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Analysis of Residual Solvents in Cannabinoid Products with Hydrogen Carrier Gas and the Agilent HydroInert Source

Using the Agilent 8697 Headspace Sampler, Agilent Intuvo 9000 GC, and Agilent 5977C MSD

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Abstract

This application note demonstrates residual solvents analysis (RSA) using headspace as a sample introduction technique on a single quadrupole GC/MS in selective ion monitoring (SIM) mode with hydrogen as the GC carrier gas. The current study followed the methodology described in Agilent application note 5994-1926EN[1] for detection of residual solvents in helium carrier gas with some modifications for hydrogen carrier gas. Using hydrogen carrier gas, an elution profile similar to previous work in helium was observed. Due to the combination of hydrogen carrier and a smaller diameter column, the run time with the current method has been reduced from 13 minutes when using helium to 9 minutes when using hydrogen. Accuracy values fell between 92.0% and 111.0%, and precision values ranged from 1.0% to 9.9% RSD. Additionally, observed results show high quality match scores, ranging from 94.4% to 99.9%, for spectra generated in hydrogen carrier gas against the NIST 23 Library. In most cases, LOD and LOQ values from the current study are well below the regulatory values published in states where cannabis is currently legal.

Introduction

Residual solvents analysis (RSA) is performed on extracted cannabis products to determine that residual solvents are not present in the product at concentration that exceed the regulatory limits.[1] RSA is typically performed using headspace as a sample introduction technique for GC-FID or GC/MS analysis with helium as the preferred carrier gas. However, recurring helium shortages and mounting costs have increased demand for applications using hydrogen as the carrier gas.

When adopting hydrogen for GC/MS analysis, there are several factors to consider. First, hydrogen is a reactive gas, and it may potentially cause chemical reactions in the inlet, column, and sometimes the MS EI source, which can change analysis results. To address potential issues in the MS source, the Agilent HydroInert source was used. Additional information can be found in the Agilent technical overview of the HydroInert source.[2] Second, for GC/MS applications, hardware changes in the gas chromatograph and mass spectrometer may be required when switching to hydrogen carrier gas. The Agilent Helium to Hydrogen Carrier Gas Conversion Guide[3] describes in detail the steps for conversion from helium to hydrogen carrier gas. Lastly, it is recommended that when working with flammable or explosive gases, laboratories maintain proper safety in gas handling and use. Further information on the safe use of hydrogen can be found in the Agilent Hydrogen Safety Manual[4] and Hydrogen Safety for the Agilent GC System Guide.[5]

Experimental

Chemicals and reagents

The residual solvents standard mix California Solvent Mixture Version 2 (DRE-GA09000698TN) was purchased from LGC (Teddington, United Kingdom). The internal standard (ISTD), α,α,α – trifluorotoluene (TFT), reagent-grade sodium chloride, and dimethyl acetamide (DMA, purity 99.5%) were purchased from Sigma-Aldrich (St. Louis, MO, US). The test matrix for calibration, cold pressed hemp seed oil (blank matrix), was obtained from Nutiva (Richmond, CA, US).

Serial dilution, internal standards, calibration standards, and sample preparation

To create calibration curves and samples, a serial dilution of the stock standard was necessary. Due to the volatile nature of the solvents, serial dilutions were made in Kimble Accuform micro-reaction vials with mininert valves obtained from DWK (Millville, NJ, US). Serial dilutions were performed first by placing the stock standard in a vial with mininert top. This vial is the highest concentration and considered to be dilution solution 12 in the current study. A serial dilution was performed for 11 additional points by combining a 50:50 ratio of the previous solution with DMA. For example, from 1 mL of stock solution, 0.5 mL of stock was combined with 0.5 mL of DMA in a new vial to form dilution solution 11. Concentrations of the dilution solutions were as follows (in descending order in parts per million (ppm)): 1000, 500, 250, 125, 62.5, 31.25, 15.63, 7.81, 3.91, 1.95, 0.98, 0.49.

Preparation of standards and samples followed the methodology described in Agilent application note 5994-1926EN[1] with one modification. 1.0 g of sample matrix was used instead of 2.5 g. Thus, the 5 mL aliquot in a sample vial represents 0.1 g of matrix and 32.1 mg/g of TFT. Thus, 32.1 mg/0.1 g = 321 mg TFT per 1 g of sample. The concentration 321.0 will be entered into Mass Hunter for the ISTD concentration.

In each calibration point, 0.1 g of matrix and 100 µL of diluted standards were used at each level. The normalized concentration (µg/g or ppm) of matrix matched calibrations points were as follows (in descending order): 1000, 500, 250, 125, 62.5, 31.25, 15.63, 7.81, 3.91, 1.95, 0.98, 0.49.

The preparation of solvent standards and calibrations levels consisted of spiking 100 µL of each diluted stock standard into an empty and capped headspace vial. The concentrations (ppm) of the solvent calibration curve were as follows (in descending order): 50, 25, 12.5, 6.25, 3.13, 1.56, 0.78, 0.39, 0.20, 0.10, 0.05.

Concentrations prepared for matrixed matched calibration should reflect the calibration range required to successfully analyze target analytes based on individual state regulations. In the current study, the objective was to calculate the lowest possible limit of detection (LOD) and limit of quantification (LOQ) for target analytes in hydrogen carrier gas. Further, the analytes chosen in this study were meant to be representative of a large range of target solvents but is not exhaustive. Thus, the purpose of this study is to show the viability of residual solvents analysis when using hydrogen as a carrier gas.

Instrumentation

The GC/MS method parameters followed the methodology described in Agilent application note 5994-1926EN[1] with some modifications for hydrogen carrier gas. As a note, for this analysis the 0.5 mL headspace sample loop (part number G4556-80105) is required to be installed in the Agilent 8697 Headspace Sampler. Further, use of the Agilent XLSI (part number G3449A) side-mount adapter makes it possible to perform terpenes analysis[6] on the same instrument with the Agilent 7650 autosampler. The GC instrument parameters can be found in Table 1, the MS instrument parameters in Table 2, and the SIM time segment parameters in Table 3. Table 4 contains a list of consumable items used for the current application.

Table 1. Headspace, GC, and backflush conditions for residual solvents analysis.

Agilent 8697 headspace parameters	
Oven temperature	80 °C
Loop temperature	80 °C
Transfer line temperature	140 °C
Vial equilibration time	12.0 minutes
Injection duration	1.0 minutes
GC cycle time	13.0 minutes
Injection loop	0.5 mL
Agilent Intuvo 9000 GC parameters	
XLSI (transfer line interface) temperature	200 °C
Inlet	EPC split/splitless
Mode	Split
Split ratio	150:1
Septum purge flow	Standard, 3 mL/minutes
Inlet temperature	200 °C
Guard chip temp	Track oven on
Bus temp	260 °C
Oven	Initial 35 °C (1 minute hold) Ramp 1: 15 °C/minuet to 155 °C
Total run time	10.1203 minute
Column 1	Agilent J&W DB-Select 624, 20 m x 0.18 mm, 1.0 µm
Control mode, flow	Constant flow, 1.5 mL/minuet
Column 2	Agilent J&W DB-Select 624, 20 m x 0.18 mm, 1.0 µm
Control mode, flow	Constant flow, 1.7 mL/minute
PSD purge flow	3 mL/minute
Agilent Intuvo 9000 GC backflush parameters	
Inlet pressure	2 psi
Backflush pressre	70 psi
Void volumes	5
Backflush time	1.1203 minute

Table 2. MS conditions for residual solvents analysis.

Agilent 5977C MSD parameters	
Source	Agilent HydroInert
Extractor lens	9 mm
Transfer line temperature	280 °C
Source temperature	250 °C
Quadrupole temperature	200 °C
Mode	SIM
EM voltage gain	Variable
Solvent delay	1.6 minuets
Tune file	*atune.u*

Table 3. Retention time, time segment, EM gain, and SIM ions used for residual solvents analysis.

