TATE & LYLE

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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

August 13, 2018

Re: Study assessing the impact of allulose on dental plaque pH for submission to Docket No. FDA-2015-P-1201-0011

Dear Commissioner Gottlieb:

Tate & Lyle Ingredients Americas LLC submits the enclosed results from a clinical trial indicating that allulose does not yield a decrease in dental plaque pH, as sucrose does, in support of its Citizen Petition (originally submitted on April 10, 2015) requesting that FDA amend 21 C.F.R. § 101.9, Nutrition Labeling of Food, to remove allulose from being included as a carbohydrate, sugar, or added sugar in the Nutrition Facts label on foods and beverages (Docket No. FDA-2015-P-1201-0011).

Tate & Lyle conducted a clinical study in order to determine the effects of allulose on dental plaque pH, with a drop in pH causing potential for dental caries. As has previously been discussed with representatives from the Agency, this study demonstrates that allulose does not operate as a sugar in terms of contributing to tooth decay, measured by changes in dental plaque pH. Under separate cover, Matsutani Chemical Industry Co., Ltd. is submitting in support of our petition its own clinical study on dental plaque pH measurements and an *in vitro* study contained in U.S. Patent No. 8,496,915, which shows that the growth of *S. mutans*, a bacterial strain causing dental caries via acid production, is suppressed when cultured with allulose. Tate & Lyle believes that in sum, these data support, and indeed supplement, the record in a more than sufficient manner to demonstrate that allulose should not be treated as a sugar, added sugar, or carbohydrate for purposes of Nutrition Facts labeling.

We further note that our petition does not request that FDA grant allulose a health claim with respect to anticariogenic effects of allulose and should not be held to that standard for purposes of the petition. However, we reserve the right to seek a health claim in the future. We are requesting FDA's response with respect to the issues addressed in the petition as quickly as possible.

Please do not hesitate to contact us with any questions.

Sincerely,

Susan M. Potter, PhD
Director, Scientific and Regulatory Affairs
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The Forsyth Institute

FINAL REPORT

Study Title: **A Clinical Study on the Effect of Allulose, a Low-Calorie Sugar, on in vivo Dental Plaque pH**

Protocol Number: **N/A**

Study Sponsor: Tate & Lyle Ingredients Americas LLC, 5450 Prairie Stone Pkwy, Hoffman Estates, Illinois 60192, USA

Study Site: The Forsyth Institute Center for Clinical and Translational Research
245 First Street, 17th Floor
Cambridge, MA 02142

Study Personnel: Principal Investigator: Hatice Hasturk, DDS, Ph.D.
Patient Recruiters and Coordinators: M. Letteri and M. Dunne
Study Staff: G. Torresyap, RDH and Constantinos Floros
Consultant: Max Goodson, DDS., PhD.

IRB Approval No/Date: #08-07/Feb 22, 2018 (Forsyth Institutional Review Board)

Study Period: Mar 12, 2018 –June 15, 2018

Conduct of Study: The study was conducted by the Forsyth Center for Clinical and Translational Research (CCTR) in compliance with the protocol, the Declaration of Helsinki, principles of Good Clinical Practice and any applicable regulatory requirement(s). In addition, the study was conducted in compliance with the United States Federal Regulations governing informed consent (21 CFR 50), Institutional Review Boards (21 CFR 56), clinical investigations, and applicable regulations governing sponsor and investigator conduct (21 CFR 312/812).

Approvals:

2 Aug, 2018
Date

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Executive Summary

Purpose

The purpose of this study was to evaluate the *in vivo* effect of Allulose, a low calorie sugar, on the pH of dental plaque.

Study Design

This study was a single center, randomized, double- blind, crossover trial with one (1) test and two (2) control arms. Subjects were randomly assigned to a rinse sequence and received water (negative control); water, 4.7% sucrose (positive control); water, 4.7% Allulose (test).

All subjects provided a signed informed consent to participate in the study and give authorization for release of relevant protected health information to the study investigators. Subjects with a good general health as evidenced by the medical history, between the ages of 18 and 75 years old and with previous high caries experience evidenced by a Decayed Missing Filled Tooth (DMFT) score of >5 were screened for pH changes after a 4.7% sucrose solution. Subjects with acidogenic plaque as demonstrated by a drop in pH to 5.7 or lower and willingness to abstain from all oral hygiene procedures including brushing, flossing, and using any other oral hygiene aides for 48 hours prior to each test day and to abstain from the use of mouthwashes during study were included in the study. Subjects with orthodontic appliances, aggressive periodontitis, acute necrotizing ulcerative gingivitis, or gross decay, systemic conditions which could influence the pH of the oral cavity (i.e., diabetes, salivary gland disorders, acid reflux or GERD, etc.), allergy or intolerance to food ingredients and products including sweeteners were excluded. Pregnant women and current smokers were also excluded from the study.

Dental plaque pH assessments were performed at 0, 2, 4, 6, 8, 10, 15, 20, 30, 40, 50, and 60 minutes using a handheld touch electrode from the mesiobuccal sites of teeth #3, 5, 8, 9,12, and 14 (per American Dental Association-ADA enumeration). The primary outcome variable was mean minimum pH during the test. Secondary outcome variables included, total area under the curve (tAUC), incremental area under the pH-versus-time curve (iAUC) and delta pH (minimum pH minus baseline pH).

A total of nine potentially eligible subjects were screened with seven qualifying subjects. These subjects were randomly assigned to a rinse sequence to test all three tests. All seven subjects completed the study without deviation/adverse events.

Study Rationale

Evidence of non-cariogenicity is required by Food and Drug Administration (FDA) for sugar substitutes. To be considered a non-cariogenic carbohydrate sweetener, FDA requires that when present in food, the food should not lower the dental plaque pH below 5.7 either during or up to 30 minutes after consumption. The purpose of this study was to demonstrate that rinsing with allulose does not lower dental plaque pH and subsequently does not produce an acidogenic plaque.

Results

No adverse events related to rinsing were reported or detected in any subject.

Allulose rinse demonstrated a mean (±SEM) minimum pH of 6.43 ± 0.12 during the study period, significantly higher than the positive control, sucrose rinse, with a mean minimum pH of 5.42 ± 0.11 ($p < 0.0001$), which was clearly under the cut-off pH value of 5.7 for cariogenicity. No

significant differences were found in mean minimum pH between allulose rinse and the negative control, water rinse (p=0.824).

Results for delta pH, total area under the curve and incremental area under the curve all indicated that allulose rinse performed significantly different compared to the positive control, sucrose rinse (p=0.001, p=0.003, p<0.0001, respectively) indicating a non-cariogenic effect similar to water rinse. No significant difference was found for the allulose rinse compared to the negative control, water rinse (p=0.998, p=1.000, p=0.987 respectively).

Conclusion

Results of this study demonstrate that allulose in an aqueous solution does not lower dental plaque pH at any tooth surfaces and at any time points during the 60-min observation period. Allulose is significantly less acidogenic than sucrose and comparable to water.

