Colgate
Oral Health Network
for Professional Education
and Development

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TRICLOSAN SAFETY EXPOSED

The purpose of this continuing education course is to:

1. Review published safety information about triclosan.
2. Discuss species-specific findings related to endocrine disruption, tumor formation and muscle function associated with triclosan exposure.
3. Discuss the effects of triclosan on antimicrobial resistance.
4. Describe important safety information regarding use of triclosan-containing dentifrice.

Introduction

Triclosan is a synthetic broad-spectrum antimicrobial agent that is found in personal care products, such as soap, antiperspirants and deodorants, antiseptics, cosmetics and toothpaste. It also is included in many other consumer products, including toys, trash bags, fabrics, bedding, kitchen utensils and cleaning supplies.1 Triclosan has been used in personal care products since the 1960s and in dental products in Europe since the 1980s. 2 In 1997, the FDA granted a new drug approval for triclosan-containing dentifrice (Colgate Total®) in the United States.

Professionals and consumers alike have encountered negative reports about potential risks associated with triclosan, calling to question whether triclosan-containing dentifrice is still a safe choice for their patients and families. Dental professionals are well-aware of the benefits of using Colgate Total® as an antiplaque and antigingivitis agent, with efficacy documented in over 80 published clinical trials. However, recent media reports and scientific publications have raised concerns about the safety of using triclosan-containing products, casting doubt about whether triclosan should be included in daily personal care. Dental professionals may be surprised by the extensive amount of published data examining the toxicity of triclosan use, and in fact, may not even be aware of this literature, as articles typically do not appear in mainstream dental publications.

When reviewing the scientific evidence, dental professionals are well-versed in how to assess the efficacy of a given chemotherapeutic agent, and look to measures that indicate a reduction in plaque scores, bleeding and/or inflammation. However, an evidence-based approach to decision-making also requires understanding how to review the evidence of potential harm, which also must be carefully weighed when recommending products to patients. The purpose of this paper is to provide dental professionals with an overview of the published toxicology literature documenting the short-term and long-term effects of exposure to triclosan.

Basic Principles of Toxicology

Toxicology is the study of deleterious effects of physical, chemical and biological substances. The body cannot distinguish between the handling of therapeutic substances, such as drugs, and toxic foreign substances, known as xenobiotics. The body handles all of these substances the same way, following similar kinetic pathways. Toxicokinetics is the study of the absorption, distribution, metabolism and excretion of toxic parent compounds and metabolic products. Toxicokinetic data is used to predict the concentration of a toxin that is able to reach the site of injury and the resultant damage that occurs from the exposure.

Toxic exposures are classified as either acute or chronic. Acute toxicity occurs as a result of a single, large exposure, and effects are usually visible within minutes to hours. Occasionally, signs of acute toxicity may not occur until several weeks to months following the initial exposure. Conversely, chronic toxicity is the effect produced over a prolonged period of time, such as with repeated or cumulative exposure to a toxic substance. Effects of chronic exposure may not appear until significant time has passed and/or after exposure to the toxin has ceased.

There are 3 main routes by which toxins can be absorbed into the body: the dermal route, through skin contact; the respiratory route, through inhalation; and the gastrointestinal route, through ingestion. For each route, the toxin must pass an epithelial barrier; therefore, toxins

tend to be lipophilic. Distribution through the body is often rapid, as toxins that enter the circulation can move freely throughout the body to gain access to their target sites of action. Rate of distribution to a given tissue is dependent upon the amount of bloodflow: highly perfused organs are more likely to be impacted by systemic exposure to a toxin. The concentration of the toxin in each tissue is determined by the affinity of the toxin for the tissue.

Molecules of toxins bind to tissue receptors, and binding strength is related to configuration of the molecule and affinity for the receptor. Toxins can act as agonists, producing the same effects as naturally-occurring substances, such as neurotransmitters, growth factors and hormones. Toxins also act as antagonists, or blockers, occupying receptor sites so that endogenous chemicals are unable to interact with the receptor to produce normal effects.

Toxins are primarily metabolized by the liver, using the cytochrome P450 hepatic enzyme system to create water soluble metabolites that can be eliminated via the kidneys. Renal excretion of toxins follows similar elimination kinetics of drugs, which can be measured by rates of clearance. Gases and volatile compounds can be eliminated via the respiratory system. Metabolites of toxins are often measured in the urine as biomarkers of exposure. Some toxins can accumulate in the body, increasing risk for continued slow release and risks for adverse health outcomes related to chronic exposure.

If the liver and kidneys are functioning properly, accumulation of any given substance is unlikely, as long as that substance can be broken down and eliminated from the body. Normal physiologic changes with aging, as well as diseases of these organs can alter these phases of kinetics. In general, accumulation of substances occurs when rate of intake exceeds rate of clearance. Accumulation also may occur with substances that have a strong binding affinity to body tissues, increasing risk for adverse effects.

Exposure risks for any substance follows a dose response curve, meaning that the greater the exposure, the greater the likelihood that adverse events will develop. From this perspective, all substances have the potential to act as toxins, even those that are seemingly innocuous, with respect to dose. A good example is water. Water is essential to life and is non-noxious with all routes of exposure, except when it is aspirated. Little thought is given to ingesting water every day, except when we have concerns that it might be contaminated with a toxic substance that could produce detrimental effects. However, ingesting excessive amounts of water can be detrimental in and of itself, even fatal, if rates of intake exceed rates of clearance. Exposure risks to humans relate to resultant adverse events, which include organ damage, effects on reproduction, and carcinogenesis.