Target analyte	Retention time (min)	Time segment	Segment start time	EM gain factor	Quantifier ion	Qualifier ion
n-Propane	1.796	1	1.60		44	43
Isobutane	1.964	2	1.90		41	57
n-Butane	2.108				58	41
2,2-Dimethylpropane	2.174				57	41
Methanol	2.338	3	2.23	20	31	29
Ethylene oxide	2.401				29	44
2-Methylbutane	2.569	4	2.47	15	43	72
n-Pentane	2.784				57	43
Ethanol	2.894				45	31
Ethyl ether	2.960				74	59
2,2-Dimethylbutane	3.160				57	43
Acetone	3.207	5	3.05		58	43
Isopropyl alcohol	3.312				45	59
Acetonitrile	3.441	6	3.37	15	41	40
2-Methylpentane	3.526				86	43
2,3-Dimethylbutane	3.530				71	55
Methylene chloride	3.541				49	84
3-Methylpentane	3.728	7	3.63		57	43
n-Hexane	3.927	8	3.85		86	43
Ethyl acetate	4.531	9	4.20		61	43
Chloroform	4.765	10	4.65		83	85
Cyclohexane	4.941	11	4.85		84	56
Benzene	5.174	12	4.99		78	51
1,2-Dichloroethane	5.224				62	64
n-Heptane	5.344				100	57
Trichloroethene	5.677	13	5.55		130	132
TFT [ISTD]	5.904	14	5.75		146	127
Toluene	6.736	15	6.65	5	91	92
Ethylbenzene	8.071	16	7.80		91	106
m+p-Xylene	8.192				91	106
o-Xylene	8.558				91	106

Table 4. Agilent consumables and part numbers used in the method for residual solvents analysis. Custom columns can be requisitioned from the Agilent GC custom columns shop.[7]

Consumable	Description	Part number
Headspace loop	Sample loop, headspace, 0.50 mL, inert	G4556-80105
Loop adaptor	Small sample loop retainer clip (quantity: 2)	G4556-20177
Inlet septum	Advanced Green septum, nonstick, 11 mm	5183-4759
Inlet liner	Universal Ultra Inert low pressure drop inlet liner	5190-2295
Guard chip	Agilent Intuvo S/SL Guard Chip	G4587-60565
Column	J&W DB-Select 624 Ultra Inert, 20 m x 180 µm x 1.0 µm (quantity: 2)	Custom Part Number
Gaskets	Intuvo polyimide gasket	5190-9072
Compression bolts	Intuvo Compression Bolts	G4581-60260
Detector tail	Intuvo MS Tail	G4590-60009
Headspace caps	crimp, aluminum, PTFE/silicone septa, 20 mm	5183-4477
Headspace vials	crimp top, amber, flat bottom, certified, 20 mL	5190-2286
50 µL syringe	Manual syringe, PTFE tipped plunger, fixed needle with bevel tip	5190-1503
100 µL syringe	Manual syringe, PTFE tipped plunger, fixed needle with bevel tip	5190-1510
250 µL syringe	Manual syringe, PTFE tipped plunger, fixed needle with bevel tip	5190-1517
500 µL syringe	Manual syringe, PTFE tipped plunger, fixed needle with bevel tip	5190-1523
1000 µL syringe	Manual syringe, PTFE tipped plunger, fixed needle with bevel tip	5190-1528
Steel tubing	Install kit for GCs, stainless steel	19199S
GC/MS source	HydroInert complete source assembly for 5977C	G7078-67930

Results and discussion

Chromatography

Figure 1 shows the SIM time segment chromatogram of calibration level 12 (1000 µg/g). Using hydrogen carrier gas, an elution profile similar to previous work in helium was observed.[1] Due to the combination of hydrogen carrier and a smaller diameter column, the run time with the current method has been reduced from 13 minutes when using helium to 9 minutes when using hydrogen. Note, the 9 mm extractor lens is the default configuration with the Agilent HydroInert source and is the recommended extractor lens for this application.
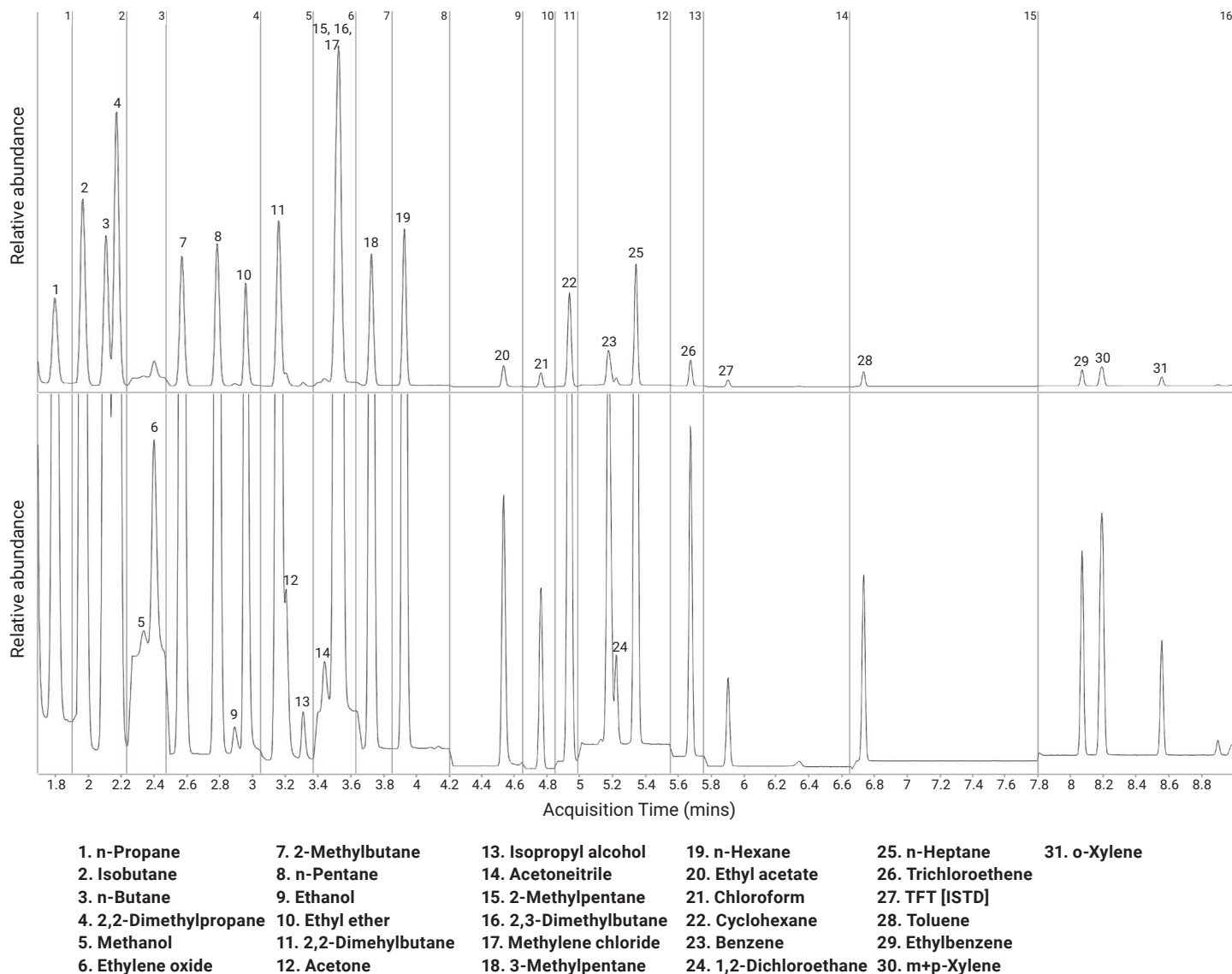

1. n-Propane	7. 2-Methylbutane	13. Isopropyl alcohol	19. n-Hexane	25. n-Heptane	31. o-Xylene
2. Isobutane	8. n-Pentane	14. Acetoneitrile	20. Ethyl acetate	26. Trichloroethene	
3. n-Butane	9. Ethanol	15. 2-Methylpentane	21. Chloroform	27. TFT [ISTD]	
4. 2,2-Dimethylpropane	10. Ethyl ether	16. 2,3-Dimethylbutane	22. Cyclohexane	28. Toluene	
5. Methanol	11. 2,2-Dimehylbutane	17. Methylene chloride	23. Benzene	29. Ethylbenzene	
6. Ethylene oxide	12. Acetone	18. 3-Methylpentane	24. 1,2-Dichloroethane	30. m+p-Xylene	

Figure 1. SIM time segment chromatogram of calibration level 12 (1000 µg/g). The top chromatogram is to scale. The bottom chromatogram is zoomed in to show small peaks.

Range and calibration

Table 5 provides the calibration range, number of calibration points, and correlation coefficient (R^2) for eight independent calibration curves. All calibration curves were fit with quadratic relationships, and 1/x weighting was used. All R^2 values were > 0.995, demonstrating excellent fit of prepared calibration standards within the chosen calibration range.