Introduction

Dietary sugars play a role in non-communicable diseases such as diabetes, metabolic syndrome and is a clear target for reduction. Several technological solutions have been introduced to replace sugar, all with benefits and limitations, for a positive impact on health. High intensity sweeteners and polyols have been used for a long time to replace sucrose. Despite no clear evidence of harm, the trend is today to look for alternatives such as sweet enhancers or alternative sugars such as allulose, which is low caloric.

Allulose is a monosaccharide, or simple sugar, that naturally presents in small quantities in fruits like figs and raisins and a variety of sweet foods like caramel sauce, maple syrup and brown sugar. Allulose is a C-3 epimer of D-fructose and considered as GRAS (generally recognized as safe) compound. It is absorbed by the small intestine and excreted in the urine without being significantly metabolized. In a study on healthy adults consuming allulose at 5 to 20 g reported urinary excretion of allulose at 66-79% and low microbial fermentability of allulose in the large intestine (Iida et al, 2010). In another study, consuming 15 g unlabeled allulose with 776 nCi of 14C-allulose showed that 86% of the radioactive dose was excreted in the urine, less than 3% excreted in feces, and almost no radioactivity was detected in expired air. Intact allulose was predominant (84%) with no other metabolites detected in the urine indicating that allulose is absorbed in the small intestine and excreted in the urine without undergoing significant metabolism (Williamson et al 2014).

Dental caries is commonly mediated by oral bacteria that digest fermentable carbohydrates, such as sucrose, glucose and fructose, resulting in high acid production and altered pH levels in dental plaque (Klein et al, 1938). Streptococcus mutans is the primary cariogenic microorganism and has a special relationship with sucrose that helps the bacteria adhere to the tooth giving it an advantage over competing organisms. With repeated exposure to sugar, the acid produced by Streptococcus mutans in this process causes demineralization of the tooth enamel and subsequent formation of subsurface carious lesions (USPHS/NIDCR 1989). Non-cariogenic sweeteners have been widely used to replace dietary sugars, such as sucrose and corn sweeteners, in foods, thereby decreasing the risk of caries (Bowen et al, 1990; Stenberg et al, 1995; Steinberg at al, 1996; Meyerowitz et al 1996). The FDA regulates health claims related to non-cariogenic carbohydrate sweeteners and dental caries (21CFR101.80). To be considered a non-cariogenic carbohydrate sweetener, FDA requires that when present in food, the food should not lower the dental plaque pH below 5.7 either during or up to 30 minutes after consumption.

Objective

The purpose of this study was to evaluate the *in vivo* effect of Allulose, a low calorie sugar, on the pH of dental plaque.

Study Design and Conduct

This study was a single center, randomized, double- blind, crossover trial with one (1) test and two (2) control arms in seven (7) subjects. Subjects were randomly assigned to receive each of the test products in a particular sequence: ACB, BCA, CAB, ABC, BAC, CBA, BAC.

- Water (negative control)
- Water, 4.7% sucrose (positive control)
- Water, 4.7% Allulose (test)

The study was conducted according to the principles of Good Clinical Practices (GCP) and the Declaration of Helsinki. The Forsyth IRB approved the study protocol and the study documents

prior to initiation of the study. All study records are being stored at the site for up to 3 years (Appendix 1).

Study Population

Subjects were recruited from existing clinical patients and subjects at Forsyth with the stipulation that their participation in this study would not affect any other study in which they may be participating. Study protocol and related study documents were approved by the Forsyth Institutional Review Board (FIRB) prior to study initiation. All subjects signed the approved informed consent document prior to study participation.

Out of a total of nine (9) volunteers screened for the study were eligible and randomized to a rinse sequence. All subjects completed all phases of the study. Subjects recruited for this study were all in good general health with the following characteristics:

Inclusion Criteria

- Subject understands the study procedures and signs forms providing informed consent to participate in the study and authorization for release of relevant protected health information to the study investigators.
- Good general health as evidenced by the medical history.
- Ages 18 to 75 inclusive.
- Caries experience in the past year.
- DMFT score of >5 demonstrating a high caries experience.
- Acidogenic plaque as demonstrated by a drop in pH to 5.7 or lower when challenged with sucrose rinse at the screening visit.
- Availability for the duration of the study.
- Willing to abstain from all oral hygiene procedures, brushing, flossing, and using any other oral hygiene aides for 48 hours prior to each test day and drink only water for the four (4) hours prior to each test.
- Willing to abstain from the use of mouthwashes during the study.

Exclusion Criteria

- Presence of orthodontic appliances.
- Systemic conditions which could influence the pH of the oral cavity (i.e., diabetes, salivary gland disorders, acid reflux or GERD, etc.).
- Use of medications that would influence the pH of the oral cavity. Specifically, concomitant use of neuroleptics, atropine, chemotherapeutic agents, diuretics, antibiotics, antihistamines, decongestants, and muscle relaxants. Also, anticipated need for intermittent use of any medications in these classes or history of use during the 72 hours immediately prior to the screening visit.
- Patients with aggressive periodontitis, acute necrotizing ulcerative gingivitis, or gross decay at discretion of PI.
- Females who by self-report are pregnant, lactating, planning to be pregnant during the study period, or women of childbearing potential who are unwilling to commit to the use of a medically approved form of contraception during the study period.
- Exposure to any investigational agent within the 30 days prior to study visit 1
- Individuals requiring prophylactic antibiotics
- Allergy or intolerance to food ingredients and products including sweeteners.

- Currently participating or have recently participated in another study that testing any oral product
- Smoking (of any kind) including e-cigarette

Subject demographic information is presented in Table 1.

Table 1. Demographic Characteristics of Study Population

Characteristic		N = 7 (100%)
Gender	Male	3 (42.9%)
	Female	4 (57.1%)
Age (years)	Mean (SEM)	52.0 (7.0)
	Median	53
	Min, Max	37, 59
Ethnicity	Not Hispanic or Latino	5 (71.4%)
	Hispanic or Latino	2 (28.6%)
Race	Black	2 (28.6%)
	White	5 (71.4%)

Subject Withdrawals and Protocol Violations

Subjects in this study could be discontinued for any of the following reasons:

- Protocol violations
- Administrative reasons
- Withdrawal of consent
- PI and or sponsor discretion

Subject disposition information is presented in Table 2.

Table 2: Subject Disposition

Number of Subjects	
Screened	9
Randomized	7 (100.0%)
Completed Study	7 (100.0%)
Did Not Complete Study	0 (0.0%)
Per Protocol Population	7 (100.0%)

All subjects who completed the study showed satisfactory level of protocol compliance.

Observations and Measurements

Assessment of Efficacy

Dental plaque pH was recorded from the mesiobuccal surfaces of 6 teeth: # 3, 5, 8, 9, 12, 14 (per American Dental Association system) or # 161, 141, 111, 211, 241, 261 (per Federation Dentaire Internationale-World Dental Federation system). If these teeth were missing the tooth distal to the missing tooth was selected. pH was recorded at time 0, 2, 4, 6, 8, 10, 15, 20, 30, 40, 50, and 60 min.

