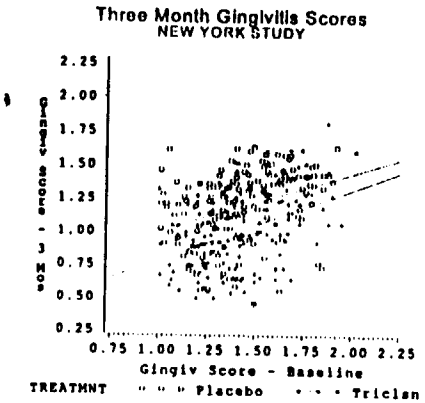

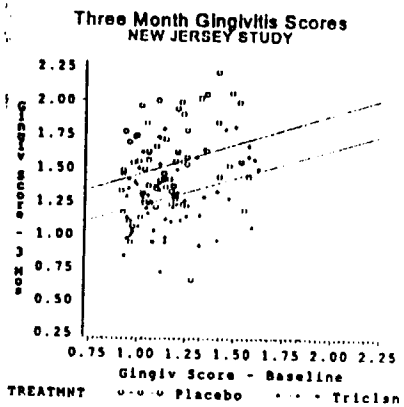

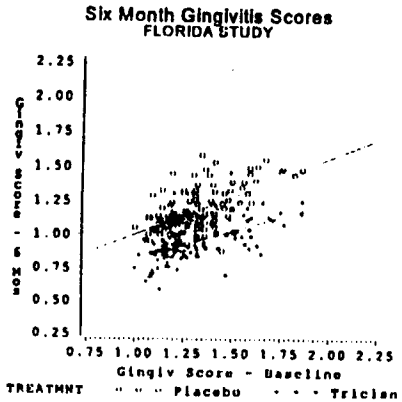

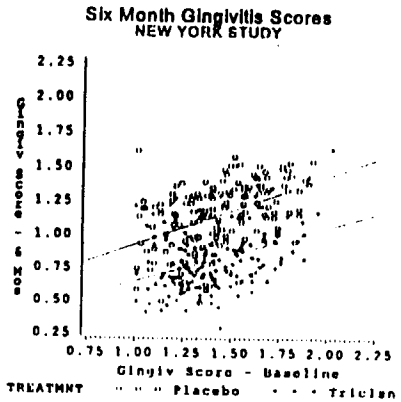

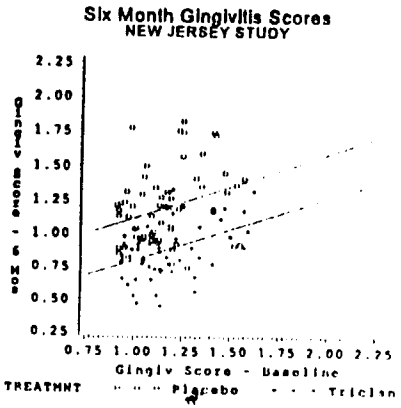

FIGURE 5.1
Colgate Triclosan Gingival Index Scores
All U.S. Studies - NDA 20231

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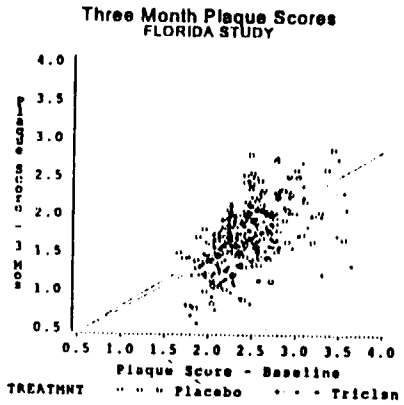

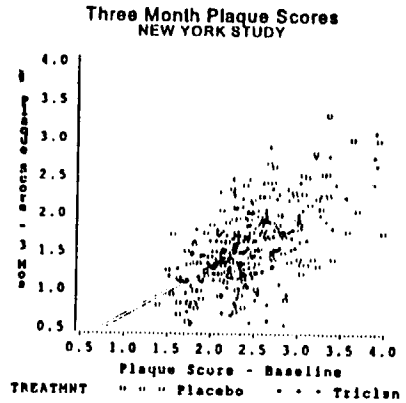

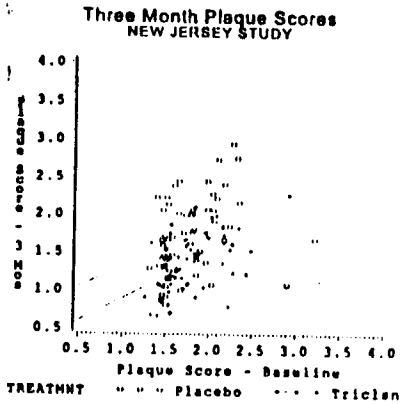

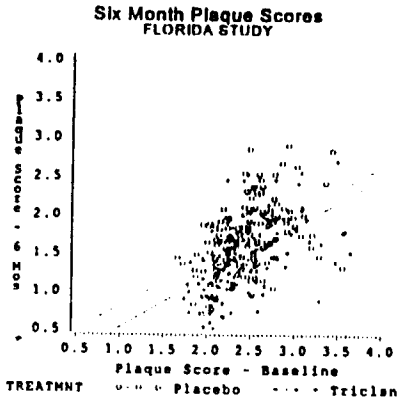

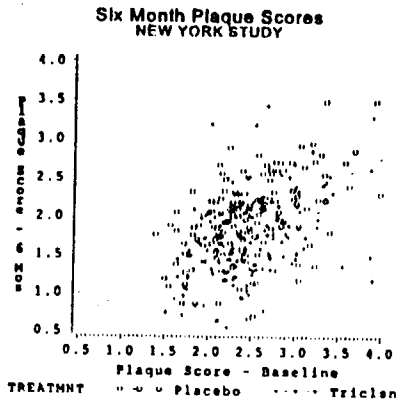

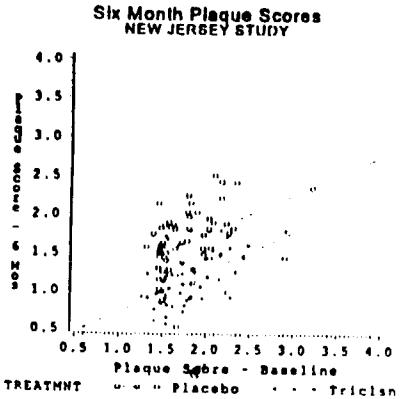

FIGURE 5.2
Colgate Triclosan Plaque Index Scores
All U.S. Studies - NDA 20231

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6.0 Reviewer's Summary

1. The California and Manchester studies would not suffice as pivotal studies in sole support of an anticaries claim. However, the results likely indicate that the triclosan dentifrice is equivalent to the NaF dentifrice in caries prevention. The safety analysis, however, indicated that irritation and/or numbing of the oral cavity occurred more frequently with those using the test dentifrice. It is recommended that the study results be used as supportive but not sole evidence for the sponsor's anticaries claim.

2. Comparison of plaque and gingivitis scores across studies using subjects with comparable baseline scores does not indicate that the New Jersey study results are inconsistent with those of the New York and Florida pivotal studies. This does not, however, rule out the existence of an active copolymer effect. Since there is a clinical basis for the copolymer ingredient to be active, a phase 4 study would be warranted

3. The sponsor's studies do not show that the anti-gingivitis effect is stronger for those individuals with high levels of baseline disease as measured by the gingival index. The results of the trials indicate the effectiveness of the triclosan dentifrice was consistent for study individuals throughout the range of baseline values.

Michael Welch, Ph.D.
Mathematical Statistician

Concur: Nancy D. Smith, Ph.D. NSmith 1/31/96

cc:
Archival: NDA 20231
HFD-160 File copy
HFD-720 File copy
HFD-550 File copy
HFD-160 Dr. Love, Dr. Cheever
HFD-550 Dr. Hyman, Dr. Blay
HFD-720 Dr. Smith, Dr. Welch
HFD-725 Dr. Harkins
HFD-701 Dr. Anello
HFD-344 Dr. Lisook

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20231

MICROBIOLOGY REVIEW(S)

DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS
MICROBIOLOGIST'S REVIEW NO. 1
November 28, 1994

MICROBIOLOGY REVIEWER: Carol K. Vincent

NOV 28 1994

A. 1. **NDA No**: 20-231

DRUG PRODUCT NAME: Total Toothpaste
(sodium fluoride USP 0.24%; triclosan 0.30%)

APPLICANT: Colgate Palmolive Company
P.O.Box 1343
909 River Road
Piscataway, NJ 08855-1343

2. **DOSAGE FORM AND ROUTE OF ADMINISTRATION**: Dentifrice

3. **METHOD(s) OF STERILIZATION**: non-sterile oral dosage form

4. **PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION**: Control of plaque / gingivitis

5. **DRUG PRIORITY CLASSIFICATION**: 4 S

B. 1. **INITIAL APPLICATION DATE**: 12-29-92

2. **APPLICATION RECEIVED FOR REVIEW**: 01-31-93

3. **RELATED DOCUMENTS**: IND

C. **REMARKS**: There are no concerns from a microbiological perspective for the manufacture, packaging, or storage (shelf life) for this drug product. Certain portions of the information relative to the oral microflora and effects of the triclosan-containing dentifrice are discussed below.

D. **CONCLUSION**: We recommend approval for NDA 20-231 from the microbiological perspective based on the above cited information.

cc:
Orig. NDA 20-231
HFD-160/ CKVincent/Hyman/JSWILLIAMS
Drafted by: CKVincent/06-15-94/08-03-94
Revised: CKVincent/11-22-94/11-28-94
R/D Init by: P. H. Cooney/11-28-94

Carol K. Vincent 11-28-94
Carol K. Vincent
Review Microbiologist, HFD-160

PHC 11/28/94

SEP 13 1996

Consultative Review for HFD-540

(Division of Topical Drug Products)

Division of Anti-Infective Drug Products (HFD-520)

Clinical Microbiology #1

REQUESTOR: Fred Hyman (HFD-540)

REASON FOR REQUEST: Microbiological review of the three pivotal studies as well as a set of "reformatted microbiology data " to specifically address "long-lasting antibacterial protection" claim .

IND/NDA Number: NDA 20231

DATE COMPLETED: 8-22-96

APPLICANT:

Colgate Palmolive Company
P. O. Box 1343
909 River Road
Piscataway, NJ 08855-1343

CONTACT PERSONS:

Paul J. Okarma, Ph.D.
Associate Director, PSR & I
Colgate Palmolive Company
P. O. Box 1343
909 River Road
Piscataway, NJ 08855-1343

PRODUCT NAMES(S): Total Toothpaste (sodium fluoride USP 0.24%; triclosan 0.30%)

SUBMISSION REVIEWED:
PROVIDING FOR:

The use of Total toothpaste for reduction and prevention of plaque, gingivitis and caries.

CHEMICAL NAME, STRUCTURAL FORMULAS, MOLECULAR FORMULA, MOL. W.T.:

This drug product contains 0.3% triclosan which is a noncationic disinfectant effective against a wide range of both Gram-positive and Gram-negative microorganisms *in vitro*.

Chemical Name: 2,4,4'-tricloro-2'-hydroxydiphenyl ether
Structural Formula: See USP Dictionary, 1996, page 721

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20231

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Triclosan 0.3% and Sodium Fluoride 0.24%
Toothpaste
TOTAL® Toothpaste
NDA 20-231, AB
Reviewer: E.D. Bashaw, Pharm.D.
APW

Colgate-Palmolive Co.
Piscataway, NJ

Submission Date:
June 18, 1997

Review of Pharmacokinetic Studies

Background

Triclosan is a topical antimicrobial commonly used in soaps and other topical products. Colgate is pursuing approval of a dentrifice containing triclosan with a label claiming that it reduces plaque and gingivitis. From a regulatory perspective the product was found to be approvable in 1996. One of the outstanding issues from the approvable letter was the relationship between the NOEL (no effect level) of triclosan seen in a carcinogenicity study in rodents and that seen in man. From Agency experience a level of 25 fold has been generally accepted as a reasonable margin of safety. Earlier estimates of this ratio were controversial due to the lack of a true in vivo biopharmaceutics estimate of absorption in man and the lack of adequate animal data.

The majority of the in vivo pharmacokinetic data available for this application comes from a Triclosan Industry Alliance report published in the early 1990's. In Jan. 1997 the applicant submitted an additional in vivo animal trial that provided a better estimate of animal exposure with daily dosing in the animal feed. In a meeting with the applicant and the clinical division (HFD-540) the applicant was reminded by Drs. Weintraub and Wilkin that the outstanding issue was "human" exposure and that there was still a need for an in vivo biopharmaceutic study. To address this issue the applicant undertook two in vivo pharmacokinetic trials to assess the degree of human exposure following an exaggerated usage pattern and to investigate the pharmacokinetics of triclosan in children.

Study Number: 97-1563-70

Study Title: Pharmacokinetic Study of A Triclosan Dentrifice in Healthy Adult Subjects

Investigator:

Study Site:

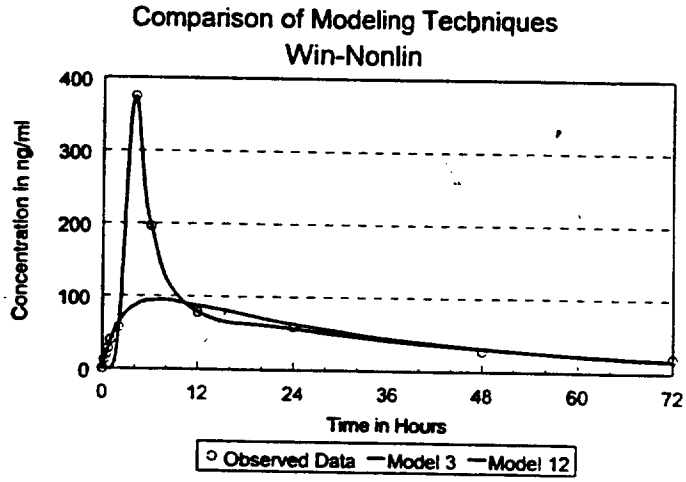
Objective: To determine the pharmacokinetics of a triclosan containing dentrifice following both single and multiple brushing administrations.

Single Dose Phase

The first phase of this trial involved the single dose administration of a 1.25gm dose of triclosan dentrifice. A total of 21 healthy adult subjects (11males, 10females) were enrolled in the trial. Upon entry into the trial all subjects were offered a breakfast consisting of bagels with cream cheese, croissants, milk and orange juice prior to dosing. All subjects were dosed with 1.25gms of dentrifice and instructed to brush without rinsing for 1 minute. At the end of this time they swallowed the "dental slurry" and rinsed their toothbrush in 100ml of distilled water. The subjects were then instructed to drink the rinse. The subjects then had timed collections of blood taken over the next 72 hours to obtain pharmacokinetic information. Attached as pages 1-7 in Appendix I are the study summary sheets, dentrifice formulation and supportive data and figures from the first phase of this study. A summary table of results is presented below:

Parameter	Mean (%CV)
AUC0-inf (ng/hr/ml)	2809 (41.7)
Cmax (ng/ml)	242.9 (35.1)
Tmax (hr)	4.0 (38.7)
Ka (1/hr)	0.765 (77.2)
Kel (1/hr)	0.0687 (41.1)
MRT (hr)	15.42

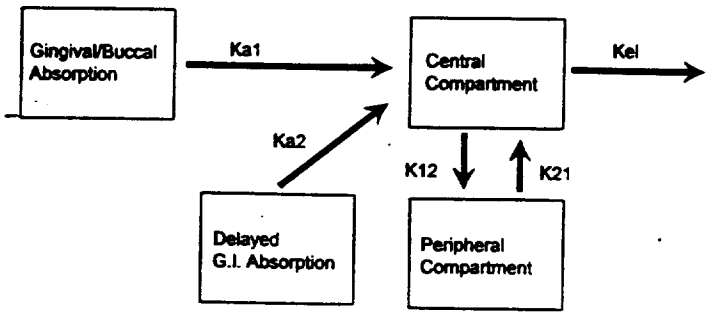
These values were obtained as part of an analysis carried out by the applicant using PC/Win-Nonlin. As part of their report the sponsor has presented the results of data fitting using model 3 (1-compartment, first order input-output). In a communication to the applicant after reviewing the draft report of this study, this reviewer informed the applicant that their analysis of the data was inadequate. Examination of the data reveals two striking features; 1., a definite two compartment characteristic to the data and 2., a complex-biphasic input. An example of the inadequacies of the model chosen by the applicant is presented graphically below for pt. #4:



Model 3, 1-Compartment, No Lag Time/Model 12, 2-Compartment, Lag Time

While the applicants analysis was initially better in providing estimates for Ka over the first hour or so, it is clear that it misses the peak and the distribution period of the drug. Model 12, the one selected by this reviewer, being a 2-compartment model, is better able to follow the distributive and elimination phases of the profiles. It appears that instead of following a simple input model, triclosan requires a more complex model such as the following to account for the pattern of absorption seen:

Proposed Pk Model For Triclsoan Toothpaste



The advantage of this model is that it allows for the input rate to change with time. It appears from examination of the data that there is initially a slow input Ka1 and, at a later point a, fast input Ka2. The clinical/pharmacokinetic significance of this model is that it can explain the relatively long Tmax values for a dosage form that contains solubilized drug. It should be noted that even though the PC/Win-Nonlin analysis was not in and of itself very useful, the pharmacokinetic parameters presented above and attached in the appendix are the result of the non-compartmental analysis module of the program. Non-compartmental analysis, by definition is unaffected by these types of concerns and as such the data is properly validated .

As for validation of the original dataset, four subjects were withdrawn from the dataset at the request of this reviewer. Two subjects were withdrawn from the analysis due to pre-dose levels (subjects 2 and 9) and an additional two subjects (#19 and 21) were be dropped from the study due to a lack of plasma samples out past 12 hours. Due to the prolonged absorption and distributional phases of triclosan the lack of plasma samples out after 12 hours tended, in this reviewers opinion to bias some of the calculated pharmacokinetic parameters (Kel, T1/2, AUC0-inf, etc.).

Using the observed AUC0-inf data and half-life, it is possible using accumulation ratio to estimate what the total AUC0-τ will be at steady-state. From the AUC and Kel collected in this trial the mean accumulation ratio is 2.73. This would provide for an total AUC0-τ of ~7700 ng/hr/ml. While this value is only a calculated value comparison of it to the value obtained at steady-state will provide some support for the claim of linear pharmacokinetics for triclosan.