Table 5. The calibration range, number of calibration points, and correlation coefficient (R^2) for eight independent calibration curves.

Target analyte	Calibration range (ppm)	Calibration points	Cal 1 (R^2)	Cal 2 (R^2)	Cal 3 (R^2)	Cal 4 (R^2)	Cal 5 (R^2)	Cal 6 (R^2)	Cal 7 (R^2)	Cal 8 (R^2)
n-Propane	15.63−1000	7	0.9989	0.9995	0.9992	0.9993	0.9987	0.9998	0.9952	0.9981
Isobutane	15.63−1000	7	0.9981	0.9996	0.9993	0.9993	0.9981	0.9995	0.9964	0.9965
n-Butane	3.91−1000	9	0.9993	0.9996	0.9993	0.9995	0.9988	0.9997	0.9963	0.9967
2,2-Dimethylpropane	0.49−1000	12	0.9987	0.9996	0.9994	0.9995	0.9989	0.9997	0.9951	0.9974
Methanol	15.63−1000	7	0.9996	0.9985	0.9992	0.9986	0.9985	0.9997	0.9995	0.9966
Ethylene oxide	15.63−1000	7	0.9997	0.9996	0.9997	0.9986	0.9965	0.9993	0.9968	0.9979
2-Methylbutane	1.95−1000	10	0.9991	0.9996	0.9994	0.9995	0.9991	0.9991	0.9954	0.9978
n-Pentane	1.95−1000	10	0.9995	0.9997	0.9993	0.9994	0.9992	0.9997	0.9951	0.9979
Ethanol	15.63−1000	7	0.9994	0.9983	0.9984	0.9985	0.9987	0.9990	0.9977	0.9988
Ethyl ether	3.91−1000	9	0.9999	0.9998	0.9997	0.9998	0.9996	0.9995	0.9977	0.9994
2,2-Dimethylbutane	0.98−1000	11	0.9995	0.9996	0.9996	0.9995	0.9995	0.9996	0.9964	0.9987
Acetone	7.81−1000	8	0.9994	0.9995	0.9994	0.9994	0.9984	0.9987	0.9990	0.9990
Isopropyl alcohol	3.91−1000	9	0.9993	0.9990	0.9995	0.9972	0.9970	0.9996	0.9973	0.9990
Acetonitrile	15.63−1000	7	0.9994	0.9995	0.9998	0.9996	0.9968	0.9991	0.9970	0.9987
2-Methylpentane	0.49−1000	11	0.9997	0.9995	0.9998	0.9982	0.9994	0.9992	0.9965	0.9989
2,3-Dimethylbutane	1.95−1000	12	0.9995	0.9998	0.9996	0.9994	0.9996	0.9998	0.9974	0.9986
Methylene chloride	0.98−1000	10	0.9999	0.9997	0.9998	0.9999	0.9995	0.9990	0.9978	0.9989
3-Methylpentane	1.95−1000	10	0.9996	0.9997	0.9996	0.9995	0.9997	0.9997	0.9973	0.9993
n-Hexane	0.49−1000	12	0.9995	0.9997	0.9995	0.9992	0.9995	0.9997	0.9987	0.9991
Ethyl acetate	1.95−1000	10	0.9996	0.9998	0.9997	0.9997	0.9991	0.9992	0.9991	0.9992
Chloroform	1.95−1000	10	0.9999	0.9997	0.9997	0.9997	0.9998	0.9994	0.9989	0.9995
Cyclohexane	0.49−1000	12	0.9999	0.9998	0.9997	0.9996	0.9997	0.9998	0.9995	0.9997
Benzene	0.49−1000	12	0.9999	0.9998	0.9999	0.9995	0.9999	0.9996	0.9995	0.9996
1,2-Dichloroethane	0.49−1000	12	0.9999	0.9996	0.9998	0.9997	0.9997	0.9994	0.9991	0.9993
n-Heptane	1.95−1000	10	0.9999	0.9998	0.9995	0.9991	0.9993	0.9996	0.9996	0.9991
Trichloroethene	1.95−1000	10	0.9998	0.9999	0.9999	0.9998	0.9997	0.9994	0.9995	0.9996
Toluene	1.95−1000	10	0.9999	0.9997	0.9999	0.9996	0.9998	0.9997	0.9994	0.9998
Ethylbenzene	7.81−1000	8	0.9984	0.9979	0.9999	0.9988	0.9983	0.9993	0.9983	0.9990
m+p-Xylene	7.81−1000	8	0.9970	0.9972	0.9998	0.9977	0.9979	0.9994	0.9981	0.9983
o-Xylene	7.81−1000	8	0.9959	0.9995	0.9994	0.9991	0.9965	0.9985	0.9969	0.9953

Limit of detection and quantification

Table 6 shows the limit of detection (LOD) and limit of quantification (LOQ) calculated using six replicate injections (n=6). The MassHunter Software calculates LOD as a method detection limits (MDL) defined as MDL = t (n-1,0.99) x SD, where t (n-1,0.99) is the one-sided Student's t-statistic at the 99% confidence limit for n-1 degrees of freedom. The calculated LOD (MDL) was further subjected to an MDL test, defined as calculated LOD < spike level < (calculated LOD x 10), to ensure the proper concentration was used to determine LOD.

Table 6. The LOD, LOQ, spike level, and MDL test results for target residual solvents.

Target analyte	LOD (µg/g)	LOQ (µg/g)	Spike level (µg/g)	MDL test
n-Propane	2.94	9.81	15.63	Passed
Isobutane	2.79	9.31	15.63	Passed
n-Butane	0.95	3.15	3.91	Passed
2,2-Dimethylpropane	0.16	0.54	0.49	Passed
Methanol	3.98	13.25	15.63	Passed
Ethylene oxide	1.75	5.20	15.63	Passed
2-Methylbutane	0.42	1.38	1.95	Passed
n-Pentane	0.69	2.31	1.95	Passed
Ethanol	10.97	36.58	31.25	Passed
Ethyl ether	0.81	2.71	3.91	Passed
2,2-Dimethylbutane	0.26	0.87	0.98	Passed
Acetone	1.76	5.86	7.81	Passed
Isopropyl alcohol	1.71	5.72	3.91	Passed
Acetonitrile	11.73	39.09	31.25	Passed
2-Methylpentane	0.20	0.65	0.98	Passed
2,3-Dimethylbutane	0.16	0.54	0.49	Passed
Methylene chloride	0.23	0.77	1.95	Passed
3-Methylpentane	0.29	0.96	1.95	Passed
n-Hexane	0.12	0.39	0.49	Passed
Ethyl acetate	0.35	1.15	1.95	Passed
Chloroform	0.18	0.60	1.95	Passed
Cyclohexane	0.16	0.54	0.49	Passed
Benzene	0.21	0.71	0.98	Passed
1,2-Dichloroethane	0.23	0.68	0.98	Passed
n-Heptane	0.49	1.63	1.95	Passed
Trichloroethene	0.19	0.62	1.95	Passed
Toluene	0.50	1.66	1.95	Passed
Ethylbenzene	2.12	7.05	7.81	Passed
m+p-Xylene	3.02	10.06	7.81	Passed
o-Xylene	4.64	15.48	7.81	Passed

Accuracy and precision

Table 7 displays the accuracy and precision data for three different calibration levels (low, mid, and high). Due to the calibration ranges being different for each target analyte, the low-level concentration is defined next to the parameter for both accuracy and precision. All accuracy values fell between 92.0% and 111.0%, and all precision values ranged from 1.0% to 9.9 %RSD.

Table 7. Accuracy as the average percent (n=8) and precision as %RSD (n=6) of a low, mid, and high-level calibration point.