Dental plaque pH was measured using a direct read-out pH meter (Orion, Model 720A). Measures of pH at the screening visit were recorded in pH units directly from the meter display as the screening measures with sucrose challenge were not blinded. However, to maintain blinding of the examiner, the subsequent study visits with test solutions (3 visits), the instrument was set to mV.

Measurements of plaque pH recorded in mV were performed *in vivo* with a hand-held touch electrode, Beetrode, model MEPH-3L (WP Instruments, New Haven CT), and a AgCL reference electrode (Fisher Scientific, Pittsburgh, PA) using a direct read-out pH meter (Orion 720A. Fisher Scientific, Pittsburgh, PA). A reference salt bridge was created by having the subject dip one finger into a KCL saturated solution containing the reference electrode.

Electrodes were calibrated immediately before and after each series of readings against standard pH buffers at pH 4.00, pH 5.00 and pH 7.00 (Fisher Scientific, Fair Lawn, NJ). Calibration measurements were recorded on CRF for each subject at each visit (Appendix 2).

Test Products

Product Use

Product Accountability

A product inventory was maintained and included details of the materials received and a clear record of when, and to whom, they were dispensed. This inventory record indicated the quantity and description of all investigational materials on hand at any time during the trial.

The test materials (dry ingredients) were kept in a secure location and at controlled room temperature of 20°C - 25°C (68°F – 77°F), RH: <50%. A separate preparation binder was kept by the unblinded staff (C-F) for preparation of the rinse solutions. This binder was kept locked and out the clinical area to maintain blinding.

Test solutions were prepared at room temperature and administered as oral rinses (15 ml for one minute) on the same day.

Electrode Failures and Replacements

One hand held touch electrode (Beetrode, model MEPH-3L, WP Instruments, New Haven CT) was assigned to each subject for use at each time point at each rinse visit (Table 3). When an electrode failed to record or was visibly broken, a new electrode was assigned to the subject and measurements were continued. Any change in electrodes during study visits was recorded on the pH Assessment CRFs.

Table 3. Number of electrodes used per subject

Subject	Number of electrodes used
1	1
2	1
3	1
4	1
5	1
6	1
7	1
Total	7

Adverse Events

Adverse events were monitored as described in the protocol throughout the study. Medical and dental history changes and medication use were reviewed at each visit and findings were recorded. In addition, extra- and intra-oral exam were performed by the study examiner at each visit.

There were no adverse events related to study or test products. All visits were conducted per original protocol and within windows.

Data Analysis

Randomization

The randomization was prepared by an independent staff and provided to the unblinded study staff. Product preparations were prepared in glass flasks and labeled as A, B, or C.

Analysis

Data entry was completed by the data manager and statistical analysis was performed by the PI and consultant (M-G). Complete data listings are included in the Appendix.

Outcome Variables

One primary outcome variable was analyzed in this study:

- minimum pH during the test

Secondary outcome variables included

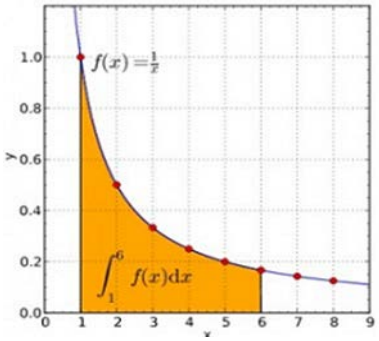
- total area under the curve (tAUC)
- incremental area under the pH-versus-time curve (iAUC)
- delta pH (minimum pH minus baseline pH)

Statistical Methods

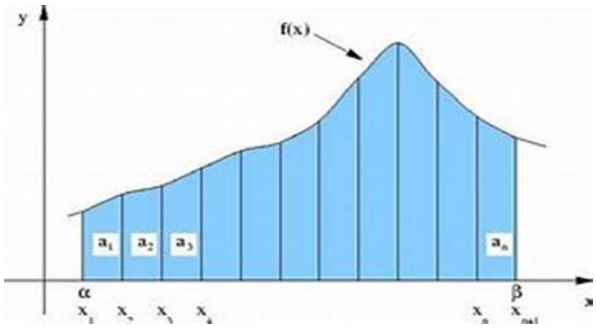
All tests of significance, unless otherwise stated, were performed at alpha = 0.05, two-sided. Assumptions of normality of residuals and heterogeneity of variance were investigated for each

response measurement. The data distribution was approximated by a normal curve. All statistical analyses and data presentations were generated using SPSS version 19.

Data recorded in mV were converted to pH by least squares fit of the function: $pH = K_1 + K_2\,mV + K_3\,Time$. For each test visit, the baseline mV was determined by averaging the pre rinse replicate measurements across the six sites for each subject. For each time point, mean pH was determined by averaging values from the six sites.



Total area under the curve



Incremental area under the curve

Total and incremental AUC was calculated using trapezoidal rule (Carstensen, Thomsen, and Hermansen, 2003) for each subject and test product. iAUC was calculated as the area between the horizontal line at baseline and the pH-versus-time graph which showed the change from baseline. Formulas are shown in the graphs above.

Descriptive statistics (number of subjects, mean, standard deviation, standard error of the mean, minimum and maximum) were presented for minimum pH, delta pH, tAUC and iAUC by study product. Repeated measures analysis of variance (ANOVA) and a post hoc test, Dunnett's test, was utilized to test for possible differences comparing allulose to sucrose and water.

Results

Summary statistics for minimum plaque pH, delta pH, total area under the curve (tAUC) and incremental area under the curve (iAUC) are presented in Table 4. The primary outcome variable, mean minimum pH value obtained post rinsing with allulose was significantly higher than the positive control (sucrose) rinse (Table 4 and Figure 1; $p<0.0001$) and well above the recognized pH of cariogenic plaque (< 5.7). Post rinse mean values for the negative control rinse (water) were not significantly different from allulose (Table 4 and Figure 1; $p=0.824$). Individual plots for pH changes during the observation period (0, 2, 4, 6, 8, 10, 15, 30, 40, 50, and 60 min) after rinsing with allulose, sucrose and water, respectively, are shown in Appendix 3.

