PRODUCT MONOGRAPH

COLGATE TOTAL
Triclosan and Sodium Fluoride Toothpaste
0.3% Triclosan and 0.243% Sodium Fluoride
Control Number 130592, DIN 02044730

COLGATE TOTAL ADVANCED HEALTH
Triclosan and Sodium Fluoride Toothpaste
0.3% Triclosan and 0.243% Sodium Fluoride
Control Number 123143, DIN 02285568

COLGATE TOTAL ADVANCED HEALTH GUM DEFENSE
Triclosan and Sodium Fluoride Toothpaste
0.3% Triclosan and 0.243% Sodium Fluoride
Control Number 144026, DIN 02364786

Anticaries – Antiplaque – Antigingivitis - Anticalculus

Colgate-Palmolive Canada Inc.
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Date of Revision:
June 25, 2013

Control Number: 163763

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Toothpaste; 0.243% sodium fluoride, 0.3% triclosan	None. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Colgate Total toothpaste is indicated for:

- Prevention of cavities
- Prevention of plaque
- Prevention of gingivitis
- Prevention of calculus

Geriatrics: No identified issues differing from a standard toothpaste

Pediatrics (< 12 years of age):
Since children under 12 years of age do not typically experience plaque, gingivitis or calculus issues, this product is not recommended for children under the age of 12 years.

CONTRAINDICATIONS

Colgate Total toothpaste contains standard toothpaste ingredients plus triclosan and fluoride. Persons with known sensitivities to any of these ingredients should avoid using the product.

WARNINGS AND PRECAUTIONS

There are no warnings or precautions required for this product.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

A very small number of consumer complaints have been received for this product, whether marketed in Canada or other countries (triclosan-containing dentifrices have been in use since 1985 and are currently marketed in many countries worldwide). Post-marketing experience reveals no adverse reactions other than those typical of dentifrice products. There were no incidents of unexpected serious reactions or adverse events attributable to a triclosan/sodium fluoride dentifrice. The frequency of complaints is very low and consistent with non-triclosan containing fluoride dentifrices. Primary complaints were of exfoliation, mild irritation of the mucosa and transient effects on taste. None of the clinical trials and consumer preference studies in which approximately 16,000 subjects were exposed to a triclosan-containing dentifrice provided any indications of significant occurrence of adverse events.

Post-Market Adverse Drug Reactions

None reported

Drug-Drug Interactions

None Known

DOSAGE AND ADMINISTRATION

For adults and children over 12 years of age: apply a ribbon of toothpaste across the head of toothbrush; brush teeth at least twice daily. Use of Colgate Total toothpaste should be in conjunction with an oral care regimen that includes a professional examination at least every six months, and flossing of the teeth.

OVERDOSAGE

The acute effects from overdosage of Colgate Total toothpaste would be those typical of most commercial dentifrice products and primarily manifest as slight gastrointestinal disturbances. Young children would be more sensitive to these effects. These effects would only be seen with ingestion of at least a full tube of toothpaste and due primarily to the base dentifrice ingredients or fluoride. No acute effects would be expected from the low level of triclosan. Treatment should consist of drinking plenty of water and treat symptomatically as needed. Even in the extreme case of prolonged exposure, serious adverse effects would not be expected from triclosan based on the wide margin of safety shown in animal studies. Colgate Total toothpaste contains 1100 ppm fluoride.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Efficacy was demonstrated in six well-controlled studies which showed statistically significant reduction in supragingival plaque and gingivitis indices in the triclosan dentifrice group versus the placebo dentifrice group after six to seven months of use, as measured by the Loe and Silness Gingival Index (Mandel-Chilton Modification) and the Quigley and Hein Plaque Index (Turesky Modification). The mean percent reduction in the Mean Gingival Index Score, the Mean Gingival Severity Index Score, the Mean Plaque Index Score, and the Mean Plaque Severity Index Score were 26% (range 20%-32%), 63% (range 48%-88%), 27% (range 12%-59%) and 48% (range 19%-98%), respectively, versus the placebo dentifrice group. The Plaque Severity Index was calculated for each subject by dividing the total number of tooth surfaces scored either 3, 4, or 5 for plaque formation, on a scale of 0 to 5, by the total number of tooth surfaces scored in the entire mouth. Similarly the Gingival Severity Index was calculated for each subject by dividing the total number of gingival sites which were surface scored 2 or 3, on a scale of 0 to 3, by the total number of sites scored for gingivitis in the entire mouth (total number of teeth scored times 6 sites per tooth). The actual reductions in these scores in the six studies were quite variable for the Mean Plaque Severity Index Score: 18.6, 19.3, 29.2, 50.8, 73.7, and 97.7%; less so for the Mean Gingival Severity Index Score, 47.6, 57.1, 57.1, 57.5, 73.6, and 87.6%.

