

**Measuring Nitrous Oxide in Dental Clinics:
Evaluating Agreement Between Three Types of Nitrous Oxide Samplers**

by

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United States Public Health Service

Indian Health Service

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CDR Edward Benchoff: I have a question sir????

CDR Charles Woodlee: Can you show me how to do that one more time?

LCDR Nicholas Schaal: So if you're not too busy I have another question for you?

Dr. Alex Stubner: Bike ride?

Dr. Cara Olsen: Statistics? Yep you got that!

Rhonda Allard: You should receive an additional salary as a professor in endnote and thesis format!

And lastly but definitely not leastly,

Graham "Steve" Clark: BLOOD AND ASHES!!! RUST AND RUIN!!! THE REDS ARE RISING!!! SPACE WOLVES!!! AND OTHER NERD STUFF!!!

Roberto "The Grouch" Sanchez-Perez: Question for You????

Warner "Wakanda" Wilson: Where you at?

Bonnie "B" Barrack: TD Tubes are gonna be the greatest thing since well since before TD tubes!

Jhermayne "Bulldog" Bullock: Find any boats yet?

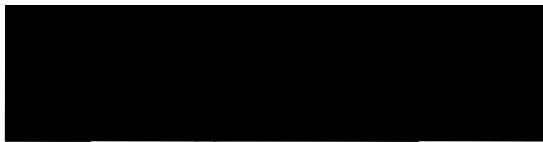
DEDICATION

I would like to dedicate this to all those fervently and passionately longing to know the agreement of the Miran SapphIRe, conventional passive dosimeter badges, and thermal desorption tubes when sampling nitrous oxide in Indian Health Clinics. I would also like to dedicate this to all those who are concerned with nitrous oxide and are earnestly seeking to accurately determine what concentrations dentist may be exposed to during procedures. All the long hours, time away from my family, and personal dedication to this study was not for a degree, accolades, or prestige but it was for you!

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May 17, 2019

ABSTRACT

Title of Thesis: Measuring Nitrous Oxide in Dental Clinics: Evaluating Agreement Between Three Types of Nitrous Oxide Samplers

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Objective: The objective of this study was to determine the agreement between a Miran SapphIRe infrared ambient analyzer, traditional passive dosimeter badges (badges), and thermal desorption tubes (TD tubes) during nitrous oxide (N₂O) sampling in Indian Health Service (IHS) dental clinics. Agreement acceptable to IHS would be $\pm 15\%$ of the Miran SapphIRe and could offer evidence for the TD tubes as being a potential alternative for future passive sampling of N₂O exposures in IHS clinics. A secondary objective of the study was to determine if there was a statistically significant difference in the sample means of each device due to the placement on the dominant and non-dominant side.

Methods: Passive sampling and direct-reading measurements were taken in the breathing zone of six dentists at three separate IHS dental clinic regions during dental procedures where N₂O was used as the anesthetic. Twenty-four sample sets were collected, each consisting of one TWA Miran SapphIRe, two badges, and three TD tubes. A repeated measures Analysis of Variance test was performed to identify statistically significant differences between the three sampling devices. A paired t-test was used to compare

measurements taken on dominant vs. non-dominant sides. The Bland-Altman method was used to investigate the level of agreement between the methods.

Results: The measurement means of all devices proved to be significantly different for the dominant side of the dentist ($p < .05$). However, when the Miran SapphIRe was compared to the non-dominant side the badge was found to not be statistically different ($p = .969$). Additional results suggest a statistically significant difference in measurement due to placement (dominant vs. non-dominant) for the badges on ($p = .003$), but no significant difference for the TD tubes ($p = .807$). When plotted using the Bland-Altman method, both the badge and the tube failed to meet terms set forth for good agreement $\pm 15\%$.

Conclusion: Despite neither of the passive samplers meeting the level of agreement ($\pm 15\%$) satisfactory to IHS, the data suggest that TD tubes are closer in agreement with the Miran SapphIRe reference method than the badges. The data also indicate that the Miran SapphIRe may report concentrations up to 13 times and 2.5 times higher than measurements obtained with the badges and TD tubes, respectively. In addition, the Miran SapphIRe showed a tendency to report higher concentrations than the badges in 46% (non-dominant) and 79% (dominant) of the 24 procedures sampled. This indicates that the badges may be underestimating the actual exposure more than 46% of the time. The Miran SapphIRe reported higher concentrations than the TD tubes for 17% (non-dominant) and 25% (dominant) of the 24 procedures sampled. Though more investigation is needed to better understand the relationship between the devices, the data in this study suggests that TD tubes may offer a more conservative estimate of the N₂O exposure to dental personnel.

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CHAPTER 1: Introduction

1.1 STATEMENT OF PURPOSE

Compare the agreement between, the Miran SapphIRe infrared analyzer, conventional passive dosimeter badges, and thermal desorption tubes during nitrous oxide sampling in Indian Health Service dental clinics.

The Indian Health Service (IHS) currently utilizes two types of devices to quantify nitrous oxide (N₂O) exposure to dental personnel, infrared analyzers and conventional passive diffusion badges. The primary purpose of this study was to compare the levels of agreement between the two current devices and an alternative type of device, thermal desorption tubes. This study also gathered environmental and operational data that IHS can use to better understand N₂O exposures, document factors that may contribute to exposures, and to make recommendations for correction as needed. Concentrations measured during this study were evaluated according to IHS policy, which is based on the American Conference of Government Industrial Hygienists (ACGIH) exposure limits. This study was conducted in five dental clinics in three of the twelve IHS Regions. The sampling devices investigated were:

- A direct reading device, the Thermo Scientific Miran SapphIRe, (Waltham MA), portable analyzer (Miran SapphIRe)
- #575 Nitrous Oxide Passive Badge, Assay Technology, (Livermore, CA) (badge)
- Stainless steel thermal desorption tubes Markes International, (Laintrisant UK) (TD tubes).

The badges and the TD tubes both used a 5-angstrom (Å) molecular sieve sorbent.

The primary research question for this study was: “Are thermal desorption tubes a viable alternative to conventional passive badge samplers for quantifying N₂O exposures in dental personnel?”

1.2 BACKGROUND

N₂O is an odorless, colorless, tasteless, stable, noncombustible gas that is approximately 1.5 times heavier than air (33). N₂O is an inorganic inhalational anesthetic, is nonirritating to the tissues, and provides the most rapid onset of anesthesia of any inhalation agent used for sedation (8). N₂O is commonly used in dentistry as it has an impressive safety record for short term use in the patient, and is excellent for providing minimal and moderate sedation for apprehensive dental patients (8).

Although N₂O has been shown to have an excellent safety record when used for short-term sedation, it has been implicated in adverse health effects for individuals who are chronically exposed (8). Chronic exposure to N₂O has been associated with reproductive, hematologic, immunological, neurological, hepatic, and nephrotic and should be a concern for dental personnel (25).

There is currently no established federal permissible exposure limit (PEL) for N₂O (37). As a result, IHS guidance is to adhere to the ACGIH threshold limit value (TLV) of 50 ppm, (90 mg/m³) as an 8 hour Time Weighted Average (TWA) (2). The ACGIH recommends the “3/5 Rule” that exposure to nitrous oxide should not exceed three times the TLV-TWA (150 ppm) for more than a total of 15 minutes at a time on no more than four occasions spaced one hour apart. The rule further recommends that exposures to N₂O should not exceed 5 times the TLV-TWA (250 ppm) under any circumstances (2).

Most IHS regions possess one Miran SapphIRe, but with each region covering multiple states and multiple clinics/hospitals, this limits the use of the Miran SapphIRe due to logistical challenges. Consequently, dental clinics use passive dosimeter badges for regular monitoring of staff exposure when the Miran SapphIRe is unavailable for annual exposure sampling. In addition to annual exposure checks, IHS Institutional Environmental Health Officers use the Miran SapphIRe to identify leaks in the systems for N₂O delivery and scavenging (collection and removal of waste anesthetic gas). As the dental staff do not have access to the Miran SapphIRe before each procedure to conduct leak checks, IHS policy specifies dental staff are to follow the American Dental Association (ADA) recommended best practices for visual equipment inspection, including a soap and bubble method to check for leaks (1).

It has been shown in studies that the use of the ADA best practices, which includes pre-checks for leaks, use of a scavenging system directly connected to the delivery system, and adequate ventilation (i.e. operatory room air changes per hour) can greatly reduce the exposure levels in the dental environment (1; 3; 7; 9; 12; 21; 44). The IHS has routinely used the Miran SapphIRe and badges interchangeably to determine if dental staff are being exposed over ACGIH recommendations. A recent study conducted by Hansen et al. (2019) found that while time weighted exposures were consistently below the 50 ppm TLV, IHS dental staff were repeatedly exposed to concentrations that exceeded the recommended excursion limit of 250 ppm (20). Hansen et al. (2019) also found that the two methods used for analysis, the Miran SapphIRe and Advanced Chemical Sensors N₂O passive dosimeter badges (Boca Raton, FL) differed by more than 25% with 95% confidence (20).

Woolfenden (2013) describes several advantages that TD tubes maintain over traditional passive dosimeter badges. TD tubes have been shown to have a higher analytical sensitivity than traditional solvent-based methods. They are robust, require very little training, and can be reused up to 100 times before their sorbent requires replacement. Although TD tubes are more expensive initially than a single badge, reuse of TD tubes may provide an overall savings in cost. Thermal desorption also precludes the need to use flammable or toxic solvents to desorb the analyte(s) of interest, as is required with the analysis of most conventional passive dosimeter badges. This increases the safety of lab personnel and minimizes environmental impact (54).

Thermal desorption tubes may provide an additional sampling alternative for IHS dental clinics as opposed to conventional badges. However, no studies investigating the levels of agreement between Miran SapphIRe, conventional passive dosimeter badges, and thermal desorption tubes, when sampling N₂O were found in the literature.

The IHS considers the Miran SapphIRe to be the reference device for sampling N₂O and as such, this study considered the Miran SapphIRe to be the reference device. The Miran SapphIRe is calibrated by the manufacturer to be accurate within $\pm 10\%$ for N₂O at 1-100 ppm (47). This means that the Miran SapphIRe reading at 1-100 ppm could be 10% higher or lower than the true concentration. The National Institute for Occupational Safety and Health (NIOSH) recommends that air-sampling devices have an accuracy of $\pm 25\%$ with 95% confidence of the true concentration (15). To ensure that the passive sampling devices meet the $\pm 25\%$ criteria set forth by NIOSH while adjusting for the $\pm 10\%$ accuracy of the Miran SapphIRe, this study set $\pm 15\%$ with 95% confidence with the Miran SapphIRe as the level to be considered “good agreement”. If

the badges or TD tubes are less than or equal to $\pm 15\%$ from the Miran SapphIRe, they will still likely be within the $\pm 25\%$ recommended by NIOSH. If good agreement, $\pm 15\%$ with 95% confidence, is observed between the Miran SapphIRe and the TD tubes and the agreement is closer than the badges, then the IHS may consider revising its policies to add the TD tubes as a viable alternative to the conventional passive badges.

The IHS institutional environmental health surveys have identified over exposure to N_2O among dental employees in past years, and Hansen et al. (2019) showed that high exposures of short duration are a concern (20). To accurately represent personnel exposure the Occupational Safety and Health Administration (OSHA) indicates that sampling within a 10-inch radius of the worker's breathing zone should be done (49; 50). Additionally, by placing all three devices within the worker's breathing zone during the procedure, the levels of agreement between the sampling devices can be determined.

Hansen et al. (2017) showed a conceptual model of how dental employees can be exposed to N_2O which can be seen in Figure 1 and also shows where sampling devices should be placed in relation to potential inhalation exposure routes (21).

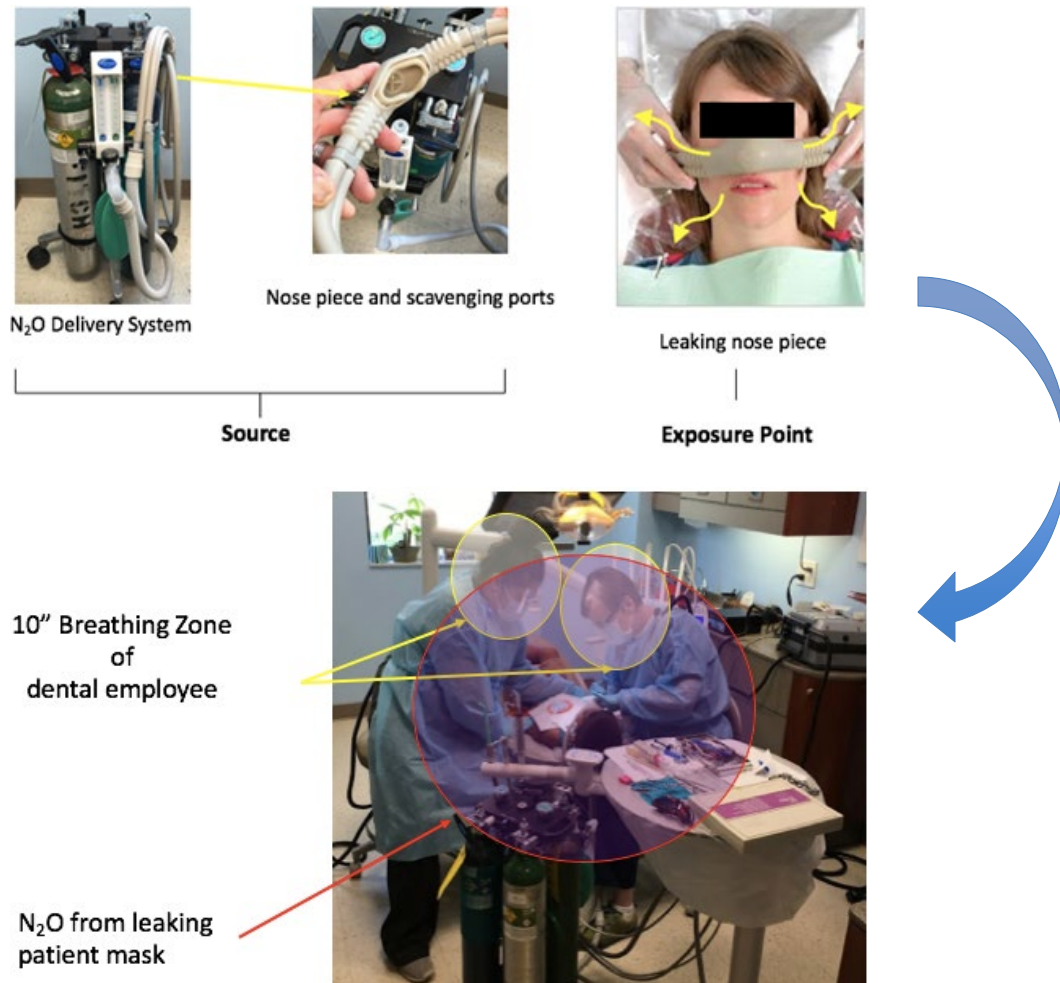


Figure 1. Conceptual model of how dental employees are exposed to N₂O (21).

In addition, OSHA states that personnel sampling in the breathing zone to be the most accurate in determining worker exposure (49). OSHA does not stipulate whether hand dominance and placement of a sampling device in relation to hand dominance may affect sampling. As dentist move about during procedures this study investigated, the relationship of placement of the sampling device in regards to hand dominance. Only one Miran SapphIRe was used during this study the Miran SapphIRe sampling tube was placed on the collar of the dominant hand for all sampling procedures.

The information from this study will help guide future IHS policy in regards to exposure assessment and it will potentially assist in making recommendations to reduce exposure.

1.3 RESEARCH QUESTIONS, HYPOTHESES, AND SPECIFIC AIMS

Research Question #1

Does the side of the dentist (dominant hand side vs. non-dominant hand side) on which the sampling device is placed have an effect on the N₂O concentration measurement?

Hypothesis #1

Placement of the sampling device on the collar of the dentist (dominant hand side or non-dominant hand side) will not result in a statistically significant difference in N₂O measurement in the Assay Technology #575 conventional passive dosimeter badges (badges) or the Markes International thermal desorption tubes (TD tubes).

Specific Aims

1. Collect samples by placing one TD tube and one badge on the collar of the dentist's dominant hand within the breathing zone. Collect samples using identical samplers placed on the collar of the non-dominant hand within the same breathing zone.
2. Use a paired t-test to determine if there is a significant difference in the mean N₂O concentrations between the dominant and non-dominant sides measured by each like pair of passive samplers.

Research Question #2

Is there a significant difference in the mean N₂O concentrations measured using two types of passive samplers (badges and TD tubes) compared to a direct reading reference method (Miran SapphIRe)?

Hypothesis #2

There is no statistically significant difference between the mean N₂O concentrations measured by the Miran SapphIRe, badges, and TD tubes.

Specific Aims

1. Perform personal N₂O sampling on dentists working in IHS dental clinics with each sampler type (1 dental procedure = 1 sampling period).
2. Use a Repeated Measures Analysis of Variance (ANOVA) to determine if there is a significant difference in the mean N₂O concentrations between sampling devices.

Research Question #3

What is the level of agreement of the badges, and TD tubes?

Hypothesis #3

Agreement in N₂O measurements between the badges and TD tubes is no worse than $\pm 15\%$ with 95% confidence.

Specific Aims

1. Use a Bland-Altman method to determine the level of agreement between badges and TD tubes.

Research Question #4

What is the level of agreement between the Miran SapphIRe and badges?

Hypothesis #4

Agreement in N₂O measurements between the Miran SapphIRe and badges is no worse than $\pm 15\%$ with 95% confidence.

Specific Aims

1. Use a Bland-Altman method to determine the level of agreement between the Miran SapphIRe and badges.

Research Question #5

What is the level of agreement between the Miran SapphIRe and TD tubes?

Hypothesis #5

Agreement in N₂O measurements between Miran SapphIRe and TD tubes is no worse than $\pm 15\%$ with 95% confidence.

Specific Aims

1. Use a Bland-Altman method to determine the level of agreement between the Miran SapphIRe and TD tubes.

CHAPTER 2: Literature Review

2.1 HEALTH EFFECTS OF N₂O

The use of N₂O as an inhalational anesthetic agent has an excellent safety record for short term sedation; however, N₂O has also been implicated in adverse health effects, especially for those who may be chronically exposed (9). Chronic exposure can produce irreversible toxic changes (bone-marrow depression) in dental employees and has been associated with neurological, immunological, reproductive, hematologic, liver, and kidney disorders (51) (25). These associations were found to be both time and dose dependent (25).

N₂O has been shown to have an adverse effect in humans and animals by interfering with vitamin B12 functions. Vitamin B12 is a nutrient that helps keep nerve and blood cells healthy, assists with making DNA, and also helps with preventing megaloblastic anemia (35). In 1978, Ames et al. showed that N₂O oxidizes the cobalt of vitamin B12 inhibiting the enzyme thymidine synthase from converting deoxyuridine to thymidine, which impairs DNA synthesis (5). This study also documented megaloblastic change to erythrocytes after exposure of up to 24 hours with N₂O seeming to interfere with the function of vitamin B12 (5). Krajewski (2007) documented significantly reduced vitamin B12 levels in surgical nurses when compared with hospital staff working outside operating theaters. This observation was the first indication that repeated occupational exposure to N₂O may disturb vitamin B12 metabolic status (29). Health care workers active under excessive occupational exposure to N₂O, might be more susceptible to development of symptomatic vitamin B12 deficiency (lethargic, loss of appetite, weight loss etc.), moreover they would likely develop hyperhomocysteinemia (abnormally high levels of homocysteine in the blood), which is a well-recognized

independent risk factor for arterial and venous thrombosis and coronary heart disease (29).

Studies have also found an association between N₂O and reproductive effects. Evidence for teratogenicity among animals has been documented; however, evidence for teratogenicity in humans is limited (6; 9; 28). Exposure to N₂O may result in adverse reproductive effects such as spontaneous abortions and reduced fertility due to long-term cumulative exposures however, the evidence is limited and further research is needed (40). Research has also shown an association between occupational exposures to greater than occupational exposure limits (OELs) of N₂O and reduced fertility in female dental assistants (43). Currently NIOSH indicates a concern for adverse reproductive effects is valid and recommends limiting exposure below OELs (36).

As a result of the associations between exposure to N₂O and the detrimental chronic health effects, it is prudent for organizations that use N₂O to monitor and control emissions so that exposure to workers is minimized.

2.2 N₂O EXPOSURE LIMITS

There is currently no established federal permissible exposure limit (PEL) for N₂O, although recommended exposure limits have been developed by the ACGIH and NIOSH (2). The recommended exposure limit (REL) promulgated by NIOSH is 25 ppm as an exposure period Time Weighted Average (TWA) and is “intended to prevent decreases in mental performance, audiovisual ability, and manual dexterity” (36).

The ACGIH Threshold Limit Value Time Weighted Average (TLV-TWA) is 50 ppm (90 mg/m³), assuming an 8 hour workday and 40-hour workweek. This limit is designed to minimize the risk of central nervous impairment, hematological effects, and

embryo/fetal damage (2). The ACGIH's "3/5 Rule" describes acceptable excursions above the TLV and is applicable to N₂O. The ACGIH transient peak exposure limits are defined as:

- 3 times the TLV-TWA value for no more than a total of 15 minutes at one time on no more than four occasions spaced one hour apart during a workday or N₂O exposures should not exceed 150 ppm for more than 30 minutes per day
- Under no circumstances may exceed 5 times the TLV-TWA, or N₂O should never exceed 250 ppm (2).

The IHS has adopted the ACGIH occupational exposure limits (OELs) (26).

2.3 DELIVERY AND SCAVENGING SYSTEMS

The American Dental Association (ADA) guidelines for N₂O delivery include recommendations to control exposure, including an active scavenging system capable of achieving an airflow rate of 45 liters per minute (LPM) and a delivery mask available in a variety of sizes to maximize proper fit on a wide range of facial dimensions (3).