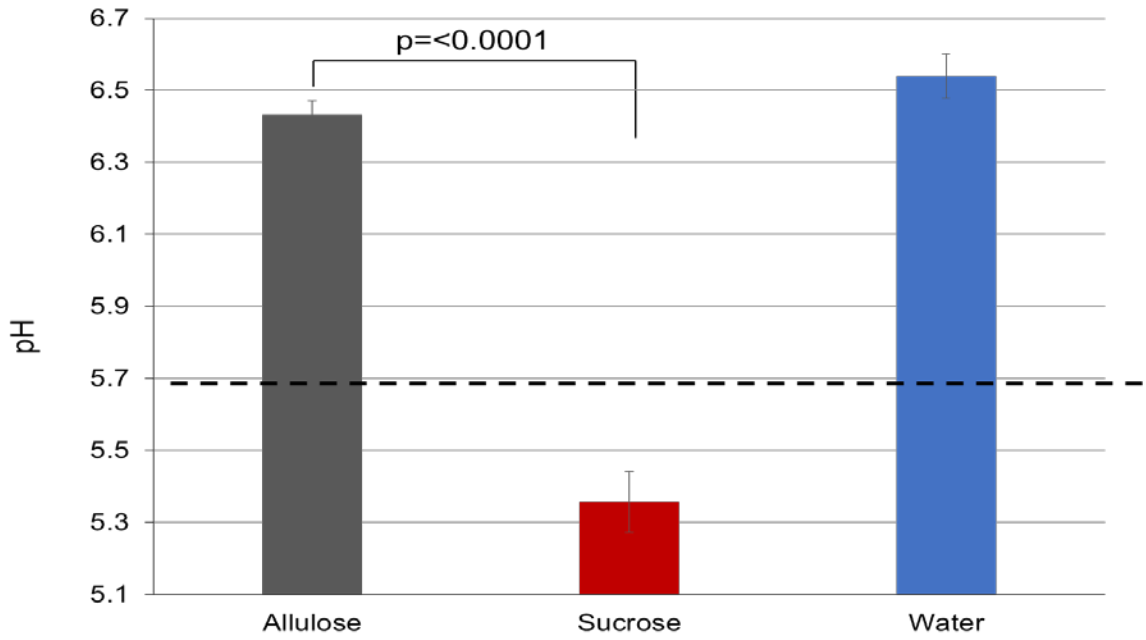


Figure 1. Average minimum plaque pH for all rinses. The minimum plaque pH following a rinse with allulose was significantly (p<0.0001) greater than that of the positive control rinse (sucrose), well above the recognized cariogenic level of pH=5.7, and not significantly different than water. Whiskers represent the standard error of the mean for each group.

The average delta pH, a secondary analysis variable that measures the minimum pH departure from baseline (change in pH after the administration of rinses at 2, 4, 6, 8, 10, 15, 20, 30, 40, 50 and 60 minutes from the pH value at time 0), showed results similar to that of the average minimum plaque pH. Allulose exhibited a significantly lower plaque pH drop than the sucrose solution at any time point (Table 4; p=0.001) and was not significantly different than water (Table 4; p=0.998).

In addition, Stephan's curve (Figure 2) was used to demonstrate the overall mean pH for all tooth sites at all time points starting at time 0 (before rinse) and 2, 4, 6, 8, 10, 15, 20, 30, 40, 50 and 60 minutes after rinse. Allulose and water rinses showed similar pH change pattern and maintained the baseline pH with slight increases which were within the normal pH range for dental plaque (6.7-8.3). Conversely, Sucrose rinse resulted in a sharp drop starting at 2 min. after the rinse and continued dropping for another 2 min where the recovery started; however, the pH levels remained at cariogenic level for up to 20 minutes.

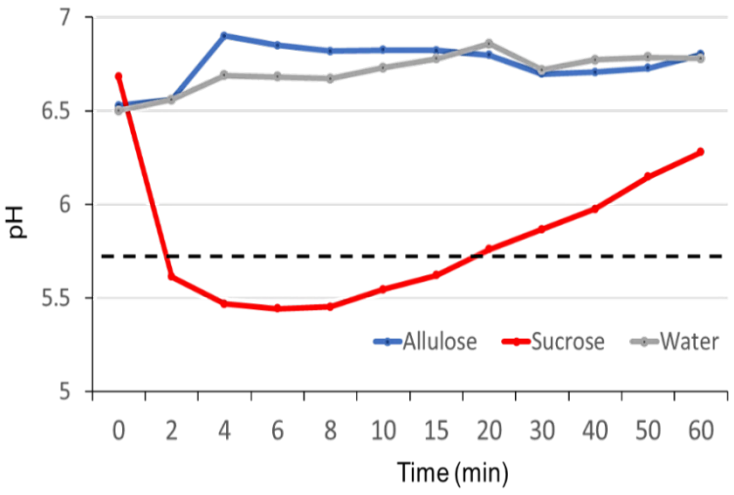


Figure 2. Stephan's Curve after 4.7% sucrose and allulose and water rinse and 48-h old dental plaque. Seven subjects were given each of the rinses in random order with one-week washout intervals. Dotted line depicts the pH of 5.7 which is critical level for cariogenicity.

The incremental and total area under the curve are the secondary analysis variables that measure the integrated cariogenic effect of each rinse. tAUC represents the pH changes over the observation period up to 60 minutes and is negatively correlated to the cariogenicity (the greater tAUC indicates lesser or non-cariogenicity) and is more suitable to determine the long-term behavior to the oral rinses, whereas iAUC more accurately describes the immediate and incremental pH response to the oral rinses at each time point and is positively correlated to the cariogenicity (negative value indicates lesser or non-cariogenic effect, where a positive value clearly indicates high cariogenicity). As with other variables, the allulose rinse was not cariogenic when compared to the sucrose rinse (iAUC; p<0.0001, tAUC; p=0.003; Table 4) and behaved like the water rinse (iAUC; p=0.987, tAUC; p=1.000, respectively, Table 4).

Table 4: Minimum plaque pH, Delta pH, Total and Incremental Area Under the Curve: Descriptive Statistics

Parameter		Allulose	Sucrose (positive control)	Water (negative control)
Minimum pH	**N**	7	7	7
	Mean (SEM)	6.43 (0.12)	5.42 (0.11)	6.54 (0.20)
	Std Dev	0.31	0.30	0.63
	Min, Max	5.82, 6.64	5.02, 5.90	5.81, 7.31
	p-value+		< 0.0001	0.824
Delta pH	**N**	7	7	7
	Mean (SEM)	-0.08 (0.12)	-1.18 (0.25)	-0.09 (0.11)
	Std Dev	0.33	0.66	0.29
	Min, Max	-3.68, 0.29	-1.99, -0.41	-1.94, 0.15
	p-value+		0.001	0.998
Incremental Area Under the Curve	**N**	7	7	7
	Mean (SEM)	-12.74 (8.4)	41.67 (8.4)	-14.27 (7.2)
	Std Dev	22.13	11.32	19.11
	Min, Max	-47.6, 23.8	-0.4, 66.8	-41.9, 66.8
	p-value+		<0.0001	0.987
Total Area Under the Curve	**N**	7	7	7
	Mean (SEM)	405.10 (9.08)	352.57 (9.08)	405.24 (12.0)
	Std Dev	24.04	24.02	31.71
	Min, Max	364.2, 437.3	323.6, 396.6	362.6, 452.4
	p-value+		0.003	1.000

+ p-values comparing to Allulose were adjusted by Dunnett's test

CONCLUSIONS

Results of this study demonstrated that allulose in an aqueous solution is no more acidogenic than a water rinse. The primary outcome, minimum pH, was significantly greater with allulose rinse compared to sucrose rinse ($p<0.0001$) and no different than water rinse. The assay response capability was demonstrated by showing that the cariogenic sweetener sucrose rinse lowered mean plaque pH below 5.7, whereas allulose rinse resulted in a similar dental plaque pH response to that of water rinse over the total observation period and at each time point compared to baseline as shown by tAUC and iAUC calculations, respectively. We conclude that allulose is non-acidogenic when used in solution and meets the criteria set by the FDA for a non-cariogenic sweetener.