Toxicokinetics of Triclosan

Triclosan can be absorbed through skin and mucosa, and via ingestion, with levels detectable in blood, urine and breast milk that correlate closely with patterns of consumer product use.3 Information about triclosan distribution following oral administration is based on studies in rodents. More than 95% of triclosan is bound to plasma proteins in mice and in humans. In rodents, at all measured timepoints and at all orally administered dosages, the highest levels of triclosan are observed in the plasma, followed by the liver, kidneys and lungs. This data reflects the lack of accumulation in major organs, which can be attributed to efficient elimination of

triclosan from the plasma. The exception occurs in mice, which exhibit higher distribution to the liver, bile and intestinal tract.

Triclosan is metabolized by the liver to parent sulfate and glucuronide conjugates in animals and humans, although there are interspecies differences in the ratio of these byproducts. Orally administered triclosan in humans undergoes the first pass effect in the liver, with virtually complete conversion of the parent compound to the sulfate or glucuronide conjugates. In humans, triclosan is primarily eliminated by the kidneys, with some minor elimination via the feces. Elimination half-life ranges from 10 to 20 hours. Similarly, half-life is approximately 13 hours in children. 1 Published data does not reflect any age or gender-related changes in triclosan pharmacokinetics. 4

Oral Route of Triclosan Exposure

Triclosan is well-absorbed regardless of whether it is ingested as a toothpaste slurry or in an aqueous solution. The amount available for systemic absorption following ingestion with oral care products is less than the applied dose, as oral care products are typically rinsed and expectorated. Absorption includes the amount retained following oral application, as well as the amount ingested all along the gastrointestinal tract, including from the buccal mucosa. 1 Studies confirm that following systemic absorption of triclosan from the oral route of exposure, triclosan is metabolized and completely removed from the body, with no evidence of adverse clinical events as there is no accumulation. 1

DeSalva et al. published the first review documenting toxicology data associated with oral exposure of triclosan in dentifrice and mouthrinse products. The review included acute and chronic toxicity studies, pharmacokinetics, and effects on reproduction and carcinogenesis. Data from 1246 subjects participating in clinical trials was included in the review, with toothpaste and mouthrinse concentrations ranging from 0.01% to 0.6% with use ranging from 1 day to 12 weeks. No differences were observed with blood, liver function, or kidney function tests between experimental and control populations. 1,5 The authors concluded that triclosan was well-tolerated across species, including man, and was deemed safe for use in oral care products. 5

Other studies have been conducted in human subjects that confirm that triclosan does not accumulate in the body or cause any clinically relevant, adverse events following exposure in oral care products. 1 To assess the buccal absorption of triclosan and retention of triclosan in dental plaque, 0.03% triclosan and placebo mouthrinses were applied twice daily for 3 weeks. Blood plasma, dental plaque and expectorated oral rinse were collected before, during and 8 days after the treatment period. Plaque samples were collected 1 hour after rinsing, and blood was drawn 4 hours after rinsing. Oral retention of the dose was calculated by subtracting the amount of triclosan remaining in the expectorated rinse. The parent compound and metabolites of triclosan were collected from the plasma samples, and total triclosan was measured in dental plaque.

Results revealed that only 7.33% of the applied triclosan dose was orally retained. Recovered triclosan in dental plaque ranged from 20.5 to 46.4 mcg per gram of dental plaque. Only small levels of free (unbound) triclosan were detected in the plasma samples; however, its metabolites were recovered at various sampling timepoints in plasma. Approximately 77% to 88% of the

metabolites were present as glucuronide conjugates (63.8 to 86.3 mcg/ml of triclosan glucuronide), while 12% to 23% were the sulfate conjugate (8.23 to 18 ng/ml of triclosan sulfate), indicating that the parent compound had undergone metabolism via the liver. These findings are consistent with previously published work that suggests that when intake from oral exposure is less than 1 mg/day, as would be assumed with use of triclosan dentifrice or mouthrinse, the glucuronide conjugate is the primary metabolite measured in plasma. 1,6

Mean total triclosan plasma concentrations ranged from 74.5 to 94.2 ng/ml, and reached a plateau after 2 days of dosing, but returned to baseline 8 days after the last triclosan oral exposure (<2 ng/ml), indicative of elimination of the metabolites via the urine. Plasma levels suggest that approximately 2 to 4% of the triclosan mouthrinse was ingested and systemically absorbed, but was completely cleared when the product was used as directed. 1,6

Similar findings have been reported with triclosan-containing dentifrice. Bagley and Lin report 3 studies where human subjects brushed with 0.3% triclosan toothpaste once or three times daily with complete ingestion of the dentifrice for 12 days; twice daily brushing with 0.2% triclosan toothpaste compared with ingestion of 20 ml of 0.01% triclosan aqueous solution for 3 weeks; and brushing twice daily with 0.02% triclosan toothpaste compared to placebo. 7 For all studies, plasma levels of triclosan reached a steady state, with no additional increases observed even after repeated brushing. In all studies, there was no accumulation even after repeated toothbrushing with ingestion of the dental slurry, confirming complete elimination of triclosan. The lack of increase in plasma triclosan level illustrates that the liver and kidneys were able to keep up with repeated dosing, by metabolizing and eliminating any systemically absorbed triclosan.