Multiple Dose Phase

This phase was begun 72 hours after administration of the first dose and following the general study design principles used in the first dosing phase. Every day of the study the subjects reported to the study unit and received a toothbrush containing a weighed out portion of

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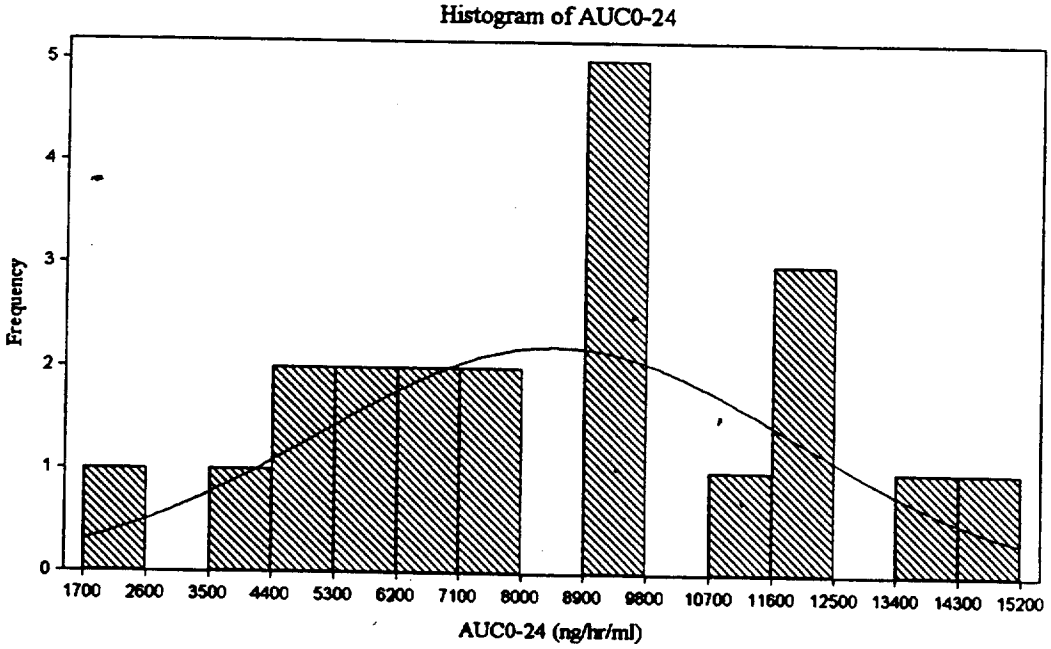
toothpaste (1.25gms). They were instructed to follow the same "dosing pattern" as they did under the single dose phase, i.e, brush for 1 minute, swallow, rinse the toothbrush, and swallow the rinse. Upon completing the morning brushing phase the subjects were given a weighed tube of toothpaste and told to brush after their mid-day meal. Upon returning to the study unit each evening, the tubes of toothpaste were weighed and the evening amount of toothpaste applied to the brush was adjusted to meet the daily dose of 3.75gms of toothpaste. This period of morning and evening supervised brushings continued for 10 days. Upon the 10th day the subjects arrived at the study unit and remained throughout the day for a day of supervised dosing and pharmacokinetic sampling. On this day each subject was "dosed" with 1.25 gms of toothpaste at 7am, 1pm, and 7pm. Attached as pages 8-12 in Appendix I are the study summary sheets and supportive data and figures from the first phase of this study. A summary table of results is presented below:

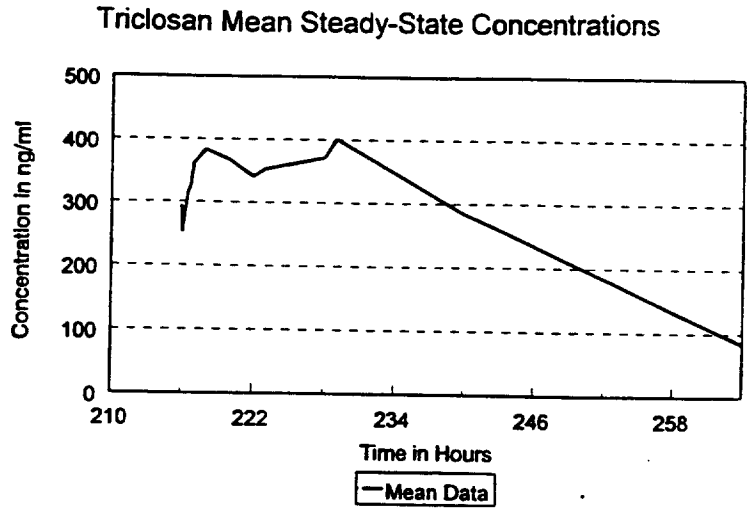
	AUC_{0-24} (ng/hr/ml)	$AUC_{0-24/3}$ (ng/hr/ml)
Mean (%CV)	8463 (40.4)	2821 (40.4)
Max		
Min		

The data from this trial is very variable showing an almost 9-fold variation between the highest and lowest AUC present in these subjects. Another way to look at the data is to plot the AUC values as a histogram with a super-imposed normal curve:



When this is done there appears to be some degree of a right shift to the data with the multiple of mean to highest being ~ 2 while the multiple of mean to lowest is ~5. This skew is

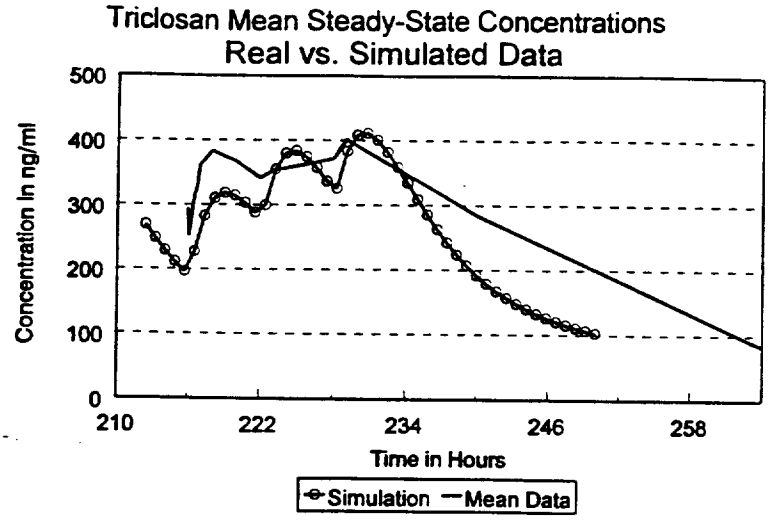
further reflected in that the median value is 9146 ng/hr/ml. Reproduced below is a plot of the mean data from this treatment interval.



From a pharmacokinetic standpoint the first issue in question is whether on not the subjects are truly at steady-state. Examination of the time 0 and 24 plasma sample concentrations indicate that the subjects were indeed at steady-state with the values being just over 3% apart (285ng/ml vs. 294ng/ml). The next issue to be resolved is whether or not the plasma sampling routine used by the applicant was sufficient to capture the peak-trough variability present in the data during a dosing interval. For this comparison, examination of the mean data curve is mis-leading as it, by definition, is a "smoothed" average of all data points at all times. Attached as Fig. 3, page 9 in Appendix I is a spaghetti plot of the data from this trial. By plotting all subjects on one graph the true nature of the variability which is not captured by the mean data is revealed. In general one can see both a tendency for the plasma concentrations to rise with time out until 16hrs or so and one can even see some trace of peak-trough cycling caused by repeat dosing over the observation interval. While additional samples are always desirable, it appears that sufficient sampling was done to obtain a reasonable estimate of the total AUC at steady-state.

Further supportive evidence of the adequacy of the sampling interval comes from the AUC0-inf value calculated from the single dose phase of the trial. Under single dose conditions an AUC0-inf value of 2809 ng/hr/ml was obtained. This value is almost identical to the split AUC0-24 value of 2821 ng/hr/ml and is further assurance of the adequacy of the plasma sampling and resultant AUC values.

As a further and final check on the adequacies of the determination of steady-state AUC for triclosan, a pharmacokinetic simulation of the data was prepared. This simulation was prepared using Win-Nonlin v1.1 and was based on the results of the single dose adult data. This information was used to produce a single dose simulation that was then adapted to mimic steady-state through the simulation of 30 dosing intervals. Each dosing interval consisted of 3.75mg of triclosan and followed the same dosing interval that was done for steady-state dosing. A comparison between the simulated data and the mean steady-state plasma level time curve is presented below:



Although obviously needing further refinement, the simulation does demonstrate that the general pattern of the data is appropriate and that the single dose data is acceptable for extrapolation purposes.

Calculation of Carcinogenicity Interval

Using the mean AUCss data from this trial the applicant obtained an carcinogenicity multiple of 58. This was done by dividing the mean AUC seen from this trial into the AUC for the no effect limit (NOEL) in mice:

AUC(mice)/AUC(man)(11.25mg exposure) = 489,200 / 8,463 = 57.8

A more conservative way, and the way preferred by this reviewer is to use the median AUC value as it is more reflective of the distribution of AUC values seen:

AUC(mice)/AUC(man)(11.25mg exposure) = 489,200 / 9,146 = 53.5

Finally, one could also calculate the extremes of the AUC values to obtain the range of ratios present:

AUC(mice)/AUC_{MAX}(man)(11.25mg exposure) = 489,200 / 15,050 = 32.5

AUC(mice)/AUC_{MIN}(man)(11.25mg exposure) = 489,200 / 1,785 = 274

Clearly the results of this trial indicate that under exaggerated dosing conditions, using large doses, more frequently than recommended by the American Dental Association, with swallowing all of the toothpaste and the resulting rinses from the toothbrush, the ratio between the amount absorbed in man under these conditions, relative to the NOEL in mice is, under worst case scenarios equal to 32.5 which is in excess of the minimum allowable 25:1 ratio. Using a more reasonable median absorption approach the resulting ratio was 53.5:1, more than double the

allowed ratio. Given that the dosing conditions which produced these ratios is very unrealistic, it is most likely that the true ratio in the general population will be much higher.

The primary purpose of the first study was to provide an in vivo assessment of the degree of accumulation of triclosan following exaggerated usage and to calculate the carcinogenicity ratio. The second study contained in this submission was a single dose administration of an oral solution of triclosan to children. The study itself was not designed to be used to calculate AUC ratios but instead to evaluate whether or not there was a significant difference between children and adults in terms of the elimination of and therefore the accumulation of triclosan.

Study Number: 97-1564-70

Study Title: Pharmacokinetic Study of A Triclosan Solution in Healthy Children 8 to 12 years of Age

Investigator:

Study Site:

Objective: The objective of this trial was to assess the disposition and the elimination of triclosan from children (8-12yrs old) relative to adults.

This study was designed as a single dose study in sixteen (8M/8F) healthy children between the ages of 8 and 12 years old. Sixteen subjects out of a pool of 30 were enrolled in the trial, fourteen showed up for dosing and of these 11subjects actually completed the trial. On the day of the study each subject consumed a light breakfast consisting of bagels with cream cheese, donuts, milk and orange juice. Following breakfast each subject received a single oral dose of 30ml of 0.03% triclosan solution (3mg) followed by 100ml of water. The subjects were then confined to the study unit for the next 12 hours while pharmacokinetic measurements were taken. After the 12 hour sample was drawn the subjects were allowed to go home. They were instructed to return the next 3 days for 24, 48, and a 72 hour sample. Attached as pages 13-20 in Appendix I are the study summary sheets, dentrifice formulation and supportive data and figures from the first phase of this study. A summary table of results is presented below:

	AUC_{0-24} (ng/hr/ml)	AUC_{0-inf} (ng/hr/ml)	Cmax (ng/ml)	Tmax (hr)	Kel (1/hr)	T1/2 (hr)	MRT (hr)
Mean (%CV)	4571 (45)	6545 (37.9)	495.9 (33.2)	1.8 (101.8)	0.0453 (31.6)	16.8 (33.3)	19.3 (24.2)
Max							
Min							

In reviewing the information present in the trial a number of minor calculation errors were noted by this reviewer in the supportive information. The most glaring example of these was the inclusion of a mean residence time of over 5000 hours for one of the subjects (see page

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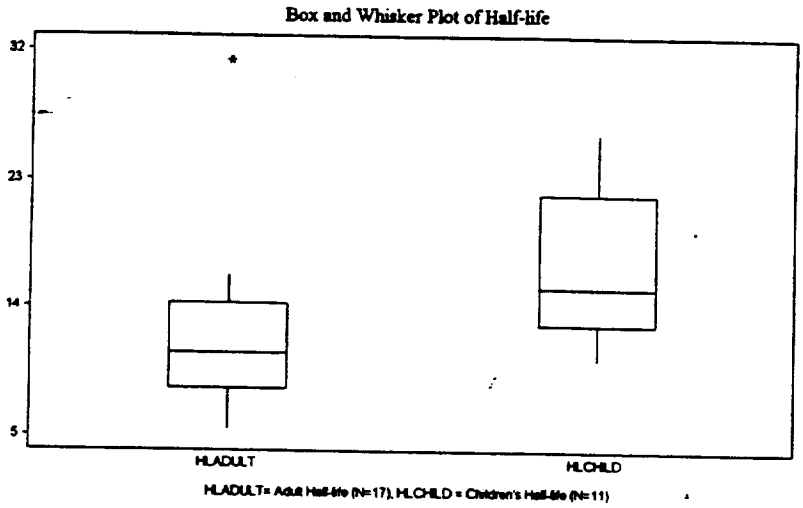
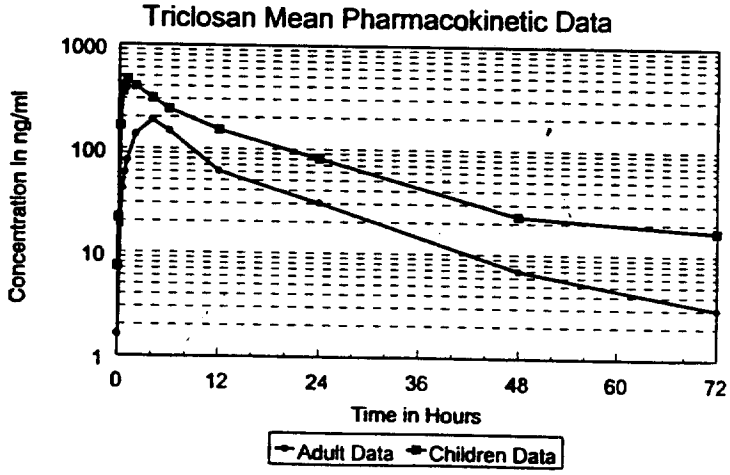
18-20, Appendix I). After looking at the raw data it appears that this value was the result of a transcription error on the applicants part. In addition during the conduct of this trial there was a communication from the sponsor indicating that three subjects dropped out of the trial due to problems encountered in the early portion of the trial. The study report makes no mention of this beyond indicating that 14 showed up for the study and 11 were enrolled. The applicant needs to properly account for all of the subjects that were eligible for this trial.

As to the comparability of the data between adults and children, if one looks at the distribution between adults and children in regards to half-life, one can see that children appear to have a longer and more variable half-life.



Whether or not this is a true difference or is a reflection of the small numbers of subjects is an open question. The problem with cross study comparisons of this kind is that very few of the pharmacokinetic parameters in question are independent of either weight or surface area. This and the fact that the absorption rate between the two dosage forms are markedly different suggests that any type of comparison can only be qualitative and not quantitative in nature. Reproduced below is a plot of the mean plasma level time curves for adults and children.



Adult Data = 3.75mg as toothpaste, Children Data = 3.0mg as solution

While not conclusive, the general appearance of the two curves suggests that there is not a marked dispositional or elimination rate difference between adults and children. This is a somewhat speculative conclusion without much supporting data. But as the objective of this trial was comparability and not bioequivalence, it is probably all that one can say.

Conclusions

The applicant has adequately demonstrated that upon repeat dosing with an exaggerated dosing scheme, the ratio of the no effect level in animals to human exposure is in excess of the FDA standard 25:1 ratio. As for the comparability of pharmacokinetics between healthy adults and children the applicant has demonstrated in a qualitative sense that the rate of elimination between adults and children is essentially the same.

Recommendation

From a pharmacokinetic standpoint the applicant has adequately assessed the absorption of triclosan from an exaggerated dosing scheme. The resulting exposure level is well above that recommended by the FDA carcinogenicity advisory committee. As to the comparability of the results from the study in children to adults, the general pattern of disposition and elimination appears to be similar between the two groups, however, differences in the formulation and in the dosing pattern limit the utility of this finding. These findings should be forwarded to the reviewing medical officer and pharmacologist for comment.

E. Dennis Bashaw, Pharm.D.
Senior Pharmacokineticist (HFD-550)
Division of Pharmaceutical Evaluation-III

for Secondary Review, John Lazor, Pharm.D.