References

Bowen WH, Young DA and Pearson SK. The effects of sucralose on coronal and root-surface caries. *J Dent Res* 1990; 69:1485-87.

Carstensen M1, Thomsen C, Hermansen K. Incremental area under response curve more accurately describes the triglyceride response to an oral fat load in both healthy and type 2 diabetic subjects. Metabolism. 2003 Aug;52(8):1034-7.

Code of Federal Regulations. Title 21, Volume 2, Revised April 1, 206: 21CFR101.80 Health Claims; dietary noncariogenic carbohydrate sweeteners and dental caries.

Jensen ME and Schachtele CF. Plaque pH measurements by different methods on the buccal and approximal surfaces of human teeth after a sucrose rinse. *J Dent Res* 1983; 62:1058-61.

Lingstrom P, Imfeld T, and Birkhed D. Comparison of three different methods for measurement of plaque-pH in humans after consumption of soft bread and potato chips. *J Dent Res* 1993; 72:865-70.

Meyerowitz C, Syrrakou EP, Raubertas RF. Effect of sucralose - alone or bulked with maltodextrin and/or dextrose- on plaque pH in humans. *Caries Res* 1996; 30:439-444.

Steinberg LM, Odusola F, Mandel ID. Effect of sucralose in coffee on plaque pH in human subjects. *Caries Res* 1996; 30:138-142.

Steinberg LM, Odusola F, Yip J, Mandel ID. Effect of aqueous solutions of sucralose on plaque pH. *Am J Dent* 1995; 8:209-211.

Wilson, W. Taubert, KA, Gewitz, M et al. Prevention of infective endocarditis: guidelines from the American Heart Association. JADA 138:739-760. 2007

Appendix 1. Study Administration

Study Conduct

The study was conducted according to the principles of Good Clinical Practices (GCP) and the Declaration of Helsinki. The investigator conducted all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities.

Institutional Review Board or Ethical Review Committee

The protocol and informed consent form was reviewed and approved on Feb 17, 2018 by the Institutional Review Board of The Forsyth Institute prior to the initiation of the study with the approval number 18-07.

Record Retention

Records will be maintained for three years per Forsyth Institutional Review Board unless a specific timeline is requested by the Sponsor or other regulatory agencies.

Appendix 2. Calibration Analysis of Probes

Calibration of probes was performed before each testing and two sets of measurements were taken each time. The averages were used as baseline value of pH in the comparison with pH values obtained at the other time points. In general, there was a 99% agreement in the probe measurements.

SUMMARY OUTPUT								
Regression Statistics								
Multiple R	0.999988744							
R Square	0.999977488							
Adjusted R Square	-3							
Standard Error	0.010249724							
Observations	1							
ANOVA								
	df	*SS*	*MS*	*F*				
Regression	3	4.66656161	1.55552054	44419.4				
Residual	1	0.000105057	0.00010506					
Total	4	4.666666667						
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*ower 95.0%*	*pper 95.0%*
Intercept							4E-219	4E-219
X Variable 1							-4E-270	-4E-270
X Variable 2	6.777579241	0.009054113	748.563606	0.00085	6.662535831	6.89262265	6.662536	6.892623
X Variable 3	-0.01743206	8.27108E-05	-210.75909	0.00302	-0.018482997	-0.0163811	-0.01848	-0.01638

		Average sum of Pre and Post					
Tip #	Subject #	Visit 2 pH	Visit 2 pH	Visit 3 pH	Visit 3 pH	Visit 4 pH	Visit 4 pH
		slope	Intercept	slope	Intercept	slope	Intercept
TL01	TL01	-0.02041	6.436475	-0.021907	6.3490822	-0.02142	6.51904
TL02	TL02	-0.01769	6.755911	-0.017536	6.8519181	-0.01748	6.87207
TL03	TL03	-0.01762	6.902289	-0.017478	6.9565344	-0.01742	6.956437
TL04	TL04	-0.0176	6.870853	-0.018266	6.7334701	-0.01825	6.746101
TL05	TL05	-0.0192	7.111493	-0.017563	6.8557755	-0.01744	6.885388
TL06	TL06	-0.01727	6.909457	-0.017292	6.9673948	-0.0173	6.970493
TL07	TL07	-0.01744	6.886655	-0.017394	6.8942683	-0.01742	6.882322

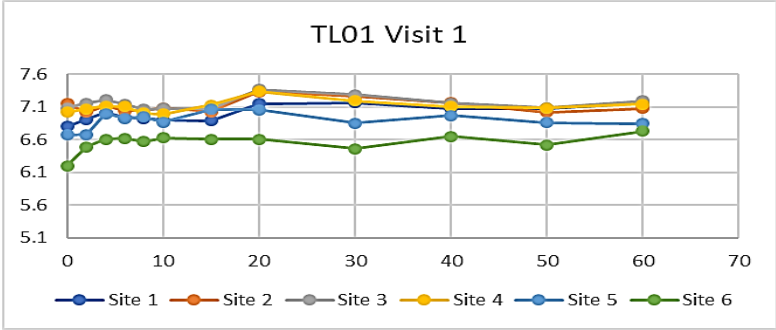
Appendix 3. Individual Plots

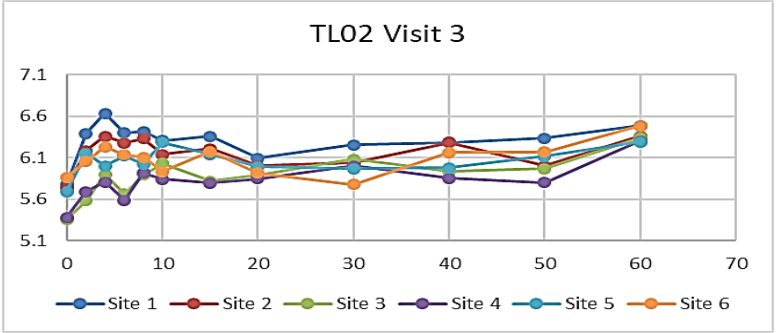
Description of plots:

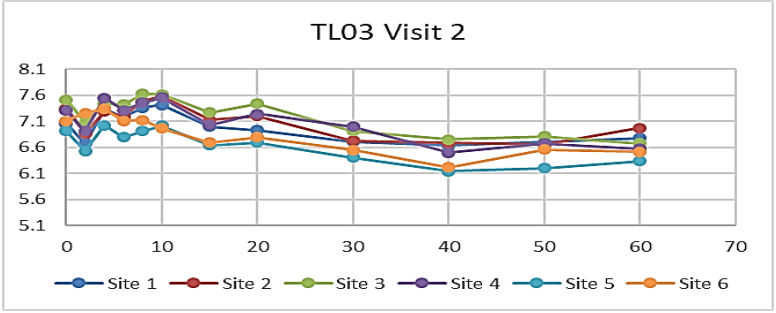
- Subjects #: TL01, TL02, TL03, TL04, TL05, TL06 and TL07
- Site 1, Site 2, Site 3, Site 4, Site 5, and Site 6 represent the tooth sites in which plaque pH was measured per protocol.
- Visit 1, Visit 2, Visit 3 refers to the order of the three treatments, which were administered in random order.
- In each plot, x axis is the minutes post rinse, y axis is pH.
- Recall that pH below 5.7 is considered acidogenic (the threshold pH used for the sucrose positive control).
- Plots are grouped below in the following order: Allulose, Sucrose, Water

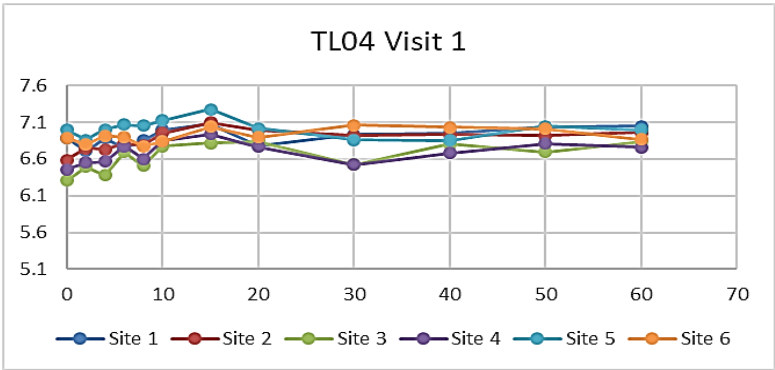
Summary of findings: A consistent reaction was obtained to the administered dose across sites within each subject on a treatment; i.e. subject #1 (TL01, Visit 1, on allulose had consistent pH reaction across all 6 teeth sites for the 60 minutes of sample collection post dose). In addition, as evident from the statistical assessment that was provided prior in the report there were clear pH differences within subject between the allulose rinse vs sucrose rinse; sucrose rinse vs water rinse; and similarity between allulose and water.

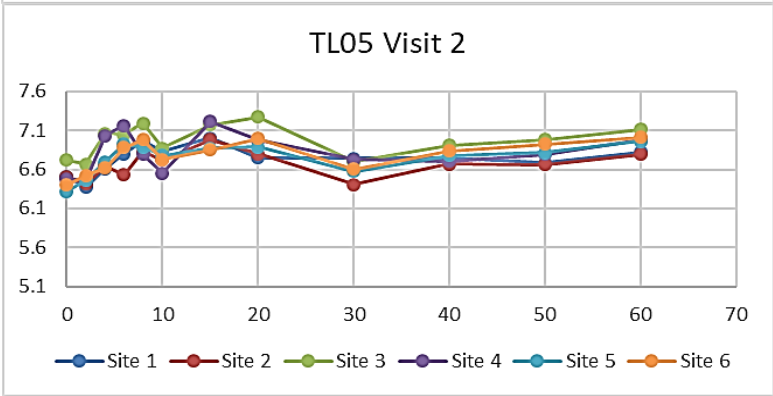
Allulose (4.7%) Rinse (n=7)

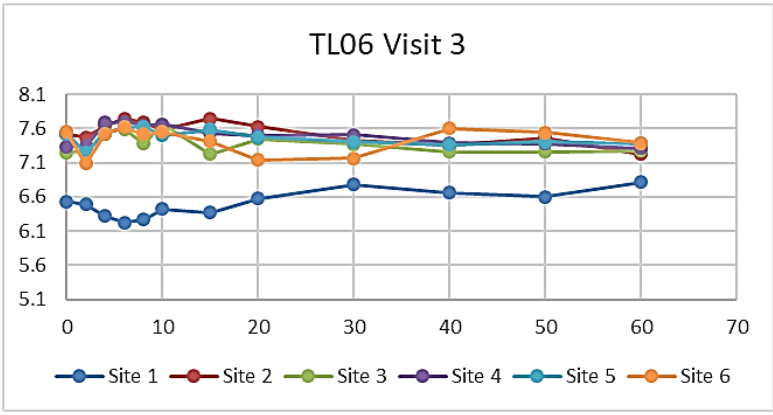


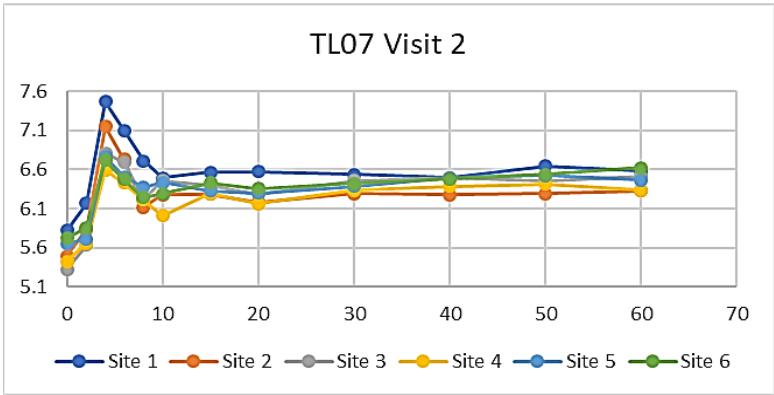




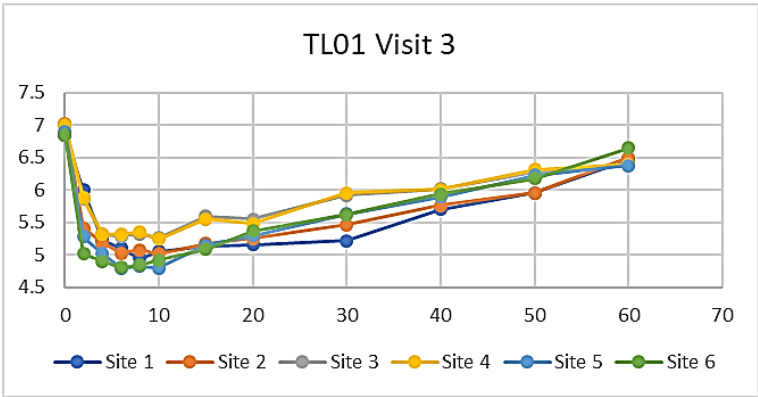

TL04 Visit 1
7.6
7.1
6.6
6.1
5.6
5.1
0
10
20
30
40
50
60
70
Site 1
Site 2
Site 3
Site 4
Site 5
Site 6