Scavenging systems can be either active or passive in nature. An active sampling system utilizes a vacuum to create negative pressure, which draws the waste (exhaled N₂O from the patient) out of the work area before exposure can occur. A passive scavenging system relies on pressure created by patient exhalation or by manual compression of a breathing system bag to sweep the waste gas into the scavenging system. Whitcher et al. (1977) showed that active scavenging of N₂O reduced exposure 29 fold among dentists without scavenging, and that the highest concentrations in the room were usually found within the dentists' breathing zones (6-10 inches of the nose)

(52). While there is a dramatic reduction in exposure when using scavenging systems, Whitcher (1977) also points out that leaks in the system are the primary source of exposure with the patient being a secondary source as a result of high concentrations of N₂O in their exhaled breath (52). Figure 2 shows an illustration of a scavenging system and key leak sources.

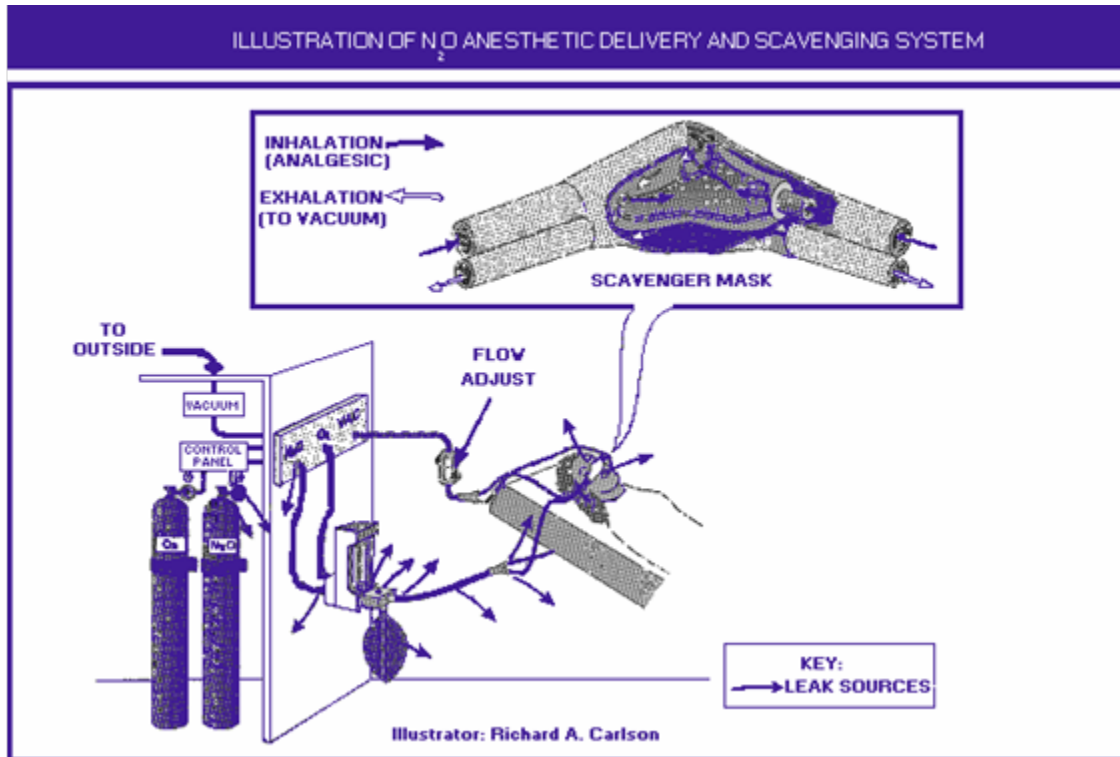


Figure 2. Illustration of N₂O Anesthetic Delivery and Scavenging System (11).

Although scavenging systems have been shown to effectively reduce N₂O concentrations, Henderson and Matthers (1999) reported peak N₂O concentrations in excess of 1,000 ppm, and a study conducted by Gilchrist et.al. (2007) found only 38% of cases studied met the recommend United Kingdom (UK) 8 hour TWA of 100 ppm (16; 22). Since the UK TWA is twice as high as the ACGIH TLV-TWA 50 ppm, the proportion of cases that exceeded 50 ppm would likely have been even greater (16; 32).

Hansen et al. (2019) found 151 instances of exposure above the maximum ACGIH 250 ppm excursion limit among dentists, and 53 excursions among dental assistants in 23 dental procedures all using an operating active scavenging system (20).

Although active measures to reduce the dentist exposure to N₂O are being taken within the IHS, there is still exposure above recommended OEL's occurring. There is still a clear need monitor dental professionals even when scavenging systems are in use.

2.4 MONITORING N₂O

Both OSHA and ADA recommend that air monitoring be performed semi-annually to characterize worker exposures for waste anesthetic gases to include N₂O (49). They allow the use of either personal, area, or source sampling, but state that “personal samples give the best estimate of a worker’s exposure”, and recommend that monitoring be performed using either “passive dosimeter/diffusive sampling” or “direct reading sampling” (1; 38).

2.4.1 Direct Reading Sampling

At the atomic and molecular level, all matter is in constant motion. By sending a beam of infrared (IR) energy through a sample at a wavelength absorbed by the sample, the concentration of the sample can be calculated in proportion to the amount of energy absorbed (47). IR analyzers, including the Thermo Scientific Miran SapphIRe, operate according to the principles of the Beer-Lambert Law (Beer’s Law). Beer’s Law describes the relationship between absorption and concentration and states that the amount of energy absorbed at a certain wavelength (light) is directly proportional to the concentration of the sample and to the path length over which the energy travels through the sample (47).

Possible interference of N₂O measurements can result from carbon dioxide, which presents a similar absorption peak at 4.43μm, and water vapor, which presents an absorption plateau that encompasses the peaks of both N₂O and carbon dioxide (52). In order to help reduce these concerns analyzers are typically placed away from the expired air stream reducing both potential water vapor and carbon dioxide breathed from those being sampled but still within the recommended 10 inch radius of the breathing zone (52).

Whitcher (1977) described use of an IR analyzer to quantify N₂O by measuring the level of absorption of IR radiation at the 4.45μm wavelength with a real-time measurement reported every 2-20 seconds depending on the setting of the instrument (52). Henry and Jerrell (1990) used a Miran 1B infrared spectrophotometer (Foxboro, South Norwalk, CT) to determine waste N₂O levels during pediatric sedations in dentist personnel's breathing zone, and to evaluate the effect of scavenging in reducing environmental exposure (23). Henry and Primosch (1991) used a Miran infrared spectrophotometer (Miran 1BD, Foxboro, South Norwalk, CT) to determine N₂O concentrations in the personal breathing zones of dental personnel attempting to determine if the size of the operating room influenced scavenger effectiveness (24). In both studies, the concern for carbon dioxide and water vapor were minimized in the same manner as described by Whitcher (1977), however the "expired air stream" or "breathing zone" was defined as 50-56 cm (20-26 in) from the nose directly above the patient's chest (23; 24; 52). Hansen et al. (2019) placed the samplers within the 10 inch radius and away from the nose as recommended by OSHA and Whitcher (19; 50).

The Miran SapphIRe has proven to be a useful and exceptional tool in quantifying exposure to N₂O in real time with dependable results, it allows for:

- Corrections to be made if leaks are detected in the N₂O delivery/scavenging systems
- Records concentrations integrated over a user-defined duration to be analyzed for each procedure as compared with one reading for a procedure (badge)
- Identifying if multiple excursions above 250 ppm occur during procedures where a badge only reports the TWA (20; 23; 24; 36).

However, the device:

- Is expensive
- Requires power to operate
- Sensitive to ambient temperature, pressure, and humidity and
- Requires user training.

Additionally, the Miran SapphIRe can be cumbersome to handle for the operator, as well as inconvenient and uncomfortable for the sampled employee (due to the attachment of a sampling hose). It also recommends calibration by the manufacturer annually and user checks to verify proper operation prior to and during use.

Hansen et al. (2019) performed a zero check before sampling but also relied on the manufacturer's calibration of the Miran SapphIRe instrument (1-100ppm). A limitation of that study was that the Miran SapphIRe was only calibrated at 1-100 ppm and some concentration measurements during the study were above 100 ppm (19). This was an significant limitation, since Thermo Scientific postulates that at higher

concentrations, above 100 ppm, there is apparent failure of Beer's Law within the Miran SapphIRe, most likely due to interaction of gas molecules with one another in the sample cell. This interaction results in inaccurate measurements at concentrations above 100 ppm (47).

2.4.2 Passive Sampling

Passive sampling is defined by Górecki, Namieśnik (2002) as the “free flow of analyte molecules from the sampled medium to a collecting medium due to chemical potentials between the two medias until equilibrium or termination by the user” (17).

Passive sampling operates according to Fick's first law of diffusion, which is described by the equation:

$$M = \frac{DA}{L} C_0 t \quad (1)$$

Where:

M = amount of analyte transported by diffusion in time (mol)

D = molecular diffusion coefficient of the analyte (cm²/s)

A = cross section of the diffusion path (cm²)

L = total length of the diffusion path (cm)

C₀ = average analyte concentration in the medium (mol/cm³)

t = time (s)

In order to maintain Fick's Law, the concentration gradient between the ambient air outside the sampler and the air inside the sampler must be preserved. This is done by selecting an appropriate sorbent that will efficiently collect and hold the analyte of interest at the boundary layer between sorbent and air. This process creates a “zero” concentration in the air immediately above the sorbent (the boundary), which preserves

the concentration gradient so that the process can continue. However, the sorbent must also be weak enough to release the sorbent of interest during analysis. A poorly chosen sorbent will either be too weak, which will allow release of weakly held analyte molecules (back diffusion), or it will be too strong, which will inhibit release of the collected molecules during analysis (17; 53).

Passive sampling devices designed for gases and vapors are classified as radial, axial (tube), or badge. The samplers rely on either diffusion or permeation to move the analyte across a barrier onto a sorbent where it is collected and held until analysis (17). The axial (tube) and badge designs will be the focus of the current study because the badge is the most consistently used passive sampler in IHS and the tube is what is of interest as a potential alternative.

Passive sampling vastly simplifies sampling and sample preparation by:

- Eliminating power requirements
- Does not require operator supervision
- Less cumbersome to handle (compared with the Miran SapphIRe)
- Not complicated to operate
- Requires no maintenance
- No pre-operational performances are needed
- Does not require a warm up time
- Are not subject to mechanical malfunction
- Ability to produce accurate results and
- Are significantly less expensive as compared to the Miran SapphIRe (17; 34).

Passive sampling does have limitations, which can affect the efficiency of analyte collection such as:

- Temperature
- Humidity
- Air movement
- Sorbent saturation.

Unless accounted for, these parameters can negatively affect the accuracy of the sampling results. Other limitations include but are not limited to: delayed results, cannot be used for leak detection, and only offers the user a TWA for the day or procedure as opposed to integrated time sampling the Miran SapphIRe is capable of.

2.4.2.1 Passive Dosimeter Badges

Badge-type samplers are open face devices, have a shorter diffusion path length with a greater cross-sectional area (compared to the axial (tube) type) and a semi-permeable, protective membrane designed to minimize the effect of air turbulence on the analyte uptake rate. Due to their larger cross-sectional area, badge-type samplers generally offer a higher uptake rate as compared to tube samplers (41; 55). While badge-type samplers exhibit higher uptake rates than their tube counterparts, badge samplers may be more inconsistent and deviate from the true concentration due to surface air velocity and possible back diffusion (53; 55).

Rossner and Farant (2004) compared charcoal tubes, passive badges, and canisters and found that badge samplers underestimated concentrations of Volatile Organic Compounds (VOC's) by 25-35% (42). Desorption and analysis of the badges was performed in the same manner as the charcoal tubes and recovery of the analyte did not

deviate from published data. Therefore, the collection of the sample was considered the primary source of error (42). The badge-type sampler is more sensitive to velocity of airflow across the sampler and the turbulence of the airflow as compared with the tube sampler, it was the conclusion of the researchers that air turbulence is what contributed to the difference (42).

Some types of badge samplers have been shown to have sampling rates that can be 10 to 200 times greater than some tube-type sampling rates. However, badges can become saturated very quickly at high concentrations or if used for long-term sampling (18; 36; 45; 55). Hansen et al. (2019) corroborated this for badge-type samplers designed to measure N₂O by finding that saturation occurred relatively quickly (< 60 minutes) in environments with concentrations approaching 500 ppm (20).

2.4.2.2 Passive Tube Samplers

Tube-type samplers are usually hollow cylindrical tubes made of glass or stainless steel and filled with a sorbent. Stainless steel tubes are usually preferred over glass as they are more durable and their cross-sectional area is slightly larger than glass (5 mm vs. 4 mm). Tube Samplers are oriented vertically during sampling with a cap at the top end that holds either a filter paper or stainless steel grid in place. Stainless steel tube samplers have a 6 mm outer diameter and a 5 mm inner diameter cross section and incorporate a precisely measured 15 mm gap diffusion path between the face of sorbent and the outer rim of the tube face (53-55). Tube samplers are affected by air turbulence when air moves over the open end of the tube. This can generate turbulence inside the tube and lead to reduction in diffusion path length, which is referred to as “wind-shortening”. However, provided that recommended guidelines for the placement of the sampler are

followed, wind speed is considered to have minimal or negligible influence on tube sampler uptake rates because of the large length-to-area ratio of the tube relative to badge-type samplers (45; 53).

2.5 EXTRACTION TECHNIQUES FOR BADGES AND TD TUBES

While some badges can use thermal desorption techniques, most use a solvent to extract the collected analyte of interest from the sorbent. Woolfenden (2013) suggests that solvent extraction results in lower extraction efficiencies (approximately 80% on average) and can result in a 1000-fold reduction in sensitivity relative to thermal desorption ($\geq 95\%$ efficiency). Dilution occurs because the collected molecules of interest are desorbed in a small volume of solvent (typically 1 mL), but only a very small portion of that solvent (generally 1 μ L, or 1/1000th of the solvent volume) is injected into the analytical system during analysis. This results in the vast majority of collected analyte being unavailable for analysis.

Conversely, extraction of the analyte of interest using thermal desorption techniques can make virtually all of the collected molecules available during analysis. Thermal desorption does not use a solvent but instead applies heat to the sorbent to stimulate release of adsorbed compounds. The released molecules are then swept out of the tube by a carrier gas. A secondary collection (focusing) trap again collects the desorbed analyte until the desorption process of the sampling tube is complete. The focusing trap is then rapidly flash heated and reaches a temperature of approximately (300 °C) within seconds, which desorbs the analyte of interest and introduces it into the analytical system in a tight band. In addition to making available virtually all of the collected molecules of interest (and its associated higher sensitivity), thermal desorption

has additional advantages over samplers that require solvent extraction including low background, elimination of the need for toxic or flammable solvents, and a sampler housing and sorbent that can be reusable for ≥ 100 heat cycles (27; 54).

CHAPTER 3: Materials and Methods

3.1 MATERIALS

Materials used during field sampling included:

- Stainless steel thermal desorption tubes (TD tubes) with a 5 Å molecular sieve sorbent (Markes International, Llantrisant, UK)
- #575 Nitrous Oxide Personal Monitoring Badges (badges) with a 5 Å molecular sieve sorbent (Assay Technology, Boardman, OH)
- Miran SapphIRe Portable IR Analyzer (Miran SapphIRe) (Thermo Scientific, Waltham, MA)
- GASCO Nitrous Oxide Calibration Gas, N₂O 99.5%, (Cal Gas Direct Incorporated, Huntington Beach CA).

3.2 METHODS

3.2.1 Sampling Method

Sampling is best described as convenience sampling. As this study was conducted within IHS a request was submitted to each Area Director to conduct sampling utilizing the three sampling devices. Sampling was considered part of normal routine sampling. After obtaining approval from each Area Director, a request was submitted to each dental clinic for a list of procedures utilizing N₂O to arrange for sampling. In total three regions, five dental clinics, and six dentist across the United States in the IHS were selected due to the number of overall cases scheduled for the sampling period. Regions were labeled numerically with Region 1 having one clinic and one dentist, Region 2 had two clinics and three dentist, and Region 3 had two clinics and two dentist. Sampling occurred in July 2019 where 24 dental procedures were sampled, additional sampling

occurred in Region 3 November 2019 to collect the remaining seven dental procedures for a total of 31 dental procedures sampled. All log transformations listed were log based 10 transformations.

3.2.2. Miran SapphIRe User Verification

Per routine IHS practice, the Miran SapphIRe received an annual factory calibration prior to the commencement of this study. Thermo Scientific stated that the calibration of the Miran SapphIRe was $\pm 10\%$ for concentrations of 1-100 ppm (47). The IHS has documented cases with exposures well above 100 ppm, therefore a procedure for developing a calibration curve across an approximate range of 1 -700 ppm was developed based on the user verification procedure recommended by Thermo Scientific (20; 47).

Equation (2) was used to determine the appropriate injection volumes of N₂O required to create the desired concentrations in the Miran SapphIRe sample cell.

$$V_1C_1 = V_2C_2 \quad (2)$$

Where:

V_1 = injected volume (μ l, ml)

C_1 = concentration (ppm) of N₂O (995,000 ppm)

V_2 = total volume of sample cell and closed loop calibration system (2.24L)

C_2 = desired concentration in ppm

Desired concentrations were selected between 1-700 ppm, and adjusted to accommodate whole value injection volumes (e.g. desired: 700 ppm = exact injection volume: 1.57 mL; adjusted injection volume: 1.6mL = actual: 716 ppm).

At each sampling Region, the prepared procedure was used to produce a calibration curve ranging from 1-700 ppm. As part of this procedure, five concentration

measurements were recorded at each calibration concentration point. Each set of five concentration measurements were then averaged to give the mean observed instrument response for each calibration point. These values were then plotted against their respective known concentrations in the instrument sample cell and checked for linearity. Since the least squares best-fit line for the data resulted in a low goodness of fit value (R^2) of 0.9792, a polynomial best-fit line was plotted with a resulting R^2 of 0.9992. Figure 3 illustrates the comparison between the linear and polynomial plots.

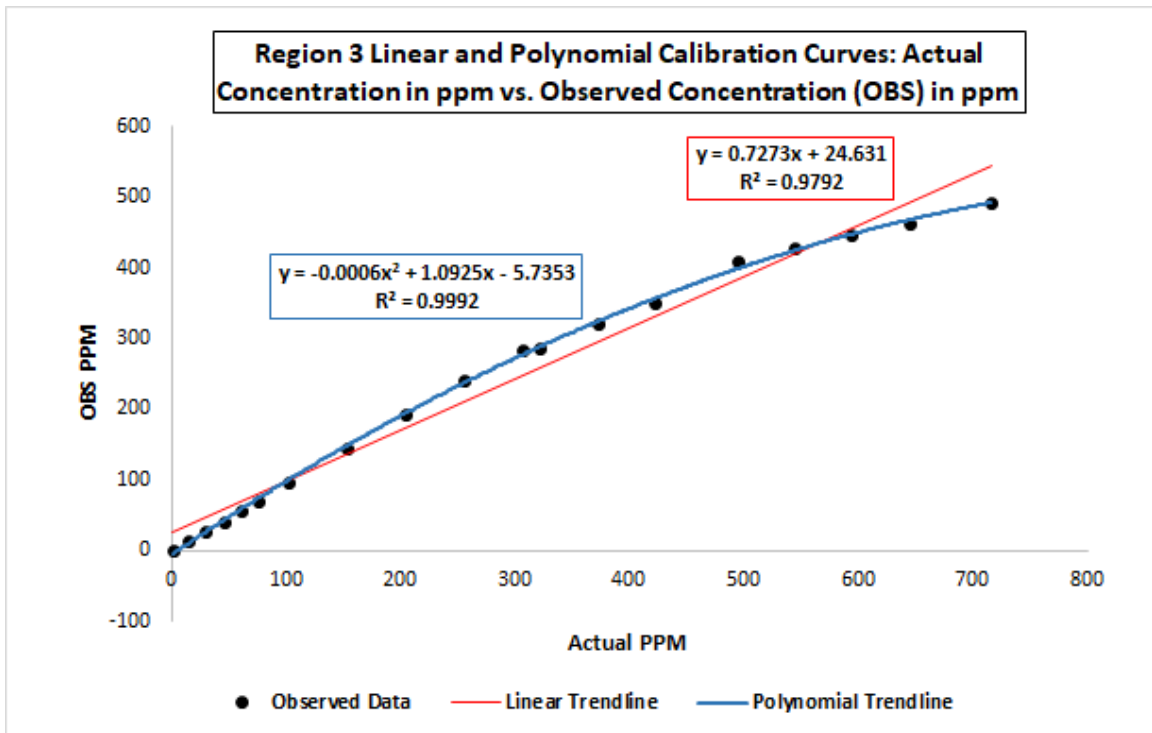


Figure 3. Miran SappHRe Calibration Curves for Region 3.

The observed concentration measurements were then inserted into the polynomial equation as the dependent variable, and the equation solved to generate a corrected observed concentration measurement (COBS). The COBS were then evaluated by calculating the percent difference between the COBS and the actual concentration

injected into the Miran SapphIRe. The average percent differences for each IHS region ranged between 2-6%. However, using concentrations over 500 ppm in the polynomial correction equation required the use of imaginary numbers making calculations infeasible for some values. Consequently, the data was log transformed to simplify the calculations. The observed concentration measurements and actual concentrations were log transformed and plotted to check for linearity. Best-fit lines were calculated for the linear relationship (red solid line) and the polynomial relationship (blue dashed line). An R^2 of 0.997 for the linear equation was calculated. The R^2 for the polynomial equation was calculated at 0.997. Figure 4 shows these two plots together.