An additional 44 supplementary studies, including more than 7700 subjects in the triclosan treatment groups, were conducted in which the following parameters were investigated: anticaries effectiveness - 9 studies (n=4517); clinical pharmacology - 3 studies (n=36); plaque/gingivitis - 9 studies (n=522); short-term effects on plaque (less than 2 weeks) - 11 studies (n=236); calculus - 4 studies (n= 458) and human safety - 9 studies (n=2211).

The caries studies demonstrated that triclosan does not interfere with the cariostatic action of fluoride. Four studies of calculus formation demonstrated the anticalculus efficacy of Colgate Total toothpaste, with mean percentage reduction of 35%, in calculus scores compared to placebo dentifrice after 12 weeks/3 months use, based on reductions of 54.7, 23.1, 26.3, and 35.6% in the individual studies. One of these studies reported a 36% reduction at 6 months, compared to the 26.3% reduction in calculus observed at 12 weeks. In vitro and in vivo studies have demonstrated that the triclosan/Gantrez copolymer inhibited crystal growth, thereby providing its anticalculus effect.

The ability of Colgate Total to reduce plaque and gingivitis in the areas between teeth has been investigated. In two long term plaque/gingivitis studies, plaque and gingivitis measured at the interproximal sites (i.e., the disto- and mesio-facial, and disto- and mesio-lingual sites on teeth, commonly scored in such studies) showed significant reductions vs. a placebo dentifrice in both the mean gingival index score and the mean plaque index score. These studies show Colgate Total also exhibits an antibacterial action in helping reduce plaque and gingivitis in the areas between teeth.

Clinical studies demonstrated that twelve hours after use of Colgate Total, triclosan concentrations in plaque were above the minimum inhibitory concentrations (MIC) for most

of the bacterial species present, and the viability of bacteria present in dental plaque was reduced by up to approximately fifty percent. These studies indicated that use of Colgate Total provides up to 12 hour antibacterial protection, helping provide protection against bacteria associated with plaque and gingivitis. When used regularly in a twice daily regime as recommended, Colgate Total should provide around the clock antibacterial action.

Pharmacokinetics

The primary metabolites of triclosan are the glucuronide and sulphate conjugates. The formation of ether or phenol metabolites occurs only when extremely high oral doses are administered (e.g., 500 mg/kg to rats). The formation of these minor metabolites likely occurs as a consequence of the saturation of primary conjugation reaction pathways and reflects metabolic overload in the presence of an exaggerated dose. Potential generation of reactive species of triclosan (i.e., arene oxide and/or free radicals) by P450 has not been demonstrated in sensitive in vitro systems that are able to detect effects of such agents.

The pharmacokinetic and metabolic profile of triclosan are species specific. Triclosan undergoes extensive first pass metabolism in all species. Enterohepatic circulation is marked (approximately 28%) in the rat but there is evidence to suggest that this occurs also in humans, albeit to a much lesser degree. The major route of excretion in humans, monkeys, rabbits, and guinea pigs is renal with conjugates (mainly the glucuronide) detectable in the urine; fecal elimination is secondary. In contrast, elimination in feces is the major route for dogs and rats. The half life in humans is approximately 15 hours.

Ingestion of 0.75 g of a 0.2% triclosan containing toothpaste twice a day (3 mg triclosan daily) for 12 weeks or brushing normally with the same dentifrice twice daily resulted in mean blood levels of 82.9 ng/mL (mean range = 39.9 - 123.1 ng/mL) and 22.6 ng/mL (mean range = 11-33 ng/mL), respectively. In both cases steady state levels were reached after 14 days. The maximum level achieved by any one individual was 180 and 44.3 ng/mL, respectively. In both cases, blood levels fell rapidly upon cessation of exposure and there was no evidence of significant storage.