Biomarkers for Triclosan Exposure

Since triclosan is eliminated by the kidneys, the presence of triclosan metabolites in urine is frequently reported as a biomarker to measure exposure in published studies. The concentration of a chemical that is measured in blood (plasma) and/or urine is known as the biomonitoring equivalent (BE). The BE value can be compared to a reference dose to determine whether the exposure dose is within levels identified as tolerable for daily intake, as published in health-based exposure guidelines, or whether the exposure dose exceeds the margin of safety. 4 Thus, BE values are often used as screening tools to evaluate population-based exposure data as a part of risk assessment. (see Triclosan and Allergy)

Key Message:

- Studies confirm that following systemic absorption of triclosan from the oral route of exposure, triclosan is metabolized and completely removed from the body, with no evidence of adverse clinical events as there is no accumulation

The oral administration of triclosan is the most important assessed route of exposure used in toxicology studies, as triclosan is readily absorbed. 4,7 This route also reflects the exposure route associated with use of triclosan-containing dentifrice and mouthrinses, so data derived from these studies is directly relevant to dental professionals. To assess the kinetics of triclosan following oral exposure, Sanborgh-Englund and colleagues measured plasma and urinary triclosan concentrations after 10 healthy volunteers swallowed a 4 mg dose of triclosan

in an oral mouthwash solution. 8 Triclosan levels accumulated in the plasma very quickly, reaching a maximum concentration in 1 to 3 hours, with a terminal half-life of 21 hours. The majority of triclosan was excreted in the urine within the first 24 hours after swallowing; however, the percentage of the dose excreted varied between subjects, ranging from 24% to 83% of the oral dose during the first 4 days after exposure. Notably, less than 1% of the excreted triclosan remained as the parent compound, reflecting the efficient metabolism of triclosan by the liver. The remaining triclosan was recovered as metabolites, predominantly as triclosan glucuronide. 8 Other studies in humans have shown that following ingestion of a single oral dose of triclosan ranging from 5 to 200 mg, approximately 40% of the dose was excreted within the first 24 hours, reaching 60% after 5 days post-exposure. 5

Both plasma levels and urinary levels of triclosan following oral administration have been shown to be useful as markers of exposure. Plasma triclosan levels appear to be more reflective of the dose that best predicts toxicity; however, the utility of using plasma level is limited, given that triclosan levels tend to be very low in humans. 4 Data from Sanborgh-Englund and colleagues confirm this finding, which demonstrated that not only did plasma levels of triclosan rise very quickly, but the entire exposure dose also was removed very quickly (in less than 24 hours). 8 Thus, caution must be used when reading studies that use plasma values for the purpose of exposure risk assessment, as the timing of the blood draw would be critical given how quickly triclosan is cleared from the blood as it is being metabolized.

Many published studies include urinary triclosan levels as relevant biomarkers for exposure. Again, data from Sanborgh-Englund and colleagues illustrates challenges with using this measure. While the majority of the single triclosan dose was eliminated within 24 hours (54%), there was tremendous variation in the range of the percentage of dose eliminated across time. However, the investigators determined that this variation was well within acceptable levels, and that variance was reflective of differences between individual human subjects. 8 Inter-individual variations in rates of excretion were also documented in other human trials following oral ingestion. 5 Biological variance is a known phenomenon among humans, including variations in rates and efficiency of distribution, metabolism and excretion of drugs and other substances. 4

Creatinine clearance also varies among individuals, and can be affected by diet, age, gender, and body mass index. 4,9,10 Cross-sectional studies often report on urinary values obtained from a single sample, and given variations in renal clearance, it is likely that the triclosan levels reported in these studies do not reflect the actual exposure. Single urinary samples can vary considerably within the same individual at different times of the day, and can be influenced by factors such as degree of hydration. Variation also occurs within an individual across multiple days; therefore, it would be more prudent to obtain multiple samples across at least one day, and preferably across several days, to better assess exposure.

Understanding that values will normally fluctuate helps to explain the variance observed in urinary levels of triclosan metabolites across studies. Higher exposure dosages will reflect a greater concentration of metabolites in the urine. An assessment of urinary metabolites performed on a single urinary sample may occasionally reveal an exposure that exceeds upper limits; however, that does not mean that the value is indicative of chronic toxicity. The measure simply reflects exposure to a higher dose at that specific point in time. 4

It is important to note that chronic exposure guidelines set upper limits of exposure that indicate the margin of safety across a lifetime of cumulative exposure. (Krishnan) Exposure guidelines for triclosan have been determined based upon toxicity studies conducted in animals, with margins of safety for dosages that reflect no observed adverse effects. In toxicology testing, animals are given dosages that are far in excess of normal daily and/or cumulative exposure to establish the dosage at which signs of toxicity appear, and to define maximum upper limits of exposure for humans. Also, BE values should not be used diagnostically or to evaluate anticipated health outcomes, as they may not reflect actual exposure levels in terms of toxicity. Further, these levels should not be used to predict the likelihood of an adverse health effect in either individuals or within a given population. 4 Individual sources of triclosan, such as from dentifrice or soap, cannot be identified from either plasma or urinary samples.

Triclosan and Endocrine Disruption

The endocrine system uses hormones as a major communication system within the body, and is critical for a variety of physiologic functions, as well as reproduction and development. 2 The endocrine system exists in a dynamic state, responding to input on a constant basis to maintain normal physiologic functions. Disruptions occur regularly within the endocrine system, which responds to these changes much like a thermostat: shutting on or off does not imply that the system has been compromised, merely, that the system is responding to the environmental conditions at the time.

Of late, there has been considerable interest paid to environmental chemicals that interfere with normal development or endocrine functions, such as reproduction or metabolism, known as endocrine disruptive chemicals (EDCs) or xenobiotics. Numerous mechanisms have been proposed to explain how these chemicals can alter endocrine function, such as interacting with hormone receptors, altering hormonal secretion or clearance, and/or interfering with normal feedback mechanisms in the hypothalamic-pituitary axis. 2

There are different definitions as to what constitutes an “endocrine disruptor;” which is broadly defined as any substance that can interact with the endocrine system to produce an effect. With this definition, an “effect” is not synonymous with an “adverse effect.” However, most national agencies conducting toxicology studies follow the more stringent definition proposed by the World Health Organization, which defines an endocrine disruptor as, “an exogenous substance or mixture that alters function(s) of the endocrine system and causes adverse health effects in an intact organism, or its progeny, or sub(populations).” 11 In this context, EDCs are evaluated in relation to causing risks to health.