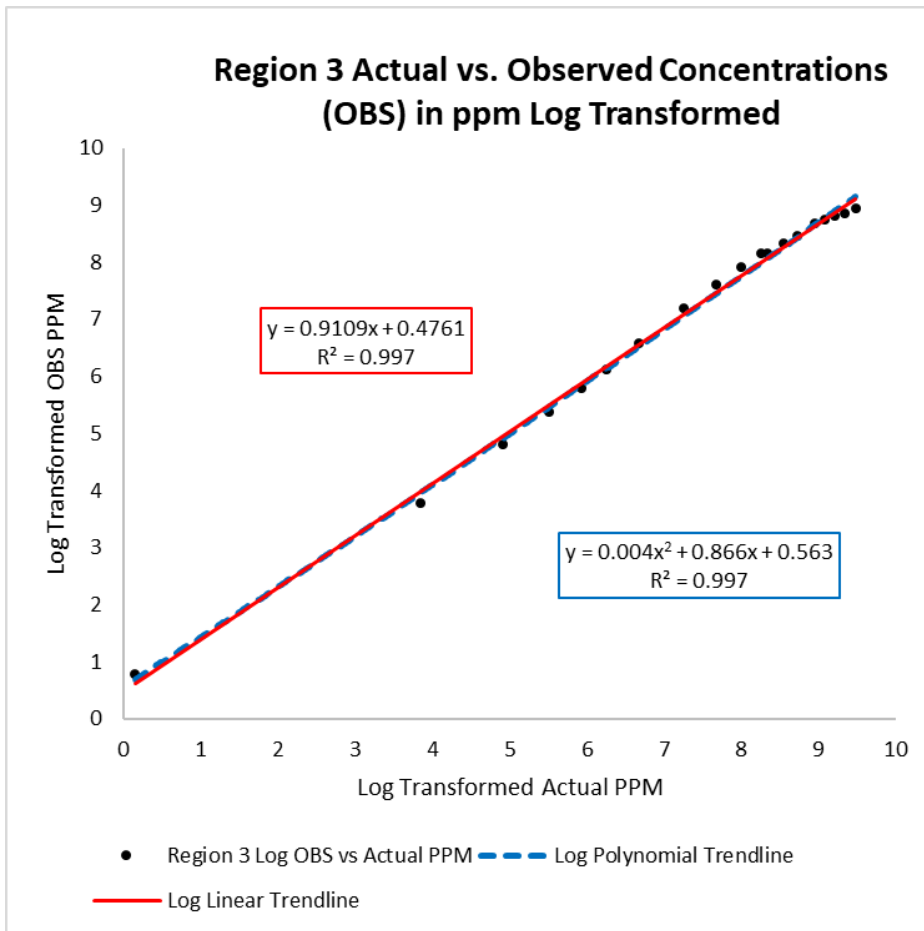


Figure 4. Log transformed Miran SapphIRe Calibration Curve region 3.

The two equations were checked for accuracy, with the linear equation giving an average percent difference (for all three regions) of 8% and the polynomial an average percent difference of 5%. The polynomial equation was selected for use in this study due to its higher accuracy and ability to improve fit of nitrous oxide concentrations above 500 ppm.

Figure 5 illustrates a comparison between the observed measurements displayed on the instrument (OBS) with the corrected observed (COBS) concentrations obtained after applying each OBS to the polynomial regression equation described above.

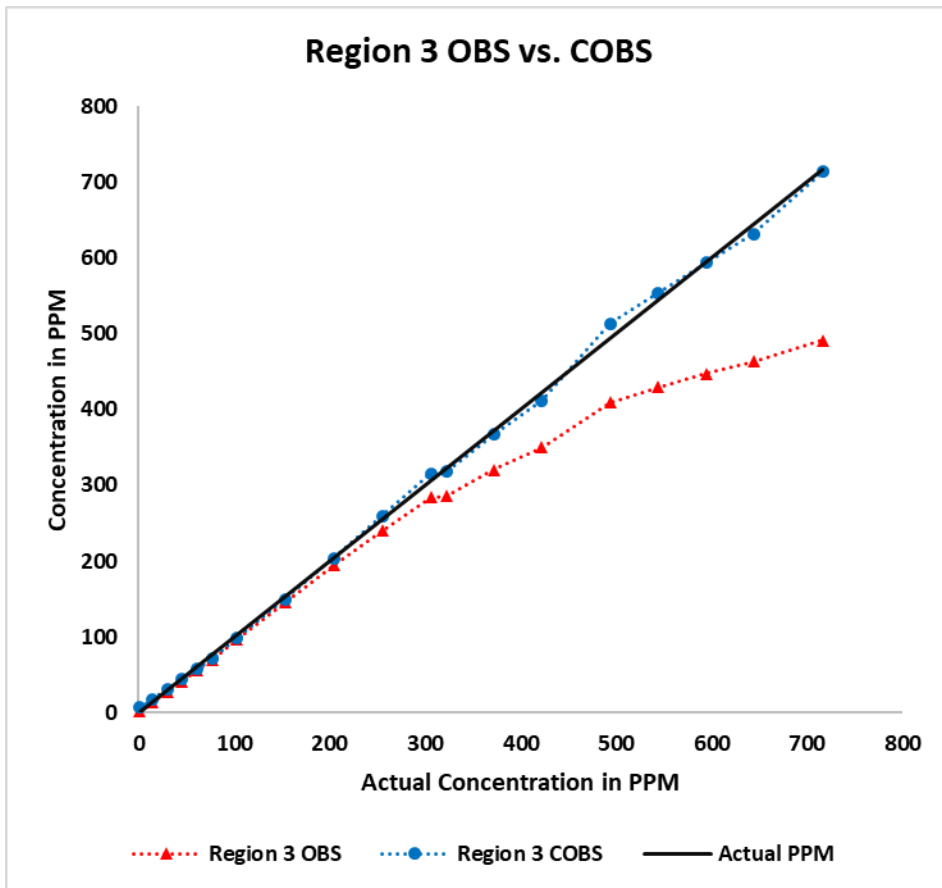


Figure 5. OBS VS COBS in relation to the actual concentration for Region 3.

The average percent difference between the actual N₂O concentrations injected in the sample cell and the observed concentrations was 20% across the entire calibration range for the three IHS regions. This difference was greatly reduced by correcting the observed concentration Miran SapphIRe readings using the calculated calibration curves created for each region. The average percent difference across regions was 5%. By applying the calibration curve for each region there is a 15% improvement for the corrected concentration. Tables and figures for each region showing the actual concentrations injected, observed concentration measurements, their respective log transformations, percent differences, OBS vs. COBS for each region, as well as the calibration equations calculated for each region can be found in Appendix A, tables 11, 12, and 13; and figures 25, 26, 27 and 28.

3.2.2.1 Miran SapphIRe Uncorrected Data

The Miran SapphIRe displayed and recorded a N₂O reading every 30 seconds during each sampling period. This reading is considered the “OBS” reading of the Miran SapphIRe. After the sampling period, the data was downloaded into a Microsoft Excel spreadsheet

3.2.2.2 Miran SapphIRe Corrected Data

Each reading was corrected using the corresponding regional calibration curve. These corrected concentrations or “COBS” were then averaged to give a procedural TWA. This corrected procedural TWA was used to compare the three sampling devices.

3.2.3 Thermal Desorption Tubes Calibration Curve

The TD tubes were analyzed at the Uniformed Services University laboratory using an Agilent 7890B/5977B gas chromatography mass spectrometer (Agilent Technologies, Santa Clara, CA). The areas under the N₂O peak were integrated and applied to the instrument's calibration curve to determine the mass of N₂O collected during sampling. The average N₂O exposure to the dental personnel was calculated by dividing the mass of N₂O collected by the product of the applicable sampling time and uptake rate (discussed below). Two separate calibration curves were reported to account for the length of time between sampling periods (July 2019 and November 2019).

TD tube calibration curve data can be found in appendix B table 14. To achieve the best fit, the data was log transformed and plotted generating a linear fit of R² 0.9956 for concentrations of 1-500 ppm. (Figure 6)

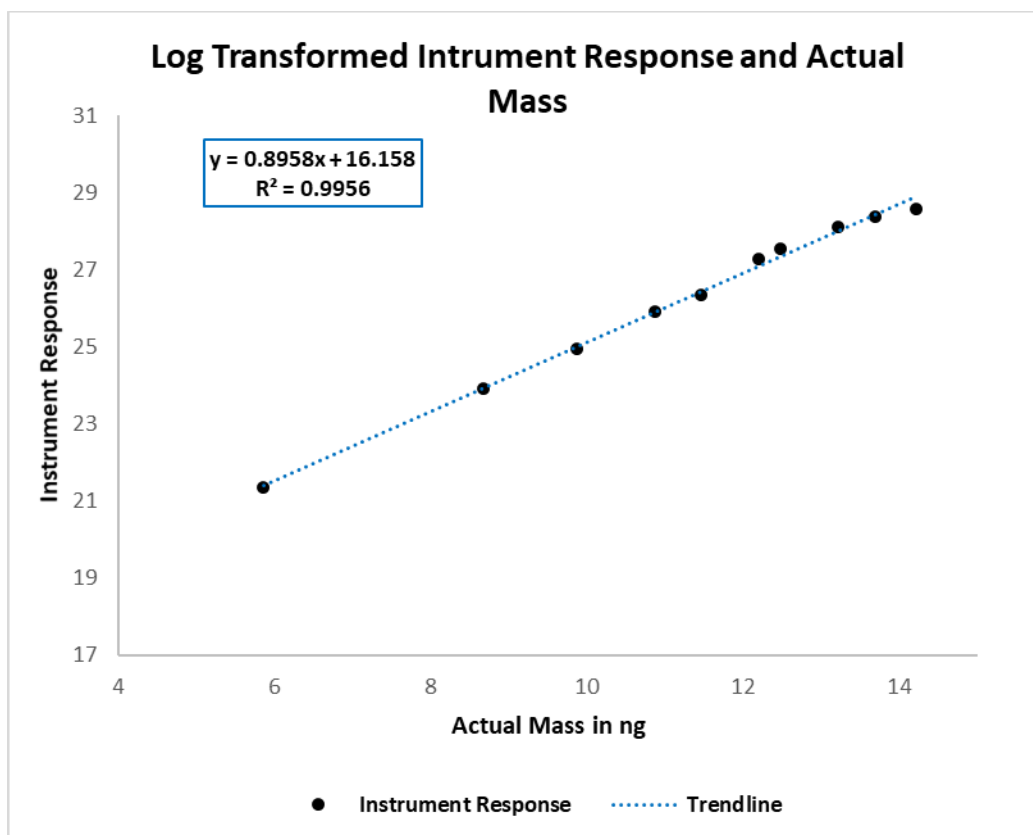


Figure 6. First sampling period TD tube calibration Curve.

Equations were derived to determine the best fit and most accurate for calculating a mass for the TD tubes. Each equation derived was used to calculate a mass then compared to the actual mass injected onto the TD tubes. The percent difference between the mass calculated using each equation and the actual mass injected onto the tube was calculated. The log transformed linear equation resulted in the lowest mean percent difference at 8%.

Appendix B table 15 shows the percent differences (PD) calculated for the polynomial (P-PD), log polynomial (LP-PD), and log linear (LL-PD), equations along with the actual masses and equivalent concentrations.

For the second sampling period (November 2019), a linear equation for 1-300 ppm was reported by the lab to conduct mass conversions. Figure 7 shows the calibration curve derived for the second sampling period.

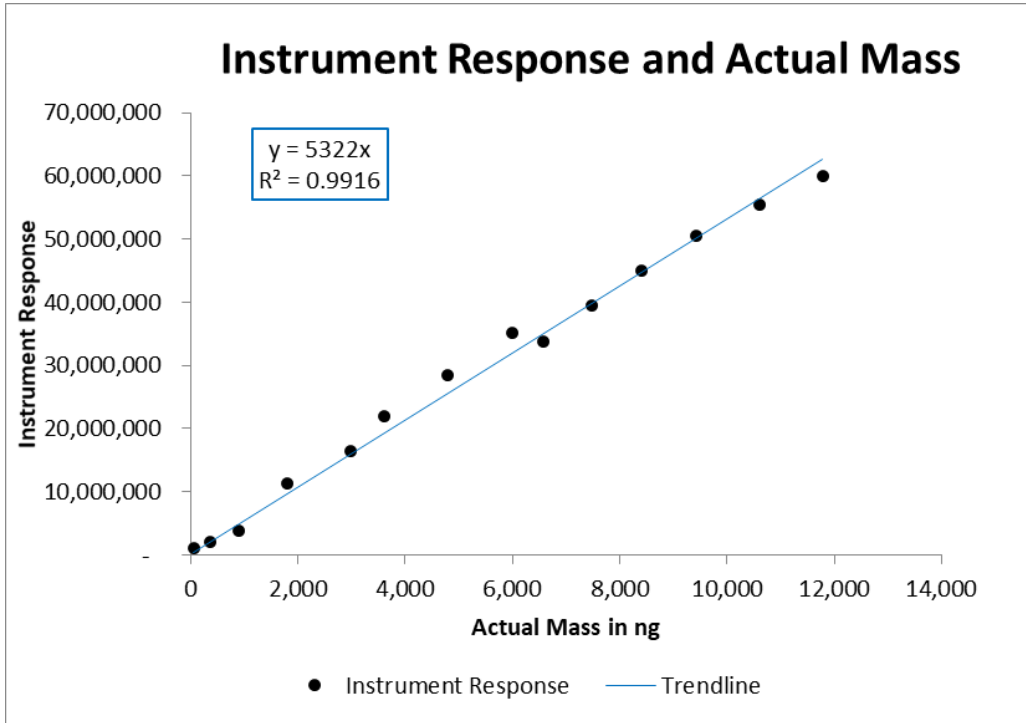


Figure 7. Second sampling period TD tube calibration curve.

The USU lab reported the figure 7 calibration curve to be the best fit and most accurate with an average percent difference of 15%. Data for the second sampling period (November 2019) can be found in appendix B table 16.

3.2.4 Calculating Mass and Concentration in ppm for Thermal Desorption Tubes

The calibration equations listed in Figures 6 & 7 were rearranged to solve for x and are shown in equation (3) first sampling period and (4) second sampling period:

$$x = (y - 16.158)/0.895 \quad (3)$$

$$x = y/5322 \quad (4)$$

Where:

y = peak area integration reported

x = mass in ng

For the first sampling equation (Figure 6 eq. 3), after the mass is calculated the anti-log must be taken before calculating a concentration.

Once the masses were calculated, concentrations were then derived for statistical comparison of differences in the means and to determine agreement of the three sampling devices. The formula used to calculate the concentration in ppm is seen in equation 5:

$$C = \frac{Mass}{Time} * 1.25 \text{ ng ppm}^{-1} \text{ mins}^{-1} \quad (5)$$

Where:

C = concentration (ppm) of N₂O

Mass = derived from appropriate equation (ng)

Time = duration of procedure in minutes

1.25 = uptake rate ng ppm⁻¹ mins⁻¹ reported by Markes International (13).

3.2.5 Badge Analysis

All badges were sent to Assay Technology (Livermore, CA) for analysis. Assay Technology's utilizes "desorption with water; headspace analysis by gas chromatography with electron capture detector"(46). The Assay Technology analysis reports included the mass (µg) collected and associated concentrations in ppm (using the badge's specific uptake rate validated by Assay Technology).

3.2.6 Pre-Sampling Activities

The N₂O delivery and scavenging systems were inspected and tested for leaks using the Miran SapphIRe. Remediation actions (tightening valves, replacement of N₂O bottles, replacement of scavenging system hoses) were taken for any measured concentrations > 0 ppm.

The Miran SapphIRe was turned on, allowed to warm for at least 30 minutes, and zeroed prior to data logging in accordance with the manufacturer's instructions (47).

All facilities sampled were built, owned, and maintained by the IHS, and all used similar operating procedures.

3.2.7 Personal Sampling Device Arrangement

Personal sampling of the dentist's breathing zone was performed using one Miran SapphIRe Portable IR Analyzer (Thermo Scientific, Waltham, MA), two #575 Nitrous Oxide Personal Monitoring Badges (Assay Technology, Livermore, CA), and three stainless steel thermal desorption tubes (Markes International, Llantrisant, UK). The breathing zone is considered a hemisphere forward of the shoulders within a radius of approximately 10 inches of the mouth and nose (39). Devices were placed according to the dentist's dominant vs non-dominant hand. Each dentist was asked whether their left or right hand was their dominant hand.

The Miran SapphIRe sampling tube, one badge, and one TD tube were placed on the collar of the dentist's dominant hand. One TD tube and one badge were placed on the collar of the dentist's non-dominant hand. In addition, one TD tube was added to the collar of the non-dominant hand for laboratory Quality Assurance/Quality Control (QA/QC) purposes. (Figure 8) In total, six sampling devices measured N₂O exposure to

each dentist during dental procedures. The dominant hand grouping of the Miran SapphIRe, one badge, and one TD tube comprised one personal sample (n = 1) of each sample type.

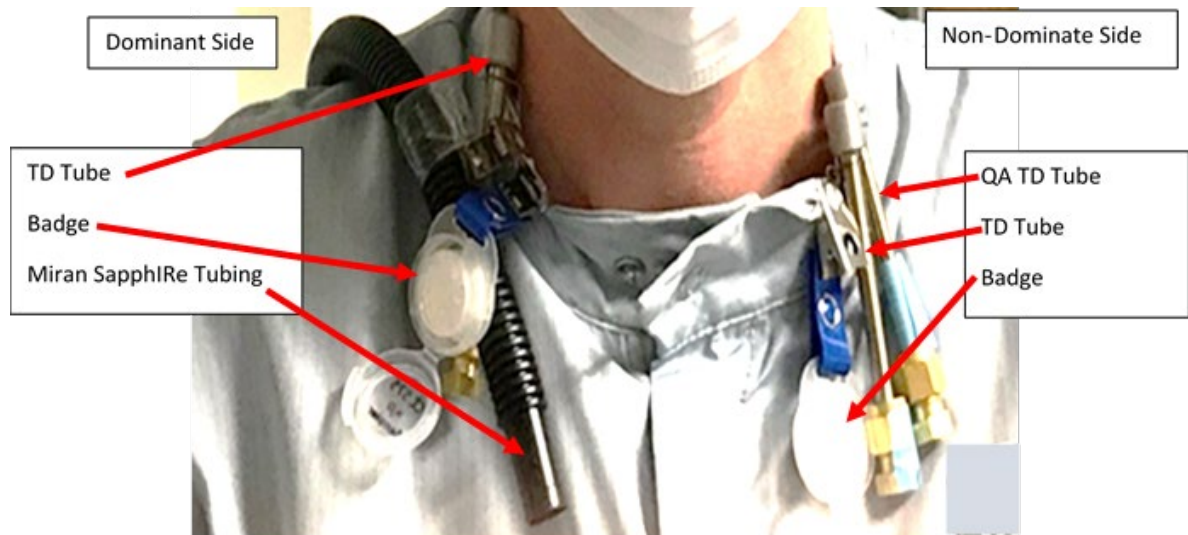


Figure 8. Arrangement of devices on dentist with head tilted up to see devices. (Dentist typically leans forward with head bent down making a picture difficult to see during sampling)

Prior to delivery of N₂O to the patient, the following steps were conducted. A sampling tube four meters in length, to allow dentist to move freely, was connected to the Miran SapphIRe with a particulate filter in-line. (Figure 9) The Miran SapphIRe tubing was placed onto the dominant collar of the dentist and recording started. Then badges and TD tubes were uncapped and placed on the dentist.

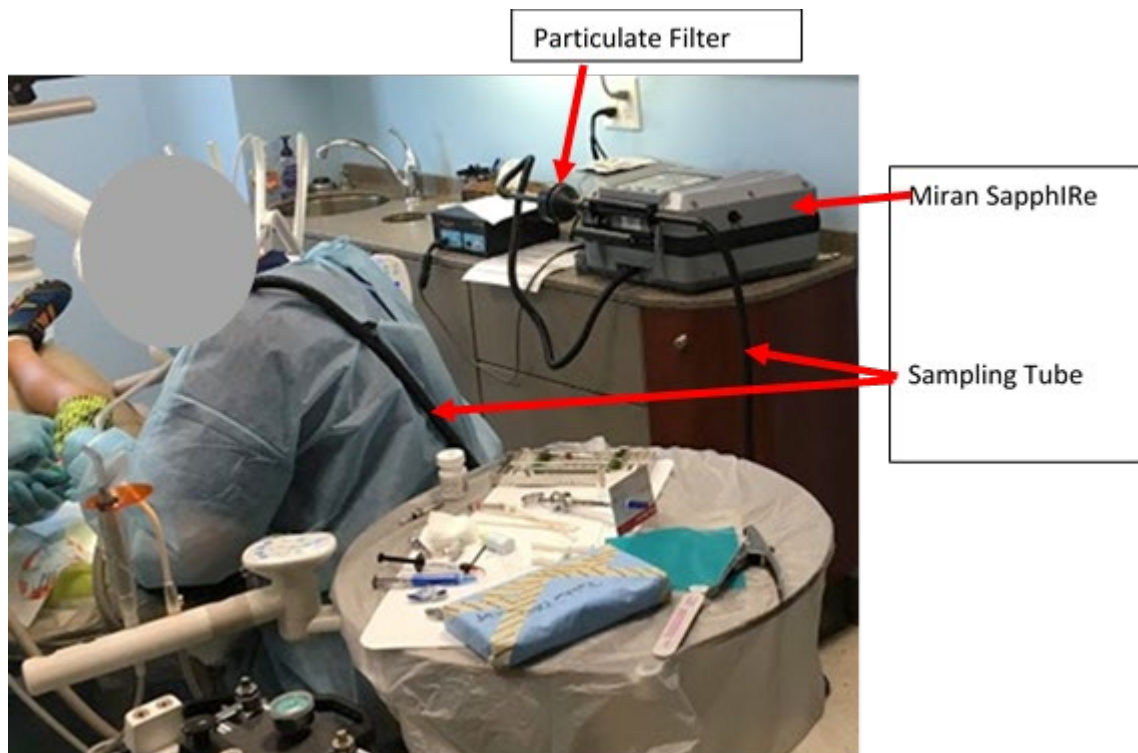


Figure 9. Miran SapphIRe sampling set up (20).