In the 3-month tooth brushing study, the average amount of toothpaste used daily was 2.46 g (range of 1.8 - 3.8 g), indicating that 4.92 mg triclosan was available for absorption. From the urinary output (mean 0.32 mg/24 hr, range of 0.16 - 0.53 mg), it was calculated that approximately 15% of the triclosan taken into the mouth during normal brushing, i.e., 0.7 - 0.8 mg/day, was absorbed. On the basis of the estimated intake of dentifrice, mean and 95th percentile intakes of triclosan associated with the use of Colgate TOTAL is estimated to be 0.0034 and 0.006 mg/kg/day, respectively, for adults and 0.075 and 0.205 mg/kg/day, respectively, for children 2 - 4 years of age. Under the proposed conditions of use, the estimated safety margins are 5000 - 8824 for adults and 146 - 400 for children.

Earlier studies suggested that there may be ethnic differences, which may be due to differential capacity of the sulphate and glucuronide metabolic pathways to inactivate the triclosan (the former being deficient in the Negro). The highest plasma level recorded in

humans was in a black subject (4000 ng/mL (parts per billion)). This value is 10-fold lower than blood levels associated with the NOAEL (26.3 mg/mL) in the chronic toxicity study in the rat, a species more sensitive to the toxic effects of triclosan than the human. Under normal use conditions, there is no evidence to suggest that glucuronide conjugation becomes saturated and, hence, incapable of detoxifying the compound.

STORAGE AND STABILITY

Store at room temperature (15 – 30˚C).

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Colgate Total toothpaste is available in the following variants:

- Clean Mint (white paste) in 85, 130, 170 mL tubes.
- Fresh Stripe (green striped gel) in a 130 mL tube.
- Whitening (blue striped gel) in 85, 130, 170 mL tubes.

Colgate Total Advanced Health toothpaste is available in the following variants in 85 and 170 mL tubes:

- Clean Between (green gel)
- Enamel Strength (white paste)
- Intense Fresh (green gel)
- Mint Gel (green gel)
- Mint Paste (white paste) also in a 18 mL tube
- Whitening (blue gel)

Colgate Total Advanced Health Gum Defense toothpaste (white paste) is available in 85 and 170 mL tubes.

All products contain the same level of active ingredients; 0.243% sodium fluoride, 0.3% Triclosan.

The non-medicinal ingredients are as follows:

Water (aqua), hydrated silica, glycerin, sorbitol, sodium lauryl sulfate, PVM/MA copolymer, sodium carboxymethylcellulose (cellulose gum), flavour, sodium hydroxide, sodium saccharin, carrageenan (*Chondrus crispus*), propylene glycol, titanium dioxide coated mica, titanium dioxide, D&C Yellow No. 10, FD&C Blue No.1.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

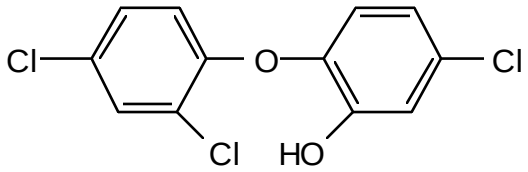
Drug Substance

Triclosan

Proper or Common Name: Triclosan (USAN 1992)

Chemical Name(s): 5-chloro-2-(2,4-dichlorophenoxy)phenol; or 2,4,4'-trichloro-2'-hydroxydiphenyl ether

Structural Formula:



Molecular Weight: 289.5

Physical Form: White to Off-White Powder

Solubility: 2.0 mg/L in water

Melting Point: 55-60 °C

Sodium Fluoride

Proper or Common Name: Sodium Fluoride (USAN 1992)

Chemical Name(s): Sodium Fluoride

Structural Formula: NaF

Molecular Weight: 41.99

Physical Form: White powder

Solubility: 4.0 g/100 mL in water

Melting Point: 993 °C

DETAILED PHARMACOLOGY

Absorption, Distribution and Excretion of Triclosan

Numerous studies were done in humans, primates, dogs, rabbits, guinea pigs, mice, and rats to assess the blood levels of triclosan and/or its glucuronide and sulfate conjugates. Triclosan blood or plasma levels, when detected, were found to be predominantly in the form of glucuronide and sulfate conjugates. In general, the major route of triclosan excretion in humans, primates, rabbits and guinea pigs is renal and the triclosan glucuronide is the main form in the urine. The secondary elimination is through the intestinal tract in the feces. In rats and dogs the feces contains the major amount. Overall the fate of triclosan is species dependent.