Target analyte	Accuracy (mean %, n=8)				Precision (% RSD, n=6)			
	Low level		Mid level	High level	Low level		Mid level	High level
	Conc (ppm)	Mean %	31.25 ppm	500 ppm	Conc (ppm)	% RSD	31.25 ppm	500 ppm
n-Propane	15.63	100.5	101.2	100.0	15.63	6.0	7.2	3.4
Isobutane	15.63	102.0	96.9	100.9	15.63	4.6	9.9	3.3
n-Butane	3.91	101.2	98.1	100.7	3.91	6.5	8.3	2.1
2,2-Dimethylpropane	0.49	105.0	100.1	100.0	0.49	6.8	7.7	2.6
Methanol	15.63	99.3	99.7	100.5	15.63	4.3	3.1	4.6
Ethylene oxide	15.63	104.6	93.3	101.6	15.63	1.5	4.8	4.1
2-Methylbutane	1.95	94.9	99.1	100.6	1.95	4.5	9.3	2.2
n-Pentane	1.95	98.7	99.2	99.5	1.95	4.0	7.8	1.5
Ethanol	15.63	96.2	102.9	100.4	15.63	4.5	5.9	3.6
Ethyl ether	3.91	103.1	99.3	100.5	3.91	5.5	5.5	2.0
2,2-Dimethylbutane	0.98	93.5	100.9	99.5	0.98	3.8	8.6	1.5
Acetone	7.81	105.6	96.3	102.1	7.81	3.1	6.4	3.1
Isopropyl alcohol	3.91	111.0	92.0	102.3	3.91	4.9	6.5	4.6
Acetonitrile	15.63	99.1	100.3	100.6	15.63	8.8	9.5	3.3
2-Methylpentane	0.98	97.3	100.1	98.8	0.98	1.9	7.4	1.7
2,3-Dimethylbutane	0.49	98.4	96.8	100.8	0.49	5.9	7.1	1.2
Methylene chloride	1.95	100.5	99.8	99.4	1.95	3.1	5.1	2.1
3-Methylpentane	1.95	93.9	100.6	99.1	1.95	5.7	6.4	1.2
n-Hexane	0.49	102.8	101.1	99.0	0.49	6.1	5.0	1.7
Ethyl acetate	1.95	102.3	96.4	101.6	1.95	3.3	5.5	1.8
Chloroform	1.95	101.5	98.3	100.9	1.95	3.5	1.4	1.5
Cyclohexane	0.49	97.6	100.0	99.3	0.49	5.7	3.4	1.1
Benzene	0.49	111.0	98.6	100.5	0.49	3.5	2.6	1.0
1,2-Dichloroethane	0.49	93.3	98.9	101.2	0.49	3.8	4.0	1.0
n-Heptane	1.95	94.2	101.4	99.0	1.95	6.6	4.6	2.1
Trichloroethene	1.95	102.4	100.4	100.6	1.95	3.6	6.1	1.8
Toluene	1.95	103.6	101.7	100.6	1.95	6.2	2.3	1.2
Ethylbenzene	7.81	94.9	104.3	101.5	7.81	3.0	2.1	3.3
m+p-Xylene	7.81	95.9	105.5	101.3	7.81	4.2	1.4	4.1
o-Xylene	7.81	93.3	106.5	101.5	7.81	4.0	2.5	6.4

Method performance using solvent standards

As described above, an eleven-point calibration curve was created using only solvent standards to evaluate the performance of the current method without the influence of matrix. Table 8 shows the calibration range, number of calibration points, linearity (R^2), LOD, and LOQ of target analytes using only solvent standard. Calibration curves for each target analyte were fit with quadratic relationships, and 1/x weighting was used. Calibration range was determined by fitting the most calibration point while maintaining a R^2 values > 0.995. For quadratic relationships a minimum of seven points was required. LOD and LOQ were calculated using the Agilent MassHunter Software onboard calculations. The calibration range, LOD, and LOQ observed in Table 8 are not normalized to matrix and thus represent the lower limits of the instrument method. In many cases, a greater number of calibration points, and thus lower levels of detection, were achieved without the influence of matrix.

Table 8. Calibration range, number of calibration points, linearity (R^2), LOD, and LOQ of target analytes using solvent standards not in matrix.

Target analyte	Calibration range (ppm)	Calibration points	R^2	LOD (n=8) ppm	LOQ (n=8) ppm
n-Propane	0.78¬−50	**7**	0.9990	0.186	0.619
Isobutane	0.10−50	10	0.9986	0.038	0.126
n-Butane	0.05−50	11	0.9981	0.014	0.045
2,2-Dimethylpropane	0.05−50	11	0.9981	0.006	0.021
Methanol	0.39−50	8	0.9993	0.081	0.270
Ethylene oxide	0.10−50	10	0.9992	0.041	0.136
2-Methylbutane	0.05−50	11	0.9985	0.012	0.041
n-Pentane	0.10−50	10	0.9986	0.019	0.064
Ethanol	0.20−50	9	0.9995	0.063	0.210
Ethyl ether	0.05−50	11	0.9987	0.013	0.043
2,2-Dimethylbutane	0.05−50	11	0.9982	0.013	0.042
Acetone	0.05−50	11	0.9990	0.018	0.059
Isopropyl alcohol	0.05−50	11	0.9999	0.011	0.036
Acetonitrile	0.39−50	8	0.9991	0.067	0.223
2-Methylpentane	0.05−50	11	0.9992	0.013	0.043
2,3-Dimethylbutane	0.20−50	9	0.9982	0.052	0.172
Methylene chloride	0.05−50	11	0.9993	0.001	0.033
3-Methylpentane	0.05−50	11	0.9986	0.012	0.040
n-Hexane	0.05−50	11	0.9985	0.015	0.049
Ethyl acetate	0.05−50	11	0.9992	0.010	0.034
Chloroform	0.05−50	11	0.9997	0.015	0.051
Cyclohexane	0.05−50	11	0.9989	0.005	0.018
Benzene	0.05−50	11	0.9993	0.014	0.046
1,2-Dichloroethane	0.05−50	11	0.9995	0.001	0.029
n-Heptane	0.05−50	11	0.9984	0.033	0.109
Trichloroethene	0.05−50	11	0.9992	0.019	0.063
Toluene	0.05−50	11	0.9995	0.017	0.055
Ethylbenzene	0.10−50	10	0.9997	0.009	0.030
m+p-Xylene	0.05−50	11	0.9996	0.006	0.020
o-Xylene	0.05−50	11	0.9997	0.012	0.041

Matrix effect

To further evaluate the effects of matrix on the detection limits of the current method, absolute matrix effect was calculated for each target analyte along with the coefficient of variance (% CV). Absolute matrix effect was calculated using the following equation:

$$\text{Absolute matrix effect (\%)} = \left(\frac{A_m}{A_s} - 1 \right) \times 100$$

where A_m is the peak area of the target analyte in spiked matrix and A_s is the peak area of the target analyte in solvent solution. Table 9 shows the absolute matrix effect and % CV of each target analyte (n=8) at the 500 ppm level. A positive percentage represents a matrix enhancement while a negative percentage represents a matrix suppression. The % CV demonstrates the variability of the enhancement or suppression. Six analytes demonstrated a matrix enhancement in hemp seed oil. All six compounds were lighter solvents with no polar R groups. All other target analytes demonstrated matrix suppression ranging from 19.9–98.1%. Analytes demonstrating the greatest matrix suppression were either heavier solvents or compounds with polar R groups. Greater matrix suppressions in target analytes have the potential to raise detection limits. It is important to note that the absolute matrix effect will be different for every analyte in every type of matrix. The current study offers only a glimpse at the potential for matrix effect and suppression to affect detection limits.

Table 9. The absolute matrix effect and coefficient of variance (% CV) of target analytes in hemp seed oil matrix.

Target analyte	Absolute matrix effect (%)	% CV
n-Propane	67.8	**21.8**
Isobutane	44.7	21.9
n-Butane	32.1	19.3
2,2-Dimethylpropane	26.3	18.9
Methanol	-96.3	14.8
Ethylene oxide	-83.5	18.1
2-Methylbutane	5.3	17.5
n-Pentane	4.5	15.5
Ethanol	-98.1	14.0
Ethyl ether	-62.1	12.8
2,2-Dimethylbutane	-20.4	13.9
Acetone	-92.2	12.3
Isopropyl alcohol	-96.5	11.8
Acetonitrile	-96.0	12.5
2-Methylpentane	-22.6	12.3
2,3-Dimethylbutane	-88.2	11.4
Methylene chloride	-22.9	14.1
3-Methylpentane	-28.1	12.4
n-Hexane	-19.9	10.6
Ethyl acetate	-91.5	10.2
Chloroform	-91.6	7.6
Cyclohexane	-58.8	9.0
Benzene	-88.7	7.6
1,2-Dichloroethane	-92.7	8.1
n-Heptane	-42.0	8.5
Trichloroethene	-88.6	6.0
Toluene	-90.7	6.2
Ethylbenzene	-91.9	6.8
m+p-Xylene	-92.3	7.6
o-Xylene	-93.4	10.4

Library match and spectral fidelity

Use of the HydroInert source greatly reduces the occurrence of redox chemistry in the MS source when using hydrogen carrier.[2] The reduction of chemical reactions in the source leads to conserved spectral fidelity, where spectra generated in hydrogen can be used with a high degree of confidence to identify target analytes from library spectra generated in helium. Table 10 shows the library match scores for spectra of target analytes generated in both helium and hydrogen against the NIST 23 library. Observed results show high-quality match scores, ranging from 94.4% to 99.9%, for spectra generated in hydrogen carrier gas against the NIST 23 Library. Hydrogen-generated spectra and the spectra from NIST 23 are shown in Figures 2–9. The match score and spectra for 2,3-dimethylbutane are absent because of the analytes close elution to 2-methylpentane and methylene chloride. The deconvolution software in MassHunter Unknowns Analysis was unable to detect the components for this analyte reliably.