CC: NDA 20-231 (ORIG),
HFD-540/DIV File
HFD-540/CSO/Blattt
HFD-880(Bashaw)
HFD-880(Lazor)
CDR. ATTN: B. Murphy
HFD-344(Viswanathan)

Appendix I

Study #	Short Summary Title	Page #
97-1563-70	Single Dose-Adults	1
97-1563-70	Multiple Dose-Adults	8
97-1564-70	Single Dose-Children	13

NDA/IND # 20-231 Suppl/Amend. # _____ Submission Date: 6/5/97 Volume: _____
Study Type: _____ Study #
Study Title: Pharmacokinetic Study of a Triclosan Dentifrice in Healthy Adult Subjects

Clinical Investigator
Site

Analytical Investigator
Site

Single Dose: Y Multiple Dose: _____ Washout Period: _____
Cross-Over N Parallel _____ Other Design _____
Fasted N Food Study N FDA High Fat Breakfast N
If fasted, how long (hrs.)? N/A

Normal Y Patients _____ Young Y Elderly _____ Renal _____ Hepatic _____

Subject Type				Male	Group	Healthy	N=	21	M=	11	F= 10
Weight	Mean	209.5	Range		Group		N=		M=		F=
Age	Mean	33.2	Range		Group		N=		M=		F=
Subject Type					Group		N=		M=		F=
Weight	Mean	165.6	Range		Group		N=		M=		F=
Age	Mean	28.5	Range		Group		N=		M=		F=

Treatment Group	Dose	Dosage Form	Strength	Lot #	Lot Size
Healthy	1.25g	Dentifrice	0.3%	LD 96482	200 Kilograms

Sampling Times

Plasma 0, 0.08, 0.25, 0.50, 0.75, 1.0, 2.0, 4.0, 6.0, 12.0, 24.0, 48.0, 72.0 hr

Urine None

Feces None

Assay Method _____

Assay Sensitivity Limit of Quantification Target: 10.0 ~~mg~~ ng/ml, Observed: 10.3 ~~mg~~ ng/ml, % CV=1.6%

Assay Accuracy QC Target/Observed/% CV: 30.1/29.5/9.5%; 251.1/251.4/10.4%; 1406.3/1419.8/6.4%

Labeling Claims From Study _____

1. The composition, and manufacturing range for the drug product, Colgate Total (triclosan 0.30%, sodium fluoride USP 0.24%) Toothpaste, formula is :

Components	Weight Percent	Manufacturing Range
Triclosan (Irgacare MP)	0.300	——
Sodium Fluoride USP	0.243	——
Deionized Water		
Dental Type Silica NF		
Glycerine USP		
Sorbitol, Non-Crystallizing		
Poly (methyl vinyl ether/maleic acid)		
Sodium Lauryl Sulfate NF		
Flavor		
Sodium Hydroxide FCC		
Propylene Glycol USP		
Titanium Dioxide USP		
Carrageenan FCC		
Saccharin Sodium USP		
Total		

2. The composition of 0.01% triclosan solution (0.1 mg/ml) is:

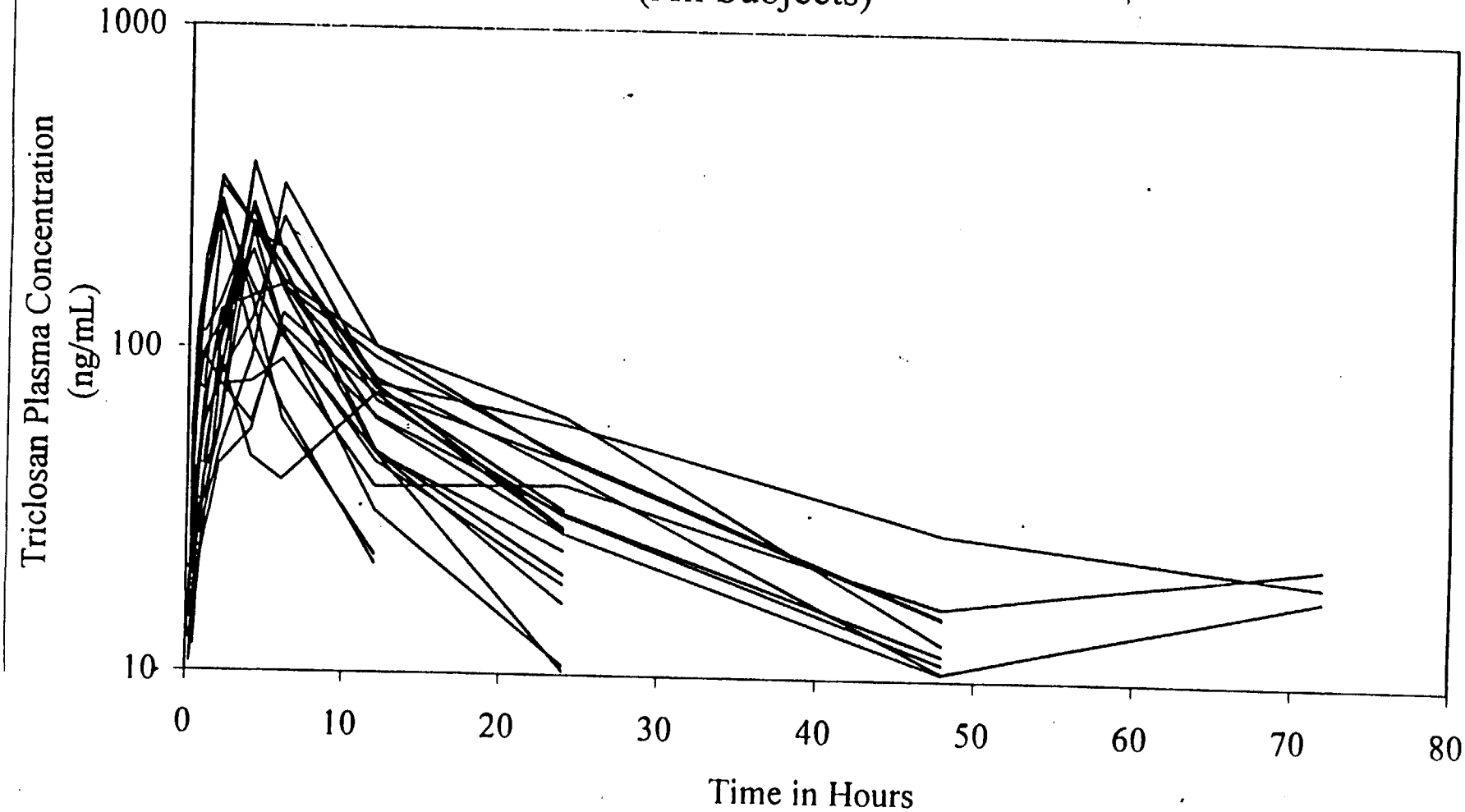
6.3 **Demographics** (Continued)

Twenty-one subjects (11 males and 10 females) entered and completed the study.

The demographics are presented below:

Subject No.	Subject Initials	Sex	Age	Race	Height (in.)	Weight (lbs.)
001	KAF	F	41	White	64.0	265.5
002	BAL	M	20	White	72.0	269.5
003	HWS	M	37	White	71.0	190.0
004	JAG	F	23	White	64.0	115.0
005	JDH	F	22	White	65.0	117.5
006	TDW	F	34	White	65.0	228.0
007	MAW	M	32	White	66.0	249.0
008	DIM	M	32	White	68.0	280.0
009	DCP	M	22	White	71.0	250.0
010	RAH	M	50	White	67.0	192.0
011	P-H	F	43	White	64.5	202.0
012	JFH	M	60	White	71.0	179.5
013	JLH	M	20	White	67.0	161.0
014	MLJ	F	19	White	63.0	141.0
015	MRJ	F	20	White	61.0	119.0
016	ALV	F	24	White	63.0	117.5
017	RMG	M	21	White	74.0	181.5
018	RDM	M	22	White	73.0	188.0
019	ESD	F	34	White	65.0	201.0
020	M-T	M	49	White	56.0	164.5
021	JRJ	F	25	White	68.0	149.0

Figure A-1: Triclosan Plasma Concentration-Time Profiles Following a Single Oral Administration of Triclosan-Containing Dentifrice (All Subjects)



BEST POSSIBLE COPY

Table 1: Triclosan Plasma Concentrations Following a Single Oral Administration of Triclosan-Containing Dentifrice

Subject	Time (hr)												
	0.0	0.08	0.25	0.50	0.75	1.0	2.0	4.0	6.0	12.0	24.0	48.0	72.0
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													
13													
14													
15													
16													
17													
18													
19													
20													
21													
Mean	1.63	1.60	17.9	40.8	58.4	76.1	136.0	188.5	148.5	61.5	30.5	6.85	2.96
SD	5.36	5.22	15.6	27.6	37.0	49.7	94.0	99.3	65.5	23.6	17.0	8.20	7.46
CV%	327.9	326.6	86.8	67.7	63.4	65.3	69.1	52.7	44.1	38.4	55.7	119.8	252.3

Plasma data that were below the limit of quantitation were expressed as 0.0.; NS = No sample.

Figure A-2: Mean Triclosan Plasma Concentration-Time Profile Following a Single Oral Adminitraion of Triclosan-Containing Dentifrice

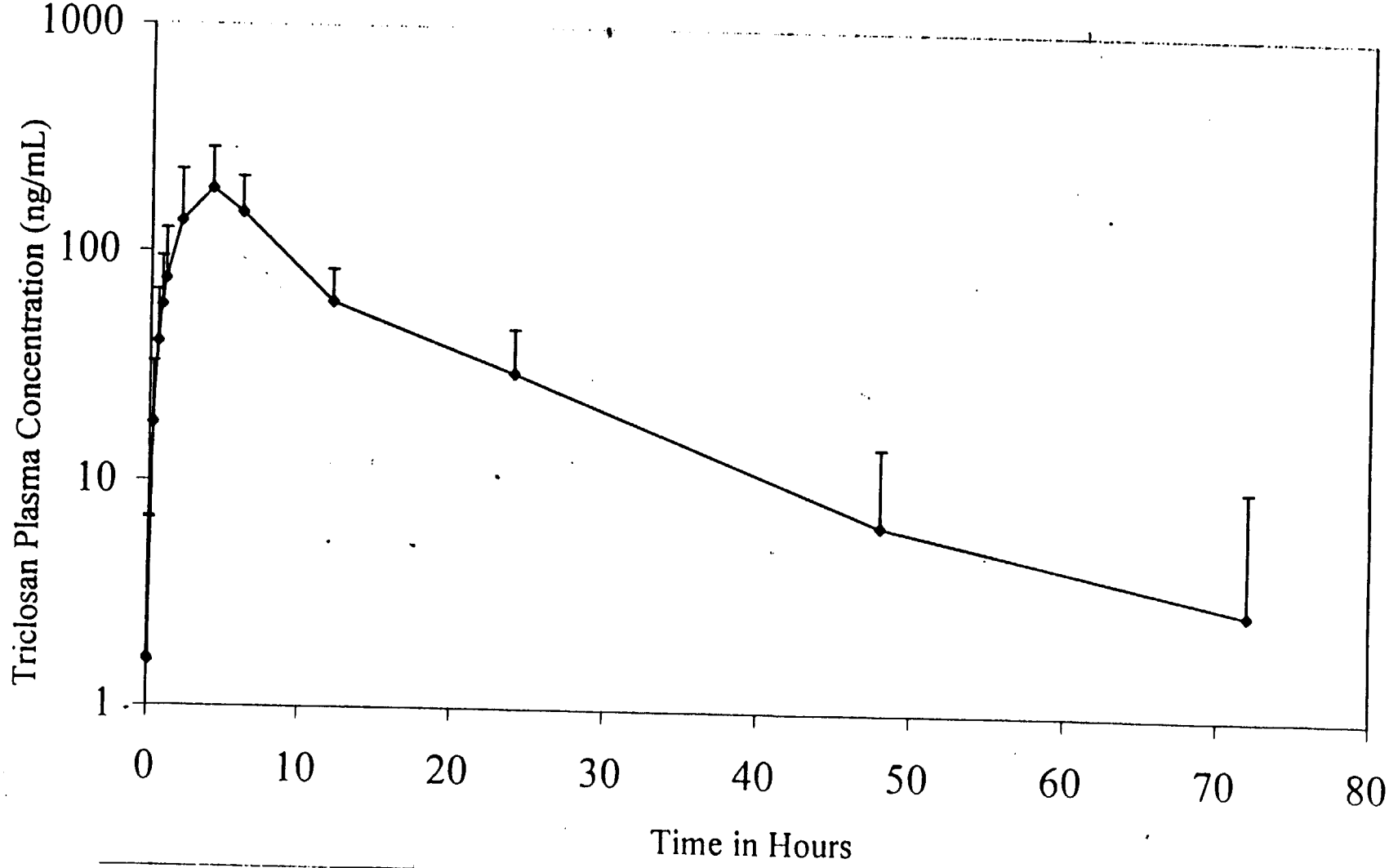


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Table 2: Triclosan Plasma Pharmacokinetic Parameters Following a Single Oral Administration of Triclosan-Containing Dentifrice

Subject	t_{max} (hr)	C_{max} (ng/mL)	K_a (1/hr)	K_{el} (1/hr)	$t_{1/2}$ (hr)	AUC_{0-inf} (ng/h/mL)	MRT (hr)	R
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								
21								
Mean	4.0	242.9	0.765	0.0687	12.1	2809	15.42	2.73
SD	1.5	85.4	0.591	0.0283	6.2	1171		
CV%	38.7	35.1	77.2	41.1	51.2	41.7		

• = Parameter Not Estimated;

t_{max} = Observed time to reach peak concentrations;
C_{max} = Observed peak plasma concentration; K_a = Absorption rate constant;
K_{el} = Elimination rate constant, $t_{1/2}$ = Terminal elimination half-life;
AUC_{0-inf} = Area under the plasma concentration-time profile from zero to infinity;
* = K_{el} and $t_{1/2}$ for subjects 2, 9, 19 and 21 were excluded from calculations;

NDA/IND # 20-231 Suppl/Amend. # _____ Submission Date: 6/5/97 Volume: _____
Study Type: _____ Study # 97-1563-70
Study Title: Pharmacokinetic Study of a Triclosan Dentifrice in Healthy Adult Subjects

Clinical Investigator _
Site _____
_____
_____

Analytical Investigato
Site
_____

Single Dose: _____ Multiple Dose: Y Washout Period: 3 Days
Cross-Over N Parallel _____ Other Design _____
Fasted N Food Study N FDA High Fat Breakfast N
If fasted, how long (hrs.)? N/A

Normal Y Patients _____ Young Y Elderly _____ Renal _____ Hepatic _____

	Subject Type		Male		Group	Healthy	N=	21	M=	11	F=	10
Weight	Mean	209.5	Range		Group		N=		M=		F=	
Age	Mean	33.2	Range		Group		N=		M=		F=	
	Subject Type				Group		N=		M=		F=	
Weight	Mean	165.6	Range		Group		N=		M=		F=	
Age	Mean	28.5	Range		Group		N=		M=		F=	

Treatment Group	Dose	Dosage Form	Strength	Lot #	Lot Size
Healthy	3.75g	Dentifrice	0.3%	LD 96482	200 Kilograms

Sampling Times

Plasma 0, 0.08, 0.25, 0.5, 0.75, 1.0, 2.0, 4.0, 6.0, 7.0, 12hr, 13hr, 24hr, 48hr

Urine None

Feces None

Assay Method: _____

Assay Sensitivity Limit of Quantification Target: 10.0 ~~mg~~ ng/ml, Observed: 10.1 ~~mg~~ ng/ml, % CV=3.5%

Assay Accuracy QC Target/Observed/% CV: 30.1/30.1/6.7%, 251.1/276.4/2.3%, 1406.3/1509.1/6.3%

Labeling Claims From Study _____

Figure A-3: Triclosan Plasma Concentration-Time Profiles at Steady-State Following TID Administration of Triclosan-Containing Dentifrice (All Subjects)

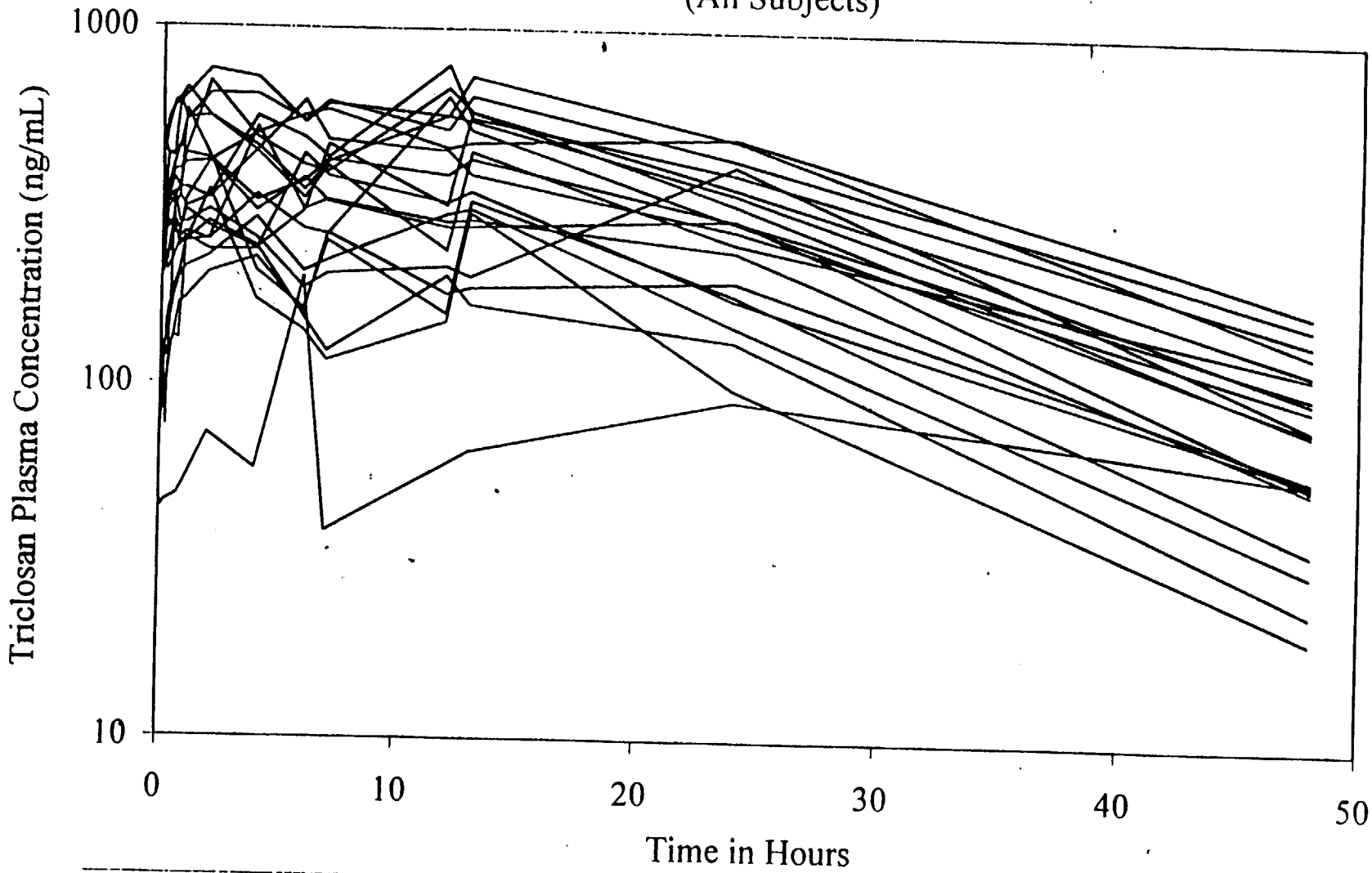

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Table 3: Triclosan Plasma Concentration at Steady-State Following TID Administration of Triclosan-Containing Dentifrice