At the end of the dental procedure, the badges and TD tubes were removed and capped and data logging for the Miran SapphIRe was halted. The badges and TD tubes were placed into their respective return containers as per laboratory instructions.

On average, each dental procedure within IHS clinics was approximately 30 minutes in duration. One blind blank of each sampler type was included with every 10 samples. One blank was included for those regions that did not have a minimum of at least 10 samples.

3.2.8 Miran SapphIRe Sampling Process Overview

The Miran SapphIRe was prepared similar to the process followed by Hansen et al. (2019) and what is typical of IHS policy and procedure (20). However, this study

included the previously described user verification check. The steps listed below were conducted for the Miran SapphIRe:

1. User verification/calibration curve conducted upon arrival to region

Immediately Prior to Sampling

2. Selected sampling mode for ambient air
3. Set instrument parameters as required for analysis, allowing for sufficient warm-up time (30 mins)
4. Purged and zeroed the Miran SapphIRe
5. Collected sample
6. Downloaded data to excel program at the end of each day
7. Sorted data by case
8. Applied region specific calibration curve.

3.2.9 Blank Correction of Badge Data

The passive badges were blank corrected by subtracting each blank's average mass reported by the lab from the mass reported for each sample. Assay Technology specified their mass reporting limit (RL) as 0.4 µg. Two samples were reported by Assay Technology as being "non-detect" (ND, meaning that the N₂O mass was below the lab's RL) before blank corrections were made. After blank correction, an additional 15 samples were considered ND (badge mass < RL). Due to the high N₂O masses reported on the blanks, a total of 17 badges were reported to be ND after blank correction.

3.2.10 Blank Correction of Thermal Desorption Tube Data

The masses from TD tube blanks were calculated using the appropriate equation (3 or 4) for mass and equation 5 for concentration. All field blanks submitted to the USU

lab produced results below the limit of quantification (LOQ). The LOQ for the first sampling period was reported to be 56 ng, and for the second sampling period was reported to be 221 ng. Nine tubes used to sample during procedures were below the LOQ and considered NDs.

3.2.11 Censored Data

Badges and TD tubes reported as NDs were treated as censored data following guidance from the American Industrial Hygiene Association (AIHA). The values substituted for the NDs, were calculated by dividing the RL or LOQ by two (4). For the badges, equation (6) below was used to convert the censored data mass into a ppm concentration:

$$C = \frac{\left(\frac{RL}{2}\right) \times \text{Molar Volume}}{\text{Molecular Weight}} \quad (6)$$

Where:

C = concentration in ppm

RL = reporting limit μg

L = volume in liters reported for each badge

Molar Volume = 24.45 L/mol

Molecular Weight = 44.013 N_2O g/mol

For the TD tubes, the LOQ was divided by two then applied to the respective calibration curve.

Statistical comparison was completed after all badges were blank corrected and after censored data was substituted.

3.3 STATISTICAL ANALYSIS

The minimum sample size required to identify a statistically significant difference in the sample means was calculated using the University of California San Francisco Clinical and Translational Science Institute's (2018) sample size calculator (48). A minimum sample size of 31 samples was calculated to ensure statistical significance at a 0.05 level of significance, with 80% power, an effect size of 0.5 ppm, and an estimated sample standard deviation of one.

The sampling data was reviewed to assess compliance with critical assumptions associated with parametric statistical tests (repeated measures ANOVA, paired t-test). Histograms of time-weighted averages were checked for normality and log transformed to approximate normal distributions to enable analysis using parametric statistical tests.

A paired t-test was used to determine the significant difference in the means between the dominant and non-dominant sides, and a repeated measures ANOVA was used to compare the three sampler types.

Bland-Altman analyses were used to measure the degree of agreement between the three sampler types. Bland-Altman analysis compares two methods quantitatively and visually by plotting the difference against the means for each procedure of the two methods (31). In this study, the three sampling devices were to be considered equivalent if their upper and lower limits of agreement were $\leq 15\%$ with 95% confidence.

To plot the Bland-Altman the following steps were taken. The bias was calculated by averaging the differences between samplers. Upper and lower levels of agreement (LOA) were also developed. The LOAs were calculated using the following equation (7):

$$LOA = Bias \pm 1.96 * \sigma \quad (7)$$

LOA = level of Agreement (either upper + or lower -)

Bias = average of the differences

1.96 = 95% Confidence Interval

σ = standard deviation of the differences

Bland and Altman (1986) recommend using log transformed data when the differences are proportional to the means, which offers an enhanced view of the data plot (31). However, the data must relate to the original scale therefore, the anti-log of the LOA's must be taken (31). Agreement acceptable to IHS was considered to exist if the upper and lower LOA's are within $\pm 15\%$ which relates to 0.85 (lower LOA) and 1.15 (upper LOA) (dimensionless) when the anti-log of the LOA's is taken. For the purposes of this study, the anti-log of the upper and lower LOA is reported in the legend respectively.

CHAPTER 4: Results

4.1 DESCRIPTIVE STATISTICS

Thirty-one procedures were sampled in three different regions, at five different clinics within the IHS, and on six separate dentists. This resulted in 31 badge sample pairs for the dominant and non-dominant hands. There were also 31 TD tube samples for each of the dominant and non-dominant hands. However, only 24 Miran SapphIRe samples were feasible due to equipment shipping problems and the backup Miran SapphIRe malfunctioning.

The duration of each individual procedure ranged from 17 minutes to 52 minutes, with an average of 33 minutes per case. Each of the three sampling regions was given a number designation. Region 1 six procedures were sampled, while Region 2 had four, and Region 3 had 21. Table 1 shows the region, total procedures sampled and average concentration in ppm sampled by device.

Table 1. Average TWA for each sampling device by region.

# Procedures and Average N₂O Concentration by Region							
Region Number	Total Procedures (n)	Miran (ppm)	Badge Dominant (ppm)	Badge Non-Dominant (ppm)	Quality Assurance TD tube (ppm)	TD tube Dominant (ppm)	TD tube Non-Dominant (ppm)
1	6	197	90	246	169	153	176
2	4	223	254	402	125	117	157
3	21	34	15	21	39	47	43

Although Region 3 had the most procedures they had a lower average across devices. This suggested that they had better control of N₂O emissions. Table 2 gives the ranges for each region by device.

Table 2. Range of concentrations by region and device in ppm.

Range of Concentrations by Site and Device in ppm						
Region	Miran Low	Miran High	Badge Low	Badge High	TD tube Low	TD tube High
1	23	438	15	592	17	301
2	1	456	ND	995	ND	253
3	1	131	ND	104	ND	159

ND-Non-Detect

4.1.1 Normality

The data was log transformed and statistically tested to determine if the data was normally distributed so that parametric statistics could be used, the results can be found in Table 3. As mentioned above the Miran SapphIRe was not available for all 31 procedures and as this study's primary focus was comparison of devices to the Miran SapphIRe the degrees of freedom reflects only those procedures where the Miran SapphIRe was used.

Table 3. Test of Normality.

Tests of Normality All Devices			
	Shapiro-Wilk		
	Statistic	df	P-value
Miran	0.928	24	0.089
Badge Dominant	0.915	24	0.045
Badge Non-Dominant	0.892	24	0.015
TD tube Quality Assurance	0.936	24	0.130
TD tube Dominant	0.915	24	0.046
TD tube Non-Dominant	0.926	24	0.081

As can be seen in Table 3, the badges resulted in $p=.045$ for the dominant side and $p=.015$ for the non-dominant side. This indicates that both sides fail to meet the assumption of normality. However, parametric statistical analysis such as the t-test and the repeated measures ANOVA can still be utilized due to the robustness of those tests and the study sample size of 31 being considered “moderate” (14). Analysis of the badge data Q-plots show that the lower ends may be cause for the non-normal distribution. (Figures 10 & 11).

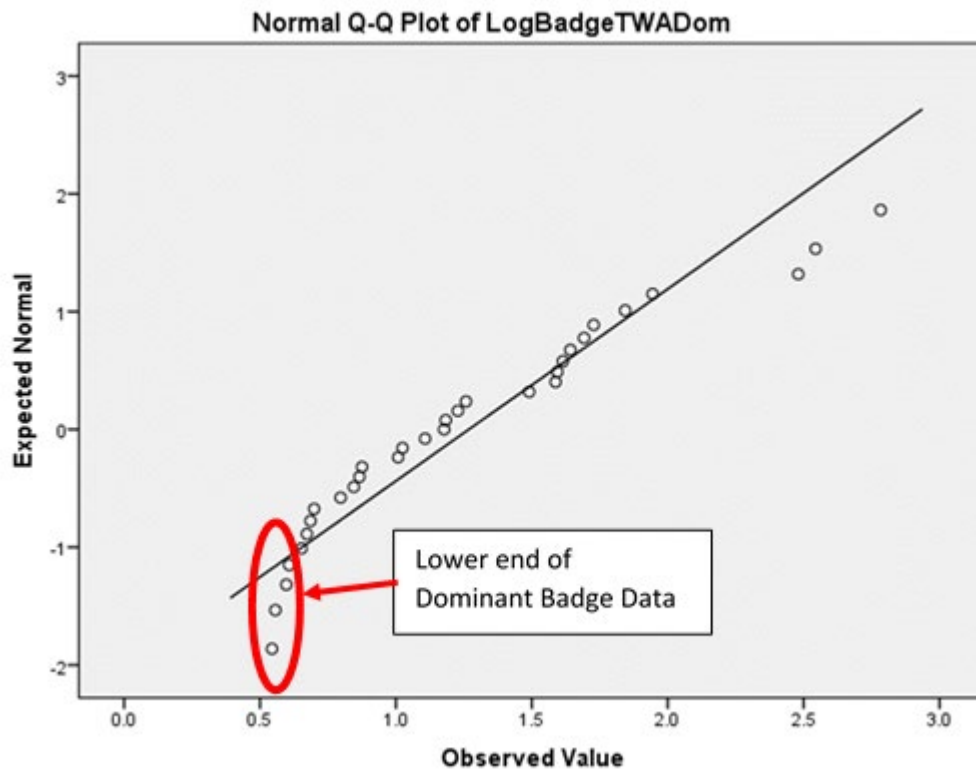


Figure 10. Q-Plot for Dominant Side Badges.

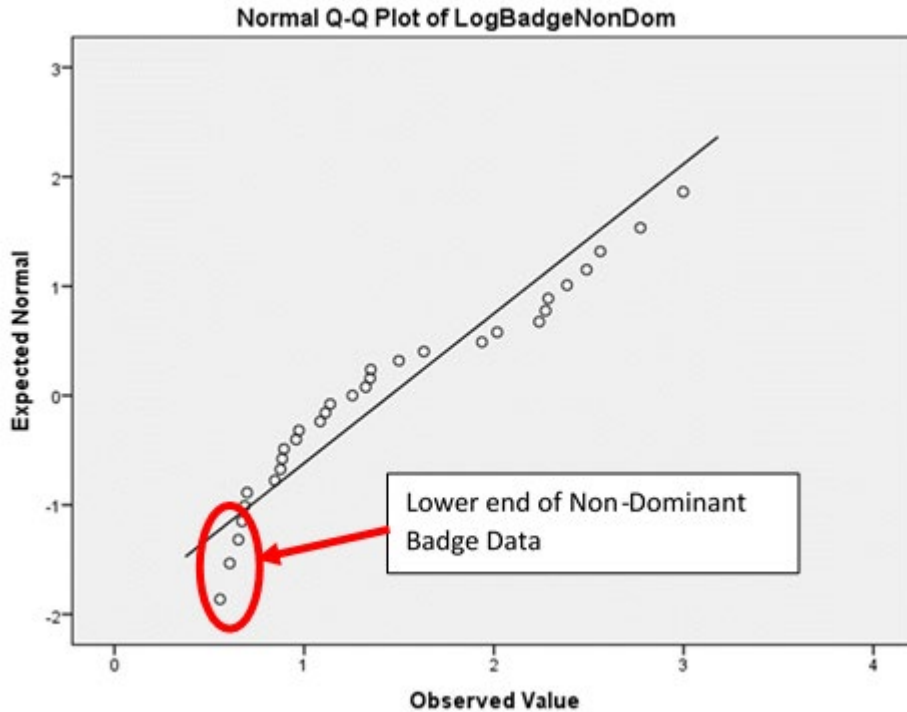


Figure 11. Q-Plot for Non-Dominant Side Badges

4.2 COMPARISON OF DEVICE PLACEMENT ON DOMINANT VS. NON-DOMINANT SIDE

Dominant hand vs non-dominant hand data for both the badges and TD tubes was investigated to determine the effect of device placement concentration measurements. Two TD tubes (one being a QA sample) were placed on the non-dominant side. A paired t-test was performed to determine if there was a significant difference in the placement of the sampling device in relation to the dominant and non-dominant hand. Table 4 shows the results of the T-test.

Table 4. Paired Samples t-test: Passive Badge and TD Tube Placement: Dominant (Dom) Hand vs Non-Dominant (Non-Dom) Hand.

Dom. Vs. Non-Dom. TD tubes and Badges Paired Samples t-test			
Device	Placement Comparison	Mean	P-Value
TD tube	QA vs Dom	-0.02	0.625
TD tube	QA vs Non-Dom	-0.02	0.728
TD tube	Dom vs Non-Dom	0.01	0.807
Badges	Dom vs Non-Dom	-0.18	0.003

Table 4 shows that there was a statistically significant difference between the means of the dominant and the non-dominant measurements that cannot be attributed to chance alone for the badges $p=.003$. There was no significant difference between the QA, dominant or non-dominant TD tubes $p>.05$. This is useful as there was missing data for the dominant side (3 tubes) due to loss of samples during analysis. Determining that there is no significant difference between the tubes, the missing data was replaced with the corresponding QA tubes for further analysis when comparing against the Miran SapphIRe and badge devices.

4.3 COMPARING DEVICES

Sampling on the dominant hand was always performed with a set of three samplers (Miran SapphIRe, badge, and TD tube). The Miran SapphIRe and the badges all reported concentration values in ppm or “non-detects”. Missing TD tube data were substituted with their corresponding QA TD tube value so that a statistical comparison could be made. A repeated measures analysis of variance (ANOVA) was then performed to investigate statistical differences between devices using the dominant side data. (Table 5) Results show there was a significant N₂O concentration differences between the three

sampling devices ($p < .05$). This suggests the difference between devices cannot be attributed to chance alone.

Table 5. Repeated Measures ANOVA Miran SapphIRe, Badge, TD tube.

Repeated Measures ANOVA Pairwise Comparisons Dominant Side			
Device		Mean Difference (Log-transformed ppm)	P-Value
Miran	Badge	0.20	0.044
	Tube	-0.12	0.035
Badge	Miran	-0.20	0.044
	Tube	-0.32	0.002
Tube	Miran	0.12	0.035
	Badge	0.32	0.002

When comparing the Miran SapphIRe to the non-dominant badge and non-dominant TD tube results show there was a significant difference between Miran SapphIRe and TD tube $p = .003$ but no significant difference between the Miran SapphIRe and badge $p = .969$ and no significant difference between the badge and TD tube $p = .153$.

Table 6. Repeated Measures ANOVA Miran SapphIRe Non-Dominant Badge and TD tube.

Repeated Measures ANOVA Pairwise Comparisons Miran and Non-Dominant Badge and TD tube			
Device		Mean Difference (Log-transformed ppm)	P-Value
Miran	Badge	0.00	0.969
	TD tube	-0.14	0.003
Badge	Miran	0.00	0.969
	TD tube	-0.13	0.153
TD tube	Miran	0.14	0.003
	Badge	0.13	0.153

4.4 LEVELS OF AGREEMENT DOMINANT SIDE

Bland-Altman plots were constructed to assess the agreement between badges and TD tubes on the dominant side; Miran SapphIRe and dominant badge; and Miran SapphIRe and dominant TD tube. As stated above there were 24 procedures sampled with the Miran SapphIRe, badges, and TD tubes however, there were a total of 31 procedures sampled with badges and TD tubes.

4.4.1 Dominant Badge and Thermal Desorption Tube LOA

Figure 12 shows the Bland-Altman plot with LOA's for the badge and TD tube. The antilog of the upper and lower LOA is reported in the legend. As can be seen the badge and TD tube do not meet the terms set for good agreement set a priori (0.85-1.15).

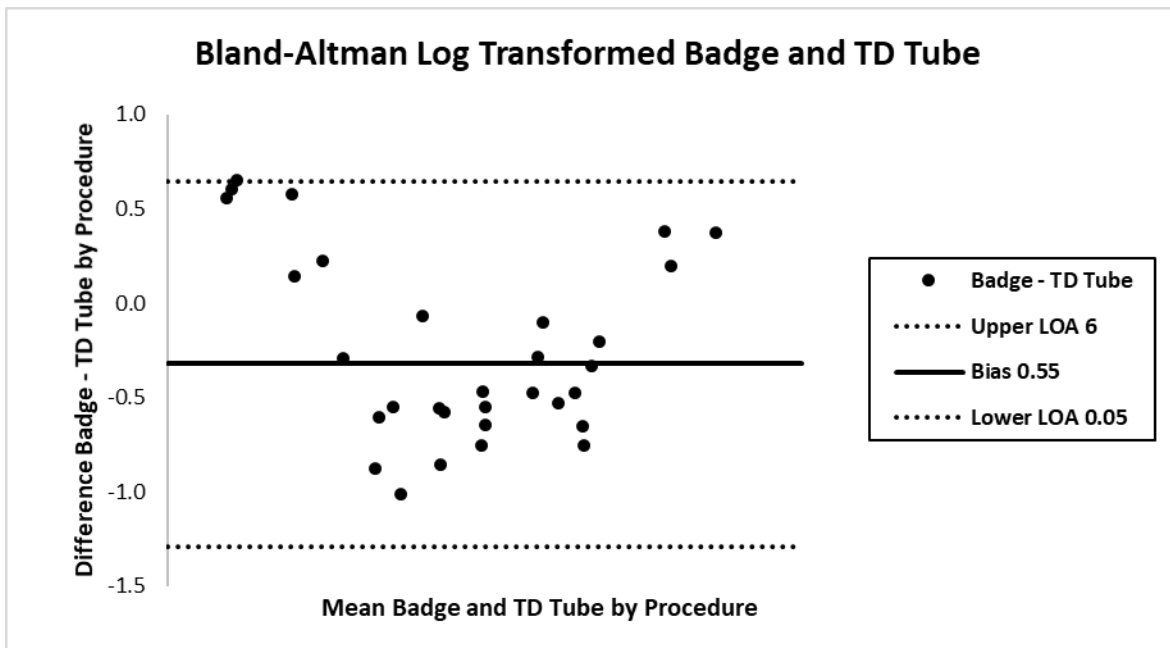


Figure 12. Bland-Altman plot dominant side badge and TD tube. The plot shows the badge minus the TD tube, as such all data points above zero on the y-axis indicate that the badge had a higher concentration measurement than the TD tube and all points below zero indicate the TD tube concentration measurements were higher than the badge.

4.4.2 Miran SapphIRe and Dominant Badge LOA

Figure 13 shows the upper and lower levels of agreement between the Miran SapphIRe and badge.

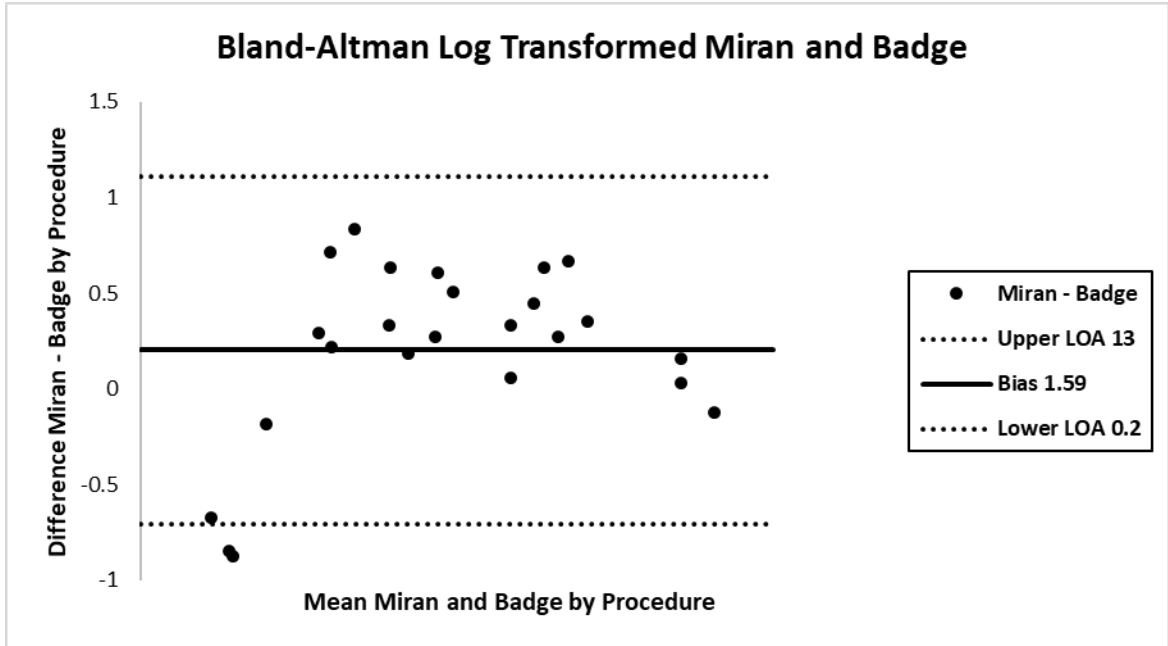


Figure 13. Bland-Altman plot Miran SapphIRe and dominant badge.