Table 10. Comparison of library match scores for spectra generated in helium and hydrogen carrier gas against the NIST 23 Library.

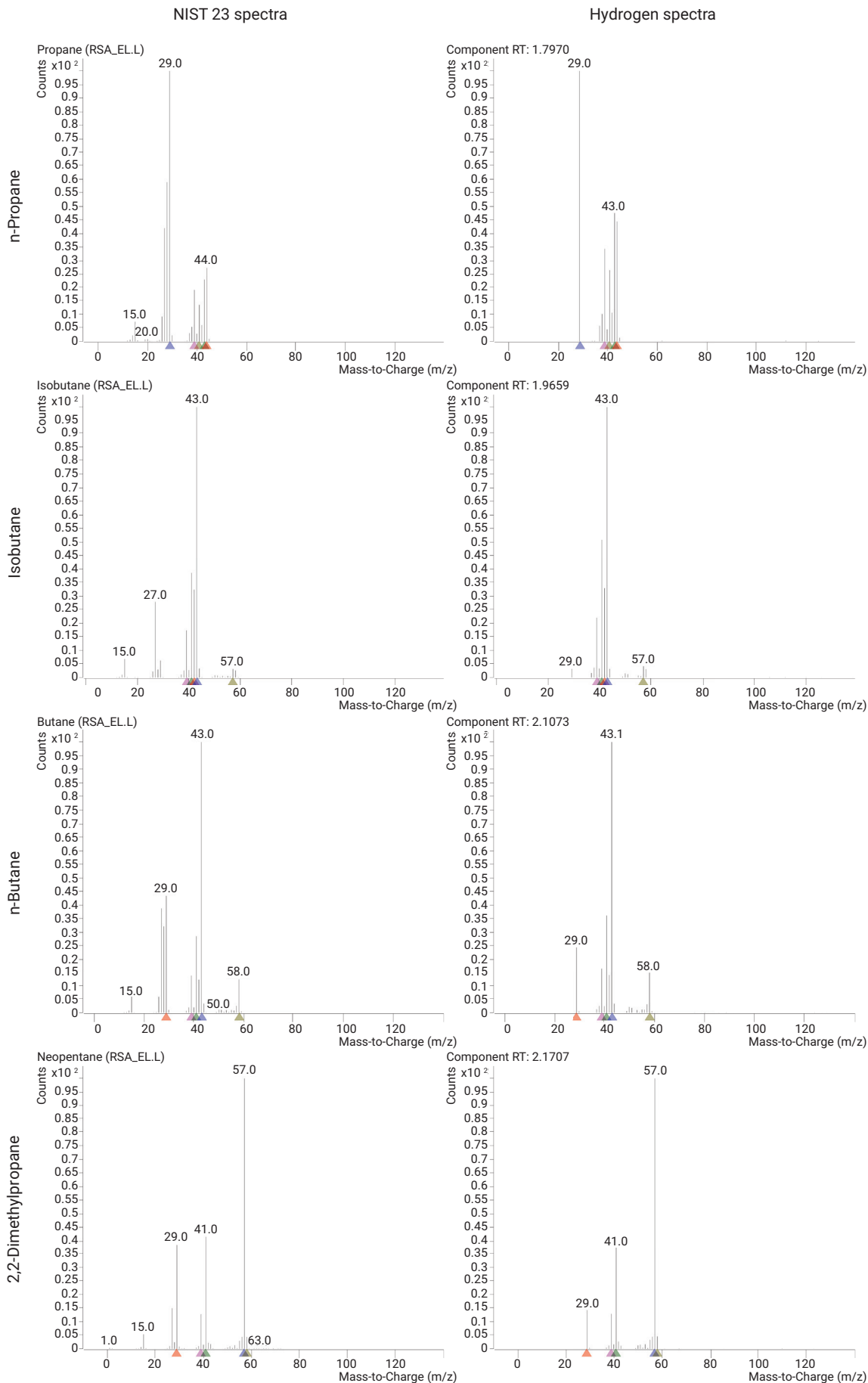| Target analyte	CAS	Helium match score (%)	Hydrogen match score (%)
n-Propane	74-98-6	98.6	94.4
Isobutane	75-28-5	99.3	97.8
n-Butane	106-97-8	98.3	97.5
2,2-Dimethylpropane	463-82-1	98.1	98.5
Methanol	67-56-1	93.2	97.1
Ethylene oxide	75-21-8	99.2	97.4
2-Methylbutane	78-78-4	97.9	98.1
n-Pentane	109-66-0	99.7	99.3
Ethanol	64-17-5	99.5	99.2
Ethyl ether	60-29-7	99.0	98.6
2,2-Dimethylbutane	75-83-2	99.5	99.5
Acetone	67-64-1	90.9	98.2
Isopropyl alcohol	67-63-0	97.5	97.7
Acetonitrile	75-05-8	98.0	99.0
2-Methylpentane	107-83-5	98.3	95.7
2,3-Dimethylbutane	79-29-8	NA	NA
Methylene chloride	75-09-2	94.4	97.1
3-Methylpentane	96-14-0	98.8	99.0
n-Hexane	110-54-3	97.2	98.4
Ethyl acetate	141-78-6	97.9	98.3
Chloroform	67-66-3	98.6	99.1
Cyclohexane	110-82-7	99.6	99.7
Benzene	71-43-2	98.1	99.1
1,2-Dichloroethane	107-06-2	93.9	98.3
n-Heptane	142-82-5	97.9	98.7
Trichloroethene	79-01-6	99.6	99.9
Toluene	108-88-3	99.2	96.2
Ethylbenzene	100-41-4	99.1	99.1
m+p-Xylene	106-42-3 & 108-38-3	99.1	99.3
o-Xylene	95-47-6	98.9	99.5