Subject	Time (hr)													
	0.0	0.08	0.25	0.50	0.75	1.0	2.0	4.0	6.0	7.0	12.0	13.0	24.0	48.0
1														
2														
3														
4														
5														
6														
7														
8														
9														
10														
11														
12														
13														
14														
15														
16														
17														
18														
19														
20														
21														
Mean	294.4	251.8	273.4	312.3	326.9	361.1	384.0	367.8	341.6	353.1	371.8	401.7	285.1	84.1
SD	160.4	129.2	140.5	143.3	160.0	164.8	178.2	170.9	153.2	162.9	199.2	176.4	123.9	43.5
CV%	54.5	51.3	51.4	45.9	49.0	45.6	46.4	46.5	44.8	46.2	53.6	43.9	43.5	51.7

Figure A-4: Mean Triclosan Plasma Concentration-Time Profile at Steady-State Following TID Administration of Triclosan-Containing Dentifrice

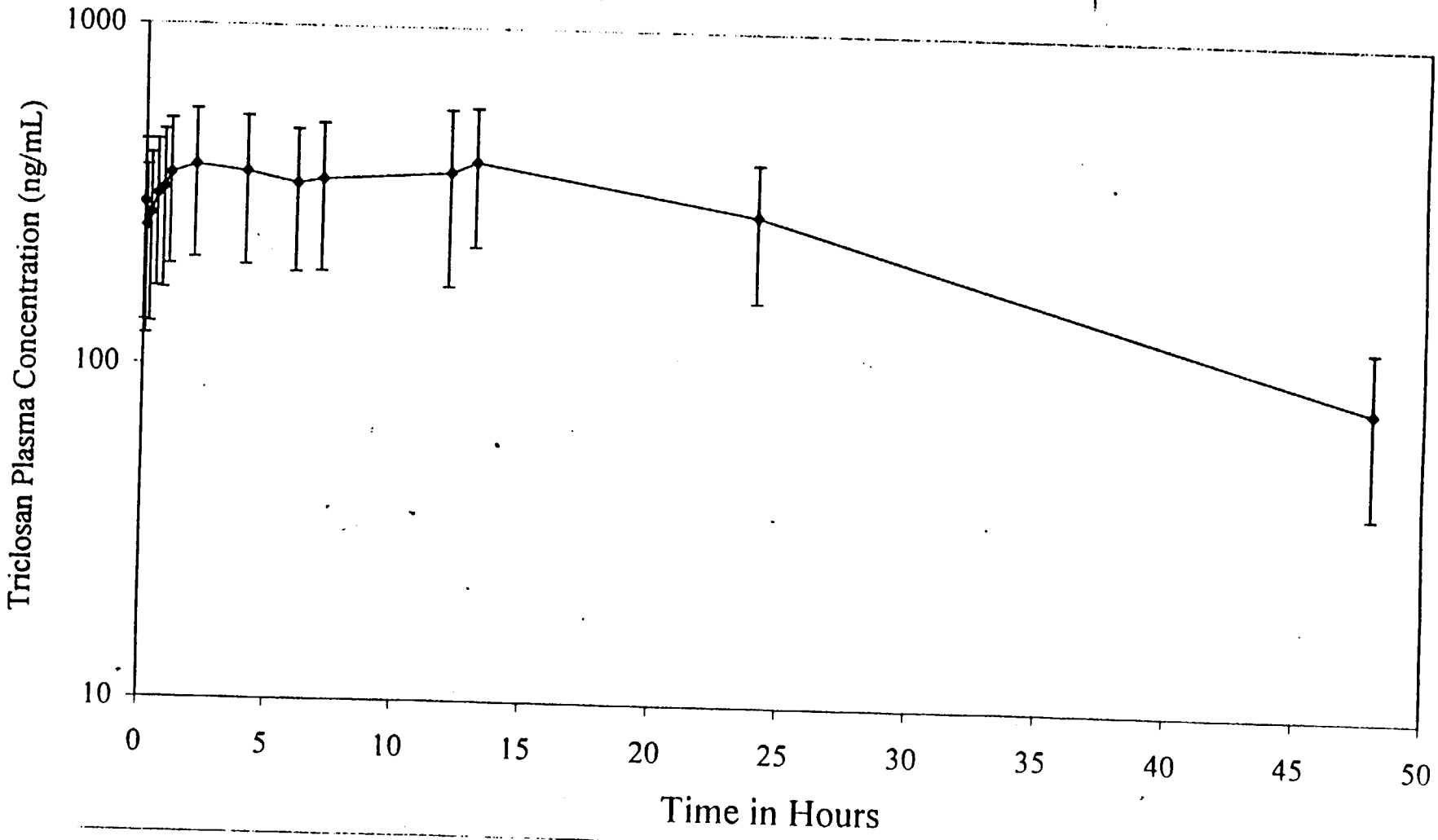

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Table 4: Triclosan Plasma Pharmacokinetic Parameters at Steady-State Following TID Administration of Triclosan-Containing Dentifrice

Subject	AUC_{24} (ng/hr/mL)	$AUC_{24}/3$ (ng/hr/mL)
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
Mean	8463	2821
SD	.3415	1138
CV%	40.4	40.4

AUC_{24}. Area under the concentration-time curve from 0 to 24 hours
$AUC_{24}/3$, AUC_{24} normalized for 3 doses administered during the 24-hour dosing period

NDA/IND # 20-231 Suppl/Amend. # _____ Submission Date: 6/5/97 Volume: _____
Study Type: _____ Study # 97-1564-70
Study Title: Pharmacokinetic Study of a Triclosan Solution in Healthy Children 8 to 12 Years of Age

Clinical Investigator _____ Analytical Investigator _____
Site _____ Site _____

Single Dose: Y Multiple Dose: _____ Washout Period: _____
Cross-Over N Parallel _____ Other Design _____
Fasted N Food Study N FDA High Fat Breakfast N
If fasted, how long (hrs.)? N/A

Normal Y Patients _____ Young Y Elderly _____ Renal _____ Hepatic _____

Subject Type				Male	Group	Healthy	N=	11	M=	7	F=	4
Weight	Mean	98.7	Range		Group		N=		M=		F=	
Age	Mean	10.7	Range		Group		N=		M=		F=	
Subject Type					Group		N=		M=		F=	
Weight	Mean	67	Range		Group		N=		M=		F=	
Age	Mean	8.5	Range		Group		N=		M=		F=	
					Group		N=		M=		F=	

Treatment Group	Dose	Dosage Form	Strength	Lot #	Lot Size
Healthy	30ml	Aqueous Solution	0.01%	1631-80	10 Kilograms

Sampling Times

Plasma 0, 0.08, 0.25, 0.50, 0.75, 1.0hr, 2.0, 4.0, 6.0hr, 12.0, 24.0, 48.0, 72.0

Urine None

Feces None

Assay Method: _____

Assay Sensitivity Limit of Quantification Target: 10.0 mg/ml, Observed: 10.4 mg/ml, % CV=3.6%

Assay Accuracy QC Target/Observed/% CV: 30.1/29.2/7.9%, 251.1/244.9/8.7%, 1406.3/1426.2/5.1

Labeling Claims From Study _____

6.3 **Demographics** (Continued)

The demographics are presented below:

Subject No.	Subject Initials	Sex	Age	Race	Height (in.)	Weight (lbs.)
101		M	12	African American/ White	60.5	94.0
102		M	11	African American	62.5	122.5
103		F	9	White	57.5	82.0
104		F	8	White	50.0	51.0
105		F	9	White	51.5	61.5
106		M	11	White	60.5	124.5
107		M	10	White	57.5	109.0
108		F	8	White	53.5	73.5
109		M	11	White	54.0	77.0
110		M	12	White	65.0	101.0
111		M	8	White	53.5	63.0

7.0 STUDY SCHEDULE

Screening: May 1, 1997
Initiation of Treatment: May 3, 1997
Completion of Blood Collection: May 6, 1997

Ju
P:

Table 1: Triclosan Plasma Concentrations in Healthy Children (8 to 12 Years of Age) Following a Single Oral Ingestion of a 30 mL Aqueous Solution of Triclosan (0.01%)

Subject	Time (hr)												
	0.0	0.08	0.25	0.5	0.75	1.0	2.0	4.0	6.0	12.0	24.0	48.0	72.0
101*													
102*													
103													
104													
105													
106													
107													
108													
109													
110													
111													
Mean	6.6	19.3	158.7	338.0	374.6	441.9	401.2	308.2	250.5	168.0	93.2	46.0	31.8
SD	11.7	31.9	78.7	136.7	127.2	155.5	159.7	200.7	188.1	87.6	42.4	72.8	71.6
CV%	-178.0	166.1	49.6	40.4	34.0	35.2	39.8	65.1	75.1	52.1	45.4	158.5	225.1

*Plasma data of subjects number 101 and 102 were excluded from calculations
†Plasma data there were below the limit of quantitation are expressed as 0.0
NR=not reportable

Figure C-1: Triclosan Plasma Concentration-Time Profiles Following a Single Oral Ingestion of 30 mL 0.01% Aqueous Solution (All Children)

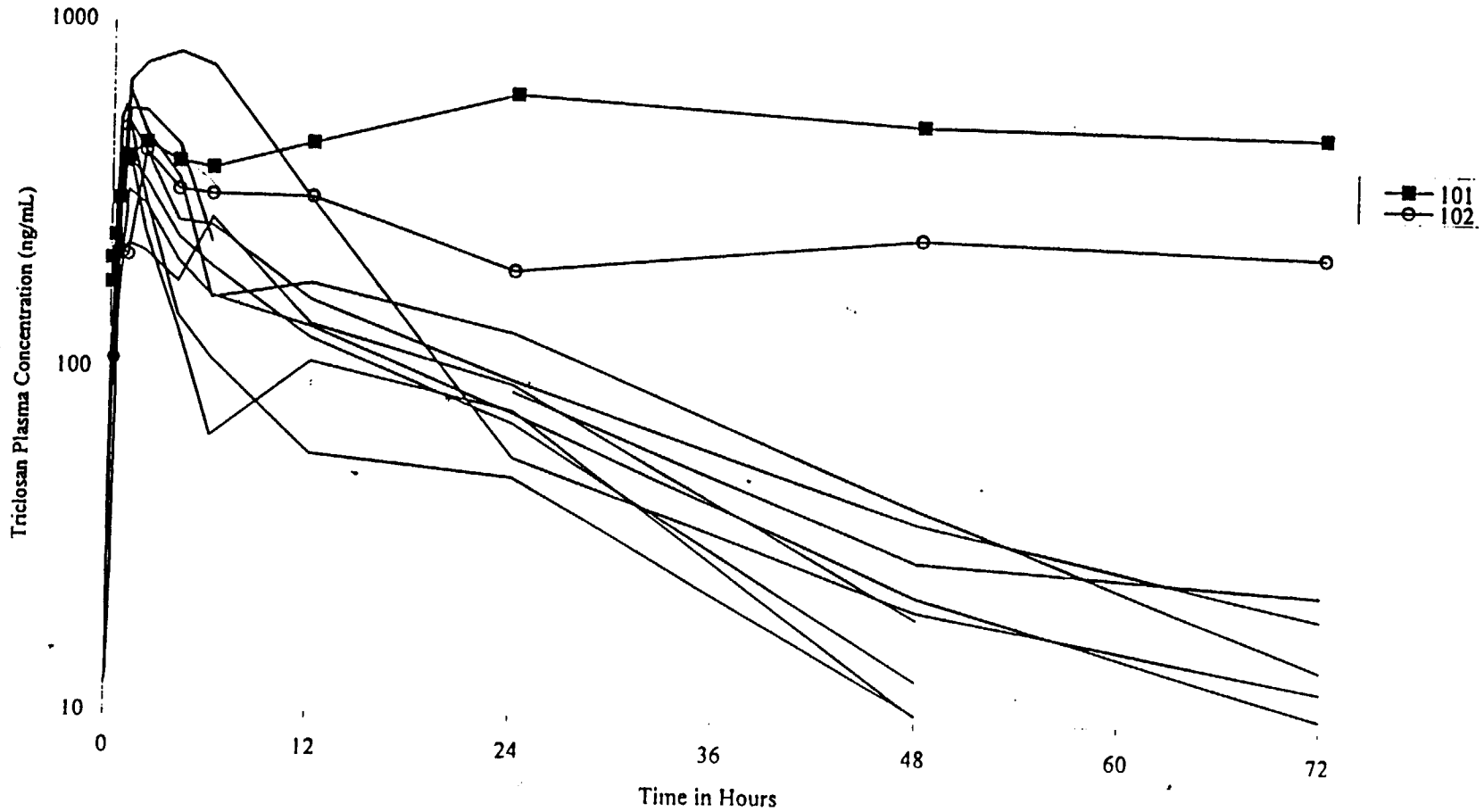

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Figure C-2: Mean Triclosan Plasma Concentration-Time Profile in Children Following a Single Oral Ingestion of 30 mL Aqueous Solution (0.01%)

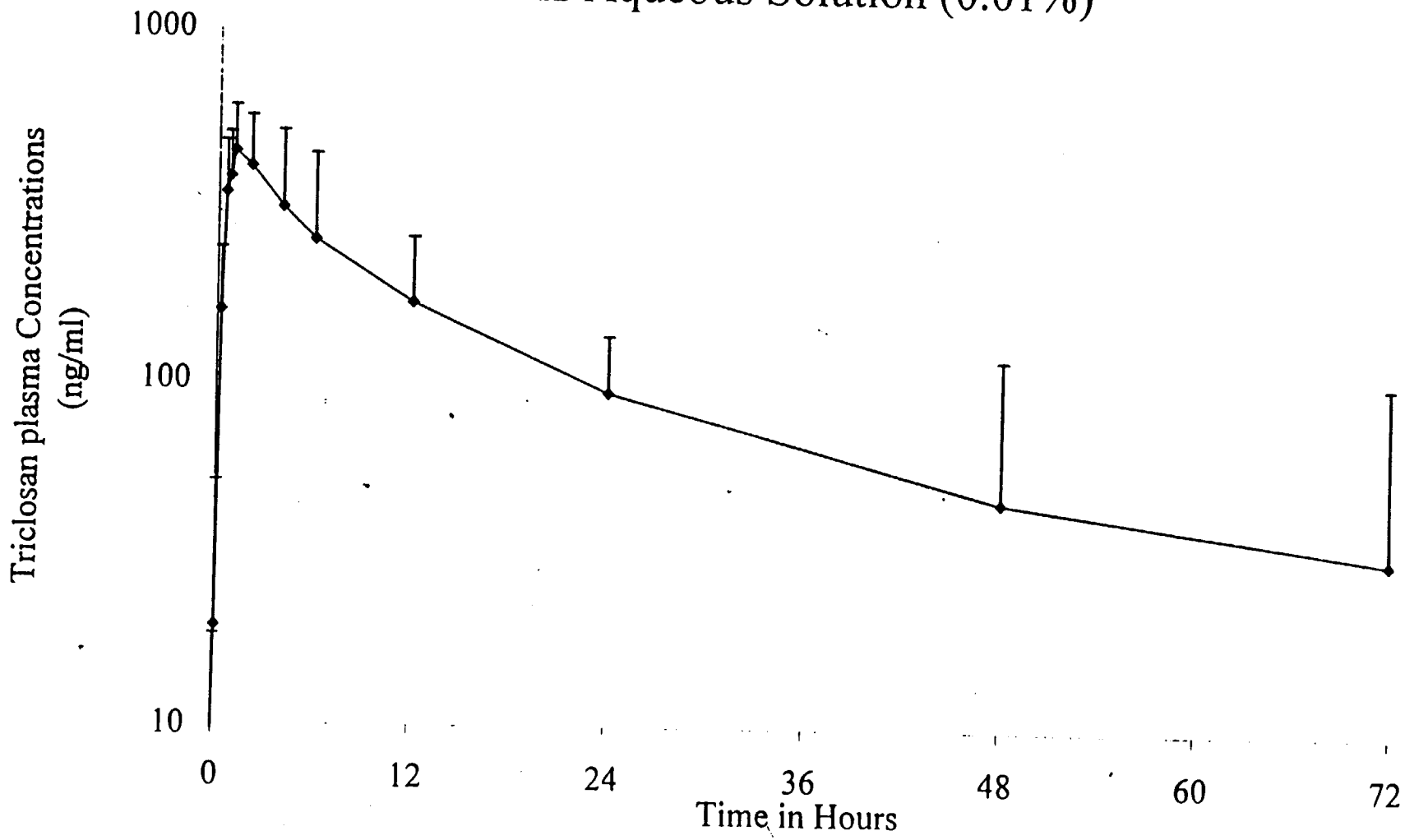

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Table 2: Triclosan Plasma Pharmacokinetic Parameters in Healthy Children (8 to 12 Years of Age) Following a Single Oral Ingestion of a 30 mL Aqueous Solution of Triclosan (0.01%)

Pharmacokinetic Parameters

Subject	t_{max} (hr)	C_{max} (ng/ml)	K_{el} (1/hr)	$t_{1/2}$ (hr)	MRT (hr)	AUC (ng/hr/mL) 0-24	AUC (ng/hr/mL) 0-inf
103							
104							
105							
106							
107							
108							
109							
110							
111							
Mean	1.8	495.9	0.0453	16.8	19.3	4571	6545
SD	1.9	164.7	0.0143	5.6	4.7	2058	2482
CV (%)	101.8	33.2	31.6	33.3	24.2	45.0	37.9

C_{max} = Observed peak plasma concentration
t_{max} = Observed Time to reach C_{max}
K_{el} = Elimination rate constant
$t_{1/2}$ = Terminal elimination half-life
MRT = Mean residence time
AUC_{0-24} = Area under the plasma concentration-time curve from 0 to 24 hours
AUC_{0-inf} = Area under the plasma concentration-time curve from 0 to infinity

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Start Time: 07:24:16 06-04-1997
End Time: 07:24:17 06-04-1997

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM (V01.2)
Core Version 26Jun96

Listing of input commands

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MODEL 200
NVARIABLES 22
NPOINTS 100
XNUMBER 9
YNUMBER 10
NCONSTANTS 1
CONSTANTS 3.75
METHOD 2  'Linear trapezoidal
BTIME 24,72
MISSING 'Missing'
NOBSERVATIONS 12
DATA 'WINNLIN.DAT'
BEGIN
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APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

WINNONLIN NONCOMPARTMENTAL ANALYSIS PROGRAM

Noncompartmental Analysis for Extravascular Administration

Linear Trapezoidal Rule Used to Compute AUC, AUMC

X		Y	Pred.	Res.	AUC	AUMC	WEIGHT
.0000		33.30			.0000	.0000	1.000
.8000E-01		90.60			4.956	.2899	1.000
.2500		217.5			31.14	5.528	1.000
.5000		435.0			112.7	39.51	1.000
.7500		314.7			206.4	96.20	1.000
1.000		551.3			314.7	194.6	1.000
2.000		546.3			863.5	1017.	1.000
4.000		437.8			1848.	3860.	1.000
6.000		230.3			2516.	6993.	1.000
24.00	*	87.70	75.25	12.45	5378.	.3837E+05	1.000
48.00	*	29.40	39.93	-10.53	6783.	.8056E+05	1.000
72.00	*	24.70	21.19	3.507	7432.	.1188E+06	1.000

*) Starred values were included in estimation of Lambda_z.