The plot shows the Miran SapphIRe minus the badge, as such all data points above zero on the y-axis indicate that the Miran SapphIRe had a higher concentration measurement than the badge and all points below zero indicate the badge concentration measurements were higher than the Miran SapphIRe.

The transformed LOA's do not fall within 0.85 to 1.15, which indicates that the Miran SapphIRe and the dominant badge do not meet the $\pm 15\%$ level of agreement acceptable to IHS. In addition, 79% of the data falls above zero on the y-axis indicating that the Miran SapphIRe reports a higher concentration than the badges for most of the procedures.

4.4.3 Miran SapphIRe and Dominant TD Tube LOA

Figure 14 shows the upper and lower levels of agreement between the Miran SapphIRe and TD tubes.

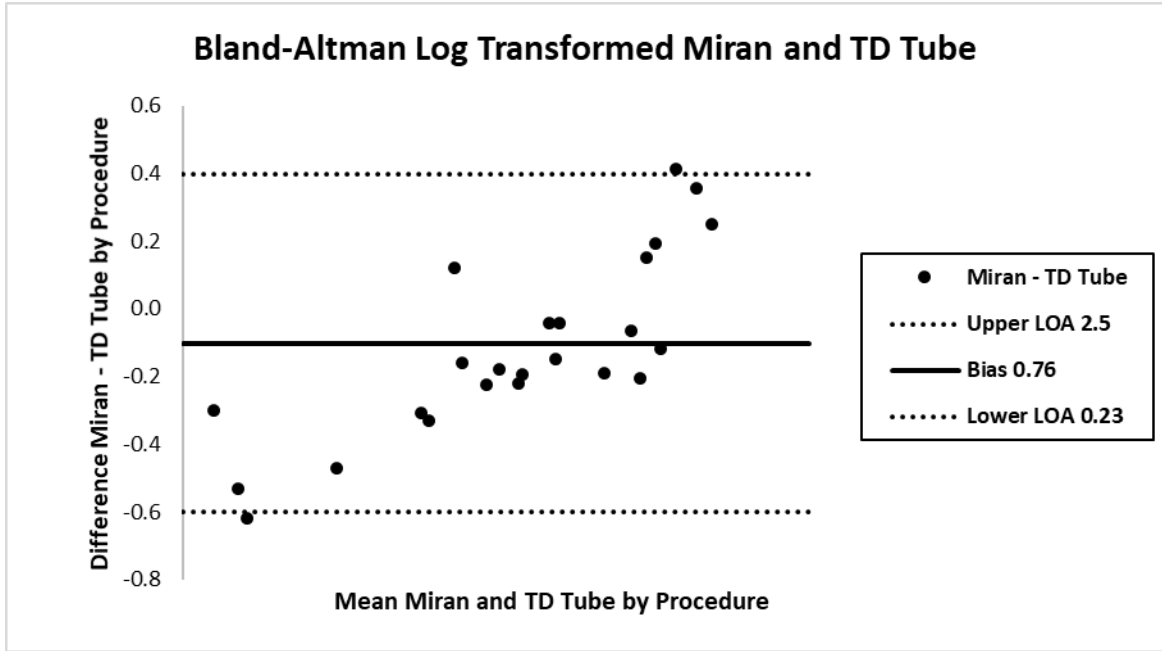


Figure 14. Bland-Altman plot Miran SapphIRe and dominant TD tube. The plot shows the Miran SapphIRe minus the TD tube, as such all data points above zero on the y-axis indicate that the Miran SapphIRe had a higher concentration measurement than the TD tube and all points below zero indicate the TD tube concentration measurements were higher than the Miran SapphIRe.

The transformed LOA's do not fall within 0.85 to 1.15, which indicates that the Miran SapphIRe and the dominant TD tube do not meet the $\pm 15\%$ level of agreement acceptable to IHS. However, the Miran SapphIRe measured concentrations higher than the TD tube for 25% of the procedures as compared to the 76% reported for the badges.

4.5 LEVELS OF AGREEMENT NON-DOMINANT SIDE

Bland-Altman plots were constructed to assess the agreement between badges and TD tubes on the non-dominant side; Miran SapphIRe and non-dominant badge; and Miran SapphIRe and non-dominant TD tube.

4.5.1 Non-Dominant Badge and Thermal Desorption Tube LOA

Figure 15 shows the Bland-Altman plot with LOA's for the badge and TD tube. As can be seen in the legend the badge and TD tube do not meet the terms set for good agreement listed above (0.85-1.15).

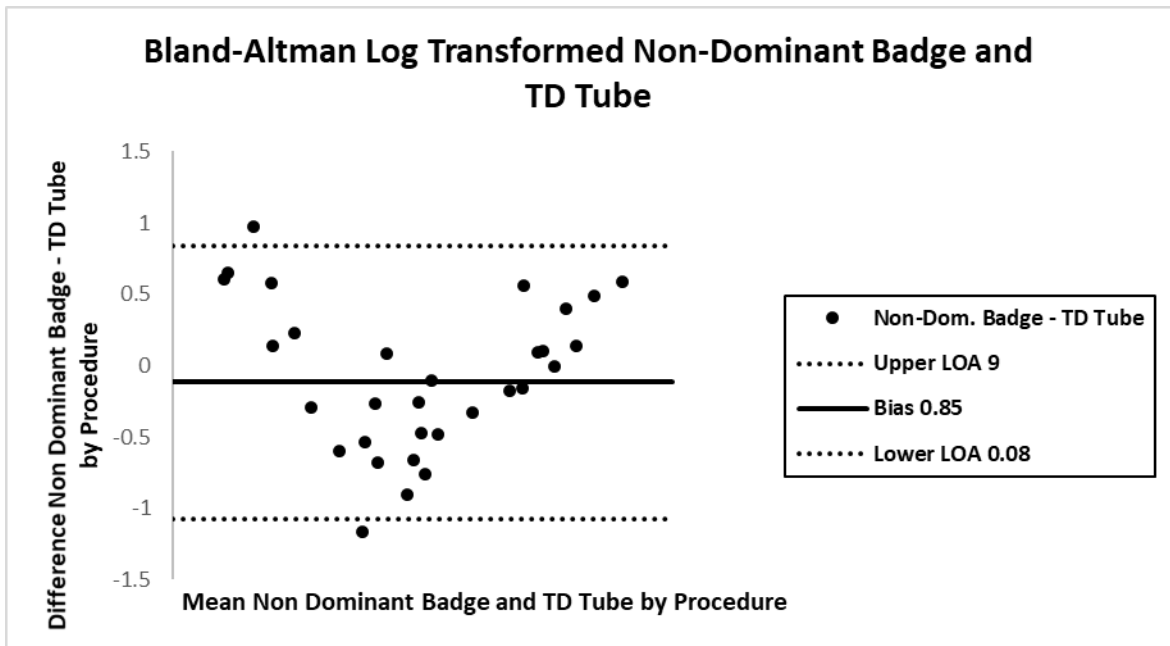


Figure 15. Bland-Altman plot non-dominant side badge and TD tube.

The plot shows the badge minus the TD tube, as such all data points above zero on the y-axis indicate that the badge had a higher concentration measurement than the TD tube and all points below zero indicate the TD tube concentration measurements were higher than the badge.

4.5.2 Miran SapphIRe and Non-Dominant Badge LOA

Figure 16 shows the upper and lower levels of agreement between the Miran SapphIRe and the non-dominant badge.

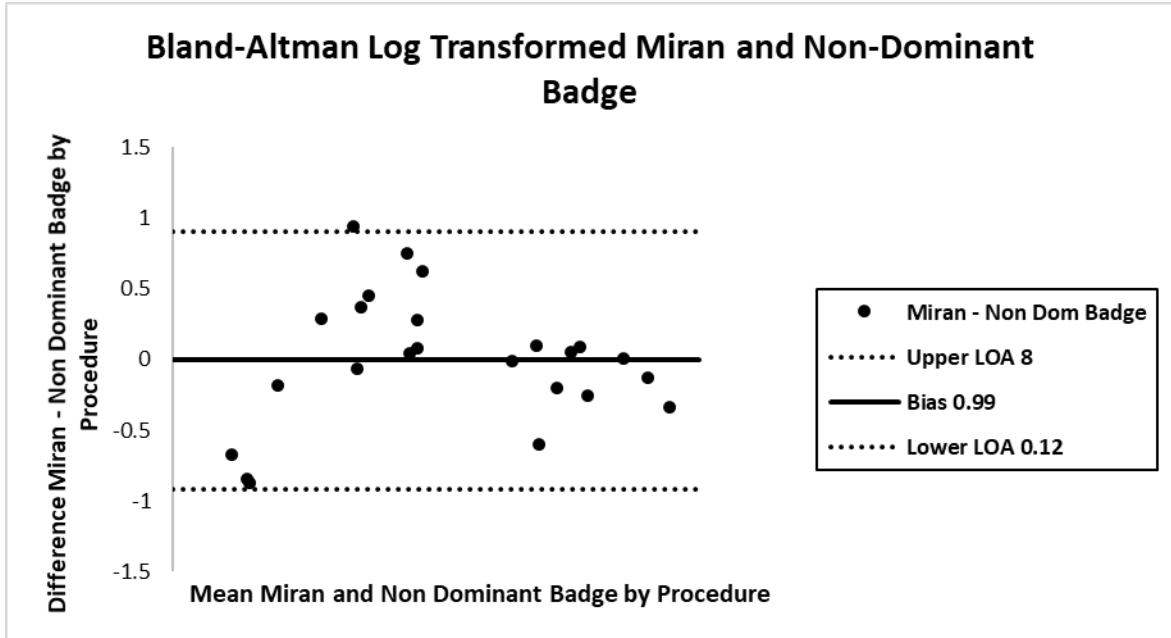


Figure 16. Bland-Altman plot Miran SapphIRe and the non-dominant badge. The plot shows the Miran SapphIRe minus the badge, as such all data points above zero on the y-axis indicate that the Miran SapphIRe had a higher concentration measurement than the badge and all points below zero indicate the badge concentration measurements were higher than the Miran SapphIRe.

The transformed LOA's do not fall within 0.85 to 1.15, which indicates that the Miran SapphIRe and the dominant badge do not meet the $\pm 15\%$ level of agreement acceptable to IHS. In addition, 50% of the data falls on or above zero on the y-axis indicating that, the Miran SapphIRe reports a higher concentration than the badges for half of the procedures.

4.5.3 Miran SapphIRe and Non-Dominant TD Tube LOA

Figure 17 shows the upper and lower levels of agreement between the Miran SapphIRe and non-dominant TD tubes.

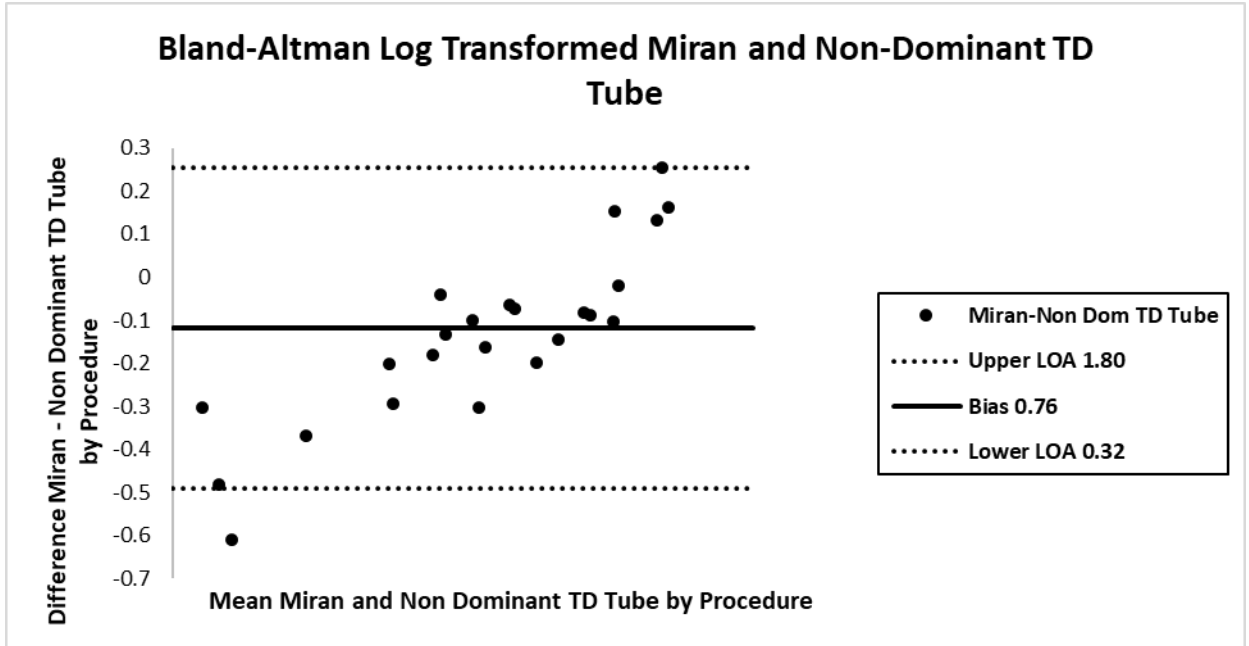


Figure 17. Bland-Altman plot Miran SapphIRe and non-dominant TD tube. The plot shows the Miran SapphIRe minus the TD tube, as such all data points above zero on the y-axis indicate that the Miran SapphIRe had a higher concentration measurement than the TD tube and all points below zero indicate the TD tube concentration measurements were higher than the Miran SapphIRe.

The transformed LOA's do not fall within 0.85 to 1.15, which indicates that the Miran SapphIRe and the dominant TD tube do not meet the $\pm 15\%$ level of agreement acceptable to IHS. However, the Miran SapphIRe measured concentrations higher than the TD tube for 17% of the procedures as compared to the 50% reported for the badges.

4.6 DEVICE COMPARISON AND AGREEMENT AT DIFFERENT CONCENTRATIONS

Using the Miran SapphIRe as the reference, the devices were divided into two groups according to concentrations between 1-50 ppm and >50 ppm to determine if the devices were significantly different and to determine the agreement. (Tables 7 and 8).

4.6.1 Device Comparison at Different Concentrations and Placement

4.6.1.1 Dominant Side

Table 7. Repeated Measures ANOVA 1-50 ppm.

Repeated Measures ANOVA Dominant 1-50 ppm All Devices			
Device	Device Compared	Mean Difference (Log-transformed ppm)	P-Value
Miran	Badge	0.08	0.663
	TD tube	-0.29	0.000
Badge	Miran	-0.08	0.663
	TD tube	-0.36	0.027
TD tube	Miran	0.29	0.000
	Badge	0.36	0.027

Table 8. Repeated Measures ANOVA >50 ppm.

Repeated Measures ANOVA Dominant >50 ppm All Devices			
Device	Device Compared	Mean Difference (Log-transformed ppm)	P-Value
Miran	Badge	-137.07	0.025
	TD tube	0.05	0.486
Badge	Miran	137.07	0.025
	TD tube	137.12	0.026
TD tube	Miran	-0.05	0.486
	Badge	-137.12	0.026

Table 7 results in no significant difference between the Miran SapphIRe and badges $p=.663$ and a significant difference between the TD tubes as compared with the Miran SapphIRe and badges on the dominant side for 1-50 ppm ($p=.000$, $p=.027$ respectively). Table 8 shows no significant difference between difference between the Miran SapphIRe and TD tube ($p=.486$) and a significant difference between the badge compared with the Miran SapphIRe and TD tube. ($p=.025$, $p=.026$ respectively).

4.6.1.2 Non-Dominant Side

Table 9. Repeated Measures ANOVA 1-50 ppm Non-Dominant Side.

Repeated Measures ANOVA 1-50 ppm Miran SapphIRe with Non-Dominant Badge and TD Tube			
Device	Device Compared	Mean Difference (Log-transformed ppm)	P-Value
Miran	Badge	-0.01	0.927
	TD tube	-0.85	0.032
Badge	Miran	0.01	0.927
	TD tube	-0.83	0.011
TD tube	Miran	0.85	0.032
	Badge	0.83	0.011

Table 10. Repeated Measures ANOVA >50 ppm Non-Dominant Side.

Repeated Measures ANOVA >50 ppm Miran SapphIRe with Non-Dominant Badge and TD Tube			
Device	Device Compared	Mean Difference (Log-transformed ppm)	P-Value
Miran	Badge	0.01	0.946
	TD tube	0.05	0.486
Badge	Miran	-0.01	0.946
	TD tube	0.04	0.786
TD tube	Miran	-0.05	0.486
	Badge	-0.04	0.786

Table 8 shows no significant difference between the Miran SapphIRE and the badge ($p=.927$) and a significant difference between the TD tube as compared to the Miran SapphIRE and badge ($p=.032$, $p=.011$ respectively). Table 9 shows no significant difference for all devices.

4.6.2 Device Agreement by Concentrations and Placement

4.6.2.1 Dominant Side

Figure 18 shows the Bland-Altman plot and for the Miran SapphIRE and dominant badge at 1-50 ppm.

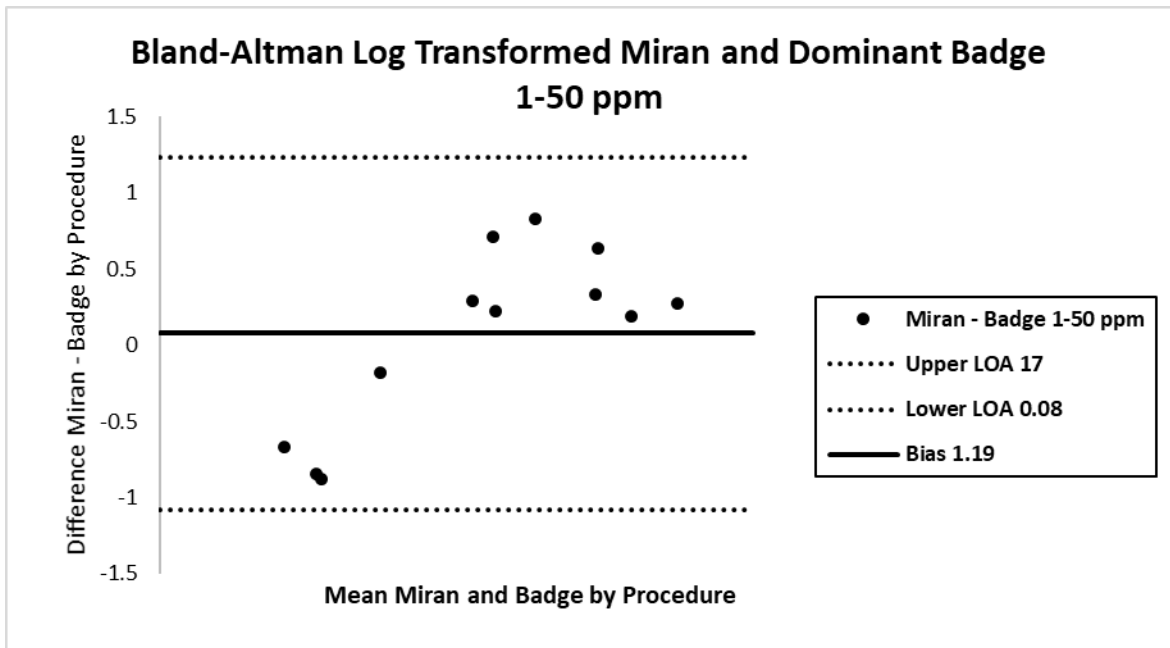


Figure 18. Bland-Altman plot Miran SapphIRE and dominant badge 1-50 ppm. The plot shows the Miran SapphIRE minus the badge, as such all data points above zero on the y-axis indicate that the Miran SapphIRE had a higher concentration measurement than the badge and all points below zero indicate the badge concentration measurements were higher than the Miran SapphIRE.

Figure 19 shows the Bland-Altman plot for the Miran SapphIRE and dominant TD tube at 1-50 ppm.