Figure 2. Comparison of NIST 23 spectra (left) to spectra observed in matrix (right) using hydrogen carrier gas for n-propane, isobutane, n-butane, and 2,2-dimethylpropane. Note: RSA_EL.L is a custom library created from the NIST 23 library for ease of analysis in MassHunter Unknowns Analysis. Spectral scale is relative and out of 100%.
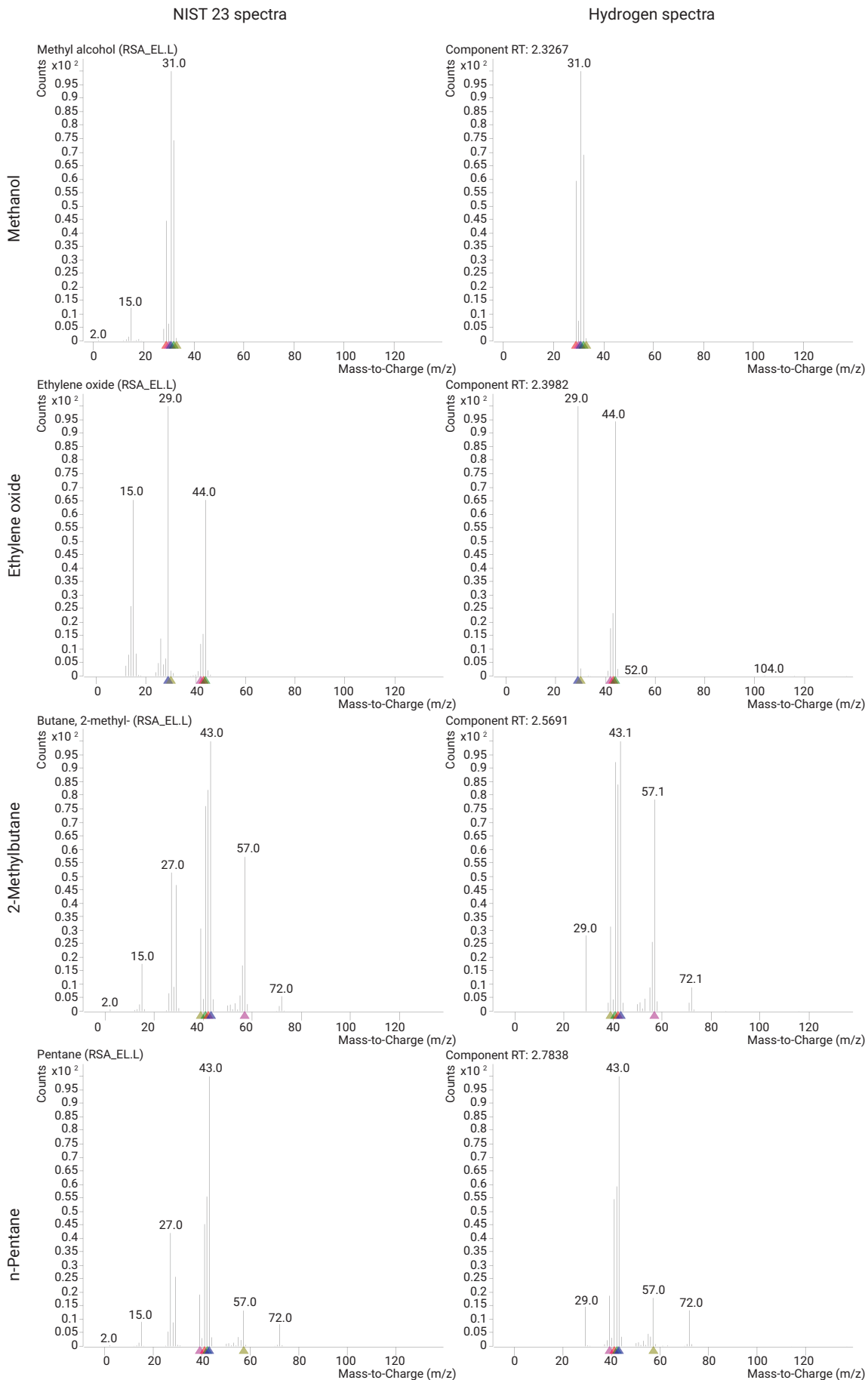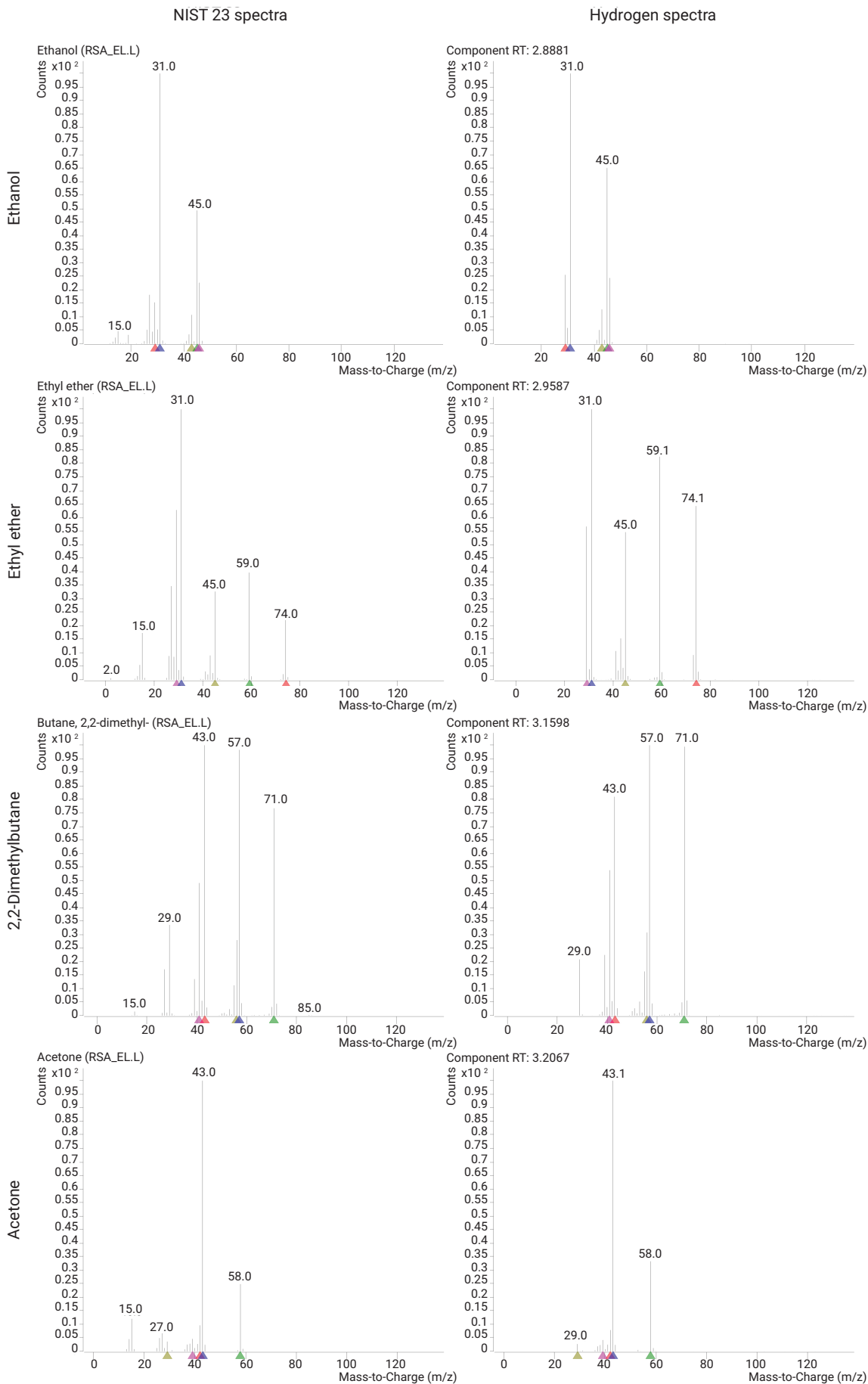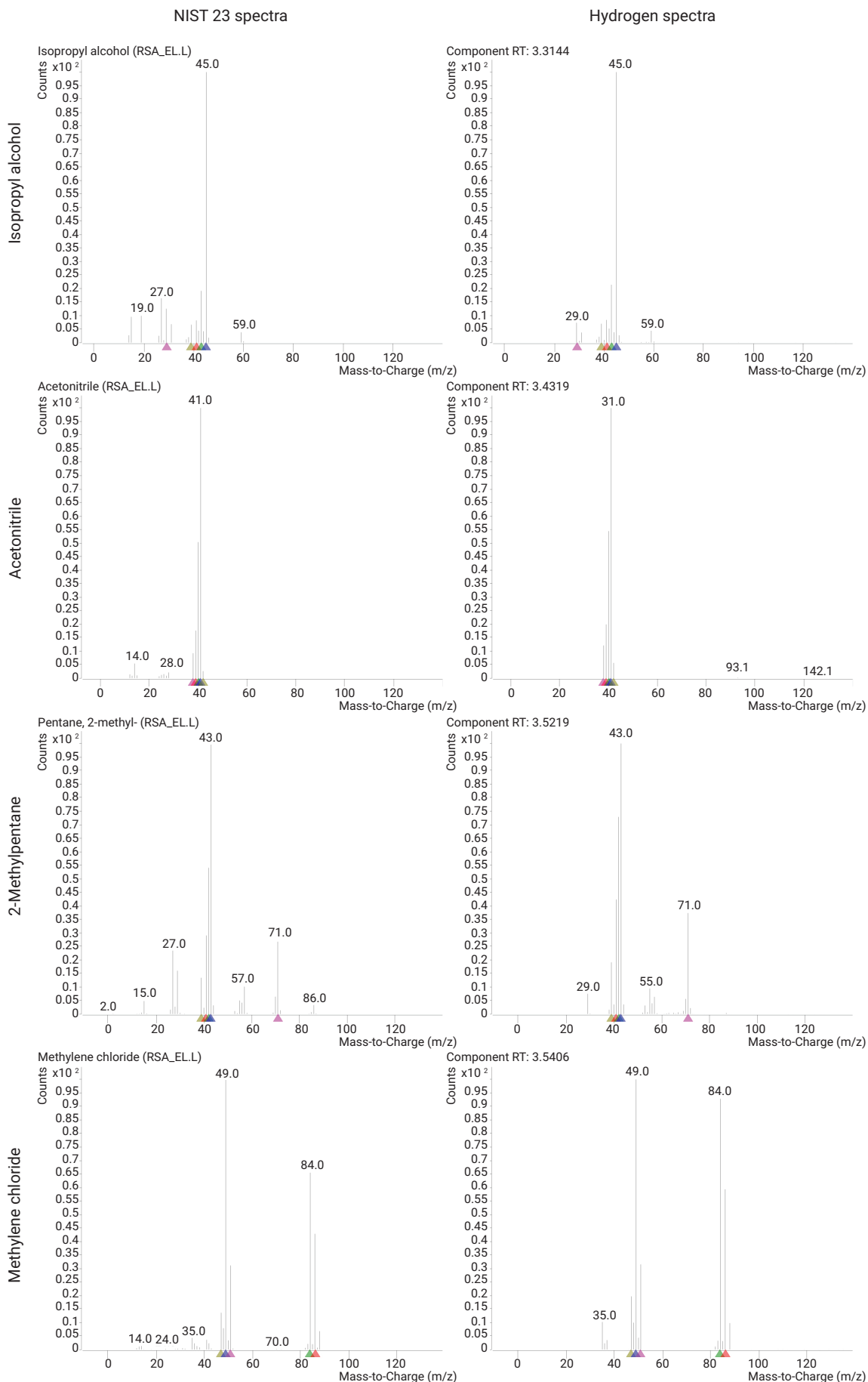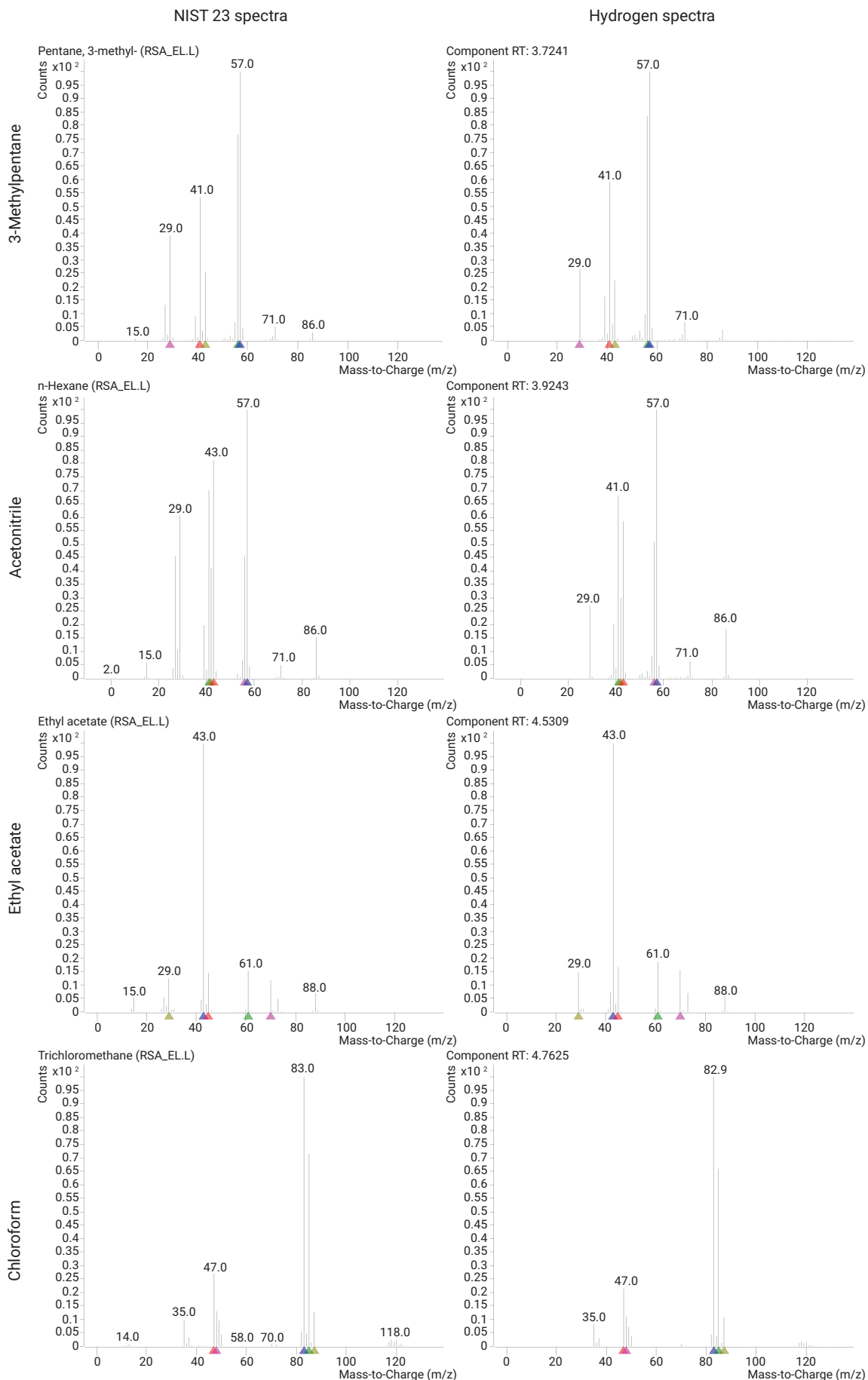
Figure 3. Comparison of NIST 23 spectra (left) to spectra observed in matrix (right) using hydrogen carrier