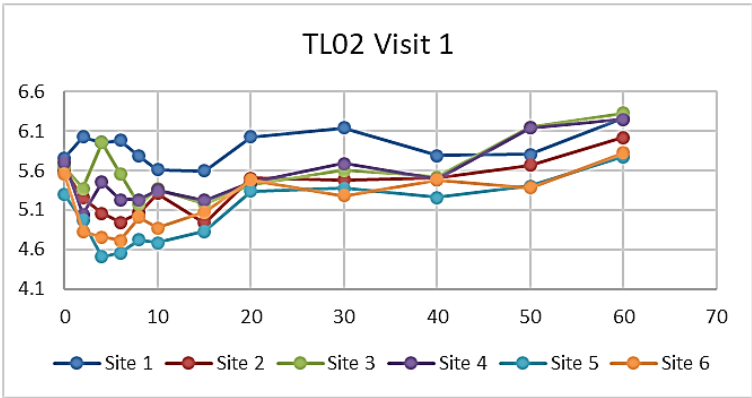

TL05 Visit 2
7.6
7.1
6.6
6.1
5.6
5.1
0
10
20
30
40
50
60
70
Site 1
Site 2
Site 3
Site 4
Site 5
Site 6

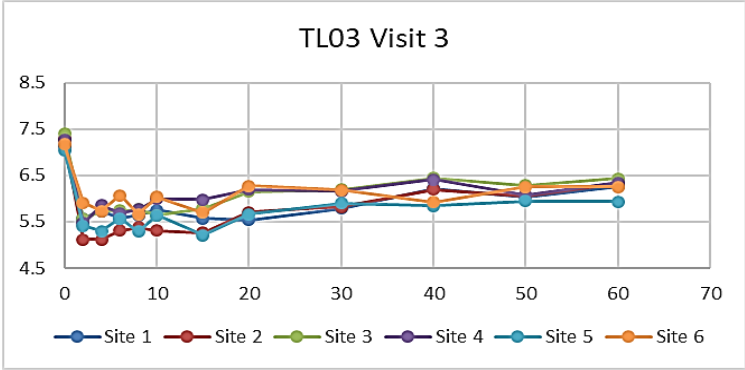

TL06 Visit 3
8.1
7.6
7.1
6.6
6.1
5.6
5.1
0
10
20
30
40
50
60
70
Site 1
Site 2
Site 3
Site 4
Site 5
Site 6

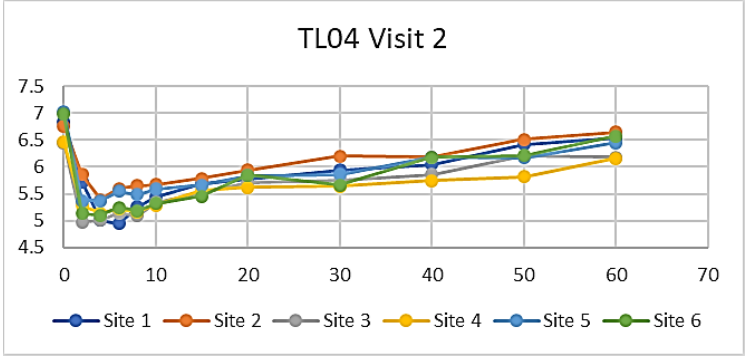

TL07 Visit 2
7.6
7.1
6.6
6.1
5.6
5.1
0
10
20
30
40
50
60
70
Site 1
Site 2
Site 3
Site 4
Site 5
Site 6

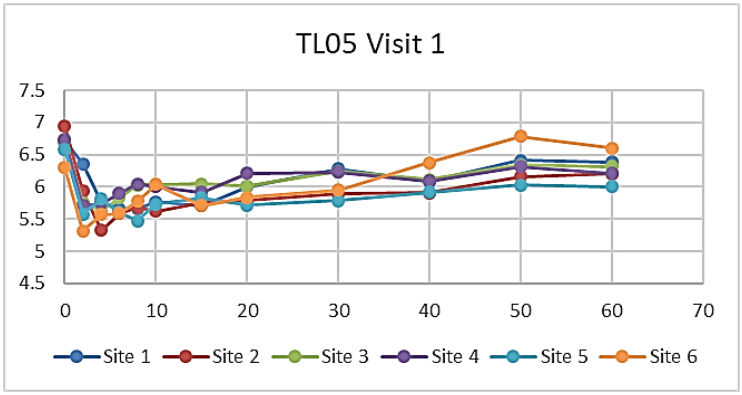
Sucrose (4.7%) Rinse (n=7)