Key Message:

- The endocrine system exists in a dynamic state, responding to input on a constant basis to maintain normal physiologic functions. Disruptions occur regularly within the endocrine system, which responds to these changes much like a thermostat: shutting on or off does not imply that the system has been compromised, merely, that the system is responding to the environmental conditions at the time.

Effects on Estrogen

The largest body of reported work has examined the ability of xenobiotics to bind to steroid hormone receptors, most notably, to estrogen receptors. Many chemicals, including triclosan, have been shown to act as "xenoestrogens," meaning that they can bind to estrogen receptors and can either modulate (agonize) or block (antagonize) estrogenic effects, as demonstrated in both in vitro and in vivo assays. 12 Xenoestrogen activities can influence estrogen-dependent health outcomes, including puberty and reproduction, and estrogen-dependent tumor growth. 13 The binding affinity of xenoestrogens, and thus, the biological activities they produce, have been reported to be "several orders of magnitude less" than those of estradiol, one of three endogenous estrogen hormones. 14

The estrogen receptor has been shown to be "promiscuous" in that many chemicals can interact with it to produce agonist or antagonist activity in vitro and in vivo. However, binding of most chemicals is less than ideal, resulting in decreased receptor affinity and a diminished response. Thus, high doses of xenoestrogens are typically required to produce an effect, referred to as a "disruption" of the endocrine pathway. 14

Four published laboratory studies in rats report on the effects of triclosan exposure on the uterus. Three of the studies found no effects on uterine weight or markers of biologic activity, 15-17 while one reported increases in both weight and marker levels.18 In rats, exposure to triclosan by itself produced no effect on the uterus; however, when given with ethinyl estradiol (a naturally produced estrogen hormone which is synthetically manufactured for birth control pills), triclosan appeared to heighten the effects of the estrogen on uterine weight and tissue changes. Interestingly, the ethinyl estradiol-induced effects were achieved within the dosage range that is used in commercially available oral contraceptives; however, the triclosan dose needed to produce these heightened estrogen effects far exceeds estimates for typical human exposure by 30- to 1000-fold. 2,15 Triclosan alone also produced a decrease in plasma levels of estradiol (another naturally produced estrogen hormone) with no effects on plasma luteinizing hormone (LH) or prolactin. 16 LH is produced by the pituitary gland and triggers ovulation. Triclosan may have potentiated the effects of estrogen by influencing estrogen binding to estrogen receptors or slowing renal estrogen clearance.16 No similar findings have been reported for female humans.

Effects on Testosterone

Triclosan also has been shown to bind to androgen receptors, calling to question whether triclosan acts as a blocker, preventing testosterone binding, and thus producing anti-androgenic effects. 2 A dose-dependent suppression of testosterone production as well as enzyme inhibition was observed in laboratory studies using Leydig cells. 19,20 In vivo studies in rats yield conflicting results. One study reported decreased plasma levels of luteinizing (LH) hormone, which is produced by the pituitary gland and stimulates Leydig cells to product testosterone, and decreased sperm production. 21 These findings are not logically related, as regulation of these hormones is controlled by a negative feedback loop, meaning that a drop in testosterone levels should initiate an increase in LH levels to stimulate testosterone production, not a decrease. Another study reported no treatment –related effects on male rat reproductive development, but decreased testosterone levels only at high triclosan dosages. 22 Results of these animal studies have been criticized due to poor design, conflicting results, sources of cells, and inconsistencies with triclosan dose-response effects as compared to previously reported studies in other types of animal models. 1 Overall, data does not support any

consistent adverse effects on male reproduction in animals. No adverse effects on testosterone or male reproduction have been reported in humans.

Effects on Human Reproduction

Epidemiologic studies in humans have found no relationship between urinary triclosan levels and adverse effects on reproduction. There are no associations with urinary triclosan levels and adverse birth outcomes. 23,24 No significant associations exist between urinary triclosan levels in girls and age of onset of menstruation or breast development. 25,26 There is no statistically significant relationship between urinary triclosan levels and male cryptorchidism (undescended testicles) or idiopathic infertility in males. 27,28

Key Message:

- Epidemiologic studies in humans have found no relationship between urinary triclosan levels and adverse effects on reproduction.

Effects on Thyroid Function

Recent studies performed in animal models suggest that oral administration of triclosan may be linked with altering hormonal regulation, specifically with thyroid function and reproduction. Because triclosan and thyroid hormone are molecules that are structurally similar, it has been hypothesized that triclosan could promote the metabolic breakdown of thyroid hormone in the liver, causing a disruptive endocrine effect that could lead to thyroid disease. Concerns about exposure to thyroid disrupting xenobiotics are related to the potential for altering the effects of thyroid hormone on brain development. 29 Multiple studies have been conducted in rats to examine the effect of exposure to triclosan on thyroid function. 16,29-33 Findings from these studies collectively demonstrate that there is a dose-dependent decrease in plasma levels of T4, no consistent effect on plasma levels of T3. No changes in thyroid stimulating hormone (TSH) were found.

Key Message:

- To date, there is no evidence to show that disruptions in thyroid function occur in humans.