gas for methanol, ethylene oxide, 2-methylbutane, and n-pentane. Note: RSA_EL.L is a custom library created from the NIST 23 library for ease of analysis in MassHunter Unknowns Analysis. Spectral scale is relative and out of 100%.
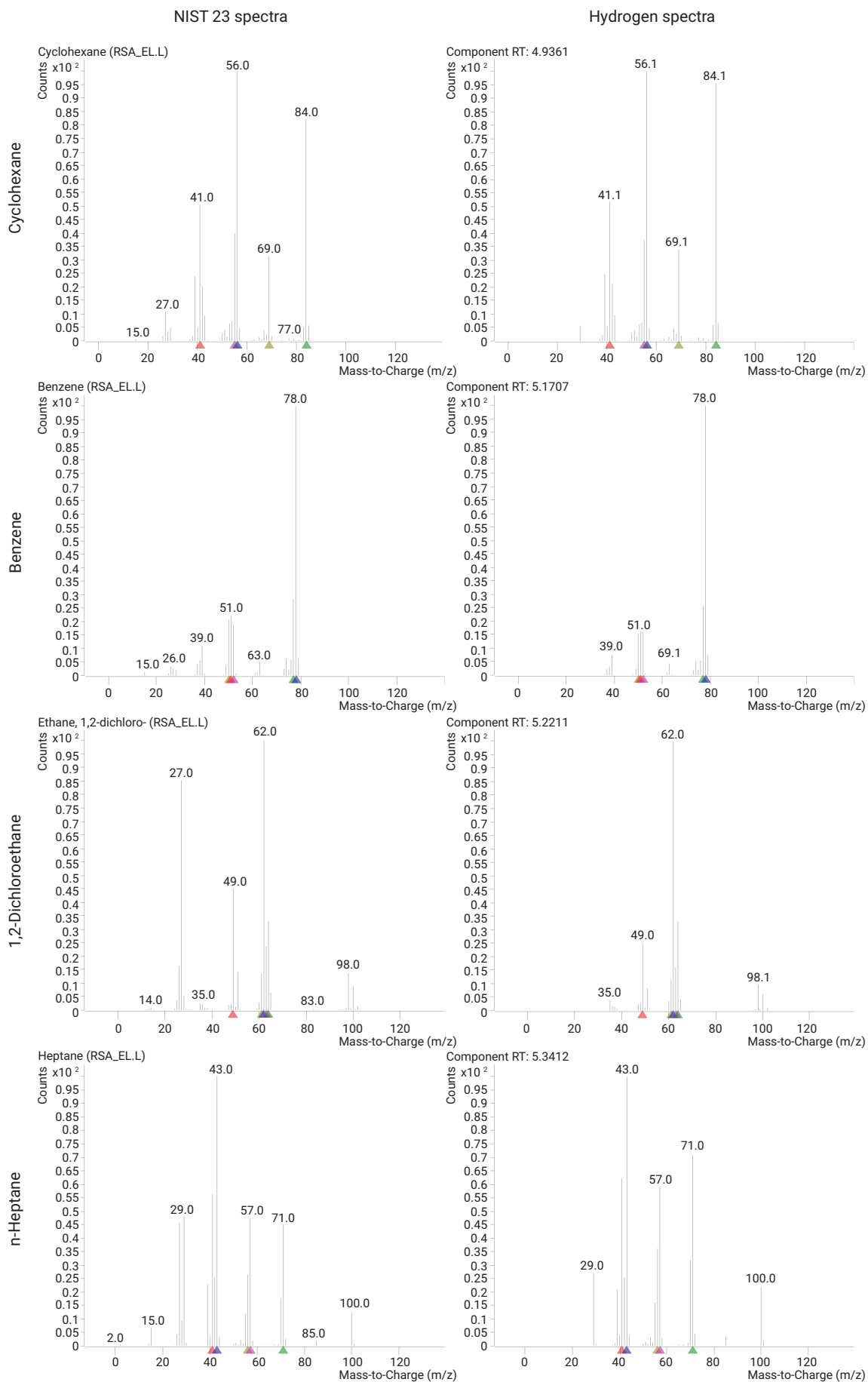
Figure 4. Comparison of NIST 23 spectra (left) to spectra observed in matrix (right) using hydrogen carrier gas for ethanol, ethyl ether, 2,2-dimethylbutane, and acetone. Note: RSA_EL.L is a custom library created from the NIST 23 library for ease of analysis in MassHunter Unknowns Analysis. Spectral scale is relative and out of 100%.