Dosing_time	.0000
Rsq	.8509
Rsq(adjusted)	.7018
Corr(x:y)	-.9224
Tlag	.0000
Tmax	1.0000
Cmax	551.3000
No._points_Lambda_z	3
Tlast	72.0000
Clast	24.7000
AUClast	7432.0695
Lambda_z	.0264
Lambda_z_lower	24.0000
Lambda_z_upper	72.0000
t1/2_Lambda_z	26.2573
AUCall	7432.0695
AUCINF(observed)	8367.7356
AUCINF(observed)/D	2231.3962
AUC_%Extrap(obs.)	11.1818
Vz(observed)/F	.0170
Cl(observed)/F	.0004
AUCINF(predicted)	8234.8940
AUCINF(predicted)/D	2195.9717
AUC_%Extrap(pred.)	9.7491
Vz(predicted)/F	.0173
Cl(predicted)/F	.0005
AUMClast	118839.9685
AUMCINF(observed)	221652.1032
AUMC_%Extrap(obs.)	46.3845
AUMCINF(predicted)	207055.2983
AUMC_%Extrap(pred.)	42.6047
MRTlast	15.9902
MRTINF(observed)	26.4889
MRTINF(predicted)	25.1437

NORMAL ENDING

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20231

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-231 SUPPL # _____

Trade Name TOTAL TOOTHPASTE Generic Name NaF/TRICLOSAN DENTIFRICE

Applicant Name COLGATE HFD- 540

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   N/A

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   N/A

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II **FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 16-985 Gleem II Dentifrice (NaF)

NDA # 17-042 FLUORINE-18 (NaF)

NDA # 16-486 P-300 Antibacterial Deodorant (Triclosan)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

NOT APPLICABLE

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /✓/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 90-TR1-0005

Investigation #2, Study # 90-TR1-0006

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

Investigation #3 YES /___/ NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

Investigation #3 YES /___/ NO /✓/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # SAME AS 2(c)

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /✓/ ! NO /___/ Explain: _____

Investigation #2

IND # YES /✓/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? NOT APPLICABLE

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

Signature Harold Blatt
Title: PROJECT MANAGER

Date JULY 8, 1997

Signature of Division Director

Date 7/10/97

cc: Original NDA Division File HFD-85 Mary Ann Holovac

US005288480A

United States Patent [19]

Gaffar et al.

[11] Patent Number: 5,288,480

[45] Date of Patent: * Feb. 22, 1994

[54] ANTIPLAQUE ANTIBACTERIAL ORAL COMPOSITION

[75] Inventors: Abdul Gaffar, Princeton; Nuran Nabi, Brunswick; John Afflitto, Brookside, all of N.J.; Orum Stringer, Yardley, Pa.

[73] Assignee: Colgate-Palmolive Co., New York, N.Y.

[*] Notice: The portion of the term of this patent subsequent to Jul. 16, 2008 has been disclaimed.

[21] Appl. No.: 964,247

[22] Filed: Oct. 21, 1992

Related U.S. Application Data

[60] Division of Ser. No. 655,571, Feb. 19, 1991, Pat. No. 5,178,851, which is a continuation of Ser. No. 398,566, Aug. 25, 1989, Pat. No. 5,032,386, which is a continuation-in-part of Ser. No. 291,712, Dec. 29, 1988, Pat. No. 4,894,220, and a continuation-in-part of Ser. No. 346,258, May 1, 1989, Pat. No. 5,043,154, which is a continuation of Ser. No. 8,901, Jan. 30, 1987, abandoned.

[51] Int. Cl.[5] A61K 7/16; A61K 7/18

[52] U.S. Cl. 424/52; 424/49

[58] Field of Search 424/49–58

[56] References Cited

U.S. PATENT DOCUMENTS

3,629,477	12/1971	Model et al.	424/340
4,022,880	5/1977	Vinson et al.	424/49
5,032,386	7/1991	Gaffar et al.	424/49
5,096,699	3/1992	Gaffar et al.	424/49
5,178,851	1/1993	Gaffar et al.	424/52
5,180,578	1/1993	Gaffar et al.	424/52
5,188,821	2/1993	Gaffar et al.	424/52
5,192,530	3/1993	Gaffar et al.	424/52
5,192,531	3/1993	Gaffar et al.	424/52
5,208,009	5/1993	Gaffar et al.	424/19

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Attorney, Agent, or Firm—Robert L. Stone; Murray M. Grill

[57] ABSTRACT

An oral composition dentifrice comprising an orally acceptable vehicle, about 5–30% by weight of a siliceous polishing agent, about 0.25–0.35% by weight of a substantially water-insoluble noncationic antibacterial antiplaque agent, such as 2,4,4'-trichloro-2'-hydroxydiphenyl ether (triclosan) and an antibacterial-enhancing agent which enhances the delivery of said antibacterial agent to, and retention thereof on, oral surfaces.

15 Claims, No Drawings

ANTIPLAQUE ANTIBACTERIAL ORAL COMPOSITION

This is a division of Application Ser. No. 07/655,571, filed Feb. 19, 1991, now U.S. Pat. No. 5,178,851, issued Jan. 12, 1993, which is a continuation of Application Ser. No. 07/398,566, filed Aug. 25, 1989, now U.S. Pat. No. 5,032,386, granted Jul. 16, 1991, which is a continuation-in-part of Application Ser. No. 07/291,712, filed Dec. 29, 1988, now U.S. Pat. No. 4,894,220, granted Jan. 16, 1990, and of Application Ser. No. 07/346,258, filed May 1, 1989, now U.S. Pat. No. 5,043,154, granted Aug. 27, 1991, which are respectively a continuation-in-part and a continuation of application Ser. No. 07/008,901, filed Jan. 30, 1987, now abandoned.

This invention relates to an antibacterial antiplaque oral composition dentifrice. More particularly, it relates to an oral composition dentifrice containing a substantially water-insoluble noncationic antibacterial agent effective to inhibit plaque.

Dental plaque is a soft deposit which forms on teeth as opposed to calculus which is a hard calcified deposit on teeth. Unlike calculus, plaque may form on any part of the tooth surface, particularly including at the gingival margin. Hence, besides being unsightly, it is implicated in the occurrence of gingivitis.

Accordingly, it is highly desirable to include antimicrobial agents which have been know to reduce plaque in oral compositions. Frequently, cationic antibacterial agents have been suggested. Moreover, in U.S. Pat. No. 4,022,880 to Vinson et al, a compound providing zinc ions as an anticalculus agent is admixed with an antibacterial agent effective to retard the growth of plaque bacteria. A wide variety of antibacterial agents are described with the zinc compounds including cationic materials such as guanides and quaternary ammonium compounds as well as non-cationic compounds such as halogenated salicylanilides and halogenated hydroxydiphenyl ethers. The noncationic antibacterial antiplaque halogenated hydroxydiphenyl ether, triclosan, has also been described in combination with zinc citrate trihydrate in European Patent Publication 0161,899 to Saxton et al. Triclosan is also disclosed in European Patent Publication 0271,332 to Davis as a toothpaste component, containing a solubilizing agent such as propylene glycol.

The cationic antibacterial materials such as chlorhexidine, benzthonium chloride and cetyl pyridinium chloride have been the subject of greatest investigation as antibacterial antiplaque agents. However, they are generally not effective when used with anionic materials. Noncationic antibacterial materials, on the other hand, can be compatible with anionic components in an oral composition.

However, oral compositions typically are mixtures of numerous components and even such typically neutral materials as humectants can affect performance of such compositions.

Moreover, even noncationic antibacterial agents may have limited antiplaque effectiveness with commonly used materials such as polyphosphate anticalculus agents which are disclosed together in British Patent Publication 22 00551 of Gaffar et al and in EP 0251591 of Jackson et al. In commonly assigned Ser. No. 07/398,605 filed on Aug. 25, 1989, titled "Antibacterial, Antiplaque Anticalculus Oral Composition", it is shown

the antiplaque effectiveness is greatly enhanced by including an antibacterial-enhancing agent (AEA) which enhances the delivery of said antibacterial agent to, and retention thereof on, oral surfaces and providing optimized amounts and ratio of polyphosphate and AEA.

Further, even when polyphosphate anticalculus agent is not present as in commonly assigned Ser. No. 07/398,606 filed on Aug. 25, 1989, titled "Antibacterial Antiplaque Oral Composition", antiplaque effectiveness on soft oral tissue is optimized by including with the AEA a solubilizing material which dissolves the noncationic antibacterial agent in saliva when the polishing agent is a siliceous polishing agent present in amount of about 5–30%. When the amount of polishing material is about 30–75% by weight, the special solubilizing material is not required, as in commonly assigned Ser. No. 07/399,669, filed on Aug. 25, 1989, titled "Antibacterial Antiplaque Oral Composition".

It is an advantage of this invention that an oral composition dentifrice containing a siliceous polishing agent, a small but effective antiplaque amount of a substantially water-insoluble noncationic antibacterial agent and an AEA is provided to inhibit plaque formation, even without requiring the presence of special solubilizing agent.

It is an advantage of this invention that the AEA enhances the delivery and retention of small but effective antiplaque amount of the antibacterial agent on teeth and on soft oral tissues.

It is a further advantage of this invention that an antiplaque oral composition is provided which is effective to reduce the occurrence of gingivitis.

Additional advantages of this invention will be apparent from consideration of the following specification.

In accordance with certain of its aspects, this invention relates to an oral composition dentifrice comprising in an orally acceptable vehicle, about 5–30% by weight of a siliceous polishing agent, about 0.25–0.35% by weight of a substantially water insoluble noncationic antibacterial agent, said oral composition dentifrice comprising at least one of a surface active-agent and a flavoring oil, and about 0.05–4% by weight of said AEA, said oral composition dentifrice being substantially free of polyphosphate anticalculus agent.

Typical examples of water insoluble noncationic antibacterial agents which are particularly desirable from considerations of antiplaque effectiveness, safety and formulation are:

HALOGENATED DIPHENYL ETHERS

2',4,4'-trichloro-2-hydroxy-diphenyl ether (Triclosan)
2,2'-dihydroxy-5,5'-dibromo-diphenyl ether.

HALOGENATED SALICYLANILIDES

4'5-dibromosalicylanilide
3,4',5-trichlorosalcylanilide
3,4',5-tribromosalicylaniiide
2,3,3',5-tetrachlorosalicylanilide
3,3',5-tetrachlorosalicylanilide
3,5-dibromo-3'-trifluoromethyl salicylanilide
5-n-octanoyl-3'-trifluoromethyl salicylanilide
3,5-dibromo-4'-trifluoromethyl salicylanilide
3,5-dibromo-3'-trifluoro methyl salicylanilide (Fluro-phene).

BENZOIC ESTERS

Methyl—p-Hydroxybenzoic Ester
Ethyl—p-Hydroxybenzoic Ester

Propyl—p-Hydroxybenzoic Ester
Butyl—p-Hydroxybenzoic Ester.

HALOGENATED CARBANILIDES

3,4,4'-trichlorocarbanilide
3-trifluoromethyl-4,4'-dichlorocarbanilide
3,3',4-trichlorocarbanilide.

Phenolic Compounds (including phenol and its homologs, mono-and poly-alkyl and aromatic halo (e.g. F,Cl,Br,I)-phenols, resorcinol and catechol and their derivatives and bisphenolic compounds). Such phenolic compounds includes inter alia:

PHENOL AND ITS HOMOLOGS

Phenol
2 Methyl—Phenol
3 Methyl—Phenol
4 Methyl—Phenol
4 Ethyl—Phenol
2,4-Dimethyl—Phenol
2,5-Dimethyl—Phenol
3,4-Dimethyl—Phenol
2,6-Dimethyl—Phenol
4-n-Propyl—Phenol
4-n-Butyl—Phenol
4-n-Amyl—Phenol
4-tert-Amyl—Phenol
4-n-Hexyl—Phenol
4-n-Heptyl—Phenol
2-Methoxy-4-(2-Propenyl)-Phenol (Eugenol)
2-Isopropyl-5-Methyl-Phenol (Thymol).

MONO- AND POLY-ALKYL AND ARALKYL HALOPHENOLS

Methyl—p-Chlorophenol
Ethyl—p-Chlorophenol
n-Propyl—p-Chlorophenol
n-Butyl—p-Chlorophenol
n-Amyl—p-Chlorophenol
sec-Amyl—p-Chlorophenol
n-Hexyl—p-Chlorophenol
Cyclohexyl—p-Chlorophenol
n-Heptyl—p-Chlorophenol
n-Octyl—p-Chlorophenol
O-Chlorophenol
Methyl—o-Chlorophenol
Ethyl—o-Chlorophenol
n-Propyl—o-Chlorophenol
n-Butyl—o-Chlorophenol
n-Amyl—o-Chlorophenol
tert-Amyl—o-Chlorophenol
n-Hexyl—o-Chlorophenol
n-Heptyl—o-Chlorophenol
p-Chlorophenol
o-Benzyl—p-Chlorophenol
o-Benzyl-m-methyl—p-Chlorophenol
o-Benzyl-m, m-dimethyl—p-Chlorophenol
o-Phenylethyl—p-Chlorophenol
o-Phenylethyl-m-methyl—p-Chlorophenol
3-Methyl—p-Chlorophenol
3,5-Dimethyl—p-Chlorophenol
6-Ethyl-3-methyl—p-Chlorophenol
6-n-Propyl-3-methyl—p-Chlorophenol
6-iso-Propyl-3-methyl—p-Chlorophenol
2-Ethyl-3,5-dimethyl—p-Chlorophenol
6-sec Butyl-3-methyl—p-Chlorophenol
2-iso-Propyl-3,5-dimethyl—p-Chlorophenol
6-Diethylmethyl-3-methyl—p-Chlorophenol
6-iso-Propyl-2-ethyl-3-methyl—p-Chlorophenol
2-sec Amyl-3,5-dimethyl—p-Chlorophenol
2-Diethylmethyl-3,5-dimethyl—p-Chlorophenol
6-sec Octyl-3-methyl—p-Chlorophenol
p-Bromophenol
Methyl—p-Bromophenol
Ethyl—p-Bromophenol
n-Propyl—p-Bromophenol
n-Butyl—p-Bromophenol
n-Amyl—p-Bromophenol
sec-Amyl—p-Bromophenol
n-Hexyl—p-Bromophenol
cyclohexyl—p-Bromophenol
o-Bromophenol
tert-Amyl—o-Bromophenol
n-Hexyl—o-Bromophenol
n-Propyl-m,m-Dimethyl—o-Bromophenol
2-Phenyl Phenol
4-chloro-2-methyl phenol
4-chloro-3-methyl phenol
4-chloro-3,5-dimethyl phenol
2,4-dichloro-3,5-dimethylphenol
3,4,5,6-terabromo-2-methylphenol
5-methyl-2-pentylphenol
4-isopropyl-3-methylphenol
5-chloro-2-hydroxydiphenylemthane.

RESORCINOL AND ITS DERIVATIVES

Resorcinol
Methyl—Resorcinol
Ethyl—Resorcinol
n-Propyl—Resorcinol
n-Butyl—Resorcinol
n-Amyl—Resorcinol
n-Hexyl—Resorcinol
n-Heptyl—Resorcinol
n-Octyl—Resorcinol
n-Nonyl—Resorcinol
Phenyl—Resorcinol
Benzyl—Resorcinol
Phenylethyl—Resorcinol
Phenylpropyl—Resorcinol
p-Chlorobenzyl—Resorcinol
5-Chloro—2,4-Dihydroxydiphenyl Methane
4'-Chloro—2,4-Dihydroxydiphenyl Methane
5-Bromo—2,4-Dihydroxydiphenyl Methane
4'-Bromo—2,4-Dihydroxydiphenyl Methane.

BISPHENOLIC COMPOUNDS

Bisphenol A
2,2'-methylene bis (4-chlorophenol)
2,2'-methylene bis (3,4,6-trichlorophenol) (hexachlorophene)
2,2'-methylene bis (4-chloro-6-bromophenol)
bis (2-hydroxy-3,5-dichlorophenyl) sulfide
bis (2-hydroxy-5-chlorobenzyl) sulfide.

The noncationic antibacterial agent is present in the oral composition in an effective antiplaque amount of about 0.25–0.35% by weight, preferably about 0.3%. The antibacterial agent is substantially water-insoluble, meaning that its solubility is less than about 1% by weight in water at 25° C. and may be even less than about 0.1%.

The preferred halogenated diphenyl ether is triclosan. The preferred phenolic compounds are phenol, thymol, eugenol, hexyl resorcinol and 2,2'-methylene bis(4-chloro-6-bromophenol). The most preferred antibacterial antiplaque compound is triclosan. Triclosan is

disclosed in aforementioned U.S. Pat. No. 4,022,880 as an antibacterial agent in combination with an anticalculus agent which provides zinc ions, and in German Patent Disclosure 3532860 in combination with a copper compound. In European Patent Disclosure 0278744 it is disclosed in combination with a tooth desitizing agent containing a source of potassium ions. It is also disclosed as an antiplaque agent in a dentifrice formulated to contain a lamellar liquid crystal surfactant phase having a lamellar spacing of less than 6.0 nm and which may optionally contain a zinc salt in published European Patent Application 0161898 of Lane et al and in a dentifrice containing zinc citrate trihydrate in published European Patent Application 0161899 to Saxton et al.