Species and Dose-route Comparison of Triclosan Pharmacokinetics.

Species	Route	t(max) (hour)	t(1/2) (hour)	Urine (% of dose)	Feces (% of dose)
Human	Oral	2-8	9-147	44-87	11-34
	Dermal	4-8	17	1-47	0.4-2
	I.V.	---	10	65	21
Monkey	Oral	12-24	---	58	25
	Dermal	15 days	---	Major	Secondary
Dog	Oral	2-8	---	8-12	68-71
	I.V.	1-2	---	13-18	67-70
Rabbit	Oral	---	---	60-74	16-22
	Dermal	---	15	1-53	>1-38
Guinea Pig	I.P.	---	13	62	14
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
	Intravag.	2-4	---	14	26
	I.P.	---	18	8	80

In clinical studies with a dentifrice containing triclosan at a concentration of 0.2, 0.3, or 0.6%, the blood levels ranged between 15 and 25 ppb. The triclosan blood levels in humans appear to reach a steady state by day 7 following normal tooth brushing with 1 gram of toothpaste twice daily, but a precise determination has not been made. Triclosan is rapidly absorbed into the blood and metabolized to the glucuronide and sulfate conjugates at about equal concentrations. In the 21-day study, the mean total triclosan blood level at 4 hours after dosing ranged between 150 to 174 ppb for the subjects taking triclosan (4 mg/day) contained in the aqueous solution. The mean total triclosan excreted in the urine ranges between 41 to 71% of the daily dose and is primarily as the glucuronide conjugate. When brushing twice a day with a toothpaste containing 2 mg triclosan, the blood level is between 15 to 21 ppb.

Four clinical pharmacokinetic studies have been conducted with oral administration of triclosan or ^{14}C-triclosan. In these studies doses of 5, 25, 100 or 200 mg of triclosan were administered. Triclosan is absorbed into the blood and the peak plasma concentration occurred at 2 to 8 hours after the dosing. The mean peak plasma concentrations were

0.025, 0.47, 1.73, and 10.5 ppm for 5, 25, 100 and 200 mg doses, respectively. The mean $t_{1/2}$ of plasma concentrations are 52, 30 and 11 hours for 5-, 25- and 100-mg doses, respectively with large intra- and inter subject ranges of 9 to 147 hours. One subject was administered 200 mg and had a blood $t_{1/2}$ of 15.6 hours. During a 48-hour period, 56, 50 and 44% of the dose is excreted in the urine for 5-, 25-, and 100-mg doses, respectively. During a 6-day period, in the subject receiving 200 mg of triclosan, 57.1% of the dose is eliminated in the urine, and 33.5% in the feces. In two other studies, with one subject each dosed with 200 mg ^{14}C-triclosan, 74 and 87% of the dose is excreted in the urine primarily as the glucuronide and 11% of the dose is found in the feces primarily as the free triclosan. The total triclosan urinary excretion ranges from 44-87% of the dose. The amount of total conjugate excreted within 48 hours varies from 25-90%, with some subjects showing distinct secondary peaks on the plasma concentration curve, indicating an enterohepatic cycle. The renal system is a primary route of excretion. In conjunction with the fecal content (34%), the total elimination of triclosan can be accounted for, and no indication of body retention of triclosan is observed

Clinical Safety and Efficacy Studies

Adequate and well-controlled clinical studies have demonstrated efficacy of triclosan (0.3%)-containing toothpastes by showing greater reductions in gingivitis and supragingival plaque in the treatment groups than in the placebo groups. The studies were of at least six months duration, and obtained comparable results using similar protocols which followed guidelines set forth by the U.S. FDA and the American Dental Association. In each study, results show that the triclosan dentifrice consistently provided highly statistically significant reductions in gingivitis and plaque while also providing a substantial evidence indicating an extremely minor incidence of adverse events associated with the dentifrice use. These events were of the type commonly associated with the inactive ingredients.