Figure 5. Comparison of NIST 23 spectra (left) to spectra observed in matrix (right) using hydrogen carrier gas for isopropyl alcohol, acetonitrile, 2-methylpentane, and methylene chloride. Note: RSA_EL.L is a custom library created from the NIST 23 library for ease of analysis in MassHunter Unknowns Analysis. Spectral scale is relative and out of 100%.
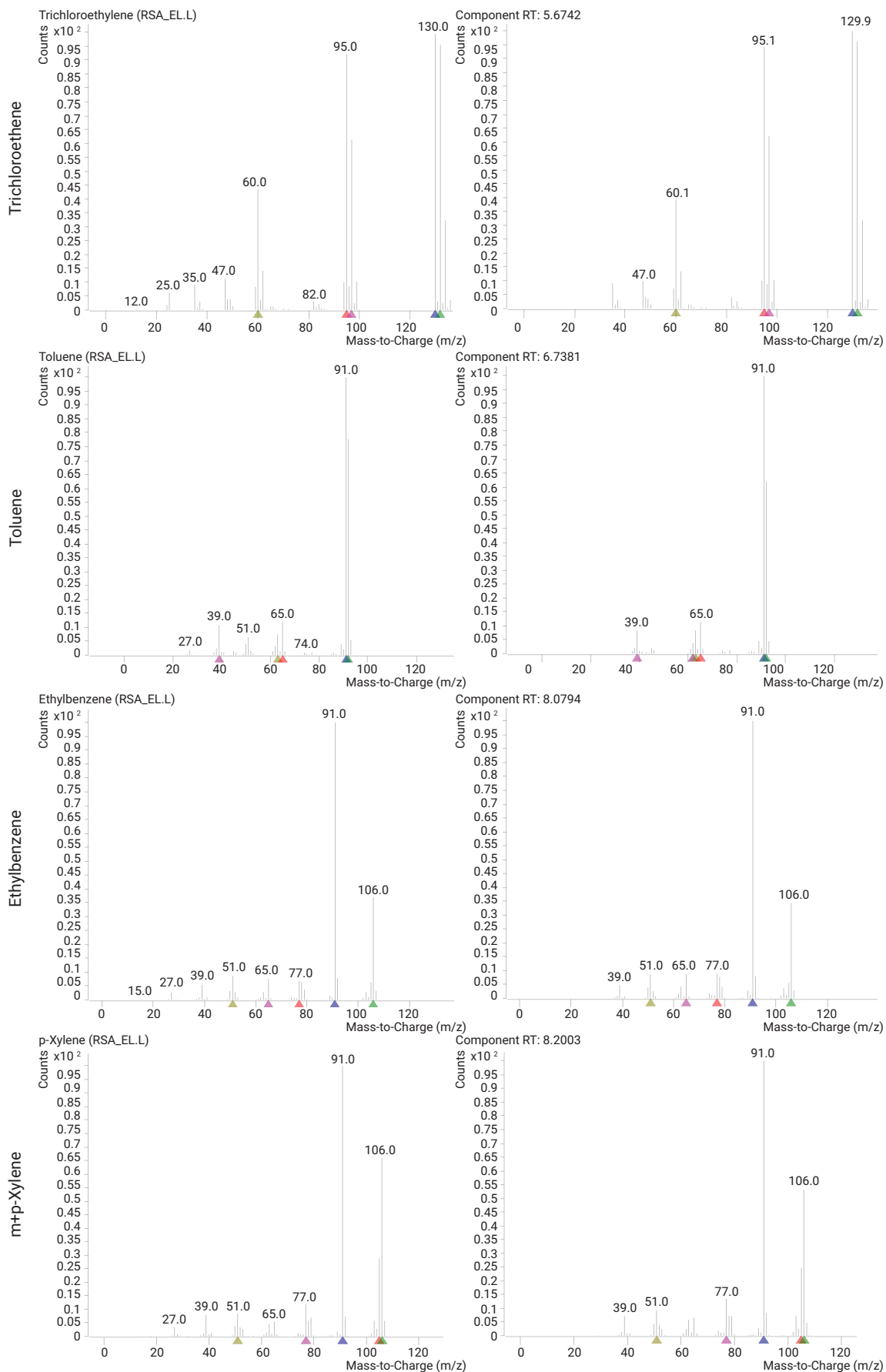
Figure 6. Comparison of NIST 23 spectra (left) to spectra observed in matrix (right) using hydrogen carrier gas for 3-methylpentane, n-hexane, ethyl acetate, and chloroform. Note: RSA_EL.L is a custom library created from the NIST 23 library for ease of analysis in MassHunter Unknowns Analysis. Spectral scale is relative and out of 100%.
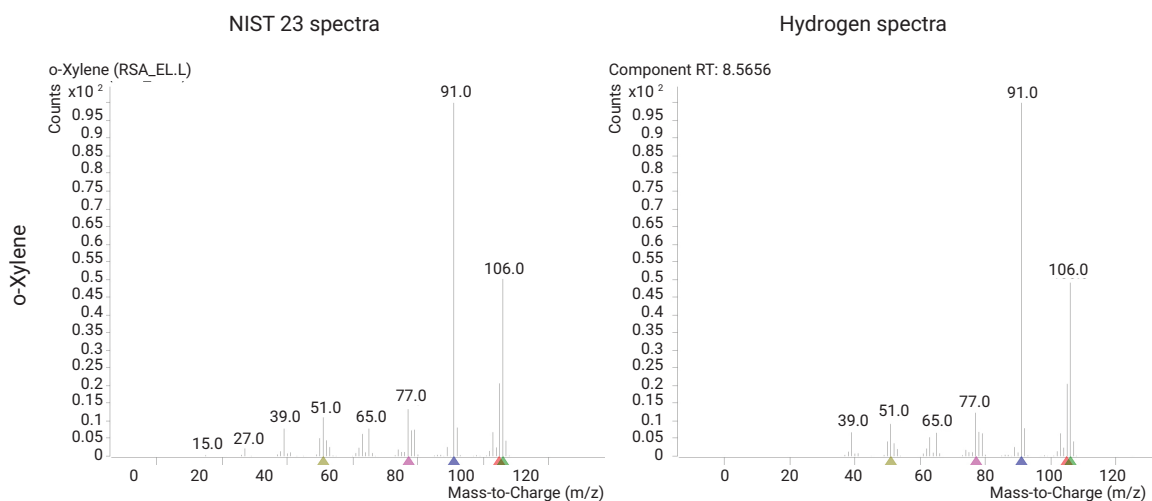
Figure 7. Comparison of NIST 23 spectra (left) to spectra observed in matrix (right) using hydrogen carrier gas for cyclohexane, benzene, 1,2-dichloroethane, and n-heptane. Note: RSA_EL.L is a custom library created from the NIST 23 library for ease of analysis in MassHunter Unknowns Analysis. Spectral scale is relative and out of 100%.

Figure 8. Comparison of NIST 23 spectra (left) to spectra observed in matrix (right) using hydrogen carrier gas for trichloroethene, toluene, ethylbenzene, and m+p-xylene. Note: RSA_EL.L is a custom library created from the NIST 23 library for ease of analysis in MassHunter Unknowns Analysis. Spectral scale is relative and out of 100%.

Figure 9. Comparison of NIST 23 spectra (left) to spectra observed in matrix (