The antibacterial-enhancing agent (AEA) which enhances delivery of said antibacterial agent to, and retention thereof on, oral surfaces, is employed in amounts effective to achieve such enhancement within the range in the oral composition of about 0.05% to about 4%, preferably about 0.1% to about 3%, more preferably about 0.5% to about 2.5% by weight.

AEA polymeric materials of the present invention include those which can be characterized as having utility as dentifrice adhesives or fixatives or dental cements. For example, U.S. Pat. Nos. 4,521,551 and 4,375,036, each to Chang et al, describe commercially available copolymer of methylvinyl ether-maleic anhydride (Gantrez) as a denture fixative. However, there has not been recognition in the prior art that adhesives, fixatives or cements when applied in water-soluble or water-swellable form together with substantially water-insoluble non-cationic antibacterial antiplaque agents could enhance the antibacterial activity of such agents. Further, in U.S. Pat. No. 4,485,090 to Chang, Gantrez AN copolymer is mentioned among polymeric anionic membrane-forming materials which attach to a tooth surface to form a hydrophobic barrier which reduces elution of a previously applied therapeutic caries prophylactic fluoride compound. Again, there is no recognition that such polymeric material could enhance the antibacterial activity of substantially water-insoluble non-cationic antibacterial antiplaque agents.

This AEA may be a simple compound, preferably a polymerizable monomer, more preferably a polymer, which latter term is entirely generic, including for example oligomers, homopolymers, copolymers of two or more monomers, ionomers, block copolymers, graft copolymers, cross-linked polymers and copolymers, and the like. The AEA may be natural or synthetic, and water insoluble or preferably water (saliva) soluble or swellable (hydratable, hydrogel forming). It has an (weight) average molecular weight of about 100 to about 1,000,000, preferably about 1,000 to about 1,000,000, more preferably about 2,000 or 2,500 to about 250,000 or 500,000.

The AEA ordinarily contains at least one delivery-enhancing group, which is preferably acidic such as sulfonic, phosphinic, or more preferably phosphonic or carboxylic, or salt thereof, e.g. alkali metal or ammonium, and at least one organic retention-enhancing group, preferably a plurality of both the delivery-enhancing and retention-enhancing groups, which latter groups preferably have the formula $-(X)_n-R$ wherein X is O, N, S, SO, SO_2, P, PO or Si or the like, R is hydrophobic alkyl, alkenyl, acyl, aryl, alkaryl, aralkyl, heterocyclic or their inert-substituted derivatives, and n is zero or 1 or more. The aforesaid "inert-substituted derivatives", are intended to include substituents on R which are generally non-hydrophilic and do not significantly interfere with the desired functions of the AEA as enhancing the delivery of the antibacterial agent to, and retention thereof on, oral surfaces such as halo, e.g. Cl, Br, I, and carbo and the like. Illustrations of such retention-enhancing groups are tabulated below.

n	X	$-(X)_nR$
0	—	methyl, ethyl, propyl, butyl, isobutyl, t-butyl, cyclohexyl, allyl, benzyl, phenyl, chlorophenyl, xylyl, pyridyl, furanyl, acetyl, benzoyl, butyryl, terephthaloyl, etc.
1	O	ethoxy, benzyloxy, thioacetoxy, phenoxy, carboethoxy, carbobenzyloxy, etc.
	N	ethylamino, diethylamino, propylamido, benzoylamido, benzoylaido, phenylacetamido, etc.
	S	thiobutyl, thioisobutyl, thioallyl, thiobenzyl, thiophenyl, thiopropionyl, phenylthioacetyl, thiobenzoyl, etc.
	SO	butylsulfoxy, allylsulfoxy, benzylsulfoxy, phenylsulfoxy, etc.
	SO_2	butylsulfonyl, allylsulfonyl, benzylsulfonyl, phenylsulfonyl, etc.
	P	diethylphosphinyl, ethylvinylphosphinyl, ethylallylphosphinyl, ethylbenzylphosphinyl, ethylphenylphosphinyl, etc.
	PO	diethylphosphinoxy, ethylvinylphosphinoxy, methylallylphosphinoxy, methylbenzylphosphinoxy, methylphenylphosphinoxy, etc.
	Si	trimethylsilyl, dimethylbutylsilyl, dimethylbenzylsilyl, dimethylvinylsilyl, dimethylallylsilyl, etc.

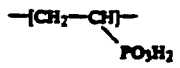
As employed herein, the delivery-enhancing group refers to one which attaches or substantively, adhesively, cohesively or otherwise bonds the AEA (carrying the antibacterial agent) to oral (e.g. tooth and gum) surfaces, thereby "delivering" the antibacterial agent to such surfaces. The organic retention-enhancing group, generally hydrophobic, attaches or otherwise bonds the antibacterial agent to the AEA, thereby promoting retention of the antibacterial agent to the AEA and indirectly on the oral surfaces. In some instances, attachment of the antibacterial agent occurs through physical entrapment thereof by the AEA, especially when the AEA is a cross-linked polymer, the structure of which inherently provides increased sites for such entrapment. The presence of a higher molecular weight, more hydrophobic cross-linking moiety in the cross-linked polymer still further promotes the physical entrapment of the antibacterial agent to or by the cross-linked AEA polymer.

Preferably, the AEA is an anionic polymer comprising a chain or backbone containing repeating units each preferably containing at least one carbon atom and preferably at least one directly or indirectly pendant, monovalent delivery-enhancing group and at least one directly or indirectly pendant monovalent retention-enhancing group geminally, vicinally or less preferably otherwise bonded to atoms, preferably carbon, in the chain. Less preferably, the polymer may contain delivery-enhancing groups and/or retention-enhancing groups and/or other divalent atoms or groups as links in the polymer chain instead of or in addition to carbon atoms, or as cross-linking moieties.

It will be understood that any examples or illustrations of AEA's disclosed herein which do not contain both delivery-enhancing groups and retention enhancing groups may and preferably should be chemically modified in known manner to obtain the preferred AEA's containing both such groups and preferably a

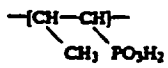
plurality of each such groups. In the case of the preferred polymeric AEA's, it is desirable, for maximizing substantivity and delivery of the antibacterial agent to oral surfaces, that the repeating units in the polymer chain or backbone containing the acidic delivery enhancing groups constitute at least about 10%, preferably at least about 50%, more preferably at least about 80% up to 95% or 100% by weight of the polymer.

According to a preferred embodiment of this invention, the AEA comprises a polymer containing repeating units in which one or more phosphonic acid delivery-enhancing groups are bonded to one or more carbon atoms in the polymer chain. An example of such an AEA is poly (vinyl phosphonic acid) containing units of the formula:



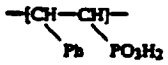
I

which however does not contain a retention-enhancing group. A group of the latter type would however be present in poly (1-phosphonopropene) with units of the formula:



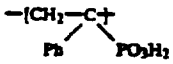
II

A preferred phosphonic acid-containing AEA for use herein is poly (beta styrene phosphonic acid) containing units of the formula:



III

wherein Ph is phenyl, the phosphonic delivery-enhancing group and the phenyl retention-enhancing group being bonded on vicinal carbon atoms in the chain, or a copolymer of beta styrene phosphonic acid with vinyl phosphonyl chloride having the units of the foregoing formula III alternating or in random association with units of formula I above, or poly (alpha styrene phosphonic acid) containing units of the formula:



IV

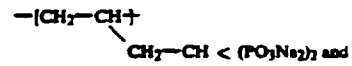
in which the delivery—and retention—enhancing groups are geminally bonded to the chain.

These styrene phosphonic acid polymers and their copolymers with other inert ethylenically unsaturated monomers generally have molecular weights in the range of about 2,000 to about 30,000, preferably about 2,500 to about 10,000, and are, with their methods of preparation disclosed and claimed in concurrently filed application Ser. No. 07/398,606 filed Aug. 25, 1989, which disclosure is incorporated here. Such "inert" monomers do not significantly interfere with the intended function of any copolymer employed as an AEA herein.

Other phosphonic-containing polymers include, for example, phosphonated ethylene having units of the formula.

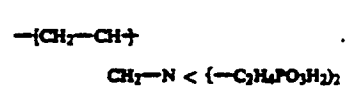
V

where n may for example be an integer or have a value giving the polymer a molecular weight of about 3,000; and sodium poly (butene-4,4-diphosphonate) having units of the formula:



VI

poly (allyl bis (phosphonoethyl) amine) having units of the formula:



VII

Other phosphonated polymers, for example poly (allyl phosphono acetate), phosphonated polymethacrylate, etc. and the geminal diphosphonate polymers disclosed in EP Publication 0321233 may be employed herein as AEA's, provided of course that they contain or are modified to contain the above-defined organic retention-enhancing groups.

According to another preferred embodiment, the AEA may comprise a synthetic anionic polymeric polycarboxylate. Although not used in the present invention to coact with polyphosphate anticalculus agent, synthetic anionic polymeric polycarboxylate having a molecular weight of about 1,000 to about 1,000,000, preferably about 30,000 to about 500,000, has been used as an inhibitor of alkaline phosphatase enzyme in optimizing the anticalculus effectiveness of linear molecularly dehydrated polyphosphate salts, as disclosed in U.S. Pat. No. 4,627,977 to Gaffar et al. Indeed, in published British Patent Publication 22 00551, the polymeric polycarboxylate is disclosed as an optional ingredient in oral compositions containing linear molecularly dehydrated polyphosphate salts and substantially water-insoluble noncationic antibacterial agent. It is further observed, in the context of the present invention that such polycarboxylate when containing or modified to contain retention-enhancing groups is markedly effective to enhance delivery and retention of the noncationic antibacterial, antiplaque agent to dental surfaces when another ingredient with which the polymeric polycarboxylate would coact (that is, molecularly dehydrated polyphosphate) is absent; for instance, when the ingredient with which the polymeric polycarboxylate coacts is especially the noncationic antibacterial agent.

Synthetic anionic polymeric polycarboxylates and their complexes with various cationic germicides, zinc and magnesium have been previously disclosed as anticalculus agents per se in, for example U.S. Pat. No. 3,429,963 to Shedlovsky; U.S. Pat. No. 4,152,420 to Gaffar; U.S. Pat. No. 3,956,480 to Dichter et al; U.S. Pat. No. 4,138,477 to Gaffar; and U.S. Pat. No. 4,183,914 to Gaffar et al. It is to be understood that the synthetic anionic polymeric polycarboxylates so disclosed in these several patents when containing or modified to contain retention-enhancing groups are operative in the compositions and methods of this invention and such disclosures are to that extent incorporated herein by reference thereto.

The synthetic anionic polymeric polycarboxylates employed herein are well known, being often employed in the form of their free acids or preferably partially or

more preferably fully neutralized water soluble or water swellable (hydratable, gel forming) alkali metal (e.g. potassium and preferably sodium) or ammonium salts. Preferred are 1:4 to 4:1 copolymers of maleic anhydride or acid with another polymerizable ethylenically unsaturated monomer, preferably methyl vinyl ether/maleic anhydride having a molecular weight (M.W.) of about 30,000 to about 1,000,000, most preferably about 30,000 to about 500,000. These copolymers are available for example as Gantrez, e.g. AN 139 (M.W. 500,000), A.N. 119 (M.W. 250,000); and preferably S-97 Pharmaceutical Grade (M.W. 70,000), of GAF Corporation.

Other AEA operative polymeric polycarboxylates containing or modified to contain retention-enhancing groups include those disclosed in U.S. Pat. No. 3,956,480 referred to above, such as the 1:1 copolymers of maleic anhydride with ethyl acrylate, hydroxyethyl methacrylate, N-vinyl-2-pyrollidone, or ethylene, the latter being available for example as Monsanto EMA No. 1103, M.W. 10,000 and EMA Grade 61, and 1:1 copolymers of acrylic acid with methyl or hydroxyethyl methacrylate, methyl or ethyl acrylate, isobutyl vinyl ether or N-vinyl-2-pyrrolidone.

Additional operative polymeric polycarboxylates disclosed in above referred to U.S. Pat. No. 4,138,477 and 4,183,914, containing or modified to contain retention-enhancing groups include copolymers of maleic anhydride with styrene, isobutylene or ethyl vinyl ether, polyacrylic, polyitaconic and polymaleic acids, and sulfoacrylic oligomers of M.W. as low as 1,000, available as Uniroyal ND-2.

Suitable generally are retention-enhancing group-containing polymerized olefinically or ethylenically unsaturated carboxylic acids containing an activated carbon-to-carbon olefinic double bond and at least one carboxyl group, that is, an acid containing an olefinic double bond which readily functions in polymerization because of its presence in the monomer molecule either in the alpha-beta position with respect to a carboxyl group or as part of a terminal methylene grouping. Illustrative of such acids are acrylic, methacrylic, ethacrylic, alpha-chloroacrylic, crotonic, beta-acryloxy propionic, sorbic, alpha-chlorsorbic, cinnamic, beta-styrylacrylic, muconic, itaconic, citraconic, mesaconic, glutaconic, aconitic, alpha-phenylacrylic, 2-benzyl acrylic, 2-cyclohexylacrylic, angelic, umbellic, fumaric, maleic acids and anhydrides. Other different olefinic monomers copolymerizable with such carboxylic monomers include vinylacetate, vinyl chloride, dimethyl maleate and the like. Copolymers ordinarily contain sufficient carboxylic salt groups for water-solubility.

Also useful herein are so-called carboxyvinyl polymers disclosed as toothpaste components in U.S. Pat. No. 3,980,767 to Chown et al; U.S. Pat. No. 3,935,306 to Roberts et al; U.S. Pat. No. 3,919,409 to Perla et al; U.S. Pat. No. 3,911,904 to Harrison, and U.S. Pat. No. 3,711,604 to Colodney et al. They are commercially available for example under the trademarks Carbopol 934, 940 and 941 of B. F. Goodrich, these products consisting essentially of a colloidally water-soluble polymer of polyacrylic acid crosslinked with from about 0.75% to about 2.0% of polyallyl sucrose or polyallyl pentaerythritol as cross linking agent, the cross-linked structure and cross-linkages providing the desired retention enhancement by hydrophobicity and/or physical entrapment of the antibacterial agent or the like. Polycarbophil is somewhat similar, being poly acrylic acid cross-linked with less than 0.2% of divinyl glycol, the lower proportion, molecular weight and/or hydrophobicity of this cross-linking agent tending to provide little or no retention enhancement. 2,5-dimethyl-1,5-hexadiene exemplifies a more effective retention-enhancing cross-linking agent.

The synthetic anionic polymeric polycarboxylate component is mainly a hydrocarbon with optional halogen and O-containing substituents and linkages as present in for example ester, ether and OH groups, and is employed in the instant compositions in approximate weight amounts of 0.05 to 4%, preferably 0.05 to 3%, more preferably 0.1 to 2%.

The AEA may also comprise natural anionic polymeric polycarboxylates containing retention-enhancing groups carboxymethyl cellulose and other binding agents gums and film-formers devoid of the above-defined delivery-enhancing and/or retention-enhancing groups are ineffective as AEA's.

As illustrative of AEA's containing phosphinic acid and/or sulfonic acid delivery enhancing groups, there may be mentioned polymers and copolymers containing units or moieties derived from the polymerization of vinyl or allyl phosphinic and/or sulfonic acids substituted as needed on the 1 or 2 (or 3) carbon atom by an organic retention-enhancing group, for example having the formula $-(X)_n-R$ defined above. Mixtures of these monomers may be employed, and copolymers thereof with one or more inert polymerizable ethylenically unsaturated monomers such as those described above with respect to the operative synthetic anionic polymeric polycarboxylates. As will be noted, in these and other polymeric AEA's operative herein, usually only one acidic delivery-enhancing group is bonded to any given carbon or other atom in the polymer backbone or branch thereon. Polysiloxanes containing pendant delivery-enhancing groups and retention enhancing groups may also be employed as AEA's herein. Also effective as AEA's herein are ionomers containing or modified to contain delivery- and retention-enhancing groups. Ionomers are described on pages 546–573 of the Kirk-Othmer Encyclopedia of Chemical Technology, third edition, Supplement Volume, John Wiley & Sons, Inc. copyright 1984, which description is incorporated herein by reference. Also effective as AEA's herein, provided they contain rare modified to certain retention-enhancing groups, are polyesters, polyurethanes and synthetic and natural polyamides including proteins and proteinaceous materials such as collagen, poly (argenine) and other polymerized amino acids.

Without being bound to a theory, it is believed that the AEA, especially polymeric AEA, is generally an anionic film forming material and is thought to attach to tooth surfaces and form a continuous film over the surfaces, thereby preventing bacterial attachment to tooth surfaces. It is possible that the noncationic antibacterial agent forms a complex or other form of association with the AEA, thus forming a film of a complex or the like over tooth surfaces. The film forming property of the AEA and the enhanced delivery and film forming property of the AEA and the enhanced delivery and retention of the antibacterial agent on tooth surfaces due to the AEA appears to make tooth surfaces unfavourable for bacterial accumulation particularly since the direct bacteriostatic action of the antibacterial agent controls bacterial growth. Therefore, through the combination of three modes of actions: 1) enhanced delivery, 2) long retention time on tooth surfaces, and 3)

prevention of bacterial attachment to tooth surfaces, the oral composition is made efficacious for reducing plaque. Similar antiplaque effectiveness is attained on soft oral tissue at or near the gum line.

In aforementioned application Ser. No. 398,606, filed on even date herewith, titled "Antibacterial Antiplaque Oral Compositions" wherein the dentifrices thereof contain about 5–30% by weight of a siliceous polishing agent, a material which solubilizes the noncationic antibacterial agent to render it effective in delivery to soft oral tissues at the gum line is employed. In the present invention, when the amount of the noncationic antibacterial agent is optimized at about 0.25–0.35% by weight, it is found that the solubilizing agent is not required; but is rather optional.