Clinical safety and efficacy studies have been conducted on a variety of dentifrice formulations containing up to 0.6% triclosan. No clinically significant adverse events were attributed to triclosan. In two of these studies where clinical chemistries (SGOT, SPGT, alkaline phosphastase, bilirubin and other standard tests) were evaluated (baseline and completion of the studies), no significant findings were reported. Changes in hematology and urinalysis were also considered unremarkable. In addition, a three year clinical, involving over 1,000 subjects using a 0.3% triclosan dentifrice, reported no treatment-related adverse observations or changes in clinical chemistry, hematology, or urinalysis after one year in an interim report.

Mean triclosan blood levels in humans were in the order of 25 parts per billion when dentifrices containing up to 0.6% triclosan were used for up to 12 weeks. A one year study in the baboon, which metabolizes triclosan in a manner similar to that of humans, given oral doses of 300 mg triclosan per kilogram body weight per day demonstrated blood levels of 100 parts per million without any associated adverse effects. Under the proposed conditions of use, the estimated mean and upper 95th percentile adult human exposures are 8824- and 5000-fold lower than the No Observed Adverse Effect Level (NOAEL) in the

baboon (30 mg/kg/day); in the case of children, the corresponding values are 400 and 146, respectively.

Blood levels of triclosan from use of a dentifrice have been shown to be generally lower than those resulting from the use of triclosan-containing soaps. In clinical studies with triclosan-containing dentifrices, mean plasma levels ranged from 28-50 parts per billion, with maximum levels ranging from 55 to 293 parts per billion. The use of triclosan-containing soaps produces mean plasma levels ranging from 10-3627 parts per billion, with maximum levels ranging from 168 to 4000 parts per billion. It has been estimated that the most likely and the upper-bound human exposure to triclosan via dermal exposure (i.e., shampoos, soaps, deodorants, etc.) are 0.13 and 0.048 mg/kg/day, respectively.

Animal Studies

In monkeys, following oral administration, the maximum blood concentration is reached at 12 to 24 hours. Following one year of dosing (30-300 mg/kg), plasma triclosan levels ranged up to 206 ppm at 300 mg/kg and were proportionate to the dose administered. In dogs, about 70% of an oral dose is eliminated in the feces, primarily as unchanged triclosan and the urinary excretion accounts for only 8 to 12% of the dose. The peak blood concentration occurs at 2 to 8 hours after oral dosing with maximum blood concentrations ranging from 4 to 9 ppm. In the rabbit, following oral (5-50 mg/kg) and dermal (0.3-11 mg/kg) administrations, the major excretion of triclosan is in the urine whereas the secondary elimination is in the feces. In guinea pigs, following intraperitoneal treatment, urinary excretion, primarily as glucuronide, accounts for 62%. Fecal elimination accounts for 14% of the dose in a 3-day period. From these data the $t_{1/2}$ is calculated to be 13 hours.

In rats, when administered orally or intravaginally, triclosan is rapidly absorbed into the blood with the first C_{max} at about 3 hours and biological half life ranging from 6 to 65 hours, and is excreted mainly in the feces as free triclosan. The AUC for the sulfate conjugate in the plasma is about twice that of the glucuronide. After intravenous administration of triclosan to biliary-fistula rats, 73% of the dose is eliminated in the bile. This finding combined with the two peak plasma concentrations observed after oral dosing suggest that a fairly considerable degree of enterohepatic circulation occurs in the rat. After 14 consecutive days of oral dosing, body retention of triclosan is very small, and there is no evidence of accumulation. Triclosan levels in blood, liver and kidney of rats in a two-year study are proportionate to the amount of drug administered in the food. Blood levels associated with hepatotoxicity were 88.6 ppm.

MICROBIOLOGY

The results of in vitro antibacterial studies with triclosan show that triclosan, solubilized in sodium lauryl sulphate, inhibited the growth of dental plaque organisms B. gingivalis, B. intermedius, A. actinomycetemcomitans, S. mutans, S. sanguis, A. viscosus and A. naeslundii at 2.5, 2.5, 5, 5, 2, 5, and 1 µg/mL, respectively. PVM/MA has no antibacterial

activity, but is added to the formulation to enhance the delivery and retention of triclosan. Tests confirmed that triclosan in Colgate Total toothpaste is a broad-spectrum antibacterial compound, an active agent against both aerobic and anaerobic gram negative as well as gram positive oral bacteria implicated in periodontal diseases. Based upon sampling of oral microflora in clinical trials conducted with triclosan-containing dentifrices for durations up to 6 months as well as extensive world-wide use of such products by all segments of the population, triclosan is not associated with any detrimental shifts in the oral microflora nor is there any evidence of triclosan resistant species emerging.