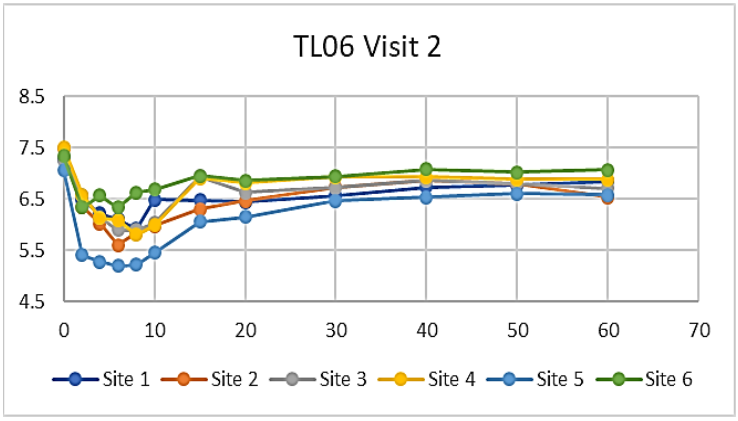


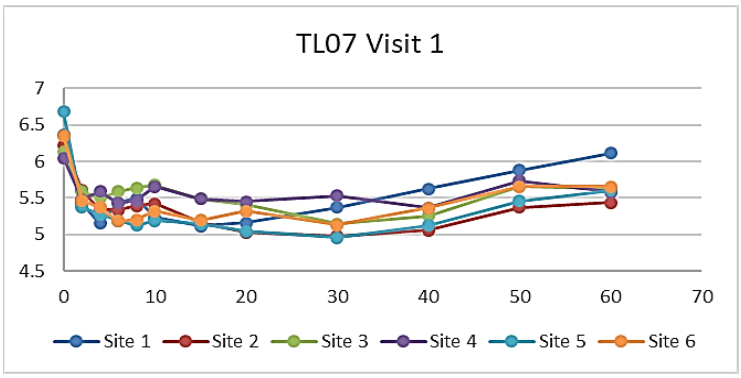




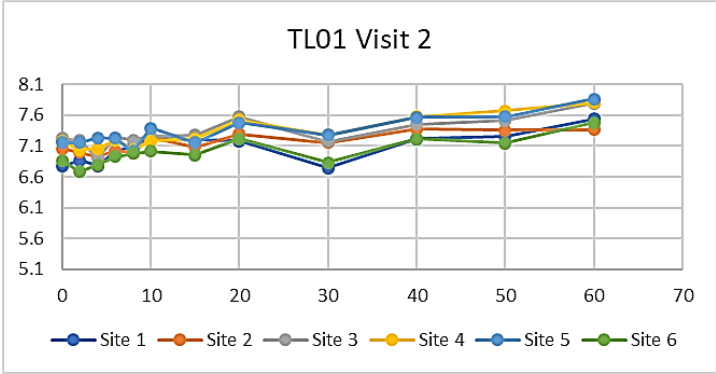


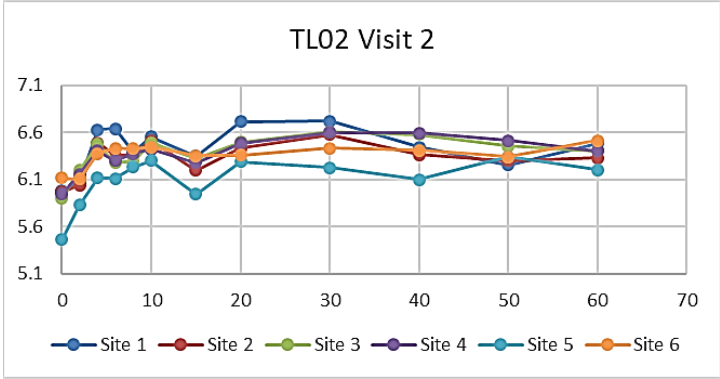

TL05 Visit 1
7.5
7
6.5
6
5.5
5
4.5
0
10
20
30
40
50
60
70
Site 1
Site 2
Site 3
Site 4
Site 5
Site 6

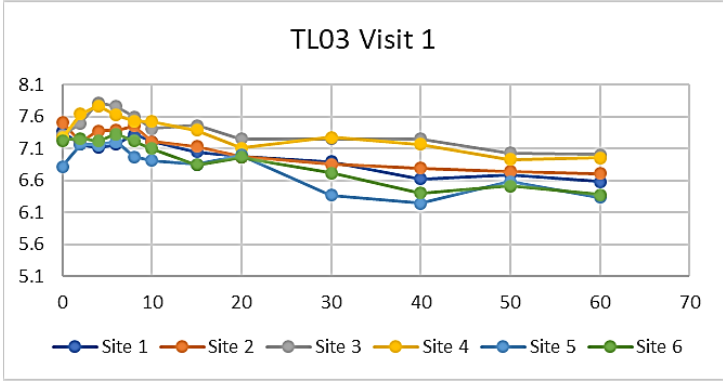

TL06 Visit 2
8.5
7.5
6.5
5.5
4.5
0
10
20
30
40
50
60
70
Site 1
Site 2
Site 3
Site 4
Site 5
Site 6

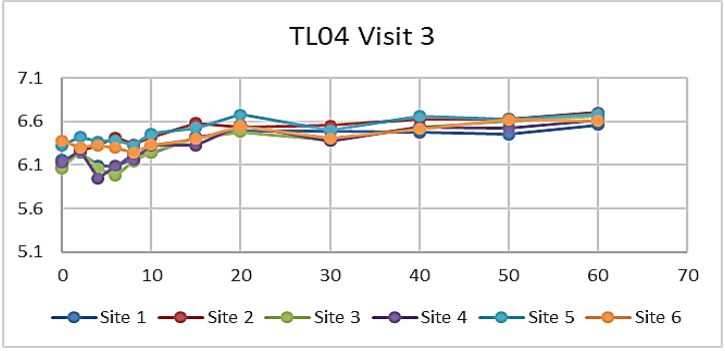

TL07 Visit 1
7
6.5
6
5.5
5
4.5
0
10
20
30
40
50
60
70
Site 1
Site 2
Site 3
Site 4
Site 5
Site 6

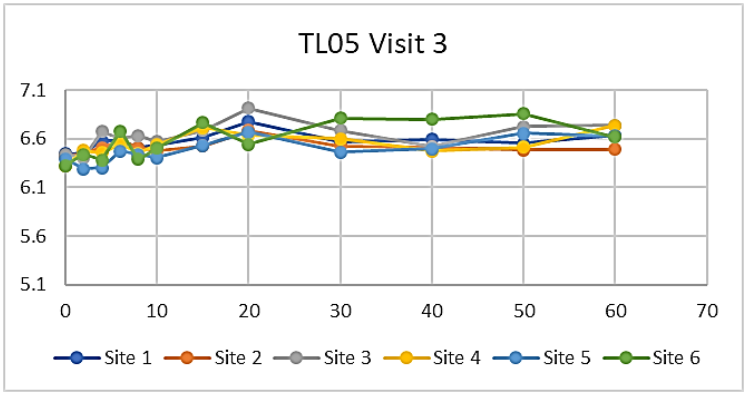
Water Rinse (n=7)

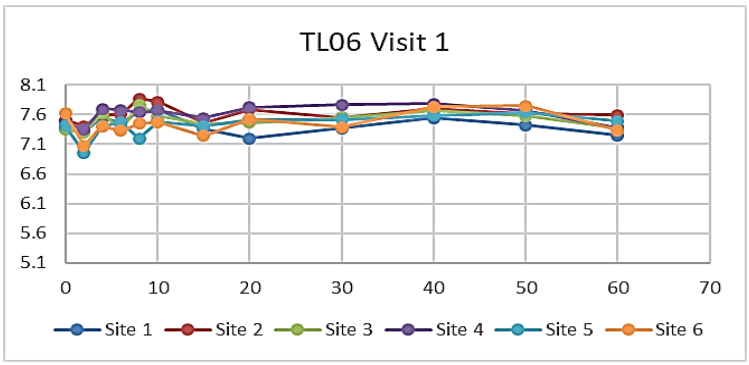


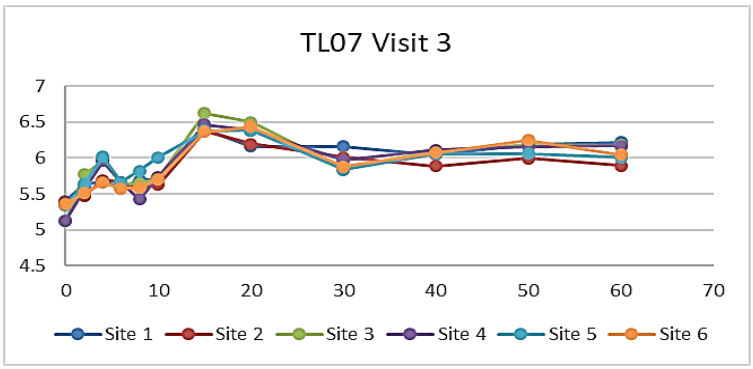







TL05 Visit 3
7.1
6.6
6.1
5.6
5.1
0
10
20
30
40
50
60
70
Site 1
Site 2
Site 3
Site 4
Site 5
Site 6


TL06 Visit 1
8.1
7.6
7.1
6.6
6.1
5.6
5.1
0
10
20
30
40
50
60
70
Site 1
Site 2
Site 3
Site 4
Site 5
Site 6


TL07 Visit 3
7
6.5
6
5.5
5
4.5
0
10
20
30
40
50
60
70
Site 1
Site 2
Site 3
Site 4
Site 5
Site 6