In the oral preparation dentifrice, an orally acceptable vehicle including a water-phase with humectant is present. Water is present typically an amount of at least about 3% by weight, generally about 3–35% and humectant, preferably glycerine and/or sorbitol, typically total about 6.5–75% or 80% by weight of the oral preparation dentifrice, more typically about 10–75%. Reference hereto to sorbitol refers to the material typically as available commercially in 70% aqueous solutions. Although not required in the present invention wherein about 0–25–0.35% of the water insoluble non-cationic antibacterial agent is present optionally, an additional ingredient which assists solubilization of the antibacterial agent in saliva may be incorporated in the water-humectant vehicle. Such optional solubilizing agents include humectant polyols such as propylene glycol, dipropylene glycol, and hexylene glycol, cellosolves such as methyl cellosolve and ethyl cellosolve, vegetable oils and waxes containing at least about 12 carbons in a straight chain such as olive oil, castor oil and petrolatum and esters such as amyl acetate, ethyl acetate and benzyl benzoate. As used herein "propylene glycol" includes 1,2-propylene glycol and 1,3-propylene glycol. Significant amounts of polyethylene glycol particularly of molecular weight of 600 or more should be avoided since polyethylene glycol effectively inhibits the antibacterial activity of the noncationic antibacterial agent. For instance, polyethylene glycol (PEG) 600 when present with triclosan in a weight ratio of 25 triclosan:1 PEG 600 reduces the antibacterial activity of triclosan by a factor of about 16 from that prevailing in the absence of the polyethylene glycol.

The pH of such oral preparation dentifrice of the invention is generally in the rental range of about 4.5 to about 9 or 10 and not preferably about 6.5 to about 7.5. It is noteworthy that the compositions of the invention may be applied orally at a pH below 5 without substantially decalcifying or otherwise damaging dental enamel. The pH can be controlled with acid (e.g. citric acid or benzoic acid) or base (e.g. sodium hydroxide) or buffered (as with sodium citrate, benzoate, carbonate, or bicarbonate, disodium hydrogen phosphate, sodium dihydrogen phosphate, etc.).

In this invention, the oral composition dentifrice may be substantially gel in character, such as a gel dentifrice. Such gel oral preparations contain siliceous dentally polishing material. Preferred polishing materials include crystalline silica having particle sized of up to about 5 microns, a mean particle size of up to about 1.1 microns, and a surface area of up to about 50,000 $cm.^2/gm.$, silica gel or colloidal silica and complex amorphous alkali metal aluminosilicate.

When visually clear or opacified gels are employed, a polishing agent of colloidal silica, such as those sold under the trademark SYLOID as Syloid 72 and Syloid 74 or under the trademark SANTOCEL as Santocel 100 or alkali metal almuinosilicate complexes (that is, silica containing alumina combined in its matrix) are particularly useful, since they are consistant with gel-like texture and have refractive indices close to the refractive indices of gelling agent-liquid (including water and/or humectant)systems commonly used in dentifices.

The polishing material is generally present in the oral composition dentifrices such as toothpaste or gel compositions in weight concentrations of about 5% to about 30%.

In a gel toothpaste, the liquid vehicle may typically comprise about 3–35% by weight of water, such as about 10–35%, and humectant in an amount ranging from about 6.5% to about 80%, such as about 10% to about 80% by weight of the preparation. In clear gels where the refractive index is an important consideration, about 3–30% of water, 0 to about 70% of glycerine and about 20–25% of sorbitol are preferably employed.

The oral composition dentifrices typically contain a natural or synthetic thickener or gelling agent in proportions of about 0.1 to about 10%, preferably about 0.5 to about 5%. A suitable thickener is synthetic hectorite, a synthetic colloidal magnesium alkali metal silicate complex clay available for example as Laponite (e.g. CP, SP 2002,D) marketed by Laporte Industries Limited. Laponite D analysis shows, approximately by weight, 58.00% SiO_2, 25.40% MgO, 3.05% Na_2O, 0.98% Li_2O, and some water and trace metals. Its true specific gravity is 2.53 and it has an apparent bulk density (g./ml. at 8% moisture) of 1.0.

Other suitable gelling agents or thickeners include Irish moss, i-carrageenan, gum tragacanth, starch, polyvinylpyrrolidone, hydroxyethypropyl-cellulose, hydroxybutyl methyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose (e.g. available as Natrosol), sodium carboxymethyl cellulose, and colloidal silica such those available as finely ground Syloid 244 and Sylodent 15.

There may be a tendency for the dentifrice to separate into liquid and solid portions when about 5% by weight or more of the optional solubilizing material such as propylene glycol is present. Furthermore, in the present invention excellent antiplaque effects can be obtained with small amounts of antibacterial agent which do not even require solubilizing agent. In the present invention, a preferred dentifrice contains about 0.3% by weight of the antibacterial agent and about 1.5–2% by weight of the polycarboxylate.

Without being bound to a theory whereby the advantages of this invention are achieved, it is believed that an aqueous, humectant vehicle is normally solubilized in surfactant micelles in the mobile phase (that is, not including gelling agent and polishing agent) of a dentfrice formula. The mobile phase solution of dentifrice during use can become diluted with saliva which causes triclosan to precipitate. However, in the present invention, it is found that even in the absence of a special solubilizing material for triclosan, when the amount of triclosan is about 0.25%–0.35% by weight and the polycarboxylate is present, sufficient triclosan is present to exert an excellent antiplaque effect on the soft tissues at the gum

line. Similar remarks apply to other water-insoluble noncationic antibacterial agents herein described.

The oral composition dentifrice may also contain a source of fluoride ions, or fluorine-providing component, as anti-caries agent, in an amount sufficient to supply about 25 ppm to 5,000 ppm of fluoride ions. These compounds may be slightly soluble in water or may be fully water-soluble. They are characterized by their ability to release fluoride ions in water and by substantial freedom from undesired reaction with other compounds of the oral preparation. Among these materials are inorganic fluoride salts, such as soluble alkali metal, alkaline earth metal salts, or example, sodium fluoride, potassium fluoride, ammonium fluoride, calcium fluoride, a copper fluoride such as cuprous fluoride, zinc fluoride, barium fluoride, sodium flourosilicate, ammonium flourosilicate, sodium fluorozirconate, ammonium fluorozirconate, sodium monofluorophosphate, aluminum mono-and di-fluorophosphate, and fluorinated sodium calcium pyrophosphate. Alkali metal and tin fluorides, such as sodium and stannous fluorides, sodium monofluorophosphate (MFP) and mixtures thereof, are preferred.

The amount of fluorine-providing compound is dependent to some extent upon the type of compound, its solubility, and the type of oral preparation, but it must be a non-toxic amount, generally about 0.0005 to about 3.0% in the preparation. In a dentifrice preparation, e.g. dental gel and an amount of such compound which releases up to about 5,000 ppm of F ion by weight of the preparation is considered satisfactory. Any suitable minimum amount of such compound may be used, but it is preferable to employ sufficient compound to release about 300 to 2,000 ppm, more preferably about 800 to about 1,500 ppm of fluoride ion.

Typically, in the cases of alkali metal fluorides, this component is present in an amount up to about 2% by weight, based on the weight of the preparation, and preferably in the range of about 0.05% to 1%. In the case of sodium monofluorophosphate, the compound may be present in an amount of about 0.1–3%, more typically about 0.76%.

It will be understood that, as is conventional, the oral preparations are to be sold or otherwise distributed in suitable labelled packages. Thus a dentifrice gel will usually be in a collapsible tube, typically aluminum, lined lead or plastic, or other squeeze, pump or pressurized dispenser for metering out the contents, having a label describing it, in substance, as a dentifrice gel or the like.

Organic surface-active agents are used in the compositions of the present invention to achieve increased prophylactic action. Moreover, they assist in achieving thorough and complete dispersion of the antiplaque antibacterial agent throughout the oral cavity, and render the instant compositions more cosmetically acceptable. Indeed, at least one of surface-active agent or flavoring oil is present to effect desired the solubilization of the antibacterial agent. The organic surface-active material is preferably anionic, nonionic or ampholytic in nature, and it is preferred to employ as the surface-active agent a detersive material which imparts to the composition detersive and foaming properties. Suitable examples of anionic surfactants are water-soluble salts of higher fatty acid monoglyceride monosulfates, such as the sodium salt of the monosulfated monoglyceride of hydrogenated coconut oil fatty acids, higher alkyl sulfates such as sodium lauryl sulfate, alkyl aryl sulfonates such as sodium dodecyl benzene sulfonate, higher alkyl sulfoacetates, higher fatty acid esters of 1,2-dihydroxy propane sulfonate, and the substantially saturated higher aliphatic acyl amides of lower aliphatic amino carboxylic acid compounds, such as those having 12 to 16 carbons in the fatty acid, alkyl or acyl radicals, and the like. Examples of the last mentioned amides are N-lauroyl sarcosine, and the sodium, potassium, and ethanolamine salts of N-lauroyl, N-myristoyl, or N-palmitoyl sarcosine which should be substantially free from soap or similar higher fatty acid material. The use of these sarcosinate compounds in the oral compositions of the present invention is particularly advantageous since these materials exhibit a prolonged and marked effect in the inhibition of acid formation in the oral cavity due to carbohydrate breakdown in addition to exerting some reduction in the solubility of tooth enamel in acid solutions. Examples of water-soluble nonionic surfactants are condensation products of ethylene oxide with various reactive hydrogen-containing compounds reactive therewith having long hydrophobic chains (e.g. aliphatic chains of about 12 to 20 carbon atoms), which condensation products ("ethoxamers") contain hydrophilic polyoxyethylene moieties, such as condensation products of poly(ethylene oxide) with fatty acids, fatty alcohols, fatty amides, polyhydric alcohols (e.g. sorbitan monosterate) and polypropyleneoxide (e.g. Pluronic materials).

Surface active agent is typically present in amount of about 0.5–5% by weight, prefereably about 1–2.5%. As indicated, surface-active agent is believed to assist in dissolving the noncationic antibacterial agent.

Various other materials may be incorporated in the oral preparations of this invention such as whitening agents, preservatives, silicones, chlorophyll compounds and/or ammoniated material such as urea, diammonium phosphate, and mixtures thereof. These adjuvants, where present, are incorporated in the preparations in amounts which do not substantially adversely affect the properties and characteristics desired. Significant amounts of zinc, magnesium and other metal salts and materials, which are generally soluble and which would complex with active components of the instant invention are to be avoided.

Any suitable flavoring or sweetening material may also be employed. Examples of suitable flavoring constituents are flavoring oils, e.g. oil of spearmint, peppermint, wintergreen, sassafras, clove, sage, eucalyptus, marjoram, cinnamon, lemon, and orange, and methyl salicylate. Suitable sweetening agents include sucrose, lactose, maltose, xylitol, sodium cyclamate, perillartine, AMP (aspartyl phenyl alanine, methyl ester), saccharine and the like. Suitably, flavor and sweetening agents may each or together comprise from about 0.1% to 5% more of the preparation. Moreover, flavoring oil is believed to aid the dissolving of the antibacterial agent, together with or even in the absence of surface-active agent.

In the preferred practice of this invention an oral composition dentifrice containing the composition of the present invention is preferably applied regularly to dental enamel and soft oral tissues, particularly at or near the gum line, such as every day or every second or third day or preferably from 1 to 3 times daily, at a pH of about 4.5 to about 9, generally about 5.5 to about 8, preferably about 6 to 8, for at least 2 weeks up to 8 weeks or more up to lifetime.

The compositions of this invention can be incorporated in lozenges, or in chewing gum or other products, e.g. by stirring into a warm gum base or coating the outer surface of a gum base, illustrative of which may be mentioned jelutong, rubber latex, vinylite resins, etc., desirably with conventional plasticizers or softeners, sugar or other sweeteners or carbohydrates such as glucose, sorbitol and the like.

The following examples are further illustrative of the nature of the present invention, but it is understood that the invention is not limited thereto. All amounts and proportions referred to herein and in the appended claims are by weight, unless otherwise indicated.

EXAMPLE 1

The following dentifrice is prepared:

	Parts	
	A	B
Glycerine	10.00	—
Propylene Glycol	—	10.00
Sorbitol (70%)	25.00	25.00
Iota carrageenan	0.60	0.60
Gantrez S-97	2.00	2.00
Sodium Saccharin	0.40	0.40
Sodium Fluoride	0.243	0.243
Sodium Hydroxide (50%)	1.00	1.00
Titanium Oxide	0.50	0.50
Silica Polishing Agent (Zeodent 113)	20.00	20.00
Silica Thickener (Sylox 15)	5.50	5.50
Sodium Lauryl Sulfate	2.00	2.00
Water	31.507	31.507
Triclosan	0.30	0.30
Flavor Oil	0.95	0.95

The above dentifrice A delivers Triclosan to the teeth and soft gum tissue essentially as well as dentifrices B containing a special solubilizing agent for Triclosan. In other words, a special solubilizing agent is not required for the dentifrice of the present invention to be effective. Further, a corresponding dentifrice in which the Gantrez polycarboxylate is absent is substantially poorer in delivering Triclosan.

In the foregoing example, improved results may also be obtained by replacing triclosan with other antibacterial agents herein described such as phenol, thymol, eugenol and 2,2'-methylene bis (4-chloro-6-bromophenol) and/or by replacing Gantrez with other AEA's such as a 1:1 copolymer of maleic anhyride and ethyl acrylate, sulfoacrylic oligomers, Carbopols (e.g. 934), and polymers of alpha or beta-styrenephosphonic acid monomers and copolymers of these monomers with each or with other ethylenically unsaturated polymerizable monomers such as vinyl phosphonic acid.

EXAMPLE 2

The following liquid phase dentifrice solutions are tested for uptake and retention of triclosan on saliva coated HA disks following the test procedures described in Example 1 with the indicated results:

	Parts			
Ingredients	A	B	C	D
Sorbitol (70% solution)	30.0	30.0	30.0	30.0
Glycerol	9.5	9.5	9.5	9.5
Propylene Glycol	0.5	0.5	0.5	0.5
SLS	20.0	20.0	20.0	20.0
NaF	0.243	0.243	0.243	0.243

-continued

	Parts			
Ingredients	A	B	C	D
Flavor Oil	0.95	0.95	0.95	0.95
Triclosan	0.3	0.3	0.3	0.3
Water	56.507	54.507	54.507	54.507
Poly (beta-styrenephosphonic acid)		2.0		
Poly (alpha-styrenephosphonic acid)			2.0	
Polyvinyl Alcohol				2.0
Adjusted to pH 6.5 with NaOH	31.0	174.0	86.0	36.0
Triclosan Uptake in Micrograms on Saliva Coated Disks				
Retention of Triclosan on Saliva Coated HA Disks After:				
Initial		183.0		
30 minutes		136.0		
1 hour		105.0		
3 hours		83.0		

The above results show that solution (D) containing polyvinyl alcohol, not an AEA hereunder, produced a triclosan uptake of only 36.0, quite similar to the 31.0 uptake of the control solution (A) without additive. In contrast, solution (C) with poly (alpha-styrenephosphonic acid) produces an uptake of 86.0, more than double that of solutions (A) and (D), and solution (B) with poly (beta-styrenephosphonic acid) produces an uptake about 5 times that of solutions (A) and (D), tending to indicate further that vicinal substitution of the delivery-enhancing group yields superior results. The above results also show the surprisingly good retention of triclosan on the HA disks over time obtained with solution (B) containing poly (beta-styrenephosphonic acid (M.W's about 3,000 to 10,000).

This invention has been described with respect to certain preferred embodiments and it will be understood that modifications and variations thereof obvious to those skilled in the art are to be included within the purview of this application and the scope of the appended claims.

We claim:

1. An oral composition for attaching, adhering or bonding a plaque-inhibiting agent to oral tooth and gum surface comprising in an orally acceptable aqueous humectant vehicle, about 5–30% by weight of a siliceous polishing agent, about 0.25%–0.35% by weight of a substantially water insoluble noncationic antibacterial agent, said oral composition comprising at least one of a surface active agent and a flavoring oil and about 0.05–4% by weight of an antibacterial-enhancing agent which contains at least one delivery-enhancing functional group and at least one organic retention-enhancing group, wherein said delivery-enhancing group enhances delivery of said antibacterial agent to oral tooth and gum surfaces and said retention-enhancing group enhances attachment, adherence or bonding of said antibacterial agent on oral tooth and gum surfaces, wherein said oral composition is free of polyphosphate anticalculus agent in an effective anticalculus amount and said vehicle is other than polyethylene glycol which reduces the antibacterial activity of said antibacterial agent.

2. The oral composition claimed in claim 1 wherein said antibacterial agent is selected from the group consisting of halogenated diphenyl ethers, halogenated salicylanilides, benzoic esters, halogenated carbanilides and phenolic compounds.

3. The oral composition claimed in claim 2 wherein said antibacterial agent is a halogenated diphenyl ether.

4. The oral composition claimed in claim 3 wherein said halogenated diphenyl ether is 2,4,4'-trichloro-2'-hydroxyphenyl ether.

5. The oral composition claims in any one of claims 1 to 4 wherein said surface active agent is present in amount of about 0.5–5% by weight.

6. The oral composition claims in any one of claims 1 to 4 wherein said flavoring oil is present in amount of about 0.1–5% by weight.

7. The oral composition according to any one of claims 1 to 4 wherein said antibacterial-enhancing agent has an average molecular weight of about 100 to about 1,000,000.

8. The oral composition according to claim 7 wherein said delivery-enhancing group is acidic.

9. The oral composition according to claim 8 wherein said delivery-enhancing group is selected from the group consisting of carboxylic, phosphoric, phosphinic, and sulfonic acids, and salts, and mixtures thereof and wherein said organic retention-enhancing group comprises the formula $-(X)_n-R$ wherein X is O, N, S, SO, SO_2, P, PO or Si, R is hydrophobic alkyl, aryl, alkaryl, alkenyl, acyl, aralkyl, heterocyclic, or inert-substituted derivatives thereof, and n is zero or 1 or more and wherein said antibacterial-enhancing agent is a natural or synthetic monomer or a polymer selected from the group consisting of oligomers, homopolymers, copolymers of two or more monomers, ionomers, block copolymers, graft copolymers and cross-linked polymers and monomers.

10. The oral composition according to claim 9 wherein said antibacterial-enhancing agent is an anionic polymer containing a plurality of said delivery-enhancing and retention-enhancing groups.

11. The oral composition according to claim 10 wherein said anionic polymer comprises a chain containing repeating units each containing at least one carbon atom.

12. The oral composition according to claim 11 wherein the unit contains at least one delivery-enhancing group and at least one retention-enhancing group bonded to the same, vicinal, or other atoms in the chain.