The FDA reviewed this data and determined that due to study design limitations, interspecies differences, and variability in routes of administration and dosing compared to those used in consumer products, the data cannot be readily extrapolated to humans. To date, there is no evidence to show that disruptions in thyroid function occur in humans. 1,3,34 One longitudinal randomized placebo-controlled clinical trial monitored thyroid function for 4 years in 132 subjects who brushed twice daily with either 0.3% triclosan dentifrice or placebo. After 4 years, continued use of triclosan dentifrice failed to produce any detectible effects on thyroid function, further lending support for long-term safety with normal use. 35 Additional research is warranted.

Triclosan and Cancer Risk

Key Messages:

- In the presence of estrogen, triclosan exerts an antiestrogenic effect that diminishes cancer cell growth.
- Evidence presented in review papers on triclosan safety demonstrates that triclosan is not genotoxic, mutagenic or carcinogenic. Collectively, these data support that triclosan is not carcinogenic to humans.

Recent concerns have arisen about the potential for triclosan to cause cancer in humans, as triclosan has been shown to bind to steroid hormone receptors, including estrogen receptors. Three studies have examined the estrogenic effects of triclosan on cultured cancer cells. 36-38 Each study used estrogen-receptor positive breast or ovarian cancer cells, or both. Two studies revealed that triclosan was able to displace estrogen from its receptor in cancer cells. 36,37 Two studies found that triclosan exposure caused cancer cells to proliferate. 37,38 However, all studies demonstrated that when cancer cells were exposed to both triclosan and estradiol, there was a reduction in cell proliferation rates. 36-38 These findings collectively suggest that triclosan alone produced an estrogenic effect leading to cell growth; but in the presence of estradiol, triclosan produced an anti-estrogenic effect, which inhibited growth. Theoretically, these findings are important as exposure to estrogen, including estradiol, is considered a risk factor for breast cancer formation, and in the presence of estrogen, triclosan could potentially lower breast cancer risk.

Increased fatty acid synthesis is another mechanism of cancer formation, including among common cancers, such as lung, pancreas and breast cancers. 39-41 Triclosan has been shown to inhibit fatty acid synthesis in cancer cells, suggesting another potential mechanism for inhibition of cancer cell growth. It is important to note that the effects of triclosan exposure on cancer formation have not been studied in humans. 13

Liver tumors have been reported in mice who are exposed to triclosan. Liver tumors are among the most frequently occurring type of spontaneous tumors in rodents, in addition to those that occur following chemical exposure. 1 In mice, toxicity data support that triclosan exposure activates peroxisome proliferation, which is a mechanism of action that is specific to rodent livers. Interestingly, triclosan increases hepatic adenomas and other cancers in mice, but not in rats or hamsters, suggesting that this pathway is species specific, even among rodents. 1

Mice and rats have similar absorption and distribution kinetics; however, their metabolism and elimination kinetics differ. For example, in mice, 48% to 73%, and in rats, 80% of orally administered triclosan is excreted by the feces. This species-specific difference suggests that enterohepatic recirculation is an important pathway for triclosan elimination, allowing for greater retention and accumulation of the parent compound in the liver. Triclosan has been shown to accumulate in the livers of mice at a higher concentration than in plasma, which has not been shown to occur in rats. Accumulation of triclosan in the liver following repeated exposure has been postulated to contribute to risk for formation of liver tumors. 1,4 The mechanism of action of peroxisome proliferation following triclosan exposure and its role in liver tumor formation is not likely relevant or predictive of development of adverse health outcomes in humans, which are likely attributable to species-specific genetic differences and differences in kinetics.

Evidence presented in review papers on triclosan safety demonstrates that triclosan is not genotoxic, mutagenic or carcinogenic. 1,3,5 Collectively, these data support that triclosan is not carcinogenic to humans. 1,3,34,42,43

Adverse Effects of Triclosan on Muscle

Key Message:

- These exposure dosages exceed anything that could be expected in humans following use of triclosan-containing consumer products. [45]
- No adverse effects on muscle tissues or on muscle function in humans have been reported.

One study reported that triclosan exposure impaired excitation-contraction coupling in both cardiac and skeletal muscle. 44 First, mice were given either a single intraperitoneal dose of triclosan or saline. The investigators reported that following injection, plasma triclosan levels increased quickly, and within 10 minutes, mice that received triclosan showed a dose-dependent decrease in cardiac output, left ventricular end-diastolic volume, and reduced pressure in the left ventricle as compared to mice that received saline. Mice that were given triclosan also demonstrated a statistically significant difference in grip strength as compared to sham-injected and saline-injected mice. Impairment in skeletal muscle function was transitory and recovery was complete within 24 hours after dosing. The investigators also exposed larval fathead minnows to various concentrations of triclosan for up to 7 days, after which the swimming activity of the fish was assessed. At the highest concentration of triclosan, swimming activity and predator avoidance and endurance were impaired. Impairment was attributed to adverse effects on striated muscle. 44 Presumably, study findings in fish reflect the potential adverse effects of environmental exposure to triclosan in water systems. (see Environmental Impact of Triclosan Exposure)

To further assess these effects observed in vivo, the investigators conducted in vitro experiments using rodent cardiac and skeletal muscle cells. Exposure to triclosan resulted in decreased excitation-contraction coupling for both muscle types, which the investigators attributed to alterations in ion influx and calcium signaling without depletion of calcium stores. The investigators cautioned that susceptible individuals may be at risk for altered muscle function with triclosan exposure. 44 The most notable limitations of these data are that the exposure routes do not reflect typical routes of either oral or dermal exposure, and the dosages used were 50- to several hundredfold greater than those used in other published chronic exposure studies in rats. These exposure dosages exceed anything that could be expected in humans following use of triclosan-containing consumer products. 45 No adverse effects on muscle tissues or on muscle function in humans have been reported.