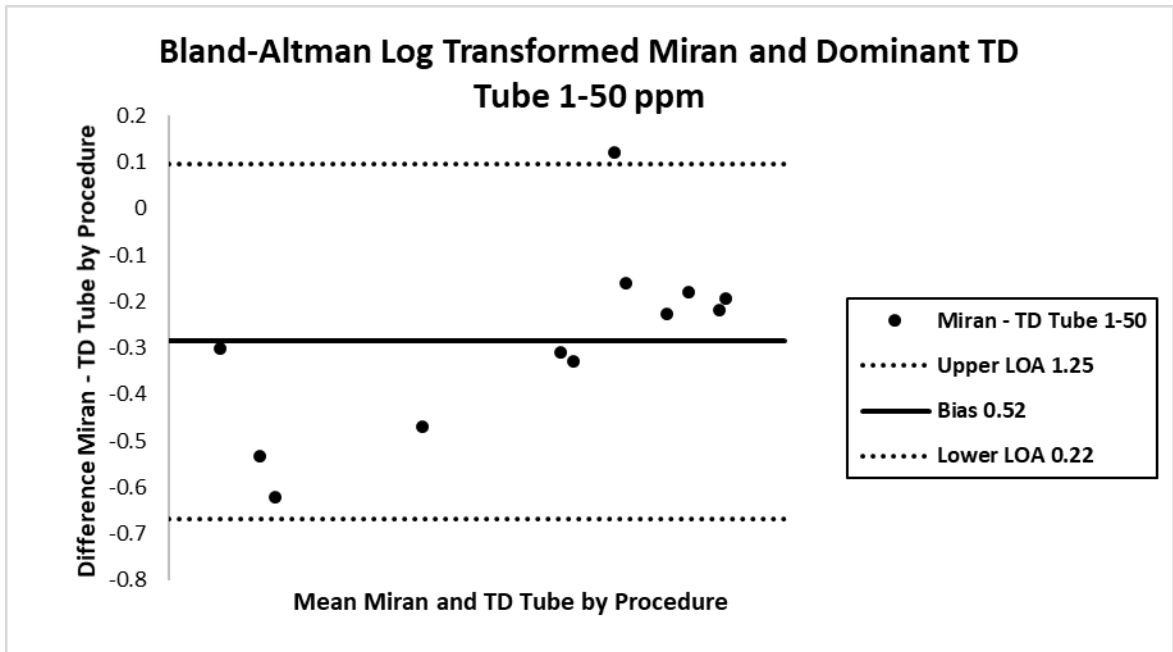


Figure 19. Bland-Altman plot Miran SapphIRE and dominant TD tube 1-50 ppm. The plot shows the Miran SapphIRE minus the TD tube, as such all data points above zero on the y-axis indicate that the Miran SapphIRE had a higher concentration measurement than the TD tube and all points below zero indicate the TD tube concentration measurements were higher than the Miran SapphIRE.

4.6.2.2 Non-Dominant Side

Figure 20 shows the Bland-Altman plot and for the Miran SapphIRE and badge at 1-50 ppm for the non-dominant side.

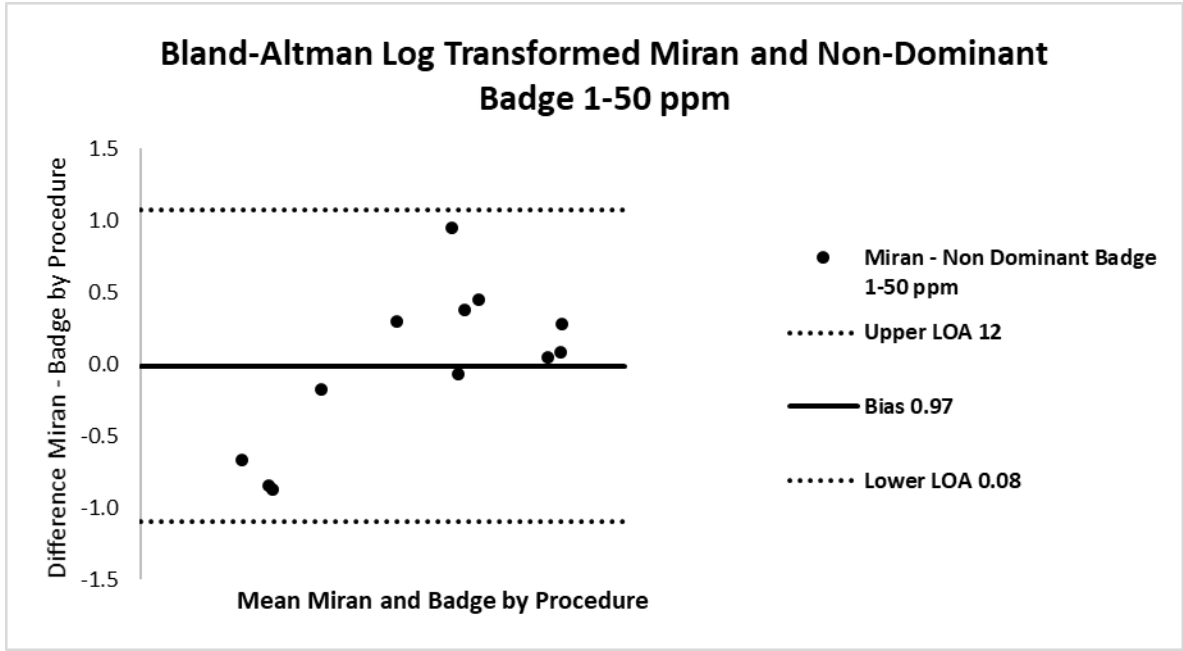


Figure 20. Bland-Altman plot Miran SapphIRE and non-dominant badge 1-50 ppm. The plot shows the Miran SapphIRE minus the badge, as such all data points above zero on the y-axis indicate that the Miran SapphIRE had a higher concentration measurement than the badge and all points below zero indicate the badge concentration measurements were higher than the Miran SapphIRE.

Figure 21 shows the Bland-Altman plot for the Miran SapphIRE and TD tube at 1-50 ppm for the non-dominant side.

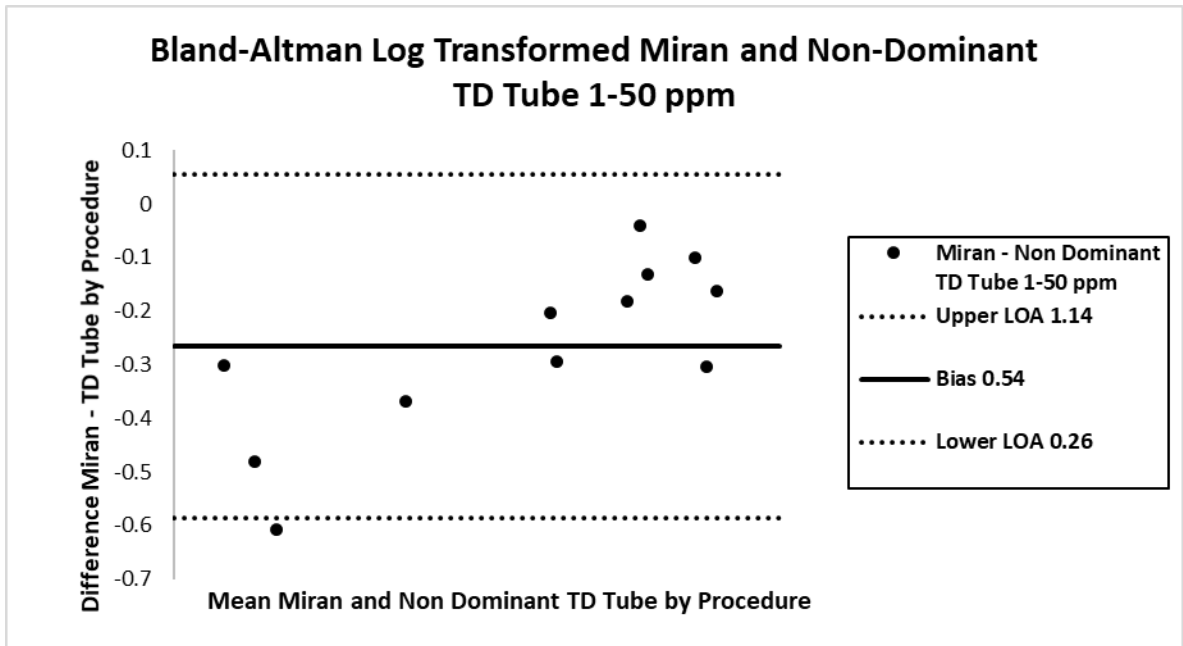


Figure 21. Bland-Altman plot Miran SapphIRE and non-dominant TD tube 1-50 ppm. The plot shows the Miran SapphIRE minus the TD tube, as such all data points above zero on the y-axis indicate that the Miran SapphIRE had a higher concentration measurement than the TD tube and all points below zero indicate the TD tube concentration measurements were higher than the Miran SapphIRE.

The Miran SapphIRE, the badges (dominant and non-dominant), and the dominant TD tubes did not meet the terms set forth as good agreement ($\pm 15\%$) set a priori. However, the non-dominant TD tubes met the upper level of agreement at 14%.

When the devices were checked for agreement at concentrations > 50 ppm none met the $\pm 15\%$. Bland-Altman figures for > 50 ppm can be found in Appendix C figures 29, 30, 31, and 32.

4.7 MIRAN SAPPHIRE OBSERVED VS. CORRECTED OBSERVED

The observed Miran SapphIRE concentration measurements (OBS) and the corrected Miran SapphIRE concentration measurements (COBS) were compared using a t-test and checked for agreement using the Bland-Altman method. A comparison of the TWA for the OBS and the COBS was done and a comparison of the number of excursions (>250 ppm). Table 11 shows the t-test results for the OBS and COBS Miran SapphIRE concentration measurements for all concentrations; for concentrations 1-100 ppm; and the number of excursions >250 ppm recorded.

Table 11. Miran SapphIRE OBS vs. COBS t-test.

Paired Samples t-test Miran Observed Concentraions (OBS) vs. Corrected Observed Concentraions (COBS)					
Test Pair	Data	Mean (Log-transformed ppm)	Std. Deviation	Std. Error Mean	P-Value
OBS vs. COBS	TWA by procedure in ppm	-0.04	0.09	0.02	0.042
OBS vs. COBS	# of Excursions by procedure	-0.12	0.16	0.05	0.032
OBS vs. COBS	TWA by procedure 1-100 ppm	-0.01	0.09	0.02	0.685

A $p=.042$ for the Miran SapphIRE OBS vs. COBS for all procedures reported TWA, indicating a significant difference in regards to using the calibration curve generated. Number of excursions >250 ppm reported a significant difference in the total amount of excursion recorded during each procedure in regards to using the calibration curve generated. For procedures recorded at 1-100 ppm no significant differences

between the means was indicated ($p=.685$), this was expected as the manufacturers calibration of the instrument to N₂O ranges from 1-100 ppm (47).

4.7.1 Bland-Altman Agreement Plots

A Bland-Altman plot (Figure 22) shows the agreement of the OBS and COBS of TWA for procedures for all data.

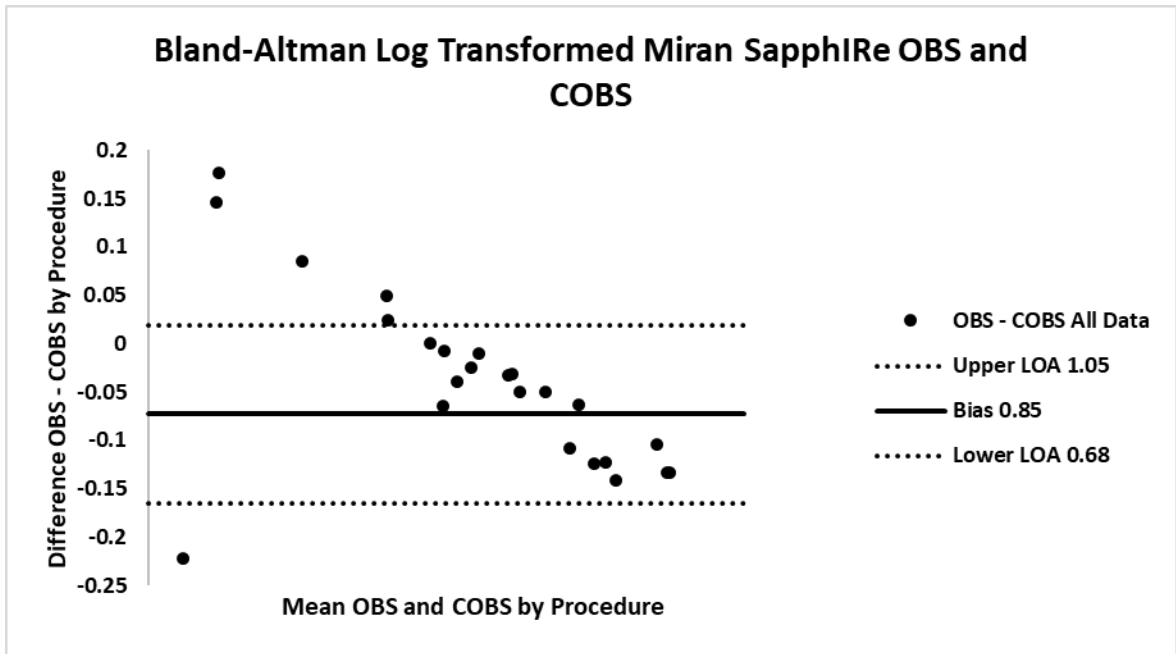


Figure 22. Bland-Altman Miran SapphIRE OBS and COBS for all 24 procedures. The COBS were subtracted from the OBS as such all data points below zero indicate that the COBS had a higher reading than the OBS.

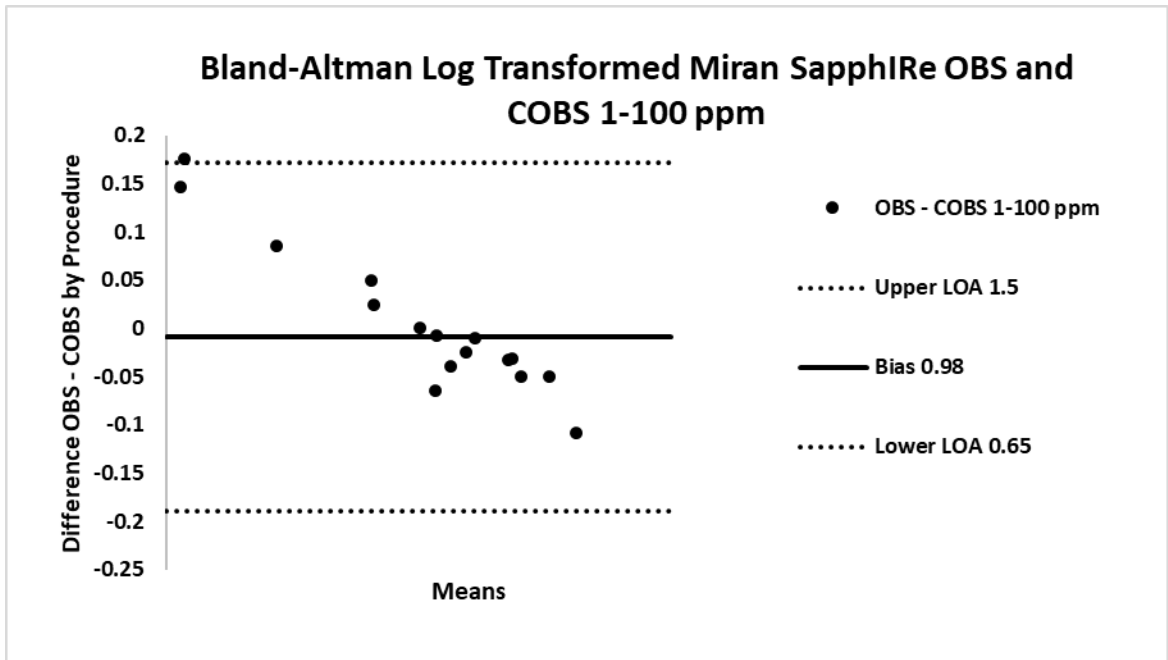


Figure 23. Bland-Altman Miran SapphIRe OBS and COBS 1-100ppm. The COBS were subtracted from the OBS as such all data points below zero indicate that the COBS had a higher reading than the OBS.

Figure 22 shows 79% of the data points are below zero, which indicates that the Miran SapphIRe OBS were underestimating the true value of the N₂O concentration.

CHAPTER 5: Discussion

5.1 PLACEMENT OF SAMPLING DEVICE

This study investigated the positioning of the sampling device (dominant vs. non-dominant hand) and found that for the badges $p=.003$, which indicated a significant difference between the dominant vs. non-dominant placement of the badge.

This study was designed to determine the agreement between devices sampling for N₂O in IHS dental clinics. The Miran SapphIRe served as the reference device to which the badges and TD tubes were compared. All devices were significantly different ($p<.05$) for all concentrations sampled on the dominant side. On the non-dominant side the Miran SapphIRe and badges were found to be not significantly different ($p=.969$) as well as the badges and TD tubes ($p=.153$) however, the Miran SapphIRe and the TD tubes were found to be significantly different ($p=.003$). None of the three devices was found to meet the minimum level of agreement of $\pm 15\%$ selected a priori by IHS regardless of placement.

5.2 MIRAN SAPPHIRE AND BADGES

This study found that there was a statistically significant difference between the sample means obtained with traditional passive dosimeter badges commonly used throughout the IHS and the measurements of the Miran SapphIRe. The Bland-Altman also indicated that the two sampling devices did not have good agreement (LOA's did not fall between 0.85 and 1.15).

5.2.1 Dominant vs. Non-Dominant Dosimeter Badges

There was a significant difference between the badges in relation to the placement of the badge (dominant vs non-dominant). The dominant mean TWA for procedure was 60 ppm and the non-dominant was 113 ppm. There are a number of variables that could have contributed to this difference and could help explain the poor agreement seen in the Miran SapphIRe and badges. Knowing that air velocities affect the badges, variables include, but are not limited to:

- Positioning of the dentist in relation to the N₂O delivery and scavenging system
- Fan placement in the room in relation to the dentist
- Movement of the dentist could have covered/blocked the badge
- Miran SapphIRe causing turbulence across the badge on the dominant side.

Figure 24 shows how the Miran SapphIRe tubing and badge placement could have affected the concentrations.

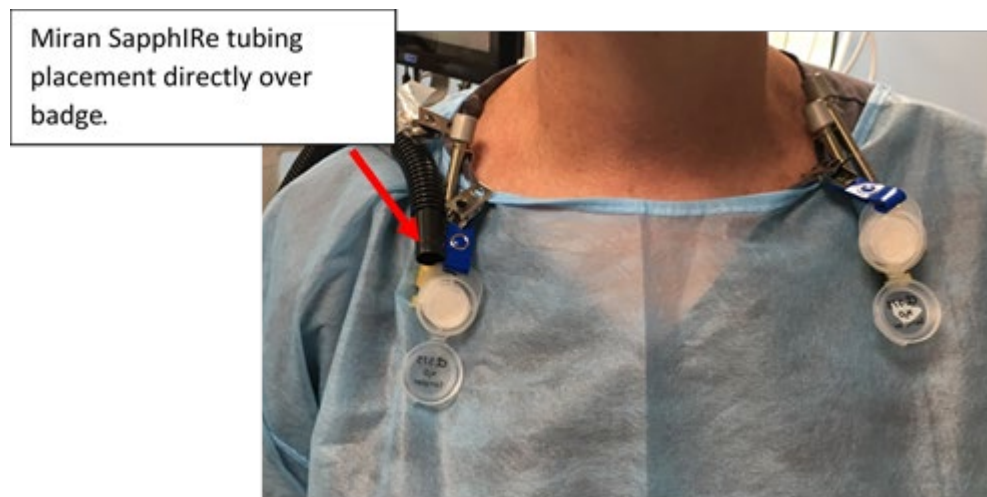


Figure 24. Miran SapphIRe tube inlet in relation to badge placement.

The Miran SapphIRe tubing and badge were placed in away as to attempt to decrease the effects of the Miran SapphIRe sampling. However, the movement of the dentist throughout the procedure did cause the Miran SapphIRe inlet to periodically reposition itself directly over the badge. The Miran SapphIRe sampling rate of 14 liters per minute could have created unanticipated turbulence or could have reduced the amount of N₂O reaching the badge

5.2.2 Miran SapphIRe and Badges Agreement

Agreement of $\pm 15\%$ with the Miran SapphIRe was not met for either the dominant or non-dominant placement of the badges. The Miran SapphIRe reported 79% of the procedure TWA concentrations higher than the dominant side badge with an average concentration of 106 ppm and 74 ppm respectively. On the non-dominant side the Miran SapphIRe reported 46% of the procedure TWA concentrations higher than the badge with an average concentration of 106 ppm and 141 ppm respectively.

The Bland-Altman showed a bias of 1.59 indicating that the mean difference between the Miran SapphIRe and badge on the dominant side was 59%. However, the upper level of agreement was calculated as 13, which indicates that the Miran SapphIRe had concentration measurements up to 13 times higher than the badge. This indicates that the actual dentist exposure could have been up to 13 times higher than what the dominant badges reported.

When the Miran SapphIRe was compared to the non-dominant side the badges there was no significant difference ($p=.969$). However, when plotted using the Bland-Altman method the bias reported a 0.99, which indicates that the mean difference between the Miran SapphIRe and non-dominant badge was 0.99%. This seems to indicate

that there is good agreement between the Miran SapphIRe and non-dominant badge. However, this is only the bias (mean) it is not all the data points the Bland-Altman reports a 95% confidence interval, which gives a better understanding of how all the data agrees as compared with the means alone. The Bland-Altman plot (figure 16) reports the upper LOA was 8. This indicates that the actual dentist exposure could have been up to 8 times higher than what the non-dominant badges reported.

This is contradictory to the findings of Hansen et al. who found that the badges used in their study tended to measure N₂O concentrations higher than the Miran SapphIRe 76% of the time (19). In this study the Miran SapphIRe tended to measure higher concentrations than the badges 79% of the time for the dominant side and measure concentrations lower than the non-dominant side 46% of the time. The badges used in their study were different than those used this study, Advanced Chemical Safety N-10 (Boca Raton, FL) (ACS N-10) compared with the Assay Technology #575 Nitrous Oxide Monitor (Livermore, CA) respectively. The ACS N-10 did not indicate the extraction method used nor the size of the molecular sieve sorbent both of which could affect the concentrations reported. Hansen et al. also indicated that they did not develop a user calibration curve for the Miran SapphIRe which may have attributed to the poor agreement found (19). The calibration curve generated in this study increased the mean concentration measurements by 22 ppm and ranged from 0-121 ppm. This wide range could indicate that the Hansen et al. study may have underestimated the actual concentrations measured with the Miran SapphIRe.