TOXICOLOGY

Toxicology

Oral toxicity

Acute oral, dermal, subcutaneous and intravenous administration of triclosan to mice, rats, rabbits and dogs indicated that it is not an acute toxicant. The acute oral LD50s ranged from 580 mg/kg(neonatal rats) to ›5000 mg/kg for adult dogs. Triclosan-containing mouthrinses and a dentifrice were also administered to the teeth and gingiva of dogs. No adverse local gingival or systemic effects were observed. When treatments were continued daily up to 13 weeks, there still was no evidence of adverse local or systemic effects. Therefore, it may be concluded that mouthrinse and dentifrice products containing triclosan are not harmful.

Dermal

Numerous formulations of dermal products containing triclosan were tested in human RIPT and Prophetic patch tests, as well as rabbit acute dermal lethality and dermal irritation evaluations. The human prophetic patch test, a 24-hour application of a test solution or slurry to the skin of human volunteers, and the Repeat Insult Patch Test (RIPT) were employed to investigate skin sensitization potential. At least 100 subjects were involved for each of the RIPT and 50 subjects were used for the prophetic test patch. There was no evidence of induced skin sensitization. Triclosan was not a skin sensitizer, phototoxicant or photosensitizer in human studies. Rabbit acute dermal lethality and skin irritation tests also indicate low levels of dermal toxicity and dermal irritation potential for these products. In summary, the findings indicate that the products with triclosan were not dermally toxic. None of the products evaluated were found to be severe irritants. In fact, most have only minimal effects indicating that triclosan at the concentrations used is not a dermal irritant.

Subacute and Subchronic Toxicity

Studies done with rats, rabbits, beagle dog, and baboons are summarized in the following tables. The time frame for these studies ranged between 3 days and 1 year, and there are multiple assessments of the test materials. In most, hematology, blood chemistry,

urinalysis and macro- and microscopic tissue measurements were performed. Several dermal studies indicated no toxicity.

Subacute and Subchronic Administration to Rats

Route	Dose (mg/kg)	Duration (wks.)	Effect
Oral Intubation	100, 300, 1000, 2000	2	Decreased weight gain at 1000 mg/kg, mortality at 3000 mg/kg
Oral Intubation	50, 100, 200, 500, 1000	4	No pathological findings
Diet	12.5, 25, 62.5, 125	13	No pathological findings
Oral Intubation	125, 250, 500, 1000	12	Toxicity for males at 500 mg/kg, Nephrosis and hepatic changes at 1000 mg/kg
Oral Intubation	50, 125, 315	13	Hepatic, thymic, and kidney changes at 125 mg/kg
Oral Diet	50, 150, 300	13	Hepatic and hematopoietic changes at 150 mg/kg and 300 mg/kg in males

Subchronic Administration to Rabbits.

Route	Dose (mg/kg)	Duration (wks.)	Effect
Oral Intubation	3, 30,150	13	Mortality and hematologic changes at 30 and 150 mg/kg
Diet	12.5, 25, 62.5, 125	13	No discernible symptoms or pathological changes
Dermal	150	2	Some skin irritation; no other toxicity
Dermal	100	0.43	No systemic toxicity
Dermal	3, 15, 30 in propylene glycol	13	Skin irritation at 15 and 30 mg/kg

Subacute and Subchronic Administration to Dogs.

Route	Dose (mg/kg)	Duration (wks.)	Effect
Diet (8 mo.old)	5, 12.5, 25	13	No symptoms or pathology
Capsule	12.5, 25, 50, 100	13	Hepatic, morphologic, and functional changes at 25, 50, and 100 mg/kg
Capsule (5 mo. old)	25, 50, 100, 200	13	Hepatic, morphologic, and functional change; nephritic and hematopoietic dysfunction at 100 and 200 mg/kg
Dermal (11 day old)	0.1% in 4.9% soap solution	3	No evidence of toxicity

Subacute and Subchronic Administration to Baboons.