Triclosan and Allergy

Exposure to EDCs, including triclosan, has been postulated to increase risk for developing allergies, as these chemicals also have been shown to affect the immune system. 46 Triclosan is known to reduce the levels of various proinflammatory cytokines and downregulate Toll-like (TLR) receptor signaling in response to bacterial endotoxin lipopolysaccharide (LPS) challenge in both acute and chronic inflammatory pathways. 47-54 Research also suggests that

alterations in the symbiotic, or commensal, relationship among human microflora may increase risk for developing allergies. 55

Some believe that among the primary reasons for the dramatic rise in asthma and allergies observed in children is that living in extremely clean households alters a young child's exposure to the flora necessary to train the immune system to mount a defense against infectious pathogens. Epidemiologic data support this "hygiene hypothesis," revealing that asthma and other allergic diseases are more common among children living in homes that have low levels of bacterial LPS. 56,57 Triclosan alters the cell membrane of both gram-positive and gram-negative microorganisms, killing bacteria that produce endotoxins, which poses questions about whether the antimicrobial properties of triclosan, in combination with its immune system effects, can contribute to allergic sensitization.

Key Message:

- Given the large prevalence of allergic disease and widespread use of triclosan-containing household and commercial products, prospective studies are needed to determine whether exposure to triclosan and other EDCs predates allergic sensitization, and if or how their antimicrobial effects influence the formation of allergic disease.

Several cross-sectional studies have shown a relationship between triclosan exposure and allergic sensitization, especially to aeroallergins, such as tree and plant pollens, and to rhinitis and asthma. 58-60 Two of these studies utilized datasets obtained from the National Health and Nutritional Examination Survey (NHANES) database to assess the effects of exposure to triclosan and other chemicals on allergic sensitization. 58,60 Data obtained from cross-sectional studies are limited by the study design. Study endpoints of asthma and wheezing were obtained through self-report, and subject recall bias is often a factor. It is also impossible for control to other irritants that may predispose subjects to allergic sensitization, such as living with pets, household pollutants such as dust mites, or other environmental exposures. Another limitation of the cross-sectional design is that investigators cannot control for the possibility of reverse causation, meaning that there is no way to determine whether results were biased because subjects with allergies may use more triclosan-containing products. 60 In households where children possess multiple allergies, it is plausible to assume that numerous antimicrobial products, including those containing triclosan, are used in an effort to promote clean living conditions.

While it is assumed that the NHANES dataset is representative of a national sample, in the Savage (2012) study, urinary levels of EDCs were not normally distributed, and exposures had to be divided into tertiles. 60 In all of these studies, an assumption was made that urinary levels of EDCs, including urinary triclosan, were appropriate biomarkers of exposure; however, as previously discussed, there are no validation studies confirming that urinary triclosan level is an accurate biomarker. Therefore, study values obtained may not represent level of actual exposure, as values were obtained from a single urinary sample from each study participant.

The most recent of these cross-sectional studies used the NHANES 2005-2006 database to assess the effects of exposure to EDCs on allergic sensitization. 60 This was the first study to examine the relationship between triclosan exposure and food allergies. Data were obtained from a subset of 860 children aged 6 to 18 years, given that allergies are more likely to develop

during childhood. Urinary EDC levels and self-reported data obtained from a respiratory disease questionnaire and medical condition questionnaire were compared to aeroallergen-specific and food-specific IgE levels. Because there is a higher prevalence of allergies in males, the data were further stratified by sex. 61

Study results revealed a significant association between urinary levels of triclosan and aeroallergens and food sensitization. 60 Further, this association was statistically significant for males only. Of the EDCs tested, those that had a positive correlation with increased sensitization all possess antimicrobial properties, and are commonly found in personal care and other household products. The authors speculated that the mechanism by which triclosan and other study EDCs contributes to allergy formation may be attributed to antimicrobial effects as opposed to endocrine effects. This speculation is supported by previously published data examining changes in gut microflora in relation to development of asthma and atophy. 55 The finding of greater allergic sensitization in males is consistent with previously published data, although the mechanism to explain this sex-based difference is not known. 61

There was no statistically significant relationship between EDCs and history of atopic asthma, wheeze or total IgE level. There also was a trend for increasing risk for atopic asthma and atopic wheeze with increasing urinary levels of triclosan which was not statistically significant. 60 These findings are limited by the fact that data obtained about asthma history and wheezing was obtained through self-report, and history of asthma was not formally physician-diagnosed. In fact, in this study, allergic sensitization was not shown to correlate clinically to manifestations of allergic disease. However, high levels of urinary triclosan were positively associated with a greater likelihood of having been diagnosed with allergies or hay fever 58 and with current rhinitis. 59

There is a substantial body of research that supports that development of clinical allergy is caused by a complex interaction of both genetic and environmental factors. 57 In today's environment, all individuals, including children, are exposed to a substantial number and diverse array of allergens. Given the large prevalence of allergic disease and widespread use of triclosan-containing household and commercial products, prospective studies are needed to determine whether exposure to triclosan and other EDCs predates allergic sensitization, and if or how their antimicrobial effects influence the formation of allergic disease. 57,60

Antimicrobial Resistance

Concerns regarding the development of resistant organisms following chronic exposure to triclosan are widespread; however, no causal relationship between triclosan use and resistance has been found. 43 Concerns about the promotion of microbial resistance are unfounded, as use of triclosan has never been shown to promote microbial resistance in any household or clinical environment. 34,42,62,63 Long-term use of triclosan dentifrice does not result in the development of microbial resistance, does not cause a shift in the normal oral microbial ecosystem, and does not cause any other adverse microbial changes, as evidenced by data collected from clinical trials of at least 6 months duration and longer. 63,64

Key Message:

- Long-term use of triclosan dentifrice does not result in the development of microbial resistance, does not cause a shift in the normal oral microbial ecosystem, and does not cause any other adverse microbial changes, as evidenced by data collected from clinical trials of at least 6 months duration and longer.

