EEA-Agilent Method 521.1

Inter-Laboratory Comparison Study

Quality Control Summary Report

Report written by

Scott Coffin, Ph.D.

California State Water Resources Control Board

Division of Drinking Water

Revised on August 6, 2024

Acknowledgments

Dr. Andy Eaton, Nilda Cox, and the rest of the team from Eurofins Eaton Analytical and Agilent Technologies are thanked for their development of the analytical method for which this report is based on (Eurofins Eaton Analytical-Agilent Method 521.1).

Dr. Syrago-Styliani Petropoulou, Dr. Arianna Kazez, Dr. William Draper (retired) and Dr. Shiyamalie Ruberu from the California Department of Public Health, Drinking Water and Radiation Laboratory, in Richmond, California, are thanked for their efforts in the optimization and intra-laboratory comparison of the EEA-Agilent Method 521.1 Revision 1.0 (2018).

Betsy Lichti (retired), Mark Bartson (retired), Dr. Maria de la Paz Carpio-Obeso, Melissa Hall, Robert Brownwood, Christopher Hand, and Andrew Hamilton from the California State Water Resources Control Board are thanked for their efforts in coordinating the inter-laboratory study and reviewing/contributing to this report.

The laboratories that voluntarily participated in the Inter-Laboratory Comparisons Study are thanked, which include Metropolitan Water District (La Verne, CA); Orange County Water District (Fountain Valley, CA); Weck Laboratories (City of Industry, CA); California Department of Public Health's Drinking Water and Radiation Laboratory (Richmond, CA); McCampbell Laboratories (Pittsburg, CA); and Eurofins Eaton Analytical, LLC (Monrovia, CA).

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Section 1: Introduction

Section 1.1 Overview and Executive Summary

This Inter-Laboratory Validation Report summarizes quality control (QC) and statistical results from the inter-laboratory comparison study of Eurofins Eaton Analytical - Agilent Method 521 Revision 1.0, 2018, *Determination of Nitrosamines in Drinking Water by Solid Phase Extraction and Capillary Column Gas Chromatography with Large Volume Injection and Chemical Ionization Tandem Mass Spectrometry (MS/MS)* (hereafter referred to as "EEA-Agilent 521.1"). Precision, accuracy, and sensitivity were evaluated by State Water Resources Control Board (State Water Board), Division of Drinking Water (DDW), staff for eight target N-nitrosamine chemicals ("nitrosamines") (Table 1) in a multi-step process involving six independent laboratories through an initial demonstration of capability (IDOC) study followed by a proficiency testing (PT) sample evaluation. Acceptance criteria (Table 3) for the initial demonstration of capability metrics (i.e., accuracy and precision requirements for 10 ppt laboratory-fortified blanks [LFBs]) were met by all laboratories for all analytes. In the case of minimum reporting limits (MRLs), five laboratories failed one or more acceptance criteria for MRLs for one or more analytes at the concentrations in which they tested (between 1 and 5 ppt, depending on each laboratory and analyte). Of the six participating laboratories, two reported verified MRLs for NDBA, three for NDEA, two for NDMA, five for NDPA, six for NMEA, four for NMOR, five for NPIP, and three for NPYR. Of the laboratories that failed to meet MRL acceptance criteria for any analyte, three re-attempted verification using higher spike LFB concentrations and were generally successful in their attempts. In the case of PTs, four laboratories met acceptance criteria for all analytes, with one laboratory failing for four analytes (NDBA, NMEA, NMOR, and NPIP), and another laboratory failing two analytes

(NDPA, and NMOR) (Tables 4-6). Despite these imperfections, this inter-laboratory comparison study considered alongside previous studies (i.e., Eaton *et al.* 2018; Kazez *et al.* 2023) provide evidence that EEA-Agilent 521.1 is robust, rugged, sensitive, selective, precise, linear, and accurate for the target analytes, and is capable of quantifying targeted nitrosamines below California's health-protective concentrations (i.e., 10 parts-per-trillion [ppt]). One improvement of EEA-Agilent 521.1 over EPA 521 is the addition of N-nitrosomorpholine (NMOR) as a target analyte. Furthermore, while this study provides recommendations to optimize the performance of EEA-Agilent 521.1, it is not necessary to modify the existing method to ensure adequate results from competent laboratories.

Table 1. Nitrosamine analytes investigated in EEA-Agilent Method 521.1 Revision 1.0.

Analyte	Acronym	Chemical Abstract Services (CAS) Registry Number
N-nitrosodimethylamine	NDMA	62-75-9
N-nitrosomethylamine	NMEA	10595-95-6
N-nitrosodiethylamine	NDEA	55-18-5
N-nitrosodi-*n*-propylamine	NDPA	621-64-7
N-nitrosomorpholine	NMOR	59-89-2
N-nitrosopyrollidine	NPYR	930-55-2
N-nitrosopiperidine	NPIP	100-75-4
N-nitrosodi-*n*-butylamine	NDBA	924-16-3

Section 1.2 Environmental Significance

Nitrosamines are produced by several industrial sources such as the manufacturing of rocket fuel, rubber products, and other industrial process (Mitch *et al.* 2003) and have been found in some community drinking water supplies in California during the United States Environmental Protection Agency's (U.S. EPA) second Unregulated Contaminant Monitoring Rule (U.S. EPA 2007). Additionally, some nitrosamines (particularly NDMA) are disinfection by-products formed from the chloramination, chlorination, and ozonation of drinking water and wastewater, therefore

making them likely to be found in drinking water beyond just industrially contaminated sources (Mitch *et al.* 2003). Furthermore, NDMA and NMOR were identified as constituents of emerging concern that present a high likelihood for occurring at levels near or exceeding health-protective concentrations in indirect potable reuse applications in California by an expert panel and were therefore recommended for consistent monitoring in recycled drinking water (Drewes *et al.* 2018).

NDMA and other nitrosamines have been identified by the National Toxicology Program as reasonably anticipated to be human carcinogens (National Toxicology Program 2016) and are among the chemicals known to the State of California to cause cancer pursuant to California's Safe Drinking Water and Toxic Enforcement Act of 1986 (California Code of Regulations 1986). Additionally, DDW has set *de minimis*[1] risk levels nitrosamines ranging from 1 to 15 nanograms per liter (ng/L or parts per trillion [ppt]), with notification levels for three nitrosamines (NDEA, NDMA, and NDPA) set at 10 ppt (State Water Resources Control Board 2022). The availability of standardized analytical methods that can reliably quantify nitrosamines at or below their notification levels is important for informing and protecting public health. Furthermore, the reliability of such analytical methods should be demonstrated adequately with transparent and accessible supporting documentation (e.g., inter-laboratory comparison studies, etc.) to ensure feasibility of providing laboratory accreditation for the use of such methods.

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[1]*De minimis* risk levels for carcinogens defined as excess lifetime cancer risk for one-in-one-million people from exposure to a single contaminant in drinking water.

Section 1.3 Background of Method Development

EPA Method 521 is a procedure developed by the U.S. EPA for determining nitrosamines in drinking water which utilizes gas chromotography-mass spectrometry (GC-MS) and has lowest concentration minimum reporting levels (LCMRLs) between 1.2 and 2.1 ppt for all analytes (Munch and Bassett 2005). Although EPA Method 521 mentions the use of a triple quadrupole GC-MS/MS, only an ion trap (GC-IT) mass spectrometer was used during method development, therefore LCMRLs for laboratories with this instrumentation were not included in the final method (Munch and Bassett 2005). Starting in the 2010's, production of new GC-IT was discontinued by major instrument manufacturers (e.g., Agilent; Eaton *et al.* 2018) to be replaced by more sensitive and selective instrumentation that utilize multiple reaction monitoring such as the GC-MS/MS, therefore questioning the current and future feasibility of using a GC-IT with Method 521 for monitoring purposes. Additionally, during the U.S. EPA's evaluation of Method 521, NMOR (a contaminant of relatively high concern in potable reuse; Drewes *et al.* 2018) presented unresolved problems with background contamination and was subsequently excluded from the analytes list (Munch and Bassett 2005).

In an effort to adapt EPA Method 521 to be used with more sensitive and advanced instrumentation (i.e., GC-MS/MS), EEA and Agilent developed a new method based on EPA Method 521 (Eaton *et al.* 2018). The new method, EEA-Agilent 521.1, contains modifications to EPA Method 521 by changing the instrumentation protocol as well as including an additional analyte (i.e., NMOR), but does not change sample preparation procedures – which (as stated by the authors) would allow the new method to be considered an equivalent alternate test procedure to Method 521 by the U.S. EPA Office

of Groundwater and Drinking Water, if the U.S. EPA were to regulate nitrosamines in drinking water (which the agency does not, at the time of writing) (Eaton *et al.* 2018).

Section 1.4 Previous Method Comparison and Validation Studies

To demonstrate the performance of EEA-Agilent 521.1 across multiple instruments and laboratories, Eaton *et al.* (2018) completed a two-part validation study, in which the method was also compared alongside EPA Method 521. In the first phase, a single laboratory compared method performance between GC/IT (using chemical ionization mode) and GC-MS/MS (using electron ionization mode) (Eaton *et al.* 2018). In the second phase, samples were split and analyzed by three independent laboratories using EEA-Agilent 521.1 with two different GC-MS/MS instruments – an Agilent 7010 and an Agilent 7000 (Eaton *et al.* 2018). The goals of the second phase included demonstrating method performance (including sensitivity and linearity of calibration curves) across three separate laboratories as well as compare the sensitivity of the method between the Agilent 7000 extractor source and the more sensitive Agilent 7010 high-efficiency extractor source (Eaton *et al.* 2018). The study demonstrated approximately 10-fold average increases in sensitivity with GC-MS/MS compared with GC/IT for all analytes, with LCMRLs ranging from 0.12 to 0.52 ppt (Eaton *et al.* 2018). The study also demonstrated additional, albeit minor, improvements in sensitivity when the high-efficiency extractor source (i.e., Agilent 7010) was utilized (Eaton *et al.* 2018). Accordingly, as confirmed in a letter from the U.S. EPA regarding the agency's technical review of EEA-Agilent 521.1, the method yields performance equivalent to EPA Method 521 (U.S. EPA 2012; Eaton *et al.* 2018).

In January 2020, DDW requested that the Chemistry Unit at the Drinking Water and Radiation Laboratory (DWRL) of the California Department of Public Health (CDPH) develop an analytical method that could quantify nitrosamines (all analytes listed in EPA Method 521 and NMOR) in water with MRLs (defined as the single-laboratory determination of the lowest true concentration for which a future recovery is expected, with 99 percent confidence, to be between 50 and 150 percent recovery) at or below 2.1 ppt for all analytes. The request further included that GC-MS/MS instrumentation be used, and that DWRL evaluate the performance of the method (including sensitivity, precision, and accuracy) through an intra-laboratory validation study. Kazez *et al.* (2023) followed the validation and quality criteria described in the U.S. EPA's Protocol for the Evaluation of Alternate Test Procedures for Organic and Inorganic Analytes in Drinking Water (U.S. EPA 2012) in addition to other method validation metrics, which included: an evaluation of the dynamic linear range of calibration; accuracy; precision; sensitivity in the form of method detection limits (MDLs) and MRLs; method ruggedness – including the use of different solvents, instruments, analysts, and consumables lot numbers; background contamination; internal standard and surrogate recoveries; sample extract suitability and sample storage stability (Kazez *et al.* 2023). Kazez *et al.* (2023) validated method performance using a ThermoFisher Scientific TSQ8000 Evo MS/MS with ExtractaBrite ion source and Trace 1310 GC. Method performance was also tested through inter-laboratory comparison studies involving an Agilent Technologies 7000 GC-MS/MS and a ThermoFisher Scientific TSQ9000 Evo instrument with advanced electron ionization ion source, which provided additional information regarding method performance differences between instruments of varying sensitivities (Kazez *et al.* 2023).

The intra- and inter-laboratory comparison studies conducted by DWRL demonstrated that EEA-Agilent 521.1 is selective, precise, linear, accurate, and robust for the target analytes, with performance equivalent to or superior to EPA Method 521 (Kazez *et al.* 2023). DWRL reported MRL values ranging from 1 ppt to 8 ppt[2] for all analytes, however, could not verify their MRL for NDPA (Kazez *et al.* 2023). Sample extracts were also found to be stable up to 28 days in dichloromethane when preserved at -20°C (Kazez *et al.* 2023). Comparable method performance was achieved across all three different instruments tested; however, higher sensitivity was demonstrated by the ThermoFisher TSQ9000 (having acceptable accuracy at 0.5 ppt for all analytes) than the TSQ8000 (which had acceptable accuracy at 1 ppt for all analytes except NDPA and NPYR – which had acceptable accuracies at 4 ppt) – results which are similar to the Agilent 7010B - as demonstrated by Eaton *et al.* (2018) (Kazez *et al.* 2023).

DWRL reviewed all aspects of the method, testing additional QC parameters, including MRLs, laboratory reagent blanks (LRBs), dilution factors, internal standard and surrogate recoveries, sample extract stability, sample storage stability, accuracy, precision, robustness, and sensitivity (Kazez *et al.* 2023). Furthermore, DWRL provided additional guidance and/or emphases to optimize the performance of the method, including (Kazez *et al.* 2023):

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[2]As tested by a ThermoFisher Scientific TSQ8000 Evo triple quadrupole MS with ExtractaBrite ion source only.

- the use of different quantitation ions for some analytes (see Table 3 in Kazez *et al.* 2023 for details);
- ensure final volume of extract ≥0.5 mL during nitrogen evaporation to prevent loss of volatile compounds (as describes in EEA-Agilent 521.1); test background contamination in each new lot numbers of solid phase extraction (SPE) cartridges – which can vary up to 7% relative percent difference between lots;
- ensure primary dilution standards in dichloromethane are prepared and stored at -20 °C and are allowed to warm to room temperature prior to analysis;
- use ultrapure reagent water that has undergone ultraviolet treatment, as other sources (e.g., water treated with ion-exchange resin, commercial ultrapure high-performance liquid chromatography grade water) have been found to contain contamination (especially NDMA); and
- always use manual SPE extraction manifolds and extract slowly to improve recovery (Kazez *et al.* 2023).

While DWRL explored two different lot numbers of SPE cartridges of the allowable type per the method (i.e., activated coconut charcoal) and found them to provide recovery for all analytes at low levels (≥70%), they did not evaluate the applicability and suitability of all possible consumables (e.g., SPE columns, isotopic reagents, etc.) (Kazez *et al.* 2023). Nonetheless, Kazez *et al.* (2023) identified that consumables can be significant contamination sources; therefore laboratories should not assume that the method is robust across all consumables. Additionally, while several laboratories have previously reported improved extraction efficiency of nitrosamines using either

Ambersorb 572[3] alone or in combination with other sorbents (Charrois *et al.* 2003; Cheng *et al.* 2004; Jenkins *et al.* 1995), the manufacture of SPE columns with this sorbent has been discontinued and could not be evaluated as an alternative to coconut charcoal by DWRL (Kazez *et al.* 2023). Additional studies and published methods would need to be validated and evaluated if alternative sorbents are to be used with alternative extraction procedures. Furthermore, the use of alternative SPE columns is not allowable in either EPA Method 521 or EEA-Agilent Method 521.1.

[3] Ambersorb 572 is a synthetic carbonaceous adsorbent that was previously manufactured by Rohm and Haas (Philadelphia, PA), and was first reported in the literature as an SPE material for the analysis of NDMA by Taguchi *et al.* (1994). Its use in EPA Method 521 or EEA-Agilent Method 521.1 is not allowable, and the mention of its use here is strictly for completeness purposes.

Section 2: Inter-laboratory Comparison Study

Section 2.1 Study Objectives

Due to the documented presence of several nitrosamines in some drinking water sources in California above or near their respective health-protective concentrations (Drewes *et al.* 2018), and the current lack of a standardized and validated analytical method capable of quantifying nitrosamines (including NMOR) at low ppt concentrations using modern instrumentation (i.e., GC-MS/MS), it is necessary to demonstrate the capabilities of such a method to enable regulatory monitoring. The principal aims of this study were to evaluate the precision, accuracy, and sensitivity of EEA-Agilent 521.1 across multiple independent laboratories against pre-determined data quality objectives (Table 3) to determine if the method would be fit-for-purpose for regulatory monitoring of drinking water. Additionally, this study was designed to support the State Water Board's Environmental Laboratory Accreditation Program in evaluating whether EEA-Agilent 521.1 is fit for accreditation purposes.

Section 2.2. Study Design

To ensure feasibility and adequacy of analytical methods for use in regulatory monitoring, DDW depends upon robust documentation demonstrating intra- and inter-laboratory performance. Previously, EEA-Agilent 521.1 underwent two independent and external stages of method validation, demonstrating its equivalency to EPA Method 521, as well as comparisons within and across qualified laboratories and instruments (Eaton *et al.* 2018; Kazez *et al.* 2023). Prior to providing laboratory accreditation for EEA-Agilent 521.1, additional demonstrations of reliable method performance with public and

commercial laboratories were desirable. Accordingly, DDW organized an inter-laboratory comparison study with volunteer laboratories using blind PT samples, as described here.

DDW's inter-laboratory comparison study was conducted in two steps, with six independent laboratories first submitting IDOC data which was reviewed and either approved or disapproved by DDW staff - followed by analysis of PT samples administrated through an independent third-party. Laboratories were invited to participate in the study if they met the following criteria: they possessed the required instrumentation to use the method (i.e., GC-MS/MS with electron ionization source); they had trained personnel for such instrumentation; they had experience with either EPA 521.1 and/or EEA-Agilent Method 521.1; they routinely analyzed drinking water matrices; and they did not have any recent or outstanding violations that would otherwise question their validity. A mixture of commercially owned laboratories (n = 3) and publicly owned laboratories (n = 3) were included.

To receive PT samples and participate in the blind performance testing portion of this study, laboratories were first required to submit acceptable IDOC data to DDW, which included accuracy and precision data based on spiking six reagent grade water samples (i.e., laboratory fortified blanks or LFBs) between 10 and 50 ppt for each target analyte, extracting the samples, and analyzing them on a single day according to the procedures defined in EEA-Agilent 521.1. In addition to reporting raw recovery data in LFBs spiked between 10 and 50 ppt, laboratories also calculated MDLs for each analyte according to the U.S. EPA method (2016), which involved extracting and analyzing seven LFBs spiked at 2 ppt, and seven LRBs and assigning an MDL to the lower of the two calculated values (i.e., based on blank contamination or spike recovery). The MDL procedure accounts for

both blank reagent water and the LFBs, ensuring that blank background is accounted for if present. Laboratories additionally calculated and reported MRLs according to the protocol defined by U.S. EPA (2004), which involves extraction and analysis of ≥ seven replicate LFBs spiked at the estimated MRL for each analyte. Each laboratory's MRL was considered validated when the mean prediction interval of results (PIR; equation 1) fell between the defined data quality objectives (i.e., 50 to 150%) and was greater than 3 times the MDL (Winslow *et al.* 2006).

Equation 1 $$\mathrm{PIR} = (\mathrm{mean} \pm s) t_{\mathrm{df},1-\left(\frac{1}{2}\right)a} \left(1 + \frac{1}{N}\right)^{1/2}$$

Where the mean is the average of seven or more replicates, *t* is the Student's *t* value with df degrees of freedom associated with an overall confidence level (1 – *α*), *s* is the standard deviation of *n* replicate samples fortified at the MRL, and *n* is the number of replicates. In equation 1, the confidence for *t* is given as (1 - [1/2] *α*) because the formula is for a two-sided interval (Winslow *et al.* 2006). For this study, a confidence level of 99% was used. If the MRL does not pass verification at the concentration tested, the analyst should either attempt to verify at a higher concentration, and/or check if recalibration is needed, and/or check if instrument maintenance is necessary.

In the second step of DDW's interlaboratory comparison study, an independent commercial provider[4] prepared and sent blind PT samples (a concentrate in methanol) to

[4] The PT provider was Absolute Standards Inc., ISO 9001 Registered, PO Box 5585, Hamden, CT 06518.

the six participating laboratories in 2021. The purpose of this step was to check the ability of laboratories to deliver accurate testing results using the methodology with independent laboratory verification. Each laboratory was tasked with: 1) following EEA-Agilent 521.1 to prepare, extract, and analyze samples (after following the provider's instruction to dilute PT samples in reagent grade water); 2) returning raw data to the independent PT provider within 6 weeks of receiving PT samples; and 3) meeting the minimum acceptance criteria for sample preparation and analysis in the method (Table 3). All six of the laboratories provided raw PT sample data to the PT provider by the submittal deadline.

While not a primary goal of the Division of Drinking Water's interlaboratory comparison study, multiple models of GC-MS/MS from several manufacturers were used during the second step, which provided preliminary insights into potential performance enhancements due to instrumentation (Table 2). Although the manufacturers of instruments and GC columns differed across laboratories, all laboratories used similar column dimensions and parameters (i.e., 30 m x 0.25 mm internal diameter fused silica capillary columns with either 0.5 or 1.0 μm bonded film of polyphenylmethylsilicone) (Table 2).[5]

[5] Both method 521 and EEA-Agilent 521.1 provide flexibility in the use of columns, stating, "any capillary column that provides adequate resolution, capacity, accuracy, and precision can be used", and further recommend that medium polarity, low bleed columns be used to provide adequate chromatography and minimize column bleed.

Table 2. Instrumentation utilized by laboratories in the inter-laboratory comparison study.

Lab ID[a]	Instrument	Column
1	GC: 7890B (Agilent) MS/MS: G7013A	Agilent VF-1701 (30 m x 0.25 mm x 1.0 µm)
2	GC: Agilent 7890A MS/MS: Agilent 7010B	Agilent DB-1701 (30 m x 0.25 mm x 1.0 µm) [Part# 122-0733]
3	GC: Agilent 7890A MS/MS: Agilent 7000 (w/EI extractor lens)	Phenomenex 7HG-G013-17 ZB-WaxPlus (30 m x 0.25 mm x 0.5 µm)
4	GC: Agilent 7890A MS/MS: Agilent 7000	Agilent DB-1701 (30 m x 0.25 mm x 1.0 µm)
5	GC: Agilent 7890B MS: Agilent 7010	Agilent DB-1701 (30 m x 0.25 mm x 1.0 µm)
6	GC: Thermo Scientific™ TSQ 9000 MS: Thermo Scientific™ Trace 1310	Thermo Scientific™ TG-1701MS (30 m x 0.25 mm x 1.0 µm)

[a]Laboratory identities were anonymized for reporting purposes.

Although instrumentation and columns differed, all participating laboratories followed the procedures in EEA-Agilent 521.1 during this inter-laboratory validation study. Laboratory ID #6 used a slower than recommended sample extraction flow rate of ~3 mL/min, instead of the approximate flow rate of ~10 mL/min recommended in section 11.4.2 of the method. The laboratory used this slower flow rate based on an in-house optimization study of the method, and results provided by the laboratory indicate that the slower flow rate did not negatively impact analyte recoveries.

Section 3: Interlaboratory Comparison Study Results and Discussion

Section 3.1: Data Evaluation

DDW staff evaluated IDOC and PT data from the six participating laboratories to ensure laboratories achieved the required method performance criteria in EEA-Agilent 521.1 for completeness, compliance, and analytical quality against pre-determined data quality objectives (Table 3). Laboratory QC that addressed both sample preparation and analysis included LRBs (also commonly referred to as 'method blanks'), LFBs, and PT

samples. Table 3 provides a summary of study acceptance criteria and a brief description of how each component was calculated. Tables 4-6 provide a summary comparison of laboratory performance by QC type, including frequencies at which the QC acceptance criteria were met. Having ≥80% of participating laboratories meeting all data quality objectives was pre-determined as a reasonable goal for demonstrating the applicability of the method for regulatory monitoring.

Table 3. Acceptance Criteria for interlaboratory comparison study applicable for all nitrosamine analytes.

Criteria	Test Procedure Description	Metric	Acceptance Criteria
Accuracy/ Precision	Extraction and analysis of six LFBs (10 ppt).	Average percentage recovery (x); relative standard deviation (RSD)	70% ≤ x ≤ 130%; RSD ≤ 20%
Method Detection Limit (MDL)[a]	Extraction and analysis of seven LFBs (spike at 2 ppt) and seven LRBs.	MDL (based on highest of MDL based on LRBs or LFBs)	MDL ≤ 10 ppt (all analytes)
Minimum Reporting Level (MRL)[b]	Extraction and analysis of ≥ seven replicate LFBs spiked at the estimated MRL for each analyte. MRL is considered validated when mean recovery falls within PIR for each analyte.	Minimum Reporting Level (MRL); Prediction Interval Range (PIR)	MRL ≤ 10 ppt (all analytes); 50% ≥ PIR ≤ 150%; must be > 3* MDL to be valid
Proficiency Testing (PT)[c]	Extraction and analysis of a single blind sample.	Reported value	70% ≥ reported value ≤ 130%

[a]MDL calculated based on U.S. EPA (2016).
[b]MRL calculated based on U.S. EPA (2004).
[c] PT samples for all analytes were between 20.1 and 45.2 ppt. While concentrations closer to notification levels (i.e., 10 ppt) were desired, DDW could not locate a PT provider providing such low-level spikes of the listed analytes.

Laboratories were asked to calculate MRLs for each analyte according to the procedures defined in EPA Method 521 (Munch and Bassett 2004). An MRL is defined as the minimum concentration that can be reported as a quantitated value for a target

analyte in a sample following analysis, which can be no lower than the concentration of the lowest calibration standard for that analyte and can only be used if acceptable quality control criteria for the analyte at that concentration are met (Munch and Basset 2004). MRLs are often used as the limit below samples are reported as non-detections and can inform DDW's development of Detection Limits for purposes of Reporting (State Water Resources Control Board 2020).

The procedure for determining an MRL involves first selecting a target concentration for an MRL based on the intended use of the method, then verifying the proposed MRL by fortifying, extracting, and analyzing 7 replicate LFBs at the proposed MRL and calculating a PIR. For example, DWRL spiked most analytes at 2 ppt based on their estimated MRLs from IDOC data (Kazez *et al.* 2023). The proposed MRLs were deemed valid if the following criteria were met (as specified in Munch and Basset 2004): the upper PIR Limit is ≤150%, the lower PIR Limit is ≥50%, and the MRL > 3 x MDL (Table 3).

Statistical analyses were performed to support the interpretation of data for specific study objectives. The R statistical programming software (version 4.3.1) was used for data visualization and statistical analyses (R Core Team 2023). The following packages were also used: *Tidyverse, multcompView (*Wickham *et al.* 2019; Hothorn *et al.* 2023*)*.

Section 3.2: Initial Demonstration of Capability

Prior to receiving blind PT samples, participating laboratories were asked to provide IDOC data for each nitrosamine analyte using EEA-Agilent 521.1[6] to ensure competency with the method and provide an opportunity to resolve challenges encountered by the laboratory prior to undergoing independent performance evaluation. This section describes the IDOC data requested of laboratories. IDOC data included background analysis using LRBs (n ≥7), recovery and precision analysis using LFBs (4 ≤ n ≤ 7)**,** determination of MDLs, and determination and confirmation of MRLs.

Section 3.2.1: Evaluation of recovery and precision

Recovery and precision at low concentrations of nitrosamines in samples were determined by each participating laboratory by extracting and analyzing four to seven replicate LFBs between 10 and 50 ppt[7] with each target analyte on a single day. Laboratories were asked to process and analyze each IDOC sample as an unknown sample. The percent recovery for each analyte in LFBs was calculated for each laboratory (Table A-1) and evaluated against the pre-defined acceptance criteria (Table 3). All laboratories met acceptance criteria for all analytes. A summary of LFB recovery data

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[6]While laboratories were expected to meet IDOC data quality objectives before receiving PT samples, several exceptions were made in the case of laboratories being unable to meet MRL data quality objectives. Based on other IDOC data provided, it was reasonable expected that these laboratories would be able to meet all other data quality objectives given sufficient time and resources, therefore they were allowed to remain in the study and participate in the PT sample component.

[7]Four out of six laboratories spiked at 10 ppt, one laboratory spiked at 40 ppt, and one other laboratory spiked at 50 ppt.

across all laboratories is presented in Table 4, with means and ranges (minimum to maximum) for accuracy and precision (i.e., relative standard deviation) reported. The raw data is reported in Table A-1, and the data are summarized in Table 4.

Table 4. Summary of recovery and precision data (6 laboratory fortified blank samples between 10 and 50 ppt) across six laboratories participating in interlaboratory comparison study.

Analyte	Average Percent Recovery (%) across Laboratories[a] (mean: min to max)	Relative Standard Deviation (%) across Laboratories[a] (mean: min to max)	Percentage of Laboratories Meeting Accuracy Acceptance Criteria (70 to 130%)	Percentage of Laboratories Meeting Precision Acceptance Criteria (%RSD: < 20%)
NDBA	102.7% (86.0% to 114.0%)	6.1% (2.0% to 10.3%)	100%	100%
NDEA	92.2% (80.3% to 112.4%)	5.0% (1.3% to 12.8%)	100%	100%
NDMA	89.4% (71.3% to 117.8%)	5.9% (0.9% to 14.1%)	100%	100%
NDPA	93.3% (82.6% to 106.6%)	5.9% (2.8% to 11.9%)	100%	100%
NMEA	92.7% (82.7% to 114.8%)	5.4% (1.1% to 13.5%)	100%	100%
NMOR	103.7% (83.9% to 127.6%)	4.7% (1.6% to 11.6%)	100%	100%
NPIP	102.2% (94.6% to 117.6%)	4.9% (1.9% to 10.5%)	100%	100%
NPYR	100.4% (88.6% to 115.5%)	4.9% (1.8% to 8.6%)	100%	100%

[a] $4 \leq n \leq 7$ samples per laboratory; n = 6 laboratories

Laboratory LFB data indicate significant differences in recovery between analytes. A one-way analysis of variance (ANOVA) test by analyte indicated significant differences between analytes ($p = 1.5 \times 10^{-5}$) (Table A-6). Tukey's *post-hoc* test revealed significantly lower recovery amongst laboratories for NDMA compared with NMOR and NPYR; as well as significantly higher recover amongst laboratories for NMOR compared with NDEA, NDMA, NDPA, and NMEA (Figure 1; Table A-7). Significance was tested at $\alpha = 0.05$.

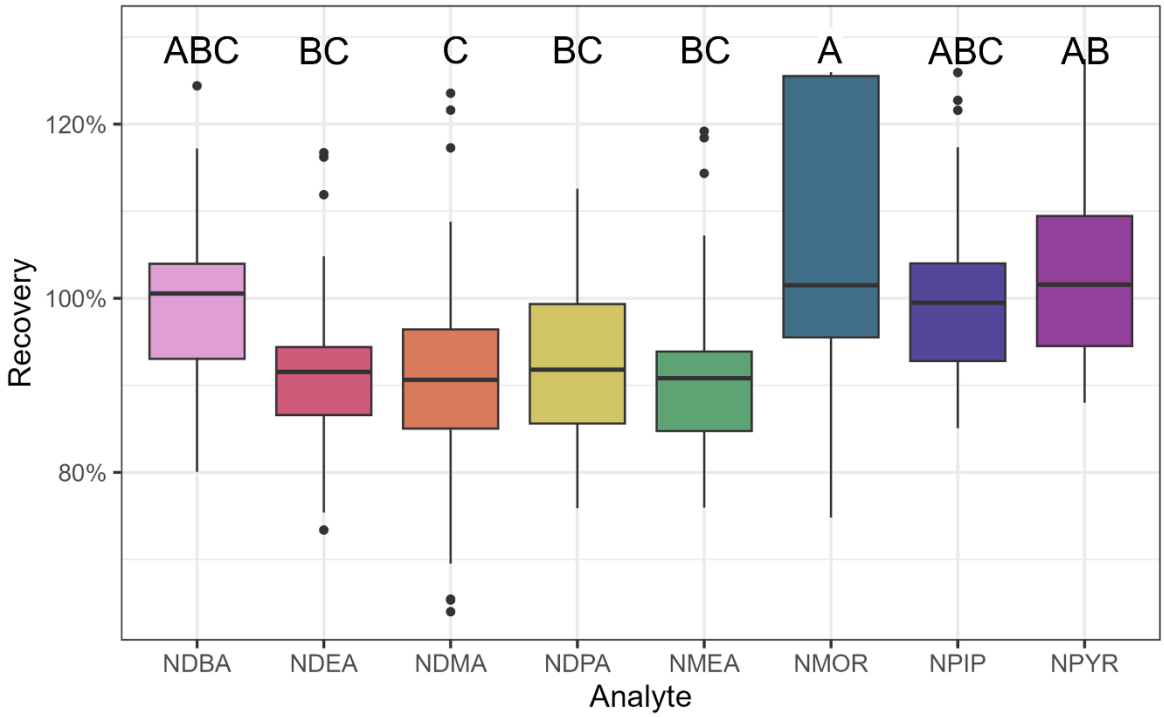

Figure 1. *Box-and-whisker plot of recovery data for each analyte across all laboratories based on LFB data submitted by laboratories (n = 4 to 7).*

Note that data from laboratory ID#4 are not used due to this laboratory only submitting summary statistic data instead of individual sample data. Boxes represent interquartile ranges of the data, with the line inside the box indicating the median. Whiskers extend the box to the minimum and maximum values. Significant differences according to Tukey's post-hoc test are annotated with letters above each analyte's boxplot. For example, NDMA has the letter "C", indicating it is significantly different from all other analytes that do not have the letter "C" (i.e., NMOR, NPYR).

As demonstrated in Table 4, all participating laboratories met both the precision (i.e., %RSD < 20%) and accuracy (i.e., 70% to 130% recovery) requirements for all analytes. Across all laboratories, the mean percentage recoveries for four analytes (i.e., NDEA, NDMA, NDPA, and NMEA) were less than nominal (i.e., 100%), and was greater than nominal for the remaining analytes (i.e., NDBA, NMOR, NPIP, and NPYR), however none of these trends could be considered statistically significant due to their 95% confidence intervals including 100% (Figure 3; Table 4). Based on these data, it can be

concluded that laboratory recovery and precision is within achievable limits at relatively

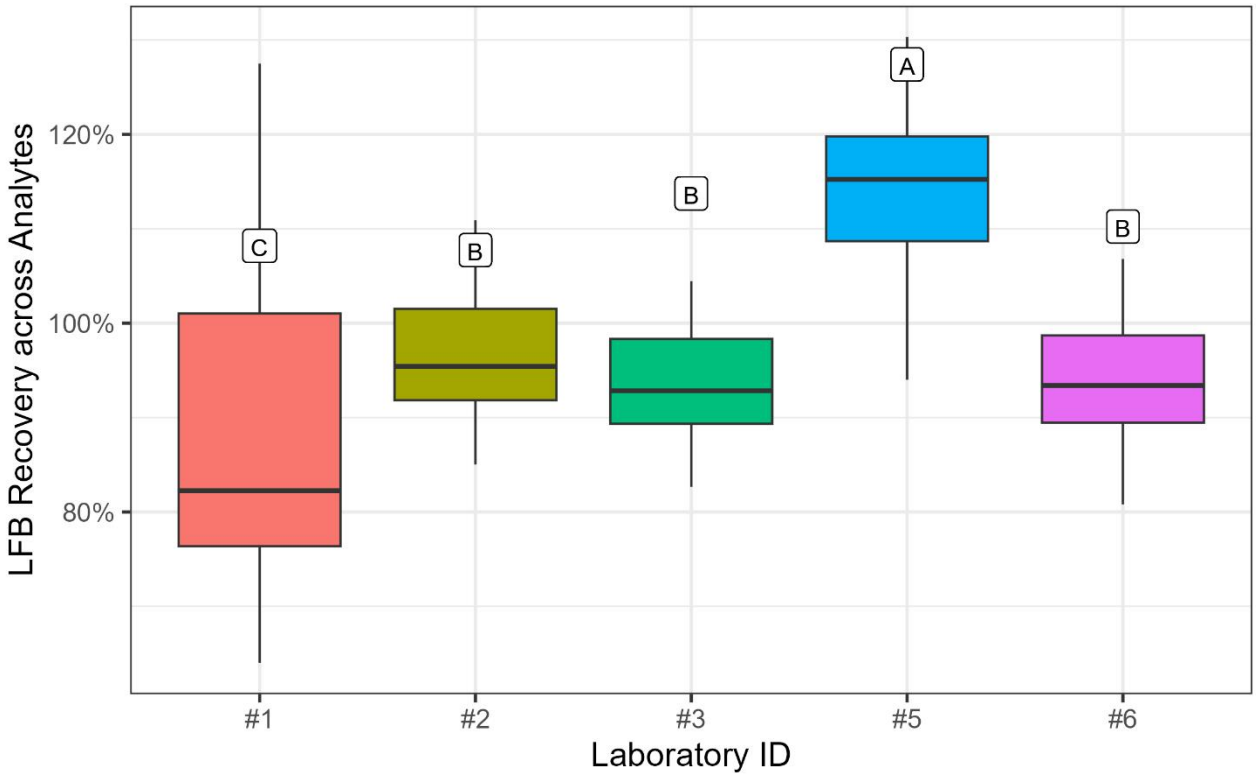

Figure 2. *Box-and-whisker plot of recovery data for each laboratory across all analytes based on LFB data submitted by laboratories (n = 4 to 7).*

Note that laboratory ID#4 is not shown due to this laboratory only submitting summary statistic data instead of individual sample data. Boxes represent interquartile ranges of the data, with the line inside the box indicating the median. Whiskers extend the box to the minimum and maximum values. This plot visually demonstrates relative laboratory bias, accuracy, and precision across all analytes in EEA-Agilent 521.1. Significant differences (Tukey's post-hoc) are annotated with letters. For example, laboratory ID #5 consistently had higher than expected recovery for all analytes compared to all other laboratories, while laboratory ID#1 had lower than expected recovery compared to other laboratories, although with relatively lower precision as well (as denoted by error bars).

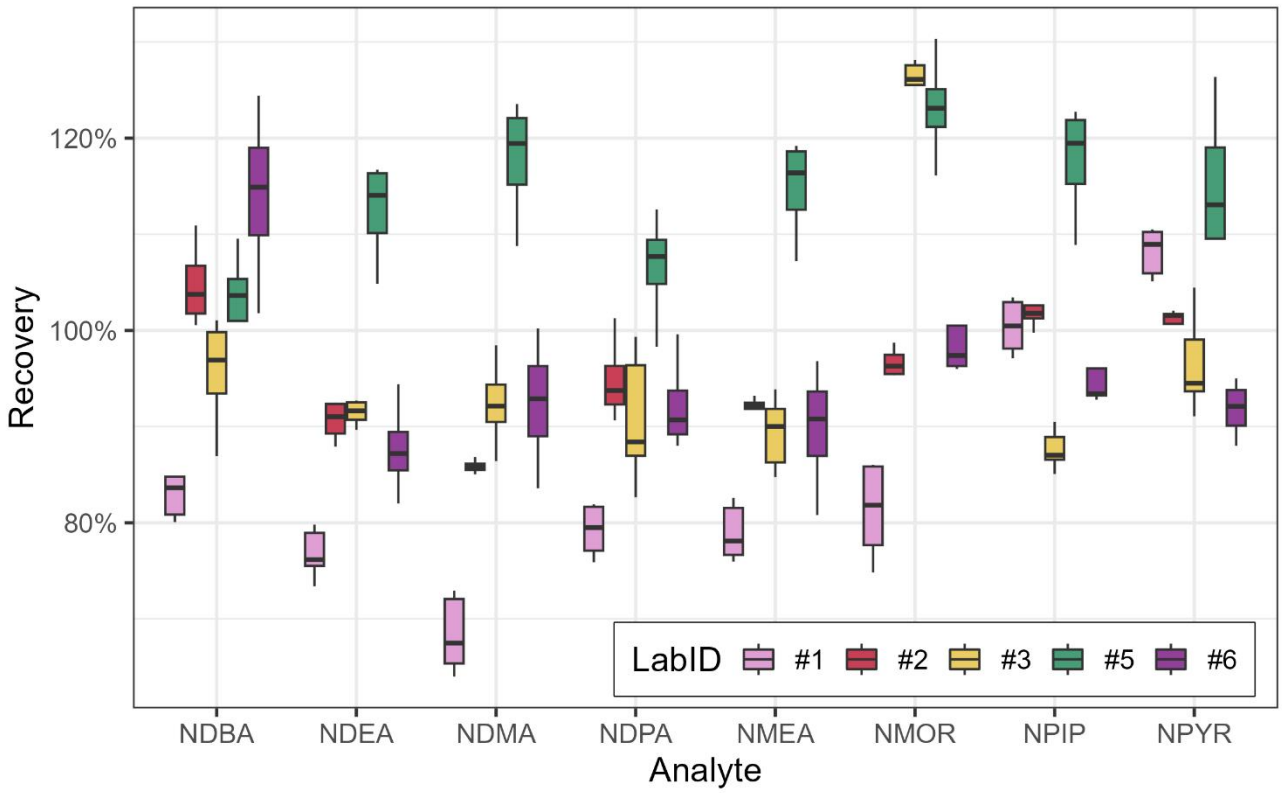

Figure 3. *Box-and-whisker plot of recovery data for each laboratory and analyte based on LFB data submitted by laboratories (n = 4 to 7).*
Note that laboratory ID#4 is not shown due to this laboratory only submitting summary statistic data instead of individual sample data. Boxes represent interquartile ranges of the data, with the line inside the box indicating the median. Whiskers extend the box to the minimum and maximum values. This plot visually demonstrates laboratory bias across one or several analytes (e.g., LabID #5 consistently had higher than expected recovery for all analytes). Significant differences (Tukey's post-hoc) are not shown in plot.

While all laboratories reported LFB data within acceptable precision and recovery data quality objectives, biases by laboratory are present. A two-way ANOVA was conducted on the LFB data[8], with the laboratory and analyte being tested as groups, as

[8]LFB data from laboratory ID#4 was excluded from these statistical tests due to this laboratory only providing summary statistic data instead of raw data.

well as the interaction term between analyte and laboratory. All terms were extremely statistically significant (i.e., p <0.001) (Table A-8), which can be readily observed visually in Figure 2 as well. No obvious explanation for differences between laboratory recovery bias are available (e.g., instrumentation differences, experience with method, etc.). For example, laboratory ID #2 and ID #5 used identical MS (Agilent 7010 – a relatively-higher sensitivity instrument), however laboratory ID #5 had consistently higher recovery than all other laboratories for nearly all analytes (Figure 3; Table A-9).

While all laboratories followed the procedures in EEA-Agilent 521.1, laboratory ID #6 extracted samples at a lower flow rate than recommended (yet still allowable) in the method (i.e., ~3 mL/min instead of ~10 mL/min). To determine if this laboratory had significantly different recoveries of LFBs compared to the other laboratories, two-sample t-tests (two-tailed) were run for each analyte (Table A-10). Laboratory #6 had significantly higher recovery for NDBA (p = 0.036), and significantly lower recovery for NDEA (p = 0.037) and NPYR (p = 0.046) compared with the rest of the laboratories (Table A-10), with no other significant differences observed for other analytes (α = 0.05). The lack of a consistent trend across analytes compared to other laboratories, as well this laboratory's relatively high performance in all aspects of the study suggests that the lower extraction flow rate did not significantly bias the laboratory's recovery data.

Section 3.2.2: Method Detection Limit

Table 5. Summary of method detection limit (MDL) data for each analyte across six laboratories.

Analyte	MDL[a] (ppt) (mean: min to max)	MDL_{Blank}[b] (ppt) (mean: min to max)	Final MDL (ppt) (mean: min to max)	Number of MDLs based on LFBs[c]	Percentage of Laboratories Meeting QC Criteria (i.e., MDL < 10 ppt)
NDBA	1.1 (0.22 to 3.5)	0.59 (0.32 to 0.78)	1.1 (0.38 to 3.5)	4	100%
NDEA	0.61 (0.13 to 1.6)	0.42 (0.13 to 1.1)	0.63 (0.13 to 1.6)	4	100%
NDMA	0.67 (0.30 to 1.3)	0.51 (0.18 to 0.99)	0.63 (0.18 to 1.3)	3	100%
NDPA	0.29 (0.07 to 0.42)	0.39 (0.16 to 0.90)	0.45 (0.31 to 0.90)	4	100%
NMEA	0.06 (0.04 to 0.08)	0.29 (0.17 to 0.45)	0.29 (0.17 to 0.45)	6	100%
NMOR	0.36 (0.07 to 0.64)	0.44 (0.18 to 1.1)	0.49 (0.25 to 1.1)	5	100%
NPIP	0.44 (0.25 to 0.62)	0.35 (0.16 to 0.62)	0.35 (0.16 to 0.62)	5	100%
NPYR	1.0 (0.68 to 1.2)	0.70 (0.25 to 1.3)	0.87 (0.44 to 1.25)	4	100%

[a]Refers to MDLs based on LFBs.
[b]Refers to MDLs based on LRBs.
[c]The final MDL for each analyte for every laboratory was determined to be the largest of each laboratory's MDLs based on values determined by both LRBs and LFBs. This value provides a general indication regarding frequency of background contamination at relevant concentrations for each analyte.

MDLs ranged from 0.1 to 3.5 ppt across laboratories, with NMEA having the lowest MDLs (mean of 0.3 ppt; range between 0.3 and 0.5 ppt), and NDBA having the highest MDLs (mean of 1.1 ppt, range between 0.4 and 3.5 ppt) (Table 5). All determined MDLs met the study's data quality objective (Table 3) of being less than 10 ppt for all analytes. For all other analytes, the maximum MDL reported by any laboratory was ≤ 1.5 ppt, with mean MDLs across laboratories ≤0.9 ppt. The majority of MDLs were based upon LFBs as expected, however, due to the potential background and minor contamination present (discussed later), some MDLs were determined based on the MDL_{Blank} results. These

results demonstrate that EEA-Agilent 521.1 can achieve similar sensitivity as the original EPA Method 521 method, which states detection limits[9] between 0.28 and 0.66 ppt (Munch and Bassett 2004).

Section 3.2.3: Minimum Reporting Level

MRLs for all laboratories and analytes are listed in Table A-3, with a summary provided in Table 6.

Table 6. Summary of minimum reporting levels for eight nitrosamines for six laboratories.

Analyte	Minimum MRL (ppt)	20th Percentile MRL (ppt)	Median MRL (ppt)	80th Percentile MRL (ppt)	Maximum MRL (ppt)	Number of Laboratories (out of 6) Meeting Acceptance Standards[a]
NDBA	1	1.6	2	5	5	2[b]
NDEA	1	1	2	2	2	3[b]
NDMA	1	1.8	2	2	2	2[b]
NDPA	1	2	2	3.8	5	5
NMEA	1	2	2	2	2	6
NMOR	1	1.8	2	3.6	4	4[b]
NPIP	1	1	2	2	2	5
NPYR	1	2	2	3.8	5	3[b]

[a]Acceptance criteria for all analytes was that MRL ≤ 10 ppt; 50% ≥ PIR ≤ 150%; and > 3 x MDL - as defined in Table 3.
[b]One or more laboratories did not meet verification requirements at the spike concentration for this analyte and did not attempt to verify at a higher spike concentration.

[9]Detection limits were calculated solely based on LFBs in Munch and Bassett (2004), and are therefore similar, but not directly comparable to the MDLs determined here.

All six laboratories provided verification data for their MRLs, however all but one laboratory failed to verify MRLs for one or more analytes (Table 6). Only NMEA had a verified MRL by all laboratories (1 or 2 ppt) (Table 6). MRLs did not meet acceptance criteria primarily due to laboratories using LFB spike concentrations that were below 3-times their MDL, with all but one remaining failure due to the lower PIR failing below the 50% acceptance criteria (Table A-3). Importantly, three laboratories that failed to verify one or more analyte's MRL at the initial LFB spike concentration attempted verification using higher concentration(s). In the case of a laboratory seeking accreditation for a given method, it is highly likely that they would attempt to verify their MRLs using higher LFB spike concentrations in the case of their first concentration failing – thus demonstrating a limitation of this study in reflecting real-world conditions in which laboratories would ordinarily dedicate additional resources to meeting method acceptance criteria. Nonetheless, the data reported in this study demonstrate that it is possible for a competent laboratory to achieve MRLs for all analytes in EEA-Agilent 521.1 well below the current notification levels of 10 ppt, as demonstrated by laboratory ID #2 (MRLs < 2 ppt for all analytes) (Table A-3). It should be noted that laboratory ID #2 used an MS/MS detector with higher sensitivity than several other laboratories (i.e., Agilent 7010B), which may have influenced results (Table 2).

Section 3.3: Proficiency Testing

The six laboratories participating in this study were sent blind PT samples and asked to extract and report within a given time frame (i.e., 6 weeks from time of receival)[10]. The PT samples contained the eight nitrosamine analytes listed in Table 1, which were prepared at concentrations unknown to the laboratories in methanol and stored in polypropylene containers with screw-cap lids. Laboratories were instructed to pipet 1 mL of the ampule solution into a 1 L flask, fill to volume with reagent grade water and mix well, then extract the entire diluted sample and analyze by gas chromatography immediately according to the procedures defined in EEA-Agilent 521.1. The true concentrations of analytes ranged from 20.1 to 45.2 ng/L (Table 7). Ideally, the PT samples used in this study would be at concentrations closer to the laboratories' lower quantitation limits to test their performance in a more rigorous manner, however the concentrations used were the lowest available in commercial PT samples. Laboratories were instructed to submit PT data directly to the PT provider (Absolute Standards, Inc.) through their online data portal, ensuring that such data were secure and verified by a third-party. Absolute Standards provided results from laboratories to DDW following completion of the study, which are reported for each individual laboratory in Table A-4 and are summarized in Table 7.

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[10] PT samples were shipped to laboratories on August 30th, 2022, and data were submitted to the vendor (Absolute Standards Inc., Hamden, CT) by October 11th, 2022.

Table 7. Summary of PT Sample concentrations, acceptable ranges, and reported values by laboratories for eight nitrosamines.

Analyte	Assigned Value (ppt) (low to high acceptance range)	Average Reported Value (ppt) (min to max)	Relative Standard Deviation across Laboratories (%)	Percentage of Laboratories Meeting Acceptable Reporting Range (70% ≤ x ≤ 130%
NDEA	25.1 (17.6 to 32.6)	22.8 (18.2 to 29.4)	19%	100%
NDMA	25.0 (17.5 to 32.5)	21.3 (17.9 to 26.9)	15%	100%
NDBA	20.1 (14.1 to 26.1)	19.2 (12.8 to 23.4)	20%	83%
NDPA	20.1 (14.1 to 26.1)	17.9 (13.8 to 21.2)	18%	83%
NMEA	30.2 (21.1 to 39.3)	26.1 (20.7 to 34.2)	19%	83%
NMOR	30.1 (21.1 to 39.1)	24.3 (18.7 to 30.8)	21%	67%
NPIP	35.0 (24.5 to 45.5)	32.8 (24.3 to 38.9)	18%	83%
NPYR	45.2 (31.6 to 58.8)	44.8 (33.5 to 51.3)	19%	100%

Four out of six laboratories met acceptance criteria for PT samples (i.e., 70% to 130% of the true value) on all analytes (Table 7). Laboratory ID #4 failed to meet acceptance criteria for four analytes (NMOR, NDBA, NMEA, and NPIP), and laboratory ID #3 failed to meet acceptance criteria for two analytes (NMOR, NDPA) (Table 7). For the other three analytes (NDEA, NDMA, and NPYR) listed as target analytes,laboratories met acceptance criteria (Table 7), including laboratory IDs #3 and #4. In all instances of laboratories failing to meet acceptance criteria, recovery was lower than expected (i.e., below the minimum threshold of 70%), with the lowest recovery being 62% for NMOR. In three cases, laboratories reported concentrations within a single percentage point of the minimum acceptable criteria (i.e., 69%) (Table A-4).

Suspected reasons for laboratories failing PT samples were reported by individual laboratories. Laboratory 4 reported that their surrogate recovery for the PT extraction

batch (~70%) was lower than over the last ~18 months (~92%). Loss during sample concentration (nitrogen blowdown) was reasonably ruled out, as other batch QCs concentrated that day exhibited no issues. The laboratory could not rule out SPE sorbent issues, as the specific lot of SPE cartridges was only used in the PT batch, however variability between SPE lots in nitrosamine extraction had been reported previously by the laboratory.

Section 4: Conclusions

This inter-laboratory study of EEA-Agilent 521.1 demonstrates relatively consistent performance across laboratories, suggesting that the method may be fit-for-purpose for monitoring nitrosamines in drinking water at or near California's health-protective concentrations of 10 ppt for all analytes. Acceptance criteria (Table 3) for recovery, precision, MDLs, and PT samples were met at a frequency of >80% by all laboratories for all analytes (Tables 4, 5, and 7). In the case of MRLs, five laboratories failed one or more acceptance criteria for MRLs for one or more analytes at the concentrations in which they tested (between 1 and 5 ppt, depending on each laboratory and analyte) (Table 6). MRL verification was heterogenous across analytes, with NDBA, NDMA, and NPYR having few laboratories reporting verified MRLs, and NDPA, NMEA, and NPIP having high verification frequencies (Table 6). The most common cause of failure for MRL verification was laboratories attempting to verify at concentrations lower than 3 times their MDL (Table A-3). Of the laboratories that failed to meet MRL acceptance criteria for any analyte, three re-attempted verification using higher spike LFB concentrations and were generally successful in their attempts (Table A-3).

Despite these imperfections, this inter-laboratory study as well as previous studies (i.e., Eaton *et al.* 2018; Kazez *et al.* 2023) demonstrate that EEA-Agilent 521.1 is sufficiently reliable for the target analytes across multiple laboratories and instrument manufacturers/models and provides equivalent performance to the method it is based upon (i.e., EPA Method 521; Munch and Bassett 2004). Furthermore, this study and Kazez *et al.* (2023) provide several recommendations for laboratories to improve their

performance of EEA-Agilent 521.1 (e.g., slower sample extraction flow rate). Analysis of laboratory performance data from this study supports these recommendations.

The data reported here and previously (Eaton *et al.* 2018; Kazez *et al.* 2023) demonstrate that the alternative analysis method (i.e., GC-MS/MS) in EEA-Agilent 521.1 provides adequate sensitivity for the targeted analytes to meet the DDW's needs (i.e., MRLs <10 ppt based on current notification levels) and is equivalent in sensitivity to EPA Method 521. Although the method may be fit-for-purpose for monitoring nitrosamines at desired concentrations, laboratories are cautioned to exercise great care to ensure accurate and reliable results are achieved.

Section 4.1 – Summary of Method Challenges

Based on the data reported in this study and previously (i.e., Munch and Bassett 2004; Eaton *et al.* 2018; Kazez *et al.* 2023), EEA-Agilent 521.1 demonstrates several challenges across laboratories, which are - background contamination, extraction efficiency, and instrument sensitivity. While such challenges should be taken into consideration by laboratories, none of these difficulties are significant enough to prevent the regular regulatory use of the analytical method for the purposes of monitoring nitrosamines in drinking water at concentrations relevant to protecting public health (i.e., ≥10 ppt).

A significant challenge with the use of EEA-Agilent 521.1 is controlling contamination. Blank contamination was observed for all analytes by at least one laboratory, and nearly all laboratories reported contamination for all analytes (Table 5; Table A-2). Likely sources of contamination were SPE cartridges (both the sorbent and

polypropylene cartridges they are packed in), reagent water that had not been treated with ultra-violet radiation (especially in the case of NDMA), and rubber products used during extraction and/or analysis such as autosamplers (Wilczak *et al.* 2003; Munch and Bassett 2004; Kazez *et al.* 2023). In the LRB data reported by laboratories (Appendix B), the maximum documented contamination for each analyte was < one-third of each laboratory's reported MRL[11] (2 ppt for all analytes; Table 6) with the exception of NDBA, NDEA, NDMA, and NPYR (Table A-5). Due to the high likelihood of contamination of most analytes in laboratory equipment and reagents, laboratories are strongly encouraged to test every new lot of materials before use, and strictly follow the QC requirements detailed in the method.

Lower than expected extraction efficiency was observed across multiple laboratories during this study. Specifically, in all cases of laboratories failing acceptance criteria for PT samples, it was always due to low recovery and never due to higher-than-expected recovery (Table 7). Multiple laboratories participating in this study reported improved (higher) extraction efficiency with the use of manual SPE manifold extraction compared to using automated extraction manifolds (e.g., "Autotrace"), which may be due to the automated methods utilizing faster than ideal elution flow rates (recommended 10 mL/min in Munch and Bassett 2004), or additional undetermined factors. During DWRL's evaluation of the ruggedness of EEA-Agilent 521.1, they

[11]EPA Method 521 and EEA-Agilent 521.1 both require that all analytes occur <one-third of the MRL in all LRBs (Munch and Bassett 2004; Eaton et al. 2018).

determined that multiple additional factors could reduce recovery rates, including the loss of volatile compounds during nitrogen evaporation of SPE eluates, and inadequate warming of primary dilution standards prior to analysis (Kazez *et al.* 2023).

Differences in instrument sensitivity may influence method performance, albeit to a relatively minor extent. Recent advances in MS/MS sensitivity offered by several major instrument manufacturers (i.e., Agilent's 7010 and Thermo Scientific's TSQ9000) have been evaluated with the EEA-Agilent 521.1 method through two comparison studies (Eaton *et al.* 2018; Kazez *et al.* 2023). Improved signal strength of ions (e.g., ~20 to 25x between Agilent's 7010 and 7000), and up to ~50% lower MRLs (e.g., <0.67 ppt for all analytes using Agilent's 7010) were documented with both instruments relative to their less sensitive counterparts (i.e., Agilent's 7000, and Thermo Scientific's TSQ8000 EVO), however the improvement in sensitivity may trigger QC issues with respect to blank contamination that would otherwise be undetectable, reducing the efficacy of this low-level enhancement (Eaton *et al.* 2018; Kazez *et al.* 2023). In summary, while more sensitive instruments can provide lower MRLs using EEA-Agilent 521.1, they are not necessary to achieve comparable performance with the original method (i.e., EPA Method 521) nor are they necessary to achieve MRLs of concentrations below California's health-protective concentrations in drinking water (State Water Resources Control Board 2022).

Section 4.2 – Summary of Recommendations for Laboratories

1. Verify every lot of SPE cartridges used to ensure minimal blank contamination.

2. Use ultra-pure reagent water that has been treated with ultra-violet radiation or purchase ultra-pure reagent water for use.
3. A maximum of 10 mL/minute of sample rate during solid phase extraction is required. Slower flow rates did not negatively impact analyte recovery.
4. Do not concentrate the extract below 0.5 mL to minimize loss of analytes.
5. Ensure all standards and samples are at room temperature prior to spiking samples as well as introduction into the GC-MS/MS.
6. Review suggested transitions as alternatives may be more sensitive depending on instrumentation used.
7. Use the 2016 MDL procedure to account for potential blank background and establish a MRL greater than potential background contamination.

Section 5: References, Acronyms, and Definitions

Section 5.1: References

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Section 5.2: Acronyms and Definitions

ANOVA = Analysis of Variance. This statistical test compares average values between different groups to determine if differences are significant or likely due to chance.

CDPH = California Department of Public Health

DDW = Division of Drinking Water. The division of the State Water Resources Control Board implementing California's Safe Drinking Water Act.

DWRL = Drinking Water and Radiation Laboratory. The chemistry unit within this laboratory at the CDPH performed method validation and participated in the interlaboratory comparison exercise for EEA-Agilent 521.1.

EEA = Eurofins Eaton Analytical. A commercial environmental monitoring laboratory based in Monrovia, California.

EEA-Agilent 521.1 = Eurofins Eaton Analytical-Agilent Method 521.1 Revision 1.0

GC = Gas Chromatography. A common type of chromatography used in analytical chemistry for separating and analyzing compounds that can be vaporized without decomposition.

IDOC = Initial Demonstration of Capability

IT = Ion Trap. A combination of electric and/or magnetic fields used to capture charged particles that is often used for mass spectrometry.

LCMRL = Lowest Concentration Minimum Reporting Limit. Defined as the lowest true concentration for which future recovery is predicted to fall, with high confidence (99%), between 50 and 150% recovery.

LFB = Laboratory Fortified Blank Sample. A reagent-grade water sample spiked with a known quantity of an analyte.

LRB = Laboratory Reagent Blank. An aliquot of reagent water that is treated exactly as a sample, including exposure to all glassware, equipment, solvents, reagents, internal standards, surrogates, and sample preservatives that are used with other samples, and extracted as if it were a sample (also commonly referred to as a ‘method blank’). The LRB is used to determine if method analytes or other interferences are present in the laboratory environment, the reagents, or the apparatus.

MRL = Minimum Reporting Level. An MRL is defined as the minimum concentration that can be reported as a quantitated value for a target analyte in a sample following analysis, which can be no lower than the concentration of the lowest calibration standard for that analyte and can only be used if acceptable quality control criteria for the analyte at that concentration is met (Munch and Basset 2004).

MS = Mass Spectrometry. An analytical technique used to measure the mass-to-charge ratio of ions.

MS/MS = Tandem Mass Spectrometry. A technique in instrumental analysis where two or more mass analyzers are coupled together using an additional reaction step.

NDEA = N-Nitrosodiethylamine

NDMA = N-Nitrosodimethylamine

NDBA = N-Nitrosodi-n-butylamine

NDPA = N-Nitrosodi-n-propylamine

NMEA = N-Nitrosomethylamine

NMOR = N-Nitrosomorpholine

NPIP = N-Nitrosopiperidine

NPYR = N-Nitrosopyrrolidine

PIR = Prediction Interval of Results. A statistical method used to test the probability of including a future observation.

PT = Proficiency Testing. A reagent grade water sample spiked and verified with a known concentration by a third-party. The sample is provided to laboratories who are blind to the concentration to determine their proficiency.

ppt = Parts per Trillion. A unit of concentration equivalent to nanograms per liter in water.

QC = Quality Control

SPE = Solid Phase Extraction. A type of chromatography used to concentrate samples.

State Water Board = State Water Resources Control Board

U.S. EPA = United States Environmental Protection Agency

Appendix A.

Table A-1. Initial demonstration of capabilities (IDOC) sample recovery concentrations of laboratory fortified blanks by laboratories for eight nitrosamines.

Lab ID Number	Analyte	Spike Quantity (ppt)	Average Recovery (ppt)	Average % Recovery	Standard Deviation (ppt)	Relative Standard Deviation (%)
1	NDBA	10	8.6	86.0%	0.9	10.3%
2	NDBA	10	8.0	80.3%	1.0	12.8%
3	NDBA	10	7.1	71.3%	1.0	14.1%
4	NDBA	10	8.3	82.6%	1.0	11.9%
5	NDBA	10	8.3	82.7%	1.1	13.5%
6	NDBA	10	8.4	83.9%	1.0	11.6%
1	NDEA	10	10.4	104.2%	1.1	10.5%
2	NDEA	10	11.0	110.0%	1.0	8.6%
3	NDEA	5	4.4	88.1%	0.1	1.7%
4	NDEA	10	10.5	104.7%	0.5	4.4%
5	NDEA	10	9.1	90.6%	0.2	2.4%
6	NDEA	10	8.6	85.9%	0.1	0.9%
1	NDMA	10	9.5	94.9%	0.5	4.8%
2	NDMA	10	9.2	92.1%	0.1	1.1%
3	NDMA	10	9.7	96.7%	0.2	1.6%
4	NDMA	10	10.2	102.1%	0.2	2.1%
5	NDMA	10	10.1	100.8%	0.2	1.8%
6	NDMA	50	42.5	85.1%	1.6	3.8%
1	NDPA	5	4.6	92.4%	0.2	4.3%
2	NDPA	5	4.5	89.3%	0.1	3.1%
3	NDPA	5	4.6	92.3%	0.2	4.0%
4	NDPA	5	4.6	91.0%	0.2	4.9%
5	NDPA	5	6.3	125.3%	0.1	0.9%
6	NDPA	5	4.8	96.5%	0.1	2.4%
1	NMEA	5	4.4	88.7%	0.3	6.5%

Lab ID Number	Analyte	Spike Quantity (ppt)	Average Recovery (ppt)	Average % Recovery	Standard Deviation (ppt)	Relative Standard Deviation (%)
2	NMEA	5	4.8	95.9%	0.3	6.2%
3	NMEA	10	10.8	108.3%	0.2	2.0%
4	NMEA	10	9.1	90.9%	0.1	1.3%
5	NMEA	10	8.6	86.4%	0.2	2.8%
6	NMEA	10	9.5	95.1%	0.3	2.8%
1	NMOR	10	8.7	87.4%	0.3	3.0%
2	NMOR	10	9.1	91.2%	0.2	2.5%
3	NMOR	10	9.9	98.6%	0.2	1.9%
4	NMOR	10	9.6	95.7%	0.5	5.3%
5	NMOR	40	53.8	134.6%	2.4	4.4%
6	NMOR	40	41.1	102.7%	2.6	6.3%
1	NPIP	40	45.0	112.4%	2.2	4.9%
2	NPIP	40	47.1	117.8%	2.6	5.6%
3	NPIP	40	42.6	106.6%	2.4	5.6%
4	NPIP	40	45.9	114.8%	2.2	4.8%
5	NPIP	40	49.3	123.2%	2.3	4.7%
6	NPIP	40	47.1	117.6%	2.5	5.3%
1	NPYR	40	46.2	115.5%	3.2	6.9%
2	NPYR	10	17.8	89.0%	1.3	7.4%
3	NPYR	10	11.4	114.0%	0.9	8.3%
4	NPYR	10	8.8	87.7%	0.5	5.8%
5	NPYR	10	9.2	92.4%	0.7	7.6%
6	NPYR	10	9.2	92.3%	0.5	5.6%

Table A-2. Method Detection Limit (MDL) concentrations by laboratories for eight nitrosamines.

Lab ID Number	Analyte	Final MDL (ppt)	MDL Based on Blanks or Spiked Samples?	MDL Spike (ppt)	MDL Based on Blanks (ppt)[a]	MDL Based on Spiked Samples (ppt)
1	NDBA	0.38	Sample	2.00	ND	0.38
2	NDBA	0.74	Sample	2.00	0.44	0.74
3	NDBA	0.68	Sample	2.00	0.68	0.68
4	NDBA	0.61	Sample	2.00	0.22	0.61
5	NDBA	0.44	Blank	2.00	0.44	0.32
6	NDBA	3.47	Blank	2.00	3.47	0.78
1	NDEA	0.22	Blank	2.00	0.34	0.22
2	NDEA	0.13	Sample	2.00	0.13	0.13
3	NDEA	0.56	Blank	2.00	0.56	0.56
4	NDEA	1.11	Sample	2.00	0.67	1.11
5	NDEA	0.23	Sample	2.00	0.13	0.23
6	NDEA	1.55	Blank	2.00	1.55	0.26
1	NDMA	0.18	Blank	2.00	0.75	0.18
2	NDMA	0.30	Sample	2.00	0.40	0.30
3	NDMA	0.99	Blank	2.00	0.99	0.99
4	NDMA	0.64	Sample	2.00	0.30	0.64
5	NDMA	0.40	Blank	2.00	0.40	0.32
6	NDMA	1.26	Blank	2.00	1.26	0.64
1	NDPA	0.37	Blank	2.00	0.39	0.37
2	NDPA	0.31	Sample	2.00	0.34	0.31
3	NDPA	0.90	Sample	2.00	0.07	0.90
4	NDPA	0.35	Sample	2.00	ND	0.35
5	NDPA	0.34	Blank	2.00	0.34	0.26
6	NDPA	0.42	Blank	2.00	0.42	0.16
1	NMEA	0.19	Blank	2.00	0.30	0.19
2	NMEA	0.24	Sample	2.00	ND	0.24
3	NMEA	0.45	Sample	2.00	0.08	0.45
4	NMEA	0.38	Sample	2.00	ND	0.38

Lab ID Number	Analyte	Final MDL (ppt)	MDL Based on Blanks or Spiked Samples?	MDL Spike (ppt)	MDL Based on Blanks (ppt)[a]	MDL Based on Spiked Samples (ppt)
5	NMEA	0.29	Sample	2.00	ND	0.29
6	NMEA	0.17	Sample	2.00	0.04	0.17
1	NMOR	0.30	Blank	2.00	0.41	0.30
2	NMOR	0.31	Sample	2.00	0.44	0.31
3	NMOR	0.25	Sample	2.00	0.22	0.25
4	NMOR	0.57	Sample	2.00	0.07	0.57
5	NMOR	0.44	Blank	2.00	0.44	0.18
6	NMOR	1.05	Sample	2.00	0.64	1.05
1	NPIP	0.27	Sample	2.00	ND	0.27
2	NPIP	0.31	Sample	2.00	ND	0.31
3	NPIP	0.62	Blank	2.00	0.62	0.62
4	NPIP	0.39	Sample	2.00	ND	0.39
5	NPIP	0.16	Sample	2.00	ND	0.16
6	NPIP	0.37	Sample	2.00	0.25	0.37
1	NPYR	1.25	Sample	2.00	0.14	1.25
2	NPYR	0.50	Sample	2.00	1.13	0.50
3	NPYR	1.20	Sample	2.00	1.19	1.20
4	NPYR	0.44	Sample	2.00	ND	0.44
5	NPYR	1.13	Blank	2.00	1.13	0.25
6	NPYR	0.68	Blank	2.00	0.68	0.57

[a] "ND" = non-detect in blanks. Accordingly, an MDL based on blanks could not be calculated according to U.S. EPA (2016).
[b]This laboratory did not provide raw blank occurrence data.

Table A-3. Minimum Reporting Level (MRL) concentrations by laboratories for eight nitrosamines.

Lab ID Number	Analyte	Spike Concentration (ppt)	Mean Recovery (%)	Lower PIR (%)	Upper PIR (%)	MRL (ppt)	QC Flags[a]
1	NDBA	2	106%	82%	131%	2	
2	NDBA	5	103%	81%	126%	5	
3	NDBA	2	110%	74%	145%	2	*m*
4	NDBA	2	89%	49%	129%	>2[b]	*l*
5	NDBA	1	136%	128%	144%	1	*m*
6	NDBA	4	117%	39%	194%	>4[b]	*l u*
1	NDEA	2	84%	70%	98%	2	
2	NDEA	2	95%	84%	107%	2	
3	NDEA	1	115%	100%	130%	1	*m*
4	NDEA	2	101%	27%	174%	>2[b]	*l u*
5	NDEA	1	106%	87%	125%	1	
6	NDEA	2	92%	76%	109%	2	*m*
1	NDMA	2	79%	67%	90%	2	
2	NDMA	2	79%	70%	87%	2	
3	NDMA	2	97%	90%	103%	2	*m*
4	NDMA	2	85%	43%	127%	>2[b]	*l*
5	NDMA	1	122%	104%	141%	1	*m*
6	NDMA	2	90%	50%	130%	2	*m*
1	NDPA	2	76%	52%	99%	2	
2	NDPA	2	119%	100%	138%	2	
3	NDPA	5	91%	66%	116%	5	
4	NDPA	2	93%	69%	117%	2	
5	NDPA	1	101%	77%	124%	1	*m*
6	NDPA	2	87%	76%	97%	2	
1	NMEA	2	88%	76%	100%	2	
2	NMEA	2	89%	79%	99%	2	
3	NMEA	2	89%	61%	117%	2	
4	NMEA	2	80%	55%	106%	2	

Lab ID Number	Analyte	Spike Concentration (ppt)	Mean Recovery (%)	Lower PIR (%)	Upper PIR (%)	MRL (ppt)	QC Flags[a]
5	NMEA	1	103%	87%	119%	1	
6	NMEA	2	80%	69%	90%	2	
1	NMOR	2	77%	58%	97%	2	
2	NMOR	2	104%	88%	121%	2	
3	NMOR	2	120%	104%	136%	2	
4	NMOR	2	87%	49%	124%	>2[b]	*l*
5	NMOR	1	112%	87%	137%	1	*m*
6	NMOR	4	99%	56%	143%	4	
1	NPIP	2	77%	61%	94%	2	
2	NPIP	2	124%	113%	134%	2	
3	NPIP	1	98%	75%	122%	1	*m*
4	NPIP	2	91%	65%	116%	2	
5	NPIP	1	102%	85%	118%	1	
6	NPIP	2	92%	69%	115%	2	
1	NPYR	2	169%	91%	248%	>2	*u m*
2	NPYR	2	124%	111%	138%	2	
3	NPYR	5	97%	77%	116%	5	
4	NPYR	2	85%	55%	115%	2	
5	NPYR	1	95%	76%	113%	1	*m*
6	NPYR	2	106%	70%	141%	2	*m*

[a]MRL fails verification if any of the following are true: lower PIR falls below 50% [*l*] ; upper PIR is greater than 150% [*u*]; average recovery is outside the defined PIR range [*a*]; MRL is less than 3 times the laboratories' MDL [*m*].

[b]Due to one or more of the PIR falling the acceptable ranges for this analyte, the laboratory failed to verify the MRL at this level and did not attempt to verify at a higher concentration. Accordingly, the MRL is reported as being greater than the listed concentration.

Table A-4. Proficiency testing (PT) sample concentrations, acceptable ranges, and reported values by laboratories for eight nitrosamines.

Lab ID Number	Analyte	Assigned Value (ng/L)	Low Acceptance Value (ng/L)	High Acceptance Value (ng/L)	Reported Value (ng/L)	Recovery (%)	Performance Evaluation[a]
1	NDBA	20.1	14.1	26.1	21.2	105.5%	Accept
2	NDBA	20.1	14.1	26.1	21.3	106.0%	Accept
3	NDBA	20.1	14.1	26.1	16.6	82.6%	Accept
4	NDBA	20.1	14.1	26.1	12.8	63.7%	Not Accept
5	NDBA	20.1	14.1	26.1	19.6	97.5%	Accept
6	NDBA	20.1	14.1	26.1	23.4	116.4%	Accept
1	NDEA	25.1	17.6	32.6	29.4	117.1%	Accept
2	NDEA	25.1	17.6	32.6	23.2	92.4%	Accept
3	NDEA	25.1	17.6	32.6	19.2	76.5%	Accept
4	NDEA	25.1	17.6	32.6	18.2	72.5%	Accept
5	NDEA	25.1	17.6	32.6	20.7	82.5%	Accept
6	NDEA	25.1	17.6	32.6	25.98	103.5%	Accept
1	NDMA	25	17.5	32.5	26.9	107.6%	Accept
2	NDMA	25	17.5	32.5	21.5	86.0%	Accept
3	NDMA	25	17.5	32.5	19.9	79.6%	Accept
4	NDMA	25	17.5	32.5	17.9	71.6%	Accept
5	NDMA	25	17.5	32.5	19.4	77.6%	Accept
6	NDMA	25	17.5	32.5	21.93	87.7%	Accept
1	NDPA	20.1	14.1	26.1	20.7	103.0%	Accept
2	NDPA	20.1	14.1	26.1	19.1	95.0%	Accept
3	NDPA	20.1	14.1	26.1	13.8	68.7%	Not Accept
4	NDPA	20.1	14.1	26.1	14.4	71.6%	Accept
5	NDPA	20.1	14.1	26.1	18	89.6%	Accept
6	NDPA	20.1	14.1	26.1	21.23	105.6%	Accept
1	NMEA	30.2	21.1	39.3	34.2	113.2%	Accept
2	NMEA	30.2	21.1	39.3	26.3	87.1%	Accept

Lab ID Number	Analyte	Assigned Value (ng/L)	Low Acceptance Value (ng/L)	High Acceptance Value (ng/L)	Reported Value (ng/L)	Recovery (%)	Performance Evaluation[a]
3	NMEA	30.2	21.1	39.3	22.8	75.5%	Accept
4	NMEA	30.2	21.1	39.3	20.7	68.5%	Not Accept
5	NMEA	30.2	21.1	39.3	23.6	78.1%	Accept
6	NMEA	30.2	21.1	39.3	29.06	96.2%	Accept
1	NMOR	30.1	21.1	39.1	30.8	102.3%	Accept
2	NMOR	30.1	21.1	39.1	25	83.1%	Accept
3	NMOR	30.1	21.1	39.1	20.1	66.8%	Not Accept
4	NMOR	30.1	21.1	39.1	18.7	62.1%	Not Accept
5	NMOR	30.1	21.1	39.1	21.6	71.8%	Accept
6	NMOR	30.1	21.1	39.1	29.83	99.1%	Accept
1	NPIP	35	24.5	45.5	38.9	111.1%	Accept
2	NPIP	35	24.5	45.5	34.8	99.4%	Accept
3	NPIP	35	24.5	45.5	26.7	76.3%	Accept
4	NPIP	35	24.5	45.5	24.3	69.4%	Not Accept
5	NPIP	35	24.5	45.5	34.8	99.4%	Accept
6	NPIP	35	24.5	45.5	37.29	106.5%	Accept
1	NPYR	45.2	31.6	58.8	51.3	113.5%	Accept
2	NPYR	45.2	31.6	58.8	48.6	107.5%	Accept
3	NPYR	45.2	31.6	58.8	34	75.2%	Accept
4	NPYR	45.2	31.6	58.8	33.5	74.1%	Accept
5	NPYR	45.2	31.6	58.8	51.3	113.5%	Accept
6	NPYR	45.2	31.6	58.8	49.86	110.3%	Accept

[a]Samples falling between the required reporting range of the true value (i.e., ≥70% and ≤130%) are deemed acceptable, while those falling outside that range are deemed unacceptable.

Table A-5. Concentrations of nitrosamines in Laboratory Reagent Blanks (LRBs) reported by laboratories.

Lab ID Number	Analyte	Average Concentration in LRBs (ppt)	Stdev of LRBs (ppt)	N[a]	Maximum Concentration Reported in LRBs (ppt)	MDL Based on LRBs
1	NDBA	ND	ND	0	ND	ND
2	NDBA	0.45	0.04	7	0.51	0.56
3	NDBA	0.69	0.28	10	NR	1.57
4	NDBA	0.14	0.03	11	0.19	0.22
5	NDBA	0.11	0.1	7	0.32	0.45
6	NDBA	1.05	0.77	7	2.5	3.47
1	NDEA	0.34	NA	1	0.34	0.34
2	NDEA	0.09	0.15	2	0.33	0.38
3	NDEA	0.04	0.02	10	NR	0.1
4	NDEA	0.32	0.13	11	0.51	0.67
5	NDEA	0.05	0.06	4	0.13	0.13
6	NDEA	0.33	0.39	7	1.16	1.55
1	NDMA	0.25	0.16	9	0.57	0.75
2	NDMA	ND	ND	0	ND	ND
3	NDMA	0.27	0.07	10	NR	0.49
4	NDMA	0.17	0.05	11	0.28	0.3
5	NDMA	0.14	0.08	9	0.28	0.4
6	NDMA	0.44	0.26	7	1.01	1.26
1	NDPA	0.39	NA	1	0.39	0.39
2	NDPA	ND	ND	0	ND	ND
3	NDPA	0.04	0.03	10	NR	0.13
4	NDPA	ND	ND	0	ND	ND
5	NDPA	0.1	0.08	9	0.22	0.34
6	NDPA	0.15	0.24	3	0.42	0.42
1	NMEA	0.2	0.03	3	0.26	0.3
2	NMEA	ND	ND	0	ND	ND
3	NMEA	0.01	0.01	10	NR	0.04
4	NMEA	ND	ND	0	ND	ND

Lab ID Number	Analyte	Average Concentration in LRBs (ppt)	Stdev of LRBs (ppt)	N[a]	Maximum Concentration Reported in LRBs (ppt)	MDL Based on LRBs
5	NMEA	ND	ND	0	ND	ND
6	NMEA	0.02	0.01	6	0.04	0.04
1	NMOR	0.41	NA	1	0.41	0.41
2	NMOR	ND	ND	0	ND	ND
3	NMOR	0.05	0.05	10	NR	0.21
4	NMOR	0.03	0.02	10	0.07	0.07
5	NMOR	0.16	0.09	9	0.3	0.44
6	NMOR	0.24	0.13	7	0.42	0.64
1	NPIP	ND	ND	0	ND	ND
2	NPIP	ND	ND	0	ND	ND
3	NPIP	0.1	0.19	10	NR	0.7
4	NPIP	ND	ND	0	ND	ND
5	NPIP	ND	ND	0	ND	ND
6	NPIP	0.25	NA	1	0.25	0.25
1	NPYR	0.14	NA	1	0.14	0.14
2	NPYR	0.35	0.15	7	0.46	0.8
3	NPYR	0.23	0.18	10	NR	0.8
4	NPYR	ND	ND	0	ND	ND
5	NPYR	0.46	0.21	9	0.75	1.13
6	NPYR	0.29	0.12	7	0.41	0.68

[A]Samples below detection limits are excluded from average and standard deviation calculations to avoid skewing data (i.e. data were not converted to zeros or otherwise). In all cases, laboratories reported between 7 and 11 blank samples. ND = non-detect; NA = not applicable; NR = raw data not reported (only summary data were reported).

Table A-6. One-way Analysis of Variance (ANOVA) results for laboratory-fortified blank recovery data by analyte.

Term	Degrees of Freedom	Sum of Squares	Mean Sum of Squares	F Statistic	*p* Value
Analyte	7	0.63	0.09	5.30	1.48E-05
Residuals	192	3.25	0.02	NA	NA

Table A-7. Tukey's Honest Significant Difference *post-hoc* tests for laboratory-fortified blank recovery data by analyte across laboratories.

	Difference	Lower 95% Confidence Interval of Difference	Upper 95% Confidence Interval of Difference	Adjusted *p* Value
NDEA-NDBA	-0.07	-0.19	0.04	4.95E-01
NDMA-NDBA	-0.09	-0.20	0.03	2.82E-01
NDPA-NDBA	-0.07	-0.18	0.05	6.18E-01
NMEA-NDBA	-0.07	-0.18	0.05	6.21E-01
NMOR-NDBA	0.07	-0.04	0.19	4.82E-01
NPIP-NDBA	0.01	-0.10	0.13	1.00E+00
NPYR-NDBA	0.04	-0.07	0.15	9.69E-01
NDMA-NDEA	-0.01	-0.13	0.10	1.00E+00
NDPA-NDEA	0.01	-0.11	0.12	1.00E+00
NMEA-NDEA	0.01	-0.11	0.12	1.00E+00
NMOR-NDEA	0.15	0.03	0.26	2.37E-03
NPIP-NDEA	0.09	-0.03	0.20	2.64E-01
NPYR-NDEA	0.11	0.00	0.22	5.74E-02
NDPA-NDMA	0.02	-0.09	0.13	1.00E+00
NMEA-NDMA	0.02	-0.09	0.13	9.99E-01
NMOR-NDMA	0.16	0.05	0.27	6.13E-04
NPIP-NDMA	0.10	-0.01	0.21	1.25E-01
NPYR-NDMA	0.12	0.01	0.24	2.06E-02
NMEA-NDPA	0.00	-0.11	0.11	1.00E+00
NMOR-NDPA	0.14	0.03	0.25	4.60E-03
NPIP-NDPA	0.08	-0.03	0.19	3.65E-01

	Difference	Lower 95% Confidence Interval of Difference	Upper 95% Confidence Interval of Difference	Adjusted *p* Value
NPYR-NDPA	0.10	-0.01	0.22	9.26E-02
NMOR-NMEA	0.14	0.03	0.25	4.66E-03
NPIP-NMEA	0.08	-0.03	0.19	3.67E-01
NPYR-NMEA	0.10	-0.01	0.22	9.34E-02
NPIP-NMOR	-0.06	-0.17	0.05	7.38E-01
NPYR-NMOR	-0.04	-0.15	0.08	9.78E-01
NPYR-NPIP	0.02	-0.09	0.14	9.98E-01

Table A-8. Two-way Analysis of Variance (ANOVA) results for laboratory-fortified blank recovery data.

Term	Degrees of Freedom	Sum of Squares	Mean Sum of Squares	F Statistic	*p* Value
LabID	4	1.34	0.34	76.08	5.16E-36
Analyte	7	0.63	0.09	20.35	2.15E-19
LabID:Analyte	28	1.20	0.04	9.74	1.89E-22
Residuals	160	0.70	0.00	NA	NA

Table A-9. Tukey's Honest Significant Difference *post-hoc* tests for laboratory-fortified blank recovery data across all analytes by laboratory.

	Difference	Lower 95% Confidence Interval of Difference	Upper 95% Confidence Interval of Difference	Adjusted *p* Value
#2-#1	0.08	0.04	0.13	1.41E-06
#3-#1	0.09	0.05	0.12	2.70E-09
#5-#1	0.26	0.22	0.30	6.11E-15
#6-#1	0.08	0.04	0.12	7.93E-06
#3-#2	0.00	-0.04	0.05	9.98E-01
#5-#2	0.18	0.13	0.22	4.05E-14
#6-#2	-0.01	-0.05	0.04	9.97E-01
#5-#3	0.17	0.13	0.21	1.30E-14
#6-#3	-0.01	-0.05	0.03	9.58E-01
#6-#5	-0.18	-0.23	-0.14	3.08E-14

Table A-10. Two-sample *t*-test comparison of laboratory-fortified blank recovery data between laboratory ID#6 and all laboratories.

Analyte	*p* Value	Lab ID#6 Mean	Lower 95% Confidence Interval of Laboratory ID#6	Upper 95% Confidence Interval of Laboratory ID#6	Mean Value of All Laboratories	Lower 95% Confidence Interval of All Laboratories	Upper 95% Confidence Interval of All Laboratories
NDBA	* 0.036	1.14	0.99	1.29	0.99	0.94	1.04
NDEA	* 0.037	0.88	0.80	0.96	0.92	0.87	0.96
NDMA	0.293	0.92	0.81	1.04	0.90	0.84	0.97
NDPA	0.171	0.92	0.84	1.00	0.92	0.88	0.96
NMEA	0.129	0.90	0.79	1.01	0.92	0.87	0.97
NMOR	0.388	0.99	0.91	1.07	1.06	0.99	1.14
NPIP	0.746	0.96	0.87	1.05	1.00	0.96	1.05
NPYR	* 0.046	0.92	0.87	0.97	1.03	0.98	1.07

Appendix B.

Excel (.xlsx) file containing raw data used to calculate MDLs, MRLs, blank contamination, and PT acceptance for each analyte by laboratory. Laboratory identities were intentionally anonymized.

Code used for statistical analysis (e.g., ANOVA, t-tests) are available at https://github.com/CAWaterBoardDataCenter/NitrosamineMethodEvaluation.git