5.3 MIRAN SAPPHIRE AND THERMAL DESORPTION TUBES

Thermal desorption tubes can also be affected by turbulent air currents, though their smaller cross-section makes them less susceptible than are conventional badges (1; 54; 55). Additionally, as can be seen in Figure 24, TD tubes were always placed in an upward position and farther away from the Miran SapphIRe inlet than was the badge.

There was no statistically significant difference between the dominant and non-dominant placement of the tubes (Table 4) indicating that the differences between the two could possibly be due to chance. Table 5 (dominant side) and 6 (non-dominant side) show a statistically significant difference between the means of the Miran SapphIRe and TD tubes ($p=.035$ and $p=.003$ respectively).

The Bland-Altman reported a bias of 0.76 indicating a mean difference of 24%. However, the upper LOA reported 2.5 and lower reported 0.23 on the dominant side. The terms set as good agreement acceptable to IHS were not met (0.85-1.15). This also indicates that the Miran SapphIRe measured some procedures 2.5 times higher than the TD tube.

For the non-dominant side the Bland-Altman reported a bias of 0.76 indicating a mean difference of 24% the same as the dominant side. However, the upper LOA reported as 1.8 and lower LOA reported as 0.32. This still does not meet the $\pm 15\%$ (0.85-1.15) acceptable to IHS but it is much closer in agreement than either the badges or the dominant tube.

The TD tubes tended to report higher concentrations by procedure than the Miran SapphIRe, 75% for the dominant side and 83% for the non-dominant side.

5.4 AGREEMENT AT DIFFERENT CONCENTRATIONS

The recommended OEL for N₂O is 50 ppm over an 8 hour TWA. As such, agreement was looked at for concentrations of 1-50 ppm and >50 ppm for both the dominant and non-dominant sides. Using the Miran SapphIRE as the reference, the devices were divided into the two groups and checked to determine if there was a significant difference between the devices at different measurements (Tables 7, 8, 9, and 10). Bland-Altman plots were also constructed to check for agreement (Figures 20, 21, 22, 23, 27, 28, 29, and 30). Agreement was not met for any of the devices at these concentrations however, for the TD tube 1-50 ppm the upper LOA reported as 1.14 indicating that that at 1-50 ppm the upper LOA meet the terms set forth as good agreement (1.15).

5.5 MIRAN SAPPHIRE MEASUREMENTS

There is a statistically significant difference between the mean OBS and COBS Miran SapphIRE concentration measurements. This was be expected as the Miran SapphIRE is calibrated by the manufacturer to N₂O concentrations ranging from 1-100 ppm (47). Calibration of the Miran SapphIRE with N₂O showed poor linearity above 200 ppm. When OBS measurements between 1 – 100 ppm were compared with the COBS, they were not statistically different $p=.685$ and the Bland-Altman plot shows a bias of 0.98 or 2%. However, a Bland-Altman plot also shows their LOAs to be between 35% (lower LOA) and 50% (upper LOA) (Figure 23). Indicating that the OBS were as different from the COBS by up to 50% on the upper end and 35% on the lower end for 95% of the procedures sampled.

This study and others (Hansen et al.(2019)) have shown that dental procedures can result in N₂O concentrations well above 100 ppm. This study has clearly shown that uncorrected Miran SapphIRe measurements become progressively less accurate as concentrations rise. It is strongly recommended that users generate their own calibration curves if maximum accuracy is of importance.

5.5.1 Excursions

The IHS adopted the ACGIH definition of excursion limits as described in Chapter 1, which state that at no time should the dentist be exposed to greater than 250 ppm (26). Uncorrected Miran SapphIRe measurements in this study identified 240 excursions above 250 ppm across all three IHS regions. When Miran values were corrected with the appropriate user-generated calibration curve the total number of excursions increased to 287 (a 20% increase).

As shown above in table 11, there is a statistically significant difference ($p=.032$) between the observed corrected and uncorrected mean excursion measurements. This again bolsters the importance of measurement correction using user-generated calibration curves.

5.6 STUDY LIMITATIONS

Random sampling was not conducted due to logistics, the low number of volunteers available, and the limited amount of time available at each location. The positioning of the dentists and their movement as they conducted dental procedures likely resulted in the blockage or covering of one or more devices. Another limitation was the loss of the Miran SapphIRe used in the first part of the study by the shipping company and the failure of the backup Miran SapphIRe. These issues resulted in missing Miran

SapphIRe data points during the last seven dental procedures, which lowered the overall power of the study.

Where results were not significant, the power within that specific test was not above the target power level of 80%. There were multiple causes of low power results, including a wide standard deviation and low significance level. However, the limited sample size due to the loss of the Miran SapphIRe was likely the main cause for power levels below 80%.

Several variables could have contributed to the poor agreement observed between the Miran SapphIRe, badges, and the TD tubes. The most obvious was the repositioning of the Miran SapphIRe, badge, and TD tube as the dentist moved about. For example, it was observed that the dentist would move in such a way as to block the devices with their smock or other articles of clothing. Also, at times the dentist would position their head in a way that would push the TD tube against their neck, which could have blocked the TD tube limiting the amount of N₂O collected. The use of censored data also could have affected the results of the study by overestimating the degree of agreement between the censored data points for each sampler.

Blank correction of some badges resulted in their reported mass falling below zero (negative mass). The supporting laboratory verified that, in this type of case, blank correction was appropriate but that samples with corrected masses less than the RL (0.4 µg) should be treated as a “non-detect”. The data that was reported as non-detect was therefore treated as censored data according to AIHA and could have altered the results of this study.

The supporting laboratory also indicated that the badges should have sampled for longer than one hour, although the technical insert included with the badges stated that acceptable sampling time ranged from 15 minutes to 8 hours (10; 46). As a result, it is possible that the sampling periods in this study were not long enough to assure collection of the minimum mass of N₂O required for reliable analysis.

Technical issues reported by the USU laboratory resulted in the TD tubes being held longer than 2 weeks. Cox and Brown (1984) reported a 27% decrease in analyte mass when held for 2 weeks (13) This could have reduced the actual amount of N₂O on the TD tubes. Also, Markes International reported uptake rate of 1.25 which was used for this study is only partially validated at the time of this study (30) .

CHAPTER 6: Conclusions

6.1 CONCLUSIONS

Neither of the passive samplers met the pre-defined Level of Agreement ($\pm 15\%$) acceptable to IHS. However, thermal desorption tubes may be a better alternative to the conventional passive dosimeter badge, as in this study they displayed closer agreement to the Miran SapphIRe for both the dominant (badge: 0.2-13; tube: 0.25-2.5) and the non-dominant (badge: 0.12-8; tube: 0.32-1.80) sides. In particular, the non-dominant 1-50 ppm TD tube reported an upper LOA of 1.14, which met the upper limit of agreement. Though this study showed that the TD tubes are closer in agreement with the reference method more research is needed.

The manufacturer of the Miran SapphIRe reported an accuracy of $\pm 10\%$ for 1-100 ppm, but analysis showed this may not be accurate under non-laboratory conditions. It is recommended that the user verification procedure and calibration curve equation be conducted/derived routinely as described in the manual to ensure that accuracy is maximized. It may be impractical to conduct the entire user verification before each dental procedure. Therefore, it is recommended that organizations using the Miran SapphIRe develop a Standard Operating Procedure (SOP) that stipulates how often the user verification should be performed. The SOP should also take into consideration barometric pressure, humidity/temperature changes, long distance traveling, and/or shipping of the device.

A study in a controlled laboratory environment should be performed to determine the level of agreement between the three methods. Controlling air velocity, elevation, and blockage/covering of the Miran SapphIRe, conventional passive dosimeter badges, and thermal desorption tubes should all be taken into consideration.

Thermo Scientific is no longer manufacturing the Miran SapphIRe. With this in consideration, the badges and TD tubes should be compared with alternatives to the Miran SapphIRe and with each other so that the most accurate method of sampling can be made available and so that organizations can determine which balance of accuracy, expense, convenience, and complexity will best suit their specific needs.

Excursions above 250 ppm appear to still be a problem within Region 1 and Region 2. Region 3 was more successful in controlling exposure however, all regions reported excursions over 250 ppm. Further analysis into the variables that could be leading to these exposures is recommended.

Raw sampling results for this study can be found in Appendix D.

Appendix A

REGION 1

Table 11. Region 1 User verification and percent difference.

Log transformations of the actual data and observed (OBS) data from the Miran SapphIRE with a percent difference. Corrected LOG OBS is the OBS applied to the calibration curve, then the antilog is taken giving a corrected OBS in ppm and a percent difference to compare with the OBS. An average percent difference is reported at the bottom.

Region 1 User Verification Check and Percent Difference							
LOG Actual	Actual PPM	OBS PPM	LOG OBS	PD OBS	Corrected LOG OBS	Corrected OBS PPM	PD
0.151197793	1.11	0.96	-0.058893689	14.54%	0.155461126	1.11	0.30%
3.851637512	14.44	12.72	3.669026766	12.64%	3.859687218	14.52	0.56%
4.906085296	29.98	25.78	4.688180359	15.08%	4.904726726	29.96	0.09%
5.508749798	45.53	38.06	5.250203656	17.87%	5.487407283	44.86	1.48%
5.932557507	61.08	50.06	5.645586386	19.83%	5.900117367	59.72	2.25%
6.25972225	76.62	62.1	5.956521363	20.94%	6.226330016	74.87	2.31%
6.674759749	102.17	84.78	6.405652061	18.60%	6.700138346	103.98	1.76%
7.25972225	153.25	123.32	6.946262984	21.64%	7.274622553	154.84	1.03%
7.674759749	204.33	162.98	7.348551126	22.52%	7.705134264	208.68	2.11%
7.996687844	255.41	202.22	7.65978188	23.25%	8.040000172	263.20	3.00%
8.25972225	306.50	238.38	7.897119389	25.00%	8.296431927	314.39	2.54%
8.331356852	322.10	240.12	7.907611763	29.16%	8.307789998	316.88	1.63%
8.539539657	372.10	273	8.092757141	30.72%	8.508513628	364.18	2.15%
8.721434916	422.10	305.34	8.254272787	32.10%	8.684089361	411.31	2.59%
8.948940774	494.20	377.48	8.560256398	26.78%	9.017922272	518.40	4.78%
9.087983678	544.20	403.76	8.657354182	29.63%	9.124192334	558.03	2.51%
9.214796124	594.20	427.64	8.740252994	32.60%	9.21505077	594.30	0.02%
9.331356852	644.20	449.38	8.811792107	35.63%	9.293554422	627.54	2.62%
9.484409342	716.29	491.12	8.939931765	37.30%	9.434391302	691.89	3.47%
			Average PD	24.52%		Average PD	1.96%

Log based 10 transformations.
 OBS-Observed Concentration Measurement.
 PD-Percent Difference.

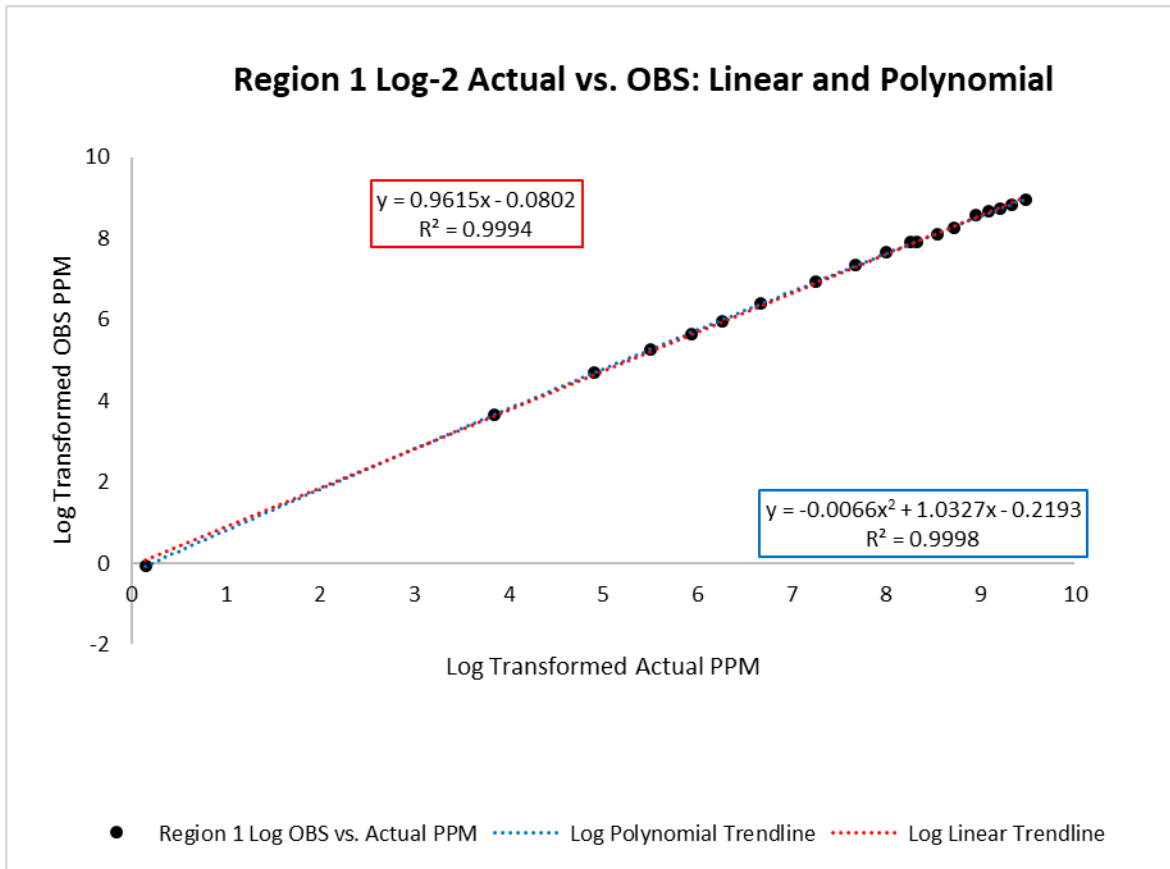


Figure 25. Log transformed Miran SapphIRe Calibration Curve Region 1. Calibration equations for the linear and polynomial with their respective R² value.

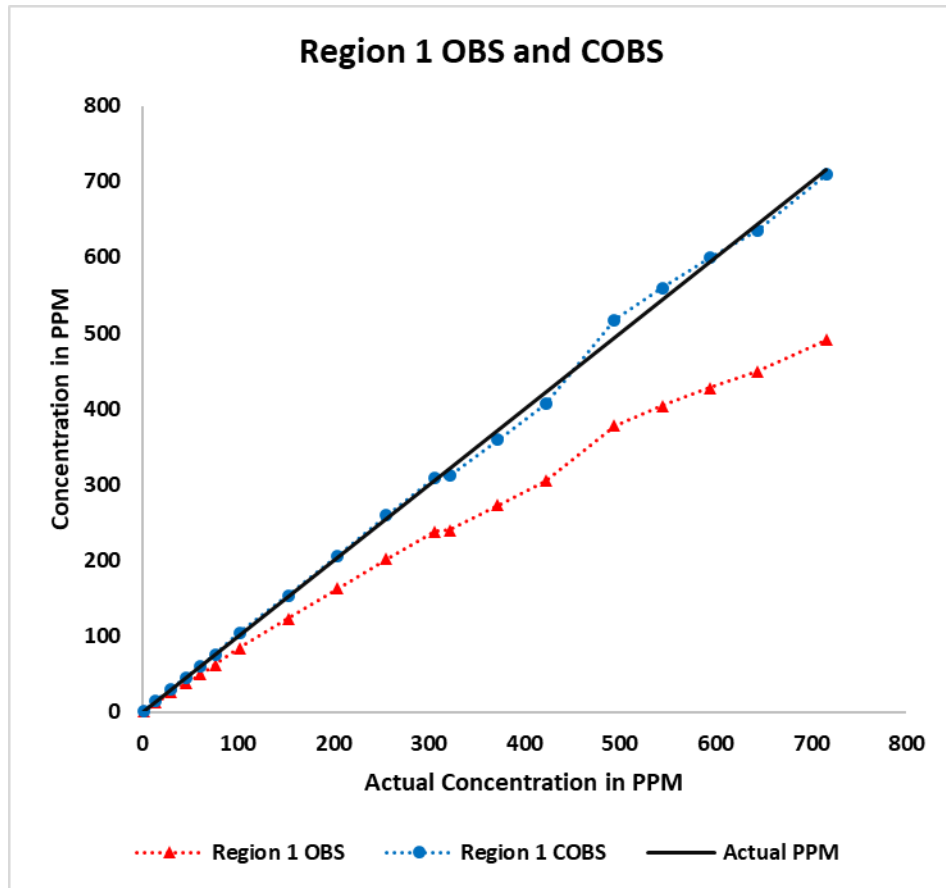


Figure 26. OBS vs. COBS in relation to the actual concentration for Region 1. This figure shows how using the formula generated corrects the OBS to the actual concentration for Region 1.

REGION 2

Table 12. Region 2 user verification and percent difference.

Log transformations of the actual data and observed (OBS) data from the Miran SapphIRe with a percent difference. Corrected LOG OBS is the OBS applied to the calibration curve, then the antilog is taken giving a corrected OBS in ppm and a percent difference to compare with the OBS. An average percent difference is reported at the bottom.

Region 2 User Verification Check and Percent Difference							
LOG Actual	Actual PPM	OBS PPM	LOG OBS	PD OBS	Corrected LOG OBS	Corrected OBS PPM	PD
0.151197793	1.11	0.58	-0.785875195	62.76%	0.177171342	1.13	1.80%
3.851637512	14.44	12.66	3.6622055	13.11%	3.865285278	14.57	0.95%
4.906085296	29.98	26.74	4.74092756	11.44%	4.862555127	29.09	3.02%
5.508749798	45.53	39.66	5.309612772	13.78%	5.409003171	42.49	6.91%
5.932557507	61.08	51.74	5.693208149	16.55%	5.786495959	55.20	10.12%
6.25972225	76.62	64.38	6.008540672	17.37%	6.102538062	68.71	10.88%
6.674759749	102.17	104.52	6.70763522	2.28%	6.823078357	113.23	10.27%
7.25972225	153.25	150.78	7.236301267	1.62%	7.387822491	167.48	8.87%
7.674759749	204.33	196.64	7.619413011	3.84%	7.808849053	224.23	9.29%
7.996687844	255.41	240.62	7.910612752	5.96%	8.13600868	281.31	9.65%
8.25972225	306.50	279.82	8.128355272	9.10%	8.384916532	334.28	8.67%
8.331356852	322.10	279.08	8.124534929	14.31%	8.380516739	333.26	3.41%
8.539539657	372.10	310.38	8.277891787	18.09%	8.558073954	376.91	1.28%
8.721434916	422.10	338.68	8.403778984	21.93%	8.705296331	417.40	1.12%
8.948940774	494.20	398.46	8.638291094	21.45%	8.983221612	506.08	2.38%
9.087983678	544.20	420.18	8.714863683	25.72%	9.075037471	539.33	0.90%
9.214796124	594.20	439.12	8.778471434	30.02%	9.151718874	568.78	4.37%
9.331356852	644.20	455.3	8.830673649	34.36%	9.214933519	594.25	8.07%
9.484409342	716.29	485.16	8.922316799	38.48%	9.326536648	642.05	10.93%
			Average PD	19.06%		Average PD	5.94%

Log based 10 transformations.
 OBS-Observed Concentration Measurement.
 PD-Percent Difference.

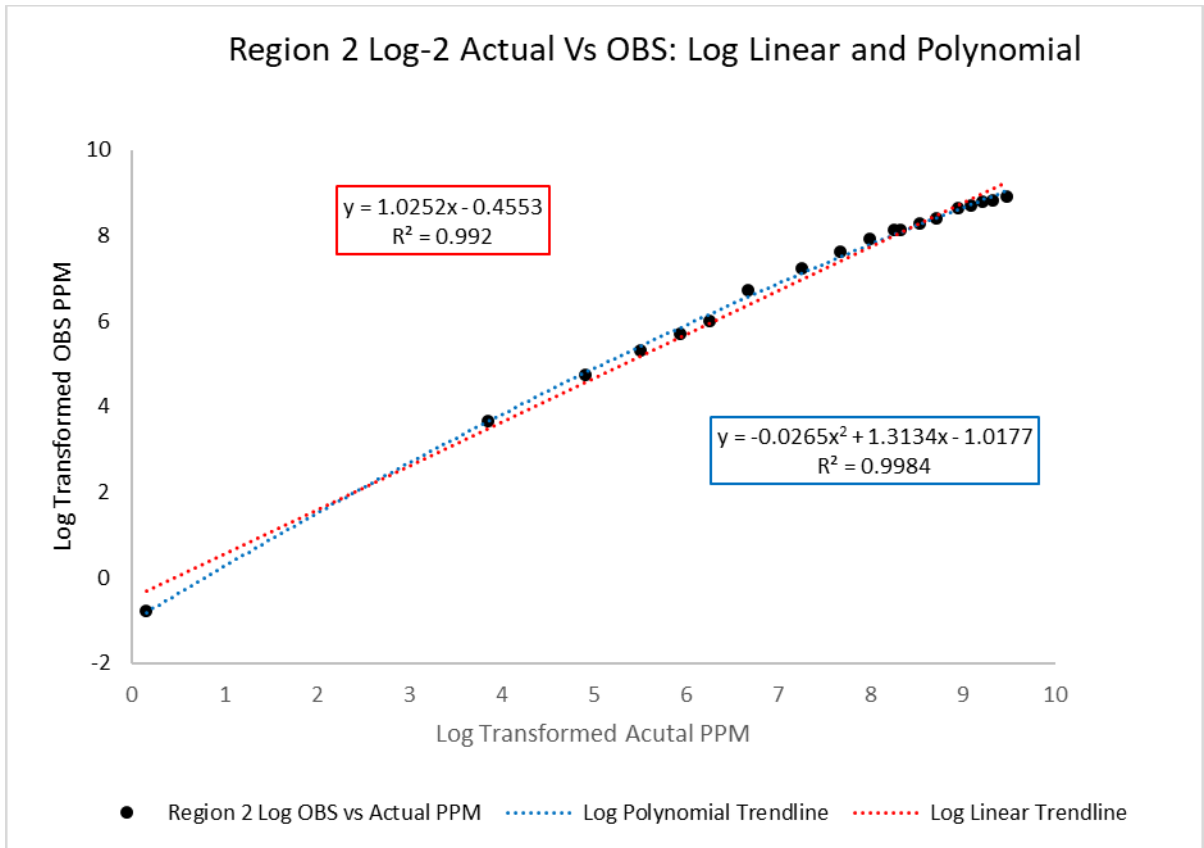


Figure 27. Log transformed Miran SapphIRe Calibration Curve Region 2. Calibration equations for the linear and polynomial with their respective R^2 value.