Triclosan in Handsoaps

Antibacterial soaps have been used since the 1940s, and grew in popularity to the extent that an estimated 75% of commercial soap brands contain triclosan. 65,66 Bathing with soaps that contain 2% triclosan is recommended for patients who carry methicillin-resistant Staphylococcus aureus (MRSA) on their skin, which helped contribute to the successful reduction in MRSA outbreaks in various clinical settings. 67-69 Recently, the governor of Minnesota signed a bill which legalizes a message to ban the sale of triclosan-containing cleaning products, with the law slated to take effect on January 1, 2017. 70 Triclosan-containing products that have obtained FDA approval for consumer use, such as triclosan dentifrice, are exempt from this legislation. Obtaining FDA-approval indicates that product use has demonstrated a positive health benefit, such as the well-documented supragingival plaque and gingivitis reduction observed with use of triclosan dentifrice. The proposed legislation reads as follows:

- Sec. 8. [145.945] CERTAIN SALES OF CLEANING PRODUCTS PROHIBITED. Subdivision 1. Prohibition. In order to prevent the spread of infectious disease and avoidable infections and to promote best practices in sanitation, no person shall offer for retail sale in Minnesota any cleaning product that contains triclosan and is used by consumers for sanitizing or hand and body cleansing.

- Subd. 2. Exception. The prohibition in subdivision 1 shall not apply to individual products for which specific United States Food and Drug Administration approval for consumer use has been secured.

This legislation came shortly after the FDA announced in December 2013 that manufacturers of antibacterial hand and body soaps have to provide evidence that use of these products is more efficacious than washing with plain soap and water to prevent and reduce spread of infection. 71 To date, there is no evidence that antibacterial soaps provide any additional health benefit besides cleaning. A model for testing the efficacy of antibacterial handwash products has been proposed. 72 Hand sanitizers, which are alcohol-based, disinfecting wipes and antibacterial

products used in healthcare settings are not affected by this FDA action. Manufacturers of hand soaps and body washes will need to provide data showing efficacy and safety data with daily long-term use by December 2014. Manufacturers who do not have studies to support their claims will be required to reformulate and/or relabel their products. The FDA will rule on whether these products are “generally recognized as safe and effective” by September 2016.

Environmental Impact of Triclosan Exposure

Widespread public perception that exposure to triclosan and potential endocrine disruption to wildlife and humans is monitored by the U.S. Environmental Protection Agency (EPA). 73 Products and manufacturing processes that contain or use triclosan are registered with the EPA, and include personal care products, soaps, plastics and textiles, paints and stains, and paper manufacturing, all of which are potential sources for triclosan to appear in water or soil. 73 Personal care products placed on the body are not sufficiently metabolized, and therefore, product ingredients have the potential to enter the environment with regular consumer use, fostering concern for bioaccumulation. 74,75 In fact, personal care products are among the most commonly identified compounds in surface water. 75 The Safe Drinking Water Act of 1996 was put into place to prevent contamination of water sources and to improve water management systems, and includes mandates for examining effects of endocrine disruptors on water systems and aquatic plants and wildlife by the EPA. 76

Monitoring data reveals that triclosan has been identified in streams and is believed to have originated from waste water treatment plants, trickle-down filtration, and sewage overflow. 73 In water, triclosan may bioaccumulate by attaching to surface solids and sediment, posing a low-to-moderate potential risk to aquatic organisms. 73

Numerous published studies support that aquatic plants, invertebrates and fish are not highly sensitive to chronic triclosan exposure; however, algae and invertebrates are more sensitive. Sensitivity in algae is thought to be caused by antibacterial mechanisms which are similar between bacteria and algae. 77,78 Using monitoring data about triclosan water levels and known toxicity values, the EPA has determined that exposure to fish does not exceed levels of concern; however, exposure does exceed levels of concern for aquatic plants. 73

Research about triclosan in water and waste water treatment plans supports that triclosan is efficiently broken down via aerobic biodegradation. EPA surface water monitoring data gathered to assess ecological risks associated with triclosan has been applied to consumers using an environmental modeling program. Results reveal that concentrations of triclosan in surface water based on EPA-registered uses do not exceed concentrations of concern for acute risk to aquatic animals and plants. 73,79 Textile manufacturers also are required to monitor how much triclosan is discharged from industrial sites. Because of potential toxicities to aquatic plants and wildlife, discharging triclosan and other chemicals into waterways by manufacturers must conform to requirements of the National Pollutant Discharge Elimination System (NPDES). 73

Triclosan also has been found in soil, where it has not been shown to dissipate. 73 Environmental toxicity studies show that any residual triclosan appearing as biosolids in the land is unlikely to produce any adverse effects in birds, mammals, invertebrates and plants. 80 Effects on soil fertility would only occur in “worst case exposures” and would likely be transient and dependent upon certain soil conditions. 80

The EPA continues to conduct risk assessments related to animal and human health hazards associated with environmental exposure to triclosan from industrial products, waste from manufacturing plants, and personal product use. National Health and Nutrition Surveys (NHANES) data from the Centers for Disease Control (CDC) are used to assess human health risks, by monitoring the urinary excretion of triclosan in humans. These data are believed to more accurately represent aggregate exposure of use of EPA and FDA registered triclosan-containing products by consumers. Further, recommendations for minimizing occupational exposure risks and requirements for use of closed delivery systems have been put into place where triclosan is used in industrial settings. 73,79

Key Message:

- The concentration of triclosan found in Colgate Total® toothpaste is 0.3%, making the impact of use on the environment negligible. Up to 98% of triclosan is removed in wastewater treatment plants following expectoration down the drain, where any remaining triclosan will continue to break down, as it is biodegradable.