Route	Dose (mg/kg)	Duration (wks.)	Effect
Oral capsule	1, 10, 30, 100	4	No toxicity
Oral capsule	3	13	No toxicity
Oral capsule	30, 100, 300	52	Emesis, diarrhea at 100 and 300 mg/kg; no pathological findings

When triclosan was given orally, it was by intubation (rat and rabbit), gelatin capsules (dog and baboon), or in the diet (rat, rabbit, and dog). In general, toxicity was more evident following oral intubation or when administered by capsule than with admixing of triclosan in the diet. Dermal application did not elicit systemic toxicity.

Triclosan in Products or Formulations - Oral Toxicity

Studies with two toothpastes containing 0.3% triclosan were conducted for Colgate-Palmolive Company. A 90-day oral toxicity study in rats examined the oral ingestion of up to 12 mg/kg triclosan in the dentifrice base (approximately 100 times expected human exposure when used 2 times daily). Parameters measured included clinical observations, food and water consumption, body and organ weights, clinical chemistries, hematology, and gross and microscopic pathology. There were no treatment related effects demonstrated for the triclosan-containing dentifrices. Additionally, the oral mucosal irritation of 0.3% triclosan dentifrices was examined compared to a placebo and commercial dentifrice product. Toothpaste was applied to the oral mucosa of rats each day for 28 days and gross and microscopic examinations made of the oral tissues. Oral irritation induced by the test product was equivalent to the control dentifrice.

Chronic Toxicity/Oncogenicity

A two-year study with Sprague-Dawley rats showed no significant compound-related effects on mortality. No evidence of carcinogenicity was seen. Animals in the highest

dose groups had reduced mean body weights relative to controls. There were some dose related reductions in RBC, hemoglobin, and hematocrit especially in females. There appeared to be an increase in clotting time for males. The blood chemistry showed dose related changes in liver enzymes, protein fraction, BUN, bilirubin, triglyceride, and glucose. The liver was the main target organ as seen by microscopic compound-related lesions in males in the highest does groups. These consisted of centrilobular hepatocyte hypertrophy and hepatocytic inclusions. This study establishes a no observed adverse effect level (NOAEL) for the rat as 50 mg/kg/day. The chemical determination of triclosan and its glucuronide and sulfate conjugates in blood, liver, and kidney of animals during the two-year study indicated that the amount detected was, in general, proportionate to the amount of drug in the food .

Total triclosan levels in kidney and liver of male rats are proportionate to dose and there is no buildup of triclosan in the tissues from the first measurement at 3 months to the final measurement at 24 months. Since liver pathology was found in rats receiving 150 mg/kg of triclosan and the 50 mg/kg level appeared to be the no observable effect level (NOEL), and the corresponding levels of total triclosan in the blood are 88.6 and 26.3 ppm, respectively it is assumed that these threshold concentrations can be used as an indicator for toxicity when studying the effects of triclosan during human clinical studies.

In a safety study, no treatment-related effects were noted in newborn rhesus monkeys bathed with 15 mL of a 0.1% triclosan liquid soap for 5 minutes daily for 90 days indicating that the neonate is not hypersusceptible to any adverse effects associated with triclosan. The use of such soaps in leukemic patients undergoing chemotherapy (estimated daily dose of 50 mg) gave no indication of increased susceptibility to triclosan. These studies indicate that neither the very young nor the debilitated patient appears to have increased susceptibility to any adverse effects associated with triclosan.

Mutagenicity

Eighteen tests were conducted to assess the mutagenic potential of triclosan , and sixteen tests showed no mutagenicity. Of the two positive tests, one was a weak response which upon repeating was found to be non-mutagenic. The other test, mammalian spot test by Fahrig, was seriously deficient. When the study was repeated, the results showed triclosan is non-mutagenic.

Reproduction and Teratology

Teratology and reproduction studies were carried out with rats, mice or rabbits by Ciba-Geigy, and are reported in their Product Master File MF-7338. These studies indicated that triclosan is neither a teratogen nor a reproductive toxin. The reproduction study was a two-generation evaluation in rats dosed with 15-150 mg/kg/day triclosan. This study identifies a NOAEL of 150 mg/kg/day for reproductive performance of adults and a NOAEL of 50 mg/kg/day for effects on the offspring. Since the developmental studies were not