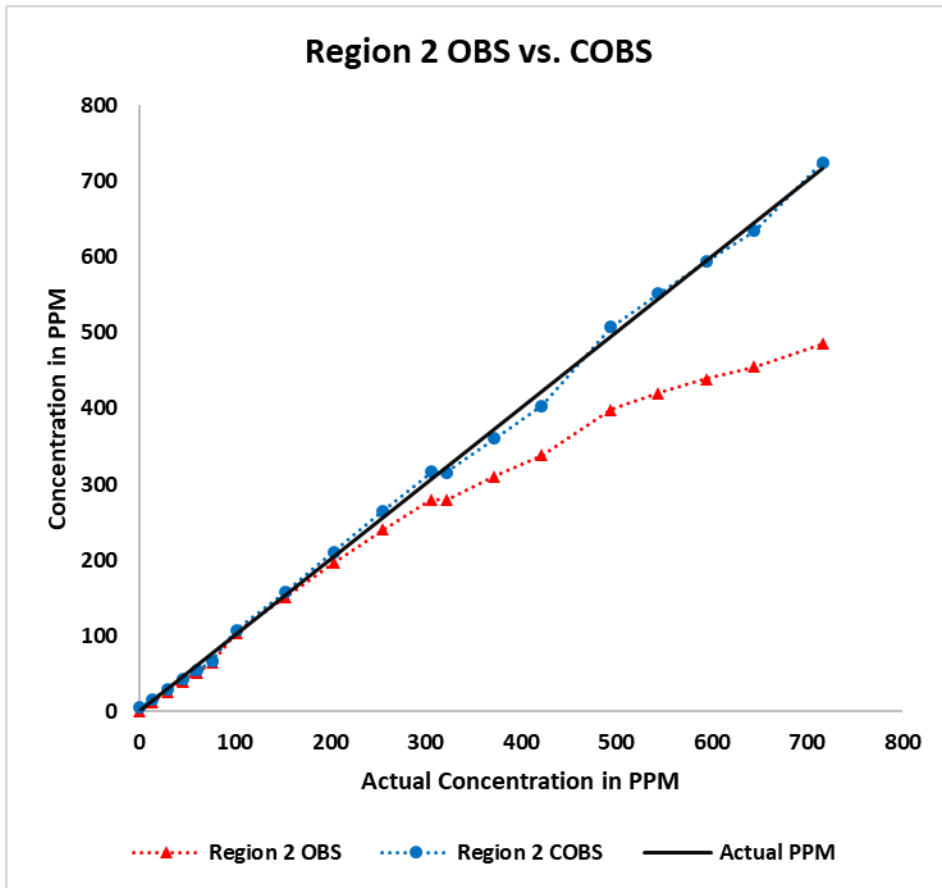


Figure 28. OBS vs. COBS in relation to the actual concentration for Region 2. This figure shows how using the formula generated corrects the OBS to the actual concentration for Region 2.

REGION 3

Table 13. Region 3 user verification and percent difference.

Log transformations of the actual data and observed (OBS) data from the Miran SapphIRe with a percent difference. Corrected LOG OBS is the OBS applied to the calibration curve, then the antilog is taken giving a corrected OBS in ppm and a percent difference to compare with the OBS. An average percent difference is reported at the bottom.

Region 3 User Verification Checks and Percent Difference							
LOG Actual	Actual PPM	OBS PPM	LOG OBS	PD OBS	Corrected LOG OBS	Corrected OBS PPM	PD
0.151197793	1.11	1.72	0.782408565	43.07%	0.252823731	1.19	7%
3.851637512	14.44	13.8	3.786596362	4.51%	3.657411266	12.62	13%
4.906085296	29.98	28.06	4.810443104	6.63%	4.793701464	27.74	8%
5.508749798	45.53	41.68	5.381283373	8.83%	5.422178594	42.88	6%
5.932557507	61.08	55.42	5.792334806	9.71%	5.872536356	58.59	4%
6.25972225	76.62	69.22	6.113117036	10.15%	6.222731532	74.68	3%
6.674759749	102.17	96.2	6.587964989	6.01%	6.739112601	106.83	4%
7.25972225	153.25	145.34	7.183288001	5.30%	7.383168239	166.94	9%
7.674759749	204.33	194.2	7.601399391	5.08%	7.833317353	228.07	11%
7.996687844	255.41	240.48	7.909773104	6.02%	8.164177575	286.85	12%
8.25972225	306.50	283.68	8.148120631	7.73%	8.419246766	342.33	11%
8.331356852	322.10	285.78	8.158761144	11.95%	8.430620463	345.04	7%
8.539539657	372.10	320.28	8.323189901	14.97%	8.606235011	389.70	5%
8.721434916	422.10	350.2	8.452035274	18.62%	8.743656809	428.65	2%
8.948940774	494.20	409	8.675957033	18.87%	8.982091076	505.68	2%
9.087983678	544.20	429.24	8.745640714	23.62%	9.056189724	532.33	2%
9.214796124	594.20	447.42	8.805485937	28.18%	9.119788332	556.33	7%
9.331356852	644.20	462.86	8.854432081	32.76%	9.171778062	576.74	11%
9.484409342	716.29	491.42	8.940812764	37.24%	9.263472623	614.59	15%
			Average PD	15.75%		Average PD	7.27%

Log based 10 transformations.
OBS-Observed Concentration Measurement.
PD-Percent Difference.

Appendix B

Table 14. Data reported by lab to use for calibration curve first sampling period.

TD Tube Calibration Data 1st Sampling Period				
PPM Equivalent	Log Actual Mass ng	Actual Mass ng	Area Units	Log Area
1	5.856181689	58	2701755	21.36546542
10	8.676592764	409	15670291	23.90152864
25	9.869237842	935	32274309	24.94388286
50	10.86923784	1871	63486543	25.91994748
75	11.45420034	2806	84817612	26.33786053
125	12.19116594	4676	163079129	27.28099692
150	12.47356567	5687	194723351	27.53685066
250	13.2136004	9499	290472947	28.11382857
350	13.68301903	13152	349287097	28.37983811
500	14.21353375	18998	401280503	28.58003582

Table 15. Percent difference comparison with actual mass in ng and equivalent concentration in ppm.

% Difference Comparison with Actual Mass in ng and Equivalent Concentration in PPM				
Mass ng	Concentration Equivalent in ppm	Polynomial Equation Percent Difference	Log-transformed Polynomial Equation Percent Difference	Log-transformed Linear Equation Percent Difference
58	1	102%	4%	3%
409	10	22%	5%	2%
935	25	1%	8%	4%
1871	50	5%	2%	2%
2806	75	16%	10%	6%
4676	125	2%	15%	16%
5687	150	3%	16%	16%
9499	250	2%	12%	9%
13152	350	1%	1%	3%
18998	500	1%	19%	24%
Average %Difference		15%	9%	8%

Table 16. Data reported by lab for calibration curve second sampling period.

TD Tube Calibration Data 2nd Sampling Period			
PPM Equivalent	Actual Mass ng	Area Average	Cal. Mass ng
1	59.40	1,177,696	221.29
10	359.98	2,013,687	378.37
26	896.36	3,821,236	718.01
48	1794.52	11,346,267	2131.96
80	2989.66	16,519,993	3104.09
96	3599.83	22,057,738	4144.63
128	4800.37	28,502,894	5355.67
160	5999.12	35,219,357	6617.69
175	6569.69	33,771,716	6345.68
200	7487.65	39,504,412	7422.85
224	8400.20	44,929,774	8442.27
251	9424.07	50,505,023	9489.86
283	10602.74	55,378,171	10405.52
314	11781.41	59,957,423	11265.96

Appendix C

BLAND-ALTMAN BY CONCENTRATION

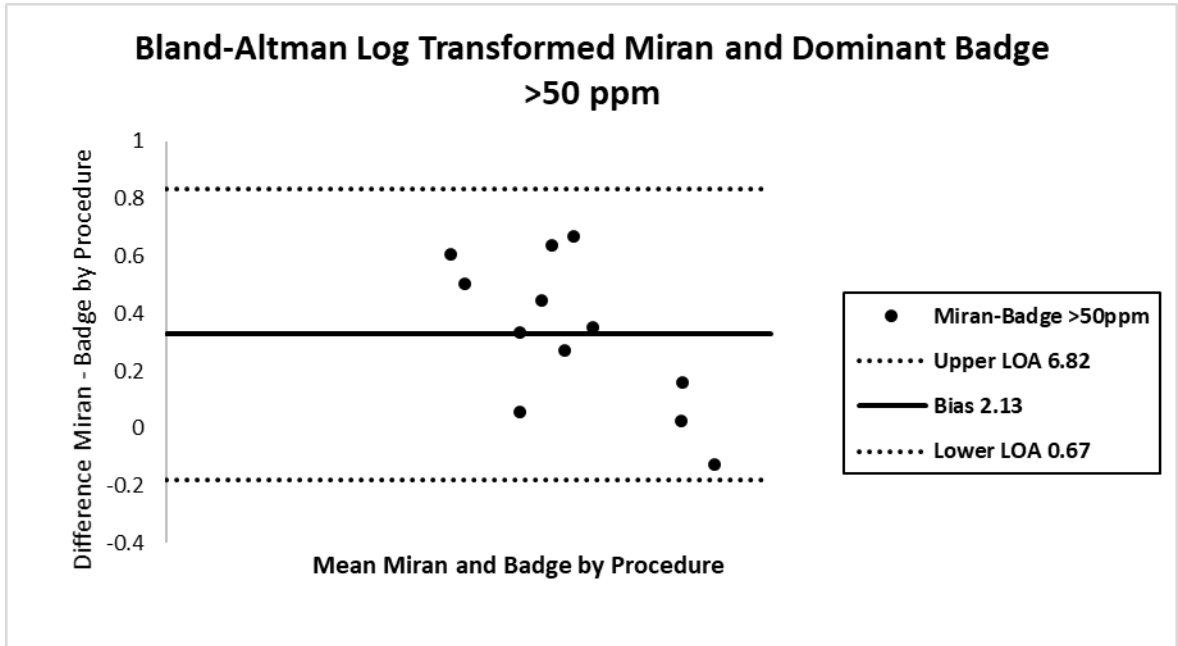


Figure 29. Log transformed Bland-Altman Miran Sapphire and dominant badge for concentrations > 50 ppm.

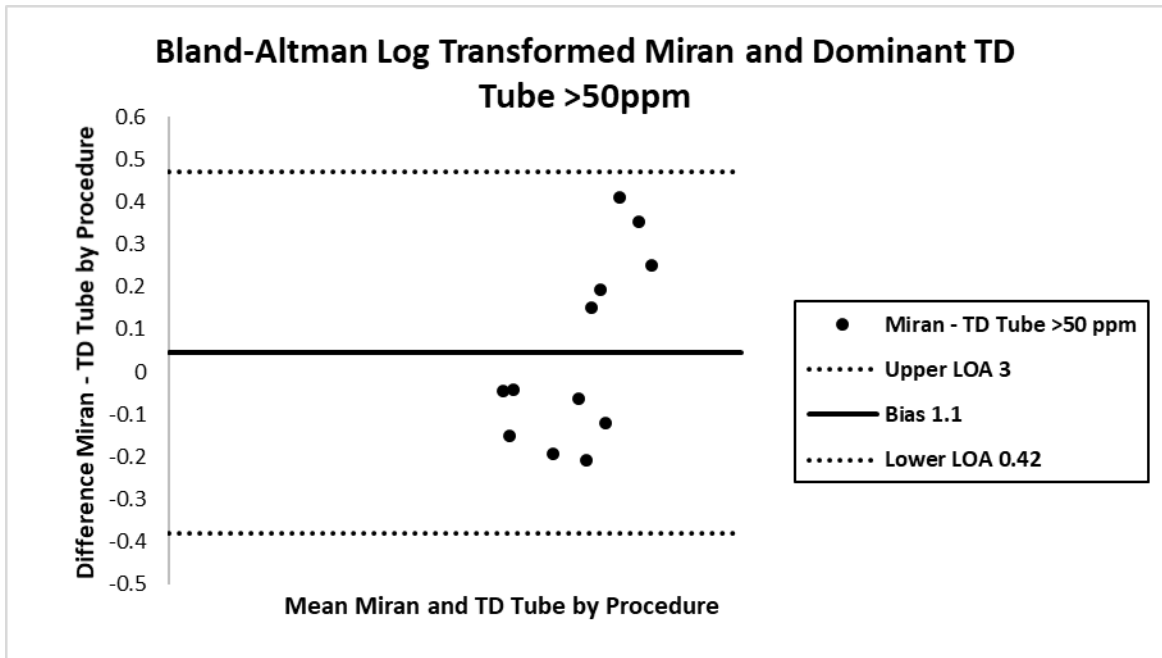


Figure 30. Log transformed Bland-Altman Miran SapphIRe and dominant TD tube for concentrations >50 ppm.

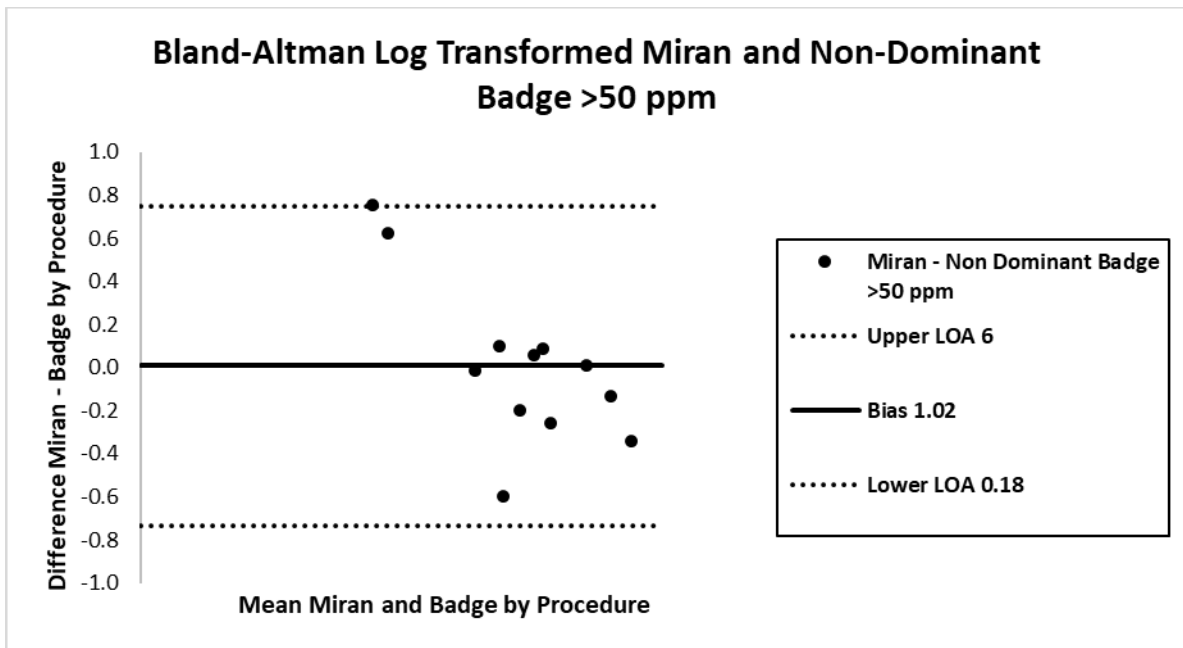


Figure 31. Log transformed Bland Altman Miran SapphIRe and non-dominant badge for concentrations > 50 ppm.

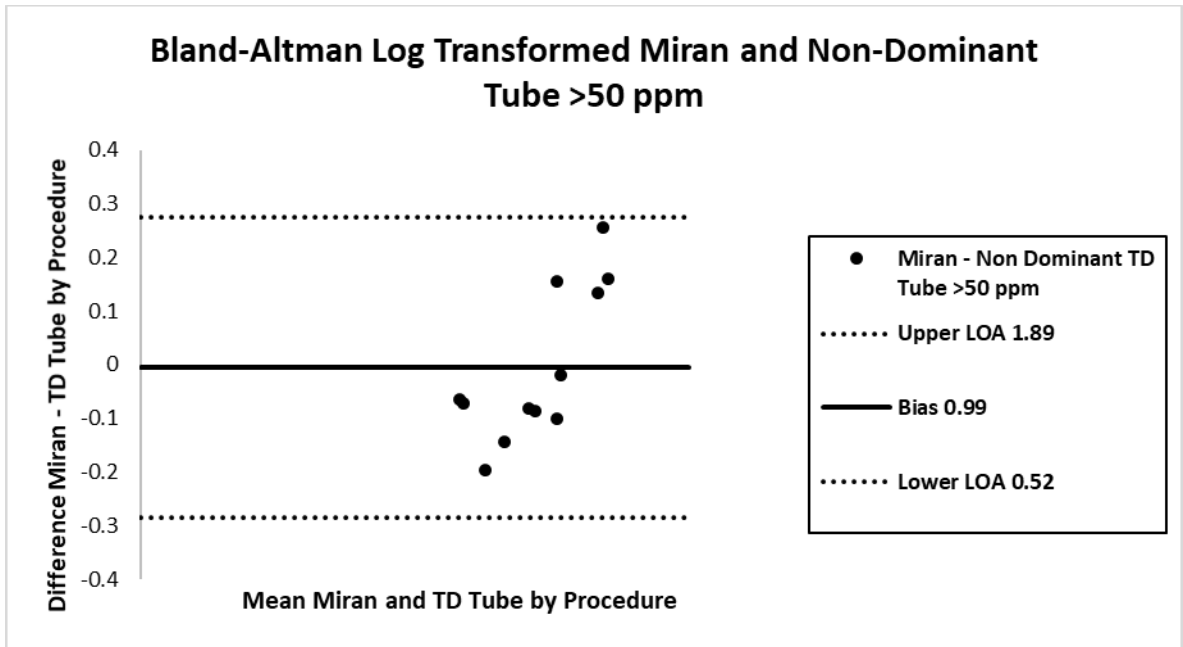


Figure 32. Bland-Altman Miran SapphIRE and non-dominant TD tube for concentrations > 50 ppm.

Appendix D

RAW DATA

Table 17. Blank corrected raw data with reported non-detects and missing TD tubes.

Raw Data Summary												
Procedure #	Date of Sample	Region	Clinic	Uncorrected Excursions	Uncorrected Miran TWA	Corrected Excursions	Corrected Miran TWA	Badge TWA Dominant	Badge Non Dominant	OA TDT	TDT Dominant	TDT Non Dominate
1	7/18/18	1	1	28	149	41	197	88	173	168	140	206
2	7/18/18	1	1	13	95	17	122	44	193	197		147
3	7/18/18	1	1	24	165	25	229	49	187	147		160
4	7/19/18	1	1	53	322	55	438	302	592	281	193	302
5	7/19/18	1	1	18	128	27	170	39	308	198	224	215
6	7/19/18	1	1	0	20	0	23	15	21	26	18	26
7	7/23/18	2	1	50	335	50	456	607	995	221	256	253
8	7/23/18	2	1	4	54	4	61	53	243	95	67	96
9	7/25/18	2	2	0	1	0	1	ND	ND	ND	ND	ND
10	7/26/18	2	1	41	294	45	373	350	364	183	145	274
11	8/6/18	3	1	0	22	0	22	10	8	19	37	30
12	8/6/18	3	1	0	2	0	1	ND	ND	3	3	3
13	8/6/18	3	1	0	18	0	18	ND	8	35	26	27
14	8/7/18	3	1	0	11	0	10	6	12	17	22	17
15	8/7/18	3	1	4	30	4	32	7	ND	47	52	40
16	8/7/18	3	1	0	1	0	1	ND	ND	4	4	4
17	8/7/18	3	1	0	4	0	3	ND	ND	8	9	7
18	8/8/18	3	2	0	50	3	54	17	13	60		64
19	8/8/18	3	2	0	48	2	52	13	9	61	73	60
20	8/8/18	3	2	0	11	0	10	ND	ND	22	20	19
21	8/8/18	3	2	0	25	0	27	ND	22	54	41	54
22	8/9/18	3	2	3	113	10	131	70	104	12	151	159
23	8/9/18	3	2	0	33	0	34	18	18	48	53	50
24	8/9/18	3	2	2	75	4	84	39	86	110	130	117
25	11/13/18	3	1	NA	NA	NA	NA	15	22		68	68
26	11/13/18	3	1	NA	NA	NA	NA	41	14	78	79	43
27	11/13/18	3	1	NA	NA	NA	NA	11	32	75	40	32
28	11/13/18	3	1	NA	NA	NA	NA	ND	ND	ND	ND	ND
29	11/14/18	3	1	NA	NA	NA	NA	31	43	129	92	92
30	11/14/18	3	1	NA	NA	NA	NA	ND	ND	ND	ND	ND
31	11/14/18	3	1	NA	NA	NA	NA	4	9	1	1	1

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