Given these findings, the EPA has stated, “Considering the low probability of triclosan being released into household wastewater and surface waters from EPA-regulated antimicrobial uses, the Agency also concluded that chronic aquatic risks are unlikely originating from consumer uses of triclosan-treated plastic and textile items. Therefore, the Agency can reasonably conclude that the antimicrobial uses of triclosan (e.g., triclosan-treated plastic and textile items in households) are unlikely to contribute significant quantities of triclosan into household wastewater and eventually in surface water.” 73 The concentration of triclosan found in Colgate Total® toothpaste is 0.3%, making the impact of use on the environment negligible. Up to 98% of triclosan is removed in wastewater treatment plants following expectoration down the drain, where any remaining triclosan will continue to break down, as it is biodegradable. 81

Safety of Colgate Total Toothpaste with Triclosan

Among oral care products available in the United States, triclosan is found in Colgate Total® toothpaste. To market Colgate Total® in the United States, the Food and Drug Administration (FDA) required Colgate to submit a New Drug Application (NDA). Colgate Total® toothpaste was approved in 1997 as safe and effective by the FDA under the Food, Drug and Cosmetic Act. 82 Because Colgate Total® toothpaste is regulated as a drug by the FDA, safety data is continuously monitored, just as it is for any other approved drug that is available on the market.

The FDA continues to support the efficacy and safety of Colgate Total® with triclosan. In a briefing for reporters conducted Dec. 16, 2013, Dr. Sandy Kweder, Deputy Director in the Office of New Drugs, FDA Center for Drug Evaluation and Research, affirmed the agency’s view that Colgate Total® is safe and effective:

> “Triclosan in toothpaste has been shown to be effective in preventing gingivitis that's caused by bacteria in the mouth. Gingivitis can really wreak havoc with people's teeth. And, they have done studies to show that use of Triclosan in that setting is safe and effective.”

The full transcript of the FDA media briefing, including the comments on Colgate Total® (see page 10 of the transcript), is available on the FDA website at: http://www.fda.gov/downloads/NewsEvents/Newsroom/MediaTranscripts/UCM378989.pdf

Numerous other regulatory agencies around the world also have reviewed the safety and efficacy data surrounding use of triclosan in various consumer products and cosmetics. 34,42,43,62,82,83 Together, these reviews confirm the safety of using triclosan where a health benefit has been demonstrated, as with dentifrice use to improve oral health.

More than 80 published clinical trials involving over 19,000 subjects have evaluated the safety and efficacy of Colgate Total® toothpaste, making it the most widely studied toothpaste in the world. These findings have been confirmed in numerous published meta-analyses and systematic reviews. 84-89

The Cochrane group recently published a systematic review to assess the effects of triclosan/copolymer containing fluoride toothpastes, compared with fluoride toothpastes, for the long-term control of caries, plaque and gingivitis in children and adults. 84 The review analyzed 30 studies containing 14,835 subjects that were published between 1990 and 2012. There were no data available for conducing a meta-analysis on adverse events; however, 22 (73%) of the 30 studies reported that there were no adverse effects caused by either the experimental or control toothpastes. The authors concluded that there was no evidence of any harmful effects or any serious safety concerns associated with use of triclosan/copolymer toothpaste in studies lasting up to 3 years in duration. This study confirms findings reported in previously published systematic reviews. 85,88,89

Key Messages:

- More than 80 published clinical trials involving over 19,000 subjects have evaluated the safety and efficacy of Colgate Total® toothpaste, making it the most widely studied toothpaste in the world. These findings have been confirmed in numerous published meta-analyses and systematic reviews. 84-89
- The Cochrane group recently published a systematic review that concluded that there was no evidence of any harmful effects or any serious safety concerns associated with use of triclosan/copolymer toothpaste in studies lasting up to 3 years in duration.

Colgate Total® toothpaste has obtained the ADA Seal of Acceptance based upon data obtained from longitudinal studies meeting rigorous scientific criteria, including criteria that require the investigators to document any safety issues that arise with long-term use. 90 Dental associations in 30 countries also have granted their seal of approval to this dentifrice.

Adverse Effects on Oral Tissues

No adverse hard or soft tissue effects have been documented with chronic use of Colgate Total® dentifrice. Triclosan has not been shown to contribute to mucosal sloughing. Sloughing may be observed in individuals who are sensitive to other ingredients that are commonly found in dentifrice formulations, including sodium lauryl sulfate, flavoring agents, and notably the pyrophosphates found in tartar-control formulations.91-93 Two studies have shown that triclosan reduces the oral mucosal inflammation and sloughing observed following exposure to

sodium lauryl sulfate in humans.94,95 It is important to note that Colgate Total® toothpaste does not contain pyrophosphates, and produces its anti-tartar effects by reducing biofilm.

Summary

Pharmacokinetic studies in humans show that following normal use of triclosan-containing dentifrice, triclosan does not accumulate in the blood or body tissues, and no adverse systemic effects have been documented following long-term use of triclosan dentifrice. 7 Even when brushing 3 times per day with full ingestion of the product, triclosan is completely eliminated from the body, mainly through excretion in the urine.1,7

In humans, the margin of safety of triclosan is very high. Triclosan-containing personal care products are appropriate for use when there is a demonstrable human health benefit, as is the case with use of triclosan-containing dentifrice for the reduction of supragingival plaque and gingivitis. Oral health professionals should feel confident in recommending use of triclosan-containing oral care products to their patients and their families.

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