13. The oral preparation according to claim 9 wherein the delivery-enhancing group is a phosphonic group or salt thereof.

14. The oral composition according to claim 13 wherein said antibacterial-enhancing agent is poly (beta-styrenephosphonic acid), poly (alpha-styrenephosphonic acid) polymer, or copolymer of either styrenephosphonic acid with the other or with another ethylenically unsaturated polymerizable monomer.

15. The oral composition according to any one of claims 1 to 4 containing a fluoride-providing source.

* * * * *

Called applicant 7-9-97 at 2:20 p.m. Applicant explained that Patent Number 5,288,480 was the correct patent number as on the most recent label submitted 5-22-97. Patent Number 5,288,480 is the one for which we have the patent information. The earlier Patent Number of 5,032,386 was incorrectly used on the diskette copy of the label submitted earlier.

DJB

Colgate-Palmolive Company

Colgate TOTAL™ (sodium fluoride USP 0.24%, triclosan 0.30%) Toothpaste

Original New Drug Application

NDA 20-231

Item 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))

Item 14. A patent certification with respect to any patant which claims the drug (21 U.S.C. 255(b)(2) or (j)(2)(A))

Paragraph II certification for the compound 2.4.4'-trichloro-2'-hydroxydiphenyl ether, triclosan, is submitted on the following pages. The patent certification states that the patent for this compound, U.S. Patent 3,455,398, May 20, 1969, expired as of May 20, 1986.

Additionally, the marketing exclusivity petition is submitted immediately following the patent certification. Copies of the Colgate-Palmolive patents for triclosan-containing dentifrices are submitted as attachments to the exclusivity petition.

For convenience in review, this information is submitted in this volume, rather than following NDA item 12.

Marketing Exclusivity

PARAGRAPH II CERTIFICATION

I, Robert L. Stone, Managing Patent Counsel of Colgate-Palmolive Company, certify on behalf of applicant Colgate-Palmolive Company, any patent that claims 2,4,4'-trichloro-2'-hydroxydiphenyl ether for which the application to which this Certification is being attached, has expired. In this regard, I call attention to U.S. Patent 3,445,398, May 20, 1969, copy attached, which expired May 20, 1986, directed to Synergistic Antibacterial Compositions (including 2,4,4'-trichloro-2'-hydroxydiphenyl ether; also known as triclosan).

Since the patent has expired, a statement under Section 314.95 (a) to notify each patent owner is unnecessary.

Robert L. Stone
Managing Patent Counsel

Attachment

State of New Jersey)
ss
County of Middlesex)

Sworn to and subscribed before me by Robert L. Stone, this 26th day of November, 1991.

Notary Public
GLORIA J. CALLOWAY
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires March 10, 1992

United States Patent Office

3,445,398

Patented May 20, 1969

1

3,445,398

SYNERGISTIC ANTIBACTERIAL COMPOSITIONS

Eric Jungermann, Chicago, and David Taber, Evanston, Ill., assignors to Armour and Company, Chicago, Ill., a corporation of Delaware

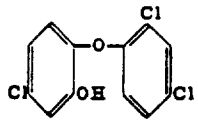
No Drawing. Filed Apr. 7, 1967, Ser. No. 629,067
Int. Cl. C11d 9/50, 3/48
U.S. Cl. 252—107 5 Claims

ABSTRACT OF THE DISCLOSURE

Compositions possessing antibacterial activity through the use of a synergistic mixture of 3,4,4'-trichlorocarbanilide and 2,4,4'-trichloro-2'-hydroxydiphenyl ether and in which the ratio of carbanilide to the diphenyl ether is from about nine to forty parts of the carbanilide to about one part of the diphenyl ether.

Background of the invention

The present invention relates to antibacterial compositions which possess synergistic activity through the use of a mixture of antibacterial agents. More specifically the present invention relates to a mixture of 3,4,4'-trichlorocarbanilide and a chlorohydroxyphenyl phenyl ether, 2,4,4' - trichloro - 2' - hydroxydiphenyl ether having the formula:



During the past decade there have been extensive investigations to develop new antibacterial agents, particularly for use in various detergent and cosmetic preparations. It is now estimated that more than 20% of the toilet bar soap sales are products which contain an antibacterial system, and this percentage is steadily increasing. A number of compounds have been suggested for use in antibacterial detergent and cosmetic preparations, and probably the most popular among these is hexachlorophene. Although hexachlorophene is an effective antibacterial agent, and retains its activity even in the presence of a detergent medium such as soap, it does have a tendency to cause discoloration in a detergent product when such product is exposed to light. According to U.S. Patent 3,177,115, hexachlorophene and certain halogenated carbanilides possess synergistic activity, that is the degree of antibacterial activity of the halogenated carbanilides and hexachlorophene in combination is far greater than the antibacterial activity of these agents when taken independently. The discovery of synergism between hexachlorophene and certain of the halogenated carbanilides was important in that it permitted soap manufacturers and others to provide detergent compositions which have a high level of antibacterial activity, but on the other hand have a greatly reduced concentration of antibacterial agents. The discovery was of further importance because one could then substantially decrease the amount of hexachlorophene employed in the antibacterial composition and thereby greatly reduce the tendency of such compositions to discolor upon prolonged exposure to light.

It has been previously found by others that antibacterial properties are imparted to various compositions by the incorporation therein of chlorohydroxyphenyl phenyl ethers. In British 1,038,185 to J. R. Geigy A.G. it is stated that such chlorohydroxyphenyl phenyl ethers are potent antibacterial agents and are active against gram positive as well as gram negative bacteria. The preparation of the aforementioned chlorohydroxyphenyl phenyl ethers are set forth in this British patent.

2

It is also known that certain of the halogenated carbanilides, particularly 3,4,4'-trichlorocarbanilide exhibit antibacterial activity.

Summary of the invention

In accordance with this invention it has been found that mixtures of 3,4,4'-trichlorocarbanilide and 2,4,4'-trichloro-2'-hydroxydiphenyl ether exhibit synergistic antibacterial activity and this activity is maintained when such mixtures are incorporated into various detergent compositions such as soap and also in cosmetic preparations.

It is therefore an object of this invention to provide antibacterial compositions which include as antibacterial agents a synergistic combination of 3,4,4'-trichlorocarbanilide and 2,4,4'-trichloro-2'-hydroxydiphenyl ether.

It is still a further object of this invention to provide antibacterial agents which are effective in soap and in other detergent and cosmetic mediums.

It is another object of this invention to provide antibacterial compositions which are effective against both gram positive and gram negative bacteria. Other objects and advantages and a fuller understanding of our invention will become apparent from the ensuing description and examples.

Description of the preferred embodiments

In a specific embodiment our invention may be exemplified by a soap composition containing as the active antibacterial ingredient a synergistic mixture of (A) 3,4,4'-trichlorcarbanilide and (B) 2,4,4'-trichloro-2'-hydroxydiphenyl ether wherein the ratio of A to B present in the soap is from about nine to forty parts of A to about one part of B.

It is found that when the halogenated carbanilide and the chlorohydroxyphenyl phenyl ether, as set forth above, are used together, a germicidal effect is achieved which is greater than the mere total of the individual effects of the individual ingredients. This has importance in cases where it is desirable to increase the activity of the carbanilide without employing higher concentrations, and in other cases, it assumes an even greater importance from an economic standpoint, since the presence of the chlorohydroxyphenyl phenyl ether enables a reduction in the total concentration of the antibacterial agent while at the same time retaining the desired level of antibacterial effect.

What the actual mechanism of the potentiating or synergistic effect is, we cannot explain. The invention relates to the synergistic cooperation of these two agents when used in minor proportions in various compositions, especially antibacterial detergent compositions such as soap, and the discovery that this synergistic phenomenon occurs even at the high pH conditions existing in soap and other detergent formulations provides one of the important aspects of this invention.

Relatively small amounts of the carbanilide and the chlorohydroxyphenyl phenyl ether are sufficient for the increased antibacterial effect. Satisfactory results can be obtained when the combined weights of the above two agents are from 0.3% to 2.5% of the total weight of the composition. A preferred range is the weight concentration of about 0.5% to 1.5% and an excellent product is one containing soap and 1% of the carbanilide and about 0.10% of the chlorohydroxyphenyl phenyl ether. It should be understood that even concentrations below the ranges set out above will provide some degree of antibacterial effect and a substantially higher concentration than those referred to will also give satisfactory results, although there are certain practical considerations such

Marketing Exclusivity

as the cost of the two agents which limits the desirability of greater amounts of the germicidal composition in the soap or other medium.

As indicated above, the ratio of the preferred range of the carbanilide to the chlorohydroxyphenyl phenyl ether is from about 9 to 40 parts of the carbanilide to about 1 part of the chlorohydroxyphenyl phenyl ether, the parts being by weight. In other words, in a soap containing an antibacterial concentration of 3,4,4'-trichlorocarbanilide, the chlorohydroxyphenyl phenyl ether is preferably used in the proportion of 1 part of the chlorohydroxyphenyl phenyl ether to from 9 to 40 parts of the carbanilide.

The term "soap" refers to the water-soluble ammonium, metallic, or organic base salts of various fatty acids, which are chiefly lauric, oleic, stearic, and palmitic acids. As used in this description, the term is intended to cover all products in which soap is a major constituent, for example, bar, flake, powdered, soft and liquid soaps; shaving creams, toothpaste, cleansing creams, etc.

The anionic type and nonionic type synthetic detergents can be used in place of the soap. The anionic type synthetics suitable for use in the invention can be described as those detergents having pronounced cleansing power and including in their molecular structure an alkyl radical containing from 6 to 18 carbon atoms and a sulfonic acid or sulfuric acid ester radical. Either organic base, ammonium, sodium or potassium salts of the anionic type detergents can be used. The main types of detergents falling within this category are alkyl-aryl sulfonates, such as sodium or potassium dodecyl benzene sulfonate, sodium or potassium octadecyl benzene sulfonate, and sodium or potassium octyl naphthalene sulfonate; the alkyl sulfates, such as sodium or potassium salts of dodecyl, hexadecyl, and octadecyl sulfates; the sulfonated fatty acid amides, such as sodium or potassium salts of the oleic acid amide of methyl taurine; and the sulfonated monoglycerides such as the mono-coconut oil fatty acid ester of sodium 1,2-hydroxypropane-3-sulfonate.

The nonionic type synthetic detergents suitable for use in the invention may be described as those detergents which do not ionize in solution but owe their water-solubility to un-ionized polar groups such as hydroxy or other linkages. The main types of detergents falling within this category are the polyoxyethylene ethers of the higher fatty alcohols and alkyl phenols; the polyethylene glycols of fatty acids; fatty alkylol amide condensation products; polymers of ethylene and propylene oxides; compounds formed by the addition of propylene oxide to ethylene diamine, followed by the addition of ethylene oxide; fatty acid ethylene oxide condensation products; condensation products of ethylene oxide and a fatty acid ester of a polyhydric alcohol or sugar; and the detergents prepared by heating together a higher fatty acid with a diethanolamine. Some examples of synthetic nonionics suitable for the purpose of this invention are ethylene oxide-tall oil fatty acid reaction products; isooctyl phenol-ethylene oxide reaction products; propylene oxide-ethylene oxide reaction products; and combinations of isooctyl phenol-ethylene oxide with coconut oil fatty acid ethylene oxide reaction products.

The synergistic combinations of the 3,4,4'-trichlorocarbanilide and the 2,4,4'-trichloro-2'-hydroxydiphenyl ether can be added to the soap and other detergents by any suitable method which results in a uniform distribution of the agents throughout the entire mass.

Specific examples illustrating the invention are set out as follows:

EXAMPLE I

A convenient and meaningful method of measuring the effectiveness of antibacterial compositions is by means of a modified agar streak method utilizing varying amounts and ratios of the individual antibacterial agents in a toilet soap medium. Briefly the test consists of making serial dilutions of soap containing varying amounts

and proportions of the antibacterial agents. All solutions are maintained at 60° C. until they are dispensed. Aliquots of the dilutions are dispensed into measured amounts of nutrient agar at 50° C. and thoroughly dispersed. Plates are poured, allowed to solidify and streaked with a standard 4 mm. loopful of a 24-hour broth culture of *Staphylococcus aureus* FDA 209. After incubation for 24 hours at 37° C., the bacteriostatic end point is determined. The bacteriostatic end point, hereinafter called the minimum inhibitory concentration, represents the minimum concentration in p.p.m. (parts per million) of the bacteriostatic agent or combination of agents necessary to inhibit all growth of the inoculant organism. No particular minimum inhibitory concentration has been established to determine the usefulness of an antibacterial agent, although the lower the end point the better the antibacterial activity and the smaller will be the amount of the agent or agents necessary to maintain a particular degree of effectiveness. The soap utilized for these evaluations was a neutral white toilet soap containing about 20% by weight of sodium coco soap and about 80% by weight of sodium tallow soap.

Using the modified agar streak method as described above, the antibacterial effectiveness of varying amounts and varying ratios of the component "active agents" was determined. In this manner a ratio study of the synergistic pair 3,4,4'-trichlorocarbanilide and 2,4,4'-trichloro-2-hydroxydiphenyl ether was carried out, the results of which are summarized in the following table.

TABLE

Initial concentration of agent in the soap		Minimum inhibitory concentration, p.p.m. of agent
TCC [1]	DPE [2]	
0.0	0.1	0.2
0.1	0.09	0.2
0.2	0.08	0.2
0.3	0.07	0.2
0.4	0.06	0.2
0.5	0.05	0.1
0.6	0.04	0.09
0.7	0.03	0.09
0.8	0.02	0.1
0.9	0.01	0.2
1.0	0.00	0.2
0.9	0.10	0.06

[1] 3,4,4'-trichlorocarbanilide.
[2] 2,4,4'-trichloro-2'-hydroxydiphenyl ether.

As shown above, synergistic results were obtained when the ratio of TCC to DPE was between 9 to 40 parts by weight of TCC to one part by weight of DPE.

The results hereinabove set out with respect to a specific soap (20% sodium coco and 80% sodium tallow soap) are obtained with soaps generally. Thus, any fatty acid soap such as sodium laurate, potassium stearate, sodium oleate, and potassium myristate will produce these results. The synergistic action is independent of the soap medium and will take place in non-detergent media as well as in anionic detergents other than soap and in nonionic systems. At the same time, soap is a system in which the synergistic components are highly effective.

While this invention has been described in and exemplified in terms of its preferred embodiments, those skilled in the art will appreciate that variations can be made without departing from the spirit and scope of the invention.

What is claimed is:

1. Antibacterial compositions consisting essentially of a detergent selected from the group consisting of fatty acid water-soluble soaps, anionic and nonionic synthetic organic detergents, and from 0.3% to 2.5% by weight of said detergent of a synergistic combination of 3,4,4'-trichlorocarbanilide and 2,4,4' - trichloro - 2' - hydroxydiphenyl ether wherein the ratio of said carbanilide to said diphenyl ether in the detergent is from about nine to forty parts of said carbanilide to about one part of said diphenyl ether, said parts being by weight.

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Nidkelling Exhibit

2. The antibacterial compositions of claim 1 wherein said detergent is a fatty acid water-soluble soap.

3. Antibacterial compositions according to claim 1 wherein said detergent is a sodium soap of higher fatty acids and wherein the total concentration of said carbanilide and said diphenyl ether is about 1.1% by weight of said detergent.

4. Antibacterial compositions according to claim 1 wherein said detergent is an anionic synthetic organic gent.

5. Antibacterial compositions according to claim 1 wherein said detergent is a nonionic synthetic organic detergent.

References Cited

UNITED STATES PATENTS

3,177,115	4/1965	Casely et al.	252—107
3,284,362	11/1966	Zussmann.	

FOREIGN PATENTS

6,401,526	8/1964	Netherlands.

HERBERT B. GUYNN, *Primary Examiner.*

P. E. WILLIS, *Assistant Examiner.*

U.S. Cl. X.R.

252—106; 424—324

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-231 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

IF_____ Trade (generic) name/dosage form: Total (triclosan / NaF) dentifrice Action: (AP) AE NA

Applicant Colgate-Palmolive Therapeutic Class OTC use

Indication(s) previously approved None

Pediatric labeling of approved indication(s) is adequate ____ inadequate ____

Indication in this application Aids in prevention of cavities, plaque, and gingivitis

(For supplements, answer the following questions in relation to the proposed indication.)

✓ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

____ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

____ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

____ b. The applicant has committed to doing such studies as will be required.
- ____ (1) Studies are ongoing,
- ____ (2) Protocols were submitted and approved.
- ____ (3) Protocols were submitted and are under review.
- ____ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

____ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

____ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Harold Slavt PM 7-10-97

Signature of Preparer and Title (PM, CSO, MO, other) Date

7/10/97

7/10/97

cc: Orig NDA/PLA # 20-231
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

135

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-231 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: Total (triclosan/NaF) dentifrice Action: AP (AE) NA

Applicant Colgate-Palmolive Therapeutic Class OTC use

Indication(s) previously approved NONE

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Prevention of plaque, caries, and gingivitis

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required. A

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

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✓ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Harold Blatt PM 8-8-96

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 20 231
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530) NLRC

From: Division of MEDICAL IMAGING		HFD- 160
Attention: PATRICIA STEWART	**Phone:** 443 - 6560	
Date: 10/2/95		
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product		
Proposed Trademark: Colgate Total™ Toothpaste	**NDA/~~ANDA~~#** 20-231	
Established name, including dosage form: Triclosan/Sodium Fluoride Toothpaste		
Other trademarks by the same firm for companion products:		
Indications for Use (may be a summary if proposed statement is lengthy): Prevent decay; prevent and reduce gingivitis; reduce formation of plaque and tartar		
Initial Comments from the submitter (concerns, observations, etc.): Please review Colgate's response to the initial review by the Labeling Committee.		

GBD
10-13-9

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. August 95

Consult #516 (HFD-550) Initial Consult #200

Colgate Total Triclosan/Sodium Fluoride Toothpaste

The use of "Total" as a trademark modifier is being used to describe both a toothbrush and toothpaste as a part of a dental hygeine system. Since the product is being sold as an OTC product, more leeway is allowed in evaluating the puffery aspects of a trademark.

The Committee does not find the use of Total to be confusing or misleading in this instance and has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

D V Boring 1/25/96 Chair