conducted by currently acceptable evaluation criteria, they were repeated with state-of-the-art study designs. In the first of these studies, mice were administered triclosan in the diet (10-350 mg/kg/day) from days 6-15 of gestation. This study established a NOAEL of 25 mg/kg/day for maternal and fetal toxicity, with no evidence of teratogenesis. In the second of these studies, a rat Segment II teratology study, animals were dosed with 15-150 mg/kg/day of triclosan from days 6-15 of gestation. There was no evidence of teratogenicity at any dose level, although there were observations of mild maternal and fetal toxicity at the highest dose. The NOAELs for both maternal and developmental toxicity was 50 mg/kg/day. Rabbits were also evaluated for possible developmental effects. Animals were dosed with 15-150 mg/kg/day of triclosan on days 6-18 of gestation. Maternal toxicity was observed only at the highest dose and no toxicity was seen in the fetuses. This study provides estimated NOAELs of 50 mg/kg/day for maternal toxicity and 150 mg/kg/day for developmental effects.

IN VITRO ANTI-INFLAMMATORY STUDIES

It has been generally assumed that triclosan in Colgate Total's effect on gingival inflammation was due to its antimicrobial action and resulting anti-plaque effect. Several in vitro studies with human gingival fibroblast cultures have shown that triclosan inhibits the formation of mediators of gingival inflammation, such as IL-1β and PGE_2. This potentially may be a means of action when triclosan is used in a toothpaste, in addition to its antibacterial effect. However, additional studies on the formation of inflammatory mediators in mononuclear blood cells, and further clinical trials investigating the effect of triclosan on levels of IL-1 β as well as PGE_2 in crevicular fluid are necessary to further support this hypothesis.

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PART III: CONSUMER INFORMATION

COLGATE TOTAL
Triclosan and Sodium Fluoride Toothpaste

COLGATE TOTAL ADVANCED HEALTH
Triclosan and Sodium Fluoride Toothpaste

COLGATE TOTAL ADVANCED HEALTH GUM DEFENSE
Triclosan and Sodium Fluoride Toothpaste

This leaflet is part III of a three-part "Product Monograph" published when Colgate Total toothpaste was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Colgate Total toothpaste. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- Prevention of cavities
- Prevention of plaque
- Prevention of gingivitis
- Prevention of calculus (tartar)

What it does:
Colgate Total contains triclosan and sodium fluoride. Triclosan is a broad spectrum antibacterial compound that will kill the bacteria in plaque that can lead to gingivitis and calculus formation. The sodium fluoride helps in making the teeth more resistant to cavities by strengthening the teeth through the remineralization process.

When it should not be used:
Colgate Total toothpaste contains standard toothpaste ingredients plus triclosan and fluoride. Persons with known sensitivities to any of these ingredients should avoid using the product.

What the medicinal ingredient is:
Sodium Fluoride, Triclosan

What the important nonmedicinal ingredients are:
Water (aqua), hydrated silica, glycerin, sorbitol, sodium lauryl sulfate, PVM/MA copolymer, sodium carboxymethyl-cellulose (cellulose gum), flavour, sodium hydroxide, sodium saccharin, carrageenan (*Chondrus crispus*), propylene glycol, colour (titanium dioxide coated mica, titanium dioxide, D&C Yellow No. 10, and/or FD&C Blue No.1).

What dosage forms it comes in:
Colgate Total toothpaste is available in 18 mL, 85 mL, 130 mL and 170 mL tubes. All products contain 0.24% sodium fluoride and 0.3% triclosan.

PROPER USE OF THIS MEDICATION

Usual dose:
For adults and children over 12 years of age: apply a ribbon of toothpaste across the head of toothbrush; brush teeth at least twice daily. Colgate Total should be used as part of an oral health program that includes regular flossing and a dental check-up every 6 months.

Overdose:
If a full tube of toothpaste is ingested the patient may experience slight gastrointestinal disturbances. Treatment should consist of drinking plenty of water and treat symptomatically as needed.

In case of accidental drug overdose, contact a health care practitioner, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

No significant side effects. As with any toothpaste there is the possibility of minor mouth irritation caused by sensitivity to standard toothpaste ingredients. If this occurs discontinue use of the toothpaste.

For any unexpected effects while taking Colgate Total toothpaste contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15 – 30˚C).

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to:**

    Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Colgate-Palmolive Canada Inc. at:
1-800-268-6757

This leaflet was prepared by Colgate-Palmolive Canada Inc.

Last revised: June 25, 2013.