

Analysis of 1,4-Dioxane in Consumer Products by Headspace-Gas Chromatography/Mass Spectrometry

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Abstract

1,4-Dioxane is an industrial chemical contaminate that may be found at trace levels in consumer products.¹⁻⁶ Government jurisdictions are beginning to regulate the amount of 1,4-dioxane allowed in consumer products. The allowable concentrations are expected to vary from state to state and country to country. Meanwhile, it has already been banned and deemed unsafe in cosmetics in Canada.¹⁻⁶ There have been several methods developed to test for 1,4-dioxane, but none of these methods are adequate to detect 1,4-dioxane in consumer products with complex mixtures and solutions.^{7,8}

The current study shows methodology for low level detection of 1,4-dioxane in consumer products including cosmetics, liquid soaps, shampoos, and cleaning products. The extraction and analysis were initially performed using an Agilent 7694E headspace sampler attached to an Agilent 7890 GC with an Agilent 5977A MSD using Agilent MassHunter software. Then, the analysis was reproduced (with minor method modifications) on a newer system consisting of an Agilent 7697A headspace sampler attached to an Agilent Intuvo 9000 GC with a 5977B MSD using MassHunter software.

The quantitation of the target analyte 1,4-dioxane was performed using isotope dilution by adding deuterated 1,4-dioxane- d_8 as an internal standard to all samples, controls, and calibrators. This method has a linear quantitation range from 10 ng/g to 20,000 ng/g (ppb). Sample size for liquid detergents was typically 2 mL and for solids was in the range of 0.1 to 2.0 g, depending on the matrix. The method detection limit was determined to be 7.1 ppb on the older system and 2.3 ppb on the newer system. Alternate qualifiers were needed for confirmation in matrix due to interferences at low levels.

Introduction

1,4-Dioxane is a heterocyclic organic compound, classified as an ether. 1,4-Dioxane (C₄H₈O₂) is a colorless liquid or solid at cool temperatures (below 53 °F) with a sweet odor like that of diethyl ether. 1,4-Dioxane is highly water-soluble, making it mobile in the environment, and it does not readily biodegrade.

Due to the myriad of problems attributed to 1,4-dioxane in the environment, it has been identified as a chemical warranting further research toward its removal from consumer products (cosmetic, personal care, and cleaning products) by California DTSC (Department of Toxic Substances Control).⁹ In New York state, there is a law in place that restricts the amount of 1,4-dioxane allowed in personal care, cleaning, and cosmetic products. The state of New York has also adopted a first-in-the-nation drinking water standard for 1,4-dioxane and set the maximum contaminant level of 1 part per billion (ppb).¹¹

1,4-Dioxane is a trace by-product formed during the synthesis of ethoxylated ingredients used in finished consumer products (cosmetic, personal care, and cleaning products). 1,4-Dioxane can form inadvertently by undesirable side reactions during ethoxylation. It can form when two consecutive ethylene oxide units are cleaved from a chain of ethylene oxides and form a ring of 1,4-dioxane. Or, it can form when the ethylene oxide ring opens to form ethylene glycol, and two ethylene glycols dimerize to form 1,4-dioxane. Both reaction pathways are shown in Figure 1. These ingredients include certain detergents, foaming agents, emulsifiers, and solvents identifiable by the prefix, suffix, word, or syllables: PEG, polyethylene, polyethylene glycol, polyoxyethylene, -eth- (e.g. laureth sulfate), or -oxynol-. The compound

1,4-dioxane is not used as an ingredient in consumer products but may be present as a trace contaminant in some.

The New York State Environmental Conservation Law has been amended to include limits on the maximum allowable concentration of 1,4-dioxane in consumer products. The limit for household cleaning and personal care products is set to 2 ppm effective December 31, 2022 and 1 ppm effective December 31, 2023. The maximum allowable concentration of 1,4-dioxane in cosmetic products will be 10 ppm effective December 31, 2022.¹⁰

There have been several methods developed to test for 1,4-dioxane, primarily for soil, water, air, cleaning products, and cosmetics. Without modification, none of the standard methods can quantify 1,4-dioxane at the single-digit parts per million (ppm) level. Consumer products are challenging to analyze due to the complex matrices associated with viscous and foaming products like gels and detergents. Due to these method demands, there is a need for developing a testing method using headspace GC and single ion monitoring (SIM) technology.^{7-8,12,13}

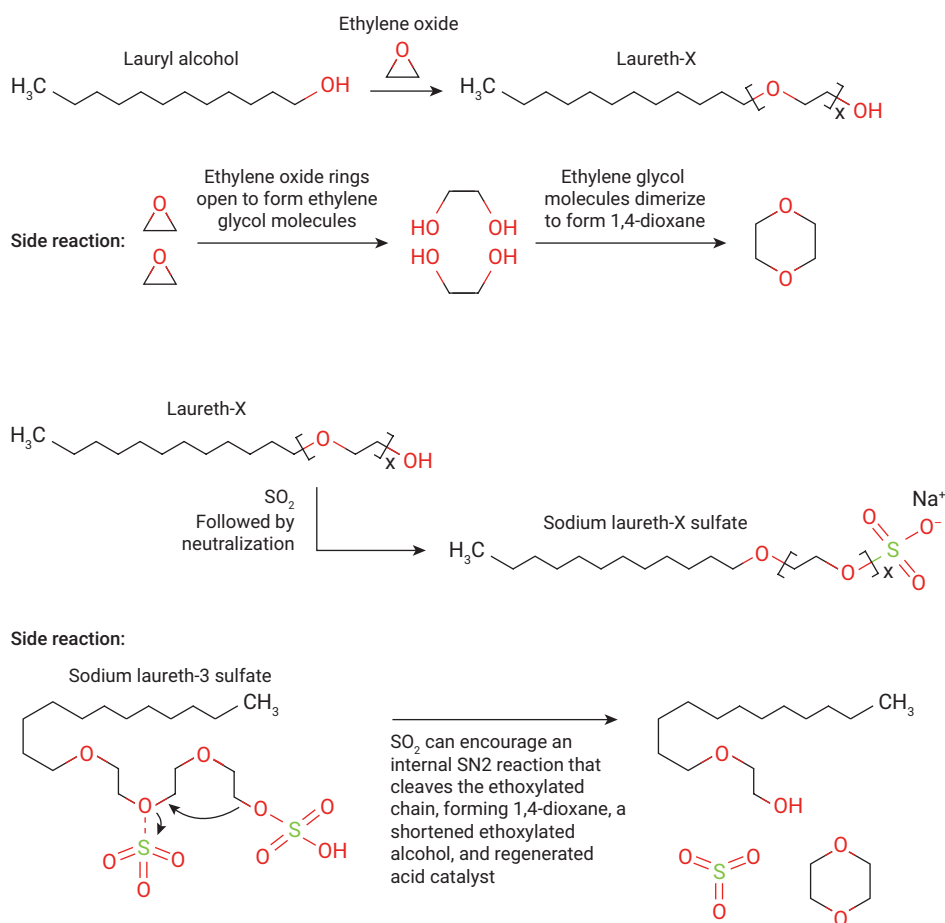


Figure 1. Two reaction pathways for synthesizing 1,4-dioxane (Environment Canada and Health Canada 2010).

Headspace has been used in several applications for analyzing volatile organic compounds with the aid of gas chromatography. In headspace analysis, the ambient volume above a sample matrix is sampled where the volatile compounds exist in gaseous form at predictable levels. In this case, the sample is typically heated to volatilize the compounds of interest into the headspace and allowed to reach equilibrium, which leads to accurate and reproducible analytical results when sampled. A major advantage of this approach is that it enables the analysis of only the volatile subset of compounds present in a sample. The complex matrix that may otherwise interfere in the case of direct injection of the sample is avoided.

Extraction techniques such as liquid-liquid extraction or solid-phase extraction may yield cleaner extracts for direct injection. However, these techniques are time and solvent-consuming and thus are unattractive compared to headspace.

The consumer products analyzed using the headspace method are highly complex and contain a myriad of volatile and semivolatile compounds that are co-extracted with the 1,4-dioxane. To compensate for these matrix effects, the isotope dilution quantitation technique is used.¹² Isotope dilution involves the addition of a known and constant amount of deuterated 1,4-dioxane (1,4-dioxane-d₈) as an internal standard to each sample, quality control, calibrator, and calibration verification. The deuterated analog of 1,4-dioxane behaves the same as 1,4-dioxane, both physically and chemically, allowing for the reproducible and accurate quantitation of 1,4-dioxane in complex matrices.

Experimental

Acquisition method

All analyses were performed on two systems. The first system was an Agilent 7890 GC equipped with an Agilent 7694E headspace sampler attached to an Agilent 5977A MSD. The second system was an Agilent Intuvo 9000 GC system equipped with an Agilent 7697A headspace sampler attached to an Agilent 5977B MSD. SIM was used to enhance sensitivity and selectivity.

After initial full autotune, a passing check tune must be performed before the start of a batch or every 24 hours. If the check tune does not pass, corrective action must be performed, and then a full autotune must be run.

GC method parameters are shown in Table 1. Headspace method details are in Table 2. MSD parameters are listed in Tables 3 and 4.

Supplies

- Volumetric flasks, Class A, 1 mL and 10 mL with ground glass stoppers
- Glass Pasteur pipets
- Volumetric air-displacement pipettes 50 to 1,000 µL with disposable tips
- 20 mL glass headspace vials with magnetic caps/PTFE-lined septa
- 12 mL screw cap glass vials
- Column dimensions: 30 m × 0.25 mm, 0.25 µm
- Ultrahigh purity helium
- Ultrahigh purity nitrogen
- Methanol: pesticide residue grade, purge and trap grade

Standard preparation

Make sure that clean glassware is used in the preparation of standards and samples. Rinse all glassware with Milli-Q water prior to use. Use certified vials to transfer neat standards if available.

Table 1. GC method parameters used for the analysis of 1,4-dioxane.

	Agilent 7890 GC System	Agilent Intuvo 9000 GC System
Inlet	60 °C	160 °C
Hold	0.1 min	
Ramp 1	500 °C/min	
Final Temperature	250 °C	
Septa Purge	3 mL/min	3 mL/min
Mode	Split 1:1	Split 10:1
Liner	Agilent inlet liner, Ultra Inert, splitless, single taper, glass wool (p/n 5190-3171)	Agilent inlet liner, Ultra Inert, splitless, straight 2 mm (p/n 5190-6068)
Oven	40 °C	40 °C
Hold	0 min	0.5 min
Ramp 1	10 °C /min	10 °C/min
Final Temperature	140 °C	140 °C
Hold	0 min	0 min
Column Flow	2 mL/min	2 mL/min
Column	GC column, like the DB-5, 30 m × 0.25 mm, 0.25 µm	Agilent J&W DB-5ms Ultra Inert Intuvo GC column module, 30 m × 0.25 mm, 0.25 µm (p/n 122-5532UI-INT)

Internal standard (1,4-dioxane-d₈)

1. Transfer an aliquot (~1 mL) of the dioxane-d₈ neat standard into a clean vial. Add 25 µL of this solution to a 25 mL volumetric flask, fill to mark with Milli-Q water, and shake well. Label this solution as 1,000 ppm dioxane-d₈ internal standard.
2. Next, transfer 25 µL of the 1,000 ppm dioxane-d₈ standard to a 25 mL volumetric flask, fill to mark with Milli-Q water, and shake well. Label this solution as 1 ppm dioxane-d₈ internal standard.

Native standard (1,4-dioxane)

1. Transfer an aliquot (~1 mL) of 1,4-dioxane neat standard into a clean vial. Add 25 µL of this solution to a 25 mL volumetric flask, fill to mark with Milli-Q water, and shake well. Label this solution as 1,000 ppm dioxane standard.
2. If needed, transfer 1 mL of the 1,000 ppm dioxane standard to a 50 mL volumetric flask, fill to mark with Milli-Q water, and shake well. Label this solution as 20 ppm dioxane standard (calibration standard 0).
3. Next, transfer 250 µL of the 1,000 ppm dioxane standard to a 25 mL volumetric flask, fill to mark with Milli-Q water, and shake well. Label this solution as 10 ppm dioxane standard (calibration standard 1).

Perform a serial dilution as described in the following protocol to make the remaining calibration standards for a seven-point calibration curve:

1. Transfer 5 mL of calibration standard 1 to a vial, add 10 mL of Milli-Q water, and mix well. Label this solution as 3.3 ppm dioxane standard (calibration standard 2).

Table 2. Headspace method parameters used for the analysis of 1,4-dioxane.

	Agilent 7694E Headspace Sampler	Agilent 7697A Headspace Sampler
Incubation Temperature	100 °C	80 °C
Incubation Time	10 min	10 min
Loop Temperature	120 °C	80 °C
Transfer Line	120 °C	140 °C
Loop Fill and Pressure	0.2 min	
Fill Pressure		15
Loop Ramp		20 psi/min
Loop Final Pressure		10
Loop Equilibrium		0.05
Vial Size	20	20
Vial Shake		5

Table 3. MSD method parameters used for the analysis of 1,4-dioxane.

	Agilent 5977A MSD	Agilent 5977B MSD
Transfer Line Temperature	280 °C	280 °C
Source Temperature	230 °C	300 °C
Tune File	Atune.u	Etune.u
Gain Factor		10

Table 4. Compound-specific parameters for the analysis of 1,4-dioxane.

Compound Parameters	SIM Ions	Retention Times
Target 1,4-Dioxane	58,87,88	2.2 & 2.27 min
IS 1,4-Dioxane-d8	96	2.22 & 2.25 min

2. Transfer 5 mL of calibration standard 2 to a vial, add 10 mL of Milli-Q water, and mix well. Label this solution as 1.1 ppm dioxane standard (calibration standard 3).
 3. Transfer 5 mL of calibration standard 3 to a vial, add 10 mL of Milli-Q water, and mix well. Label this solution as 0.37 ppm dioxane standard (calibration standard 4).
 4. Transfer 5 mL of calibration standard 4 to a vial, add 10 mL of Milli-Q water, and mix well. Label this solution as 0.12 ppm dioxane standard (calibration standard 5).
 5. Transfer 5 mL of calibration standard 5 to a vial, add 10 mL of Milli-Q water, and mix well. Label this solution as 0.04 ppm dioxane standard (calibration standard 6).
 6. Transfer 5 mL of calibration standard 6 to a vial, add 10 mL of Milli-Q water, and mix well. Label this solution as 0.013 ppm dioxane standard (calibration standard 7).
 7. If desired, transfer 5 mL of calibration standard 6 to a vial, add 5 mL of Milli-Q water, and mix well. Label this solution as 0.0065 ppm dioxane standard (calibration standard 8).
- Transfer 2 mL of each calibration standard into a headspace vial. To each vial, add 2 mL of 1 ppm dioxane-d₈ internal standard and mix well. The standards are ready for analysis.

Initial calibration verification (ICV)

A second source standard should be analyzed to verify the accuracy of the calibration. A certified reference material (CRM) containing 2,000 µg/mL of 1,4-dioxane (Sigma-Aldrich part number CRM48367) is used. The analyst may prepare any one (or all) of the following ICV standards for analysis.

- **ICV at 10 ppm:** Transfer 10 µL of CRM stock to a headspace vial containing 1990 µL of Milli-Q water. Add 2 mL of 1 ppm dioxane-d₈ internal standard and mix well.
- **ICV at 1 ppm:** Dilute the CRM stock to 20 µg/mL by combining 10 µL of stock with 990 µL of Milli-Q water in a 2 mL autosampler vial. Transfer 100 µL of CRM at 20 µg/mL to a headspace vial containing 1,900 µL of Milli-Q water. Add 2 mL of 1 ppm dioxane-d₈ internal standard and mix well.
- **ICV at 0.1 ppm:** Dilute the CRM stock to 20 µg/mL by combining 10 µL of stock with 990 µL of Milli-Q water in a 2 mL ASV. Transfer 10 µL of CRM at 20 µg/mL to a headspace vial containing 1,990 µL of Milli-Q water. Add 2 mL of 1 ppm dioxane-d₈ internal standard and mix well.

Continuing calibration verification

A midlevel calibration standard (standard 4) should be injected after every 10 samples and at the end of the sequence.

Method blank

A method blank must be analyzed with each preparatory batch of samples. In this case, 2 mL of Milli-Q water is mixed with 2 mL of 1 ppm dioxane-d₈ internal standard in a headspace vial and analyzed.

Laboratory control spike (LCS)

An LCS should be analyzed per preparatory batch. The concentration of the LCS should be greater than LOQ and less than the midlevel calibration. A spiked water sample at 0.5 ppm concentration is prepared and analyzed as follows:

Transfer 100 µL of 1,4-dioxane standard at 10 ppm to 1,900 µL of Milli-Q water. Add 2 mL of 1 ppm dioxane-d₈ internal standard and mix well.

Matrix spike and matrix spike duplicate

A matrix spike should be performed one per preparatory batch. The following procedure describes the spiking of a sample with 1 ppm of 1,4-dioxane.

Combine 100 µL of the 1,000 ppm 1,4-dioxane standard with 900 µL of Milli-Q water in a 2 mL ASV to prepare a 100 ppm 1,4-dioxane standard. Next, spike 2 mL of a sample with 20 µL of the 100 ppm standard in a headspace vial. Add 2 mL of 1 ppm dioxane-d₈ internal standard and mix well.

Prepare a duplicate spiked sample following the same procedure for analysis.

Sample preparation and analysis

For liquid samples, measure 2 mL into a headspace vial along with 2 mL of 1 ppm dioxane-d₈ internal standard and mix well.

For semisolid or solid samples, measure between 0.1 to 2 g depending on the matrix into a headspace vial. It may be necessary to add water to the sample to form a slurry if the sample is thick. Add 2 mL of 1 ppm dioxane-d₈ internal standard to the sample and mix well prior to analysis.

Results and discussion

7890 GC system with 7694E headspace sampler

A seven-point calibration curve was used for quantification in the range of 13 ppb to 10 ppm. Based on five calibration curves (spanning three years), the R² value was greater than 0.997 in each calibration. The average response factor of the curves was 1.13 with a relative standard deviation (RSD) of 11.6%. Calibration data are shown in Figure 2.

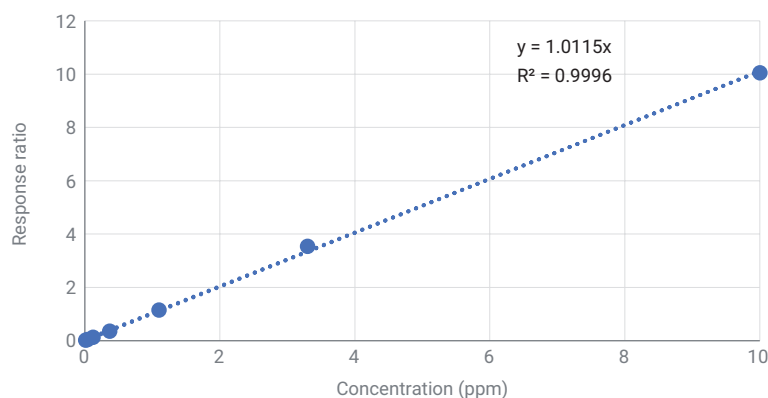


Figure 2. Calibration curve for 1,4-dioxane analysis on the Agilent 7890 GC system with Agilent 7694E headspace sampler.

The initial calibration was verified with the use of a certified reference material that was diluted and analyzed at 10, 1, and 0.1 ppm. In each case, the percent difference was less than 10%. For continuing calibration verification, a midlevel calibration standard (standard 4) was repeatedly injected over a period of five days from the initial calibration. The percent difference was less than 13.5%.

Quality control for this method was monitored throughout data collection. Method blanks yielded nondetectable levels to ensure that there was no carry over. Three laboratory control spikes were analyzed, and the accuracy ranged from 90 to 110%. Finally, a matrix spike and matrix spike duplicate were analyzed. The matrix spike samples were analyzed after spiking with a known amount (1 ppb) of 1,4-dioxane. The results are shown in Table 5.

The method detection limit (MDL) for 1,4-dioxane was calculated based on EPA methodology (EPA 821-R-16-006). The MDL was determined by spiking a detergent (predetermined to contain nondetectable levels of 1,4-dioxane) at a concentration of 50 ppb 1,4-dioxane. Ten replicates of the spiked sample were injected over three days, an example chromatogram is shown in Figure 3. The MDL was determined to be 7.1 ppb, as detailed in Table 6.

Table 5. Matrix spike and matrix spike duplicate results for 1,4-dioxane analysis on the Agilent 7890 GC system with Agilent 7694E headspace sampler.

Type	Concentration (ppm)	Percent Recovery	Percent Deviation
Sample	1.69		
Matrix Spike	2.63	94	
Matrix Spike Duplicate	2.58	90	1.6%

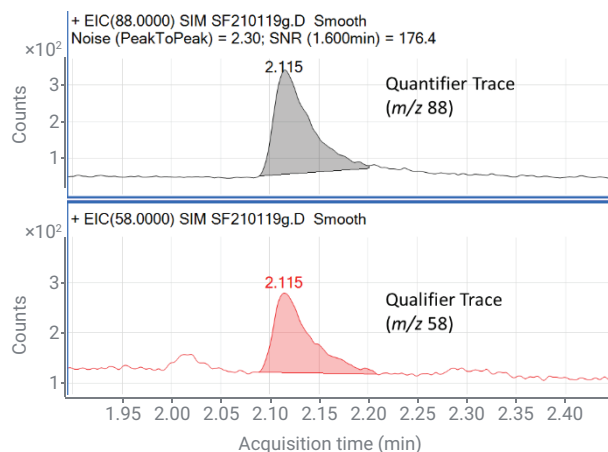


Figure 3. Example chromatography from one of the ten spiked sample injections used for method detection limit (MDL) calculation of 1,4-dioxane on the Agilent 7890 GC system with Agilent 7694E headspace sampler.

Table 6. Method detection limit (MDL) for the analysis of 1,4-dioxane on the Agilent 7890 GC system with Agilent 7694E headspace sampler.

Name	Retention Time (min)	SIM Ions	Concentration Injected	Average Measured Concentration	Standard Deviation	Method Detection Limit	Limit of Quantitation
1,4-Dioxane	2.115	88, 58	50 ppb	49 ppb	0.0025	7.1 ppb	13 ppb

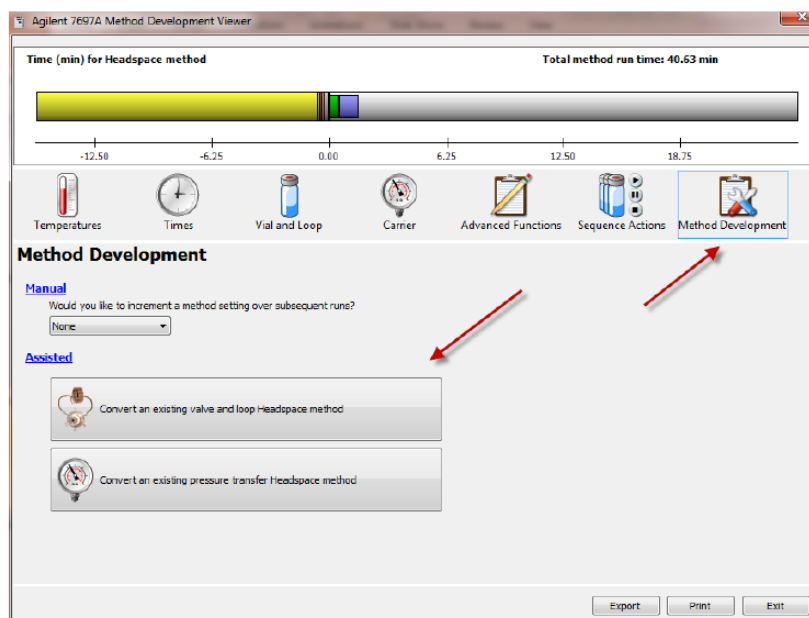
Intuvo 9000 GC system with 7697A headspace sampler

Method parameters from the 7890 GC system with 7694E headspace sampler can be transferred to the Intuvo 9000 GC system with 7697A headspace sampler. The conditions for the 7697A headspace sampler need minimal optimization. The 7697A has onboard pneumatics control to achieve active backpressure control. This difference changes the loop fill behavior and requires new method parameters. The use of the method conversion wizard (Figure 4) will give recommended starting conditions, which then can be optimized.¹⁴

A nine-point calibration curve was used for quantification in the range of 6.5 ppb to 20 ppm. Based on five calibration curves (spanning nine days), the R^2 value was greater than 0.9979, as shown in Figure 5. Average response factor of the curves was 1.1 with an RSD of 5.44%.

The initial calibration was verified with the use of a certified reference material that was diluted and analyzed at 10, 1, and 0.1 ppm. In each case, the percent difference was less than 10%. For continuing calibration verification, a midlevel calibration standard (standard 4) was repeatedly injected over a period of nine days from the initial calibration, and the percent difference was less than 10%.

Quality control for this method was also monitored throughout data collection. Method blanks yielded nondetectable levels, proving there was no system carry over. Three laboratory control spikes were analyzed, and the accuracy ranged from 90 to 110%. A matrix spike and matrix spike duplicate were also analyzed. The matrix spike samples were analyzed after spiking with a known amount (1 ppm) of 1,4-dioxane. The results are shown in Table 7.



Standalone or as part of headspace driver

Figure 4. Screen capture from the method conversion wizard for the Agilent 7697A headspace sampler.

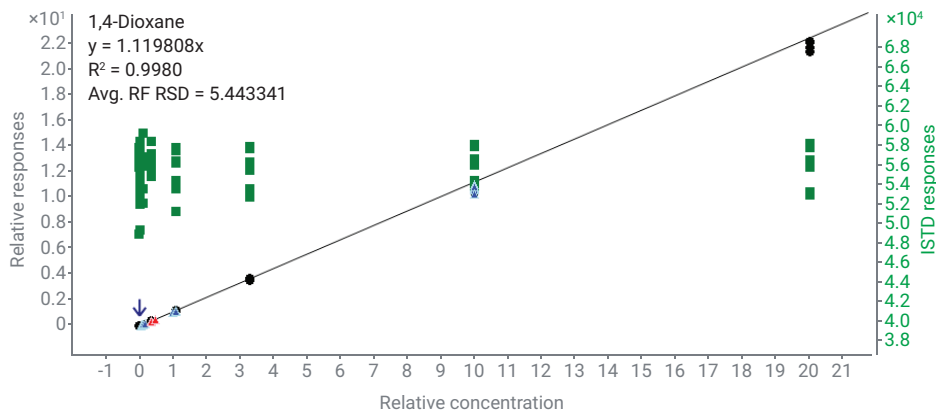


Figure 5. Calibration curve for 1,4-dioxane analysis on the Agilent Intuvo 9000 GC system with an Agilent 7697A headspace sampler.

Table 7. Matrix spike and matrix spike duplicate results for 1,4-dioxane analysis on the Agilent Intuvo 9000 GC system with Agilent 7697A headspace sampler.

Type	Concentration (ppm)	Percent Recovery
Sample	0.0	
Matrix Spike	0.994	94.2
Matrix Spike Duplicate	0.995	95.4

The MDL for 1,4-dioxane was calculated based on EPA methodology (EPA 821-R-16-006). The MDL was determined by spiking a detergent (predetermined to contain nondetectable levels of 1,4-dioxane) at a concentration of 50 ppb 1,4-dioxane. Thirty replicates of the spiked sample were injected over nine days, representative data are shown in Figure 6. The MDL was determined to be 2.3 ppb (Table 8).

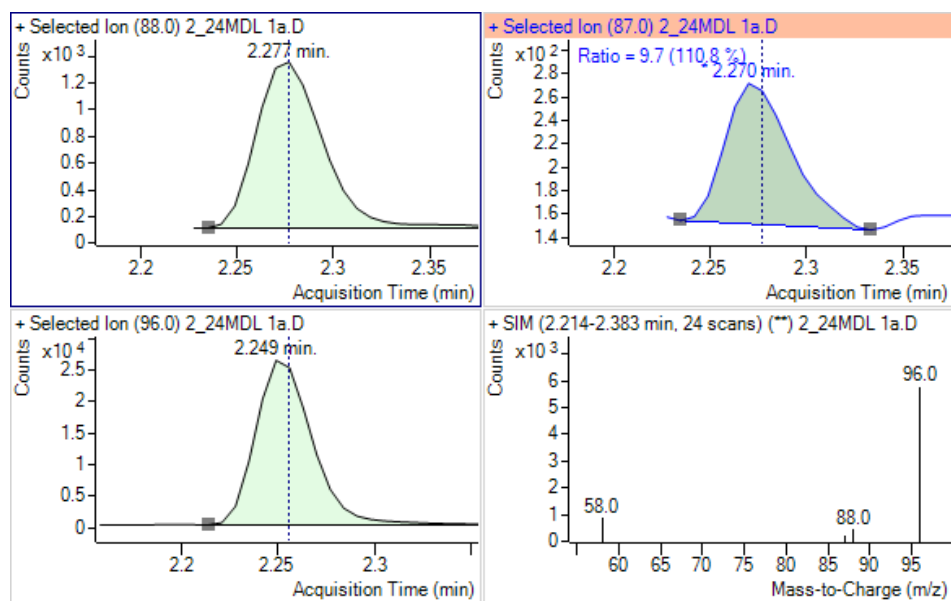


Figure 6. Example chromatography from one of the 30 spiked sample injections used for method detection limit (MDL) calculation of 1,4-dioxane on the Agilent Intuvo 9000 GC system with an Agilent 7697A headspace sampler.

Table 8. Method detection limit (MDL) for the analysis of 1,4-dioxane on the Agilent Intuvo 9000 GC system with an Agilent 7697A headspace sampler.

Name	Retention Time (min)	SIM Ions	Concentration Injected	Average Measured Concentration	Standard Deviation	Method Detection Limit	Limit of Quantitation
1,4-Dioxane	2.277	88, 87, 58	50 ppb	52.55 ppb	0.9	2.3 ppb	9.3 ppb

Best practices

Table 9. Best practices for the analysis of 1,4-dioxane.

Instrument Measure	Frequency	Requirement	Correction
Initial Calibration Verification (ICV)	Immediately after calibration	ICV $\pm 30\%$ true value	Reanalyze ICV, rerun calibration, corrective action
Continuing Calibration Verification (CCV)	Before batch and after every 10 analytical runs excluding blanks	CCV $\pm 30\%$ true value	Reanalyze CCV, rerun calibration, corrective action
Internal Standard (ISTD)	Added to every sample, standard, blank, and QC sample		
Retention Time (RT)	Evaluate in every sample	ISTD RT ± 0.33 min Analyte RT < 10 s To midpoint ICAL or first CCV	Inspect and perform instrument maintenance
Matrix Blank (MB)	With every batch of 10 or fewer samples	Analyte $< \text{LOQ}$	Reanalyze, corrective action
Laboratory Control Spikes (LCS)	With every batch of 10 or fewer samples	Spike recovery $\pm 30\%$	Reanalyze, corrective action
Matrix Spike and Matrix Spike Duplicate (MS/MSD)	With every batch of 10 or fewer samples	Spike recovery $\pm 30\%$ RDP of MS/MSD $< 20\%$	Reanalyze, corrective action

Replace reference materials when responses do not pass criteria, are low compared to past calibrations, or reach their expiration date.

Recalibrate when the continuing calibration verification no longer passes within 20% of true value, or when maintenance has been performed.

Conclusion

These methods present a sensitive, robust, and selective method to determine 1,4-dioxane in consumer products including: cosmetic, personal care, and cleaning products. The benefits of using the Agilent 5977 MSD SIM capabilities with the headspace sampler cannot be underestimated in reducing sample matrix interference and improving signal-to-noise. This instrument configuration provides high selectivity and sensitivity with a more confidence-driven solution for the analysis of 1,4-dioxane. Lower detection limits cannot be achieved due to the myriad of interferences in the gel, viscous, and foaming mixtures. One approach to reduce matrix interferences and achieve lower detection limits would be the use of a triple quadrupole GC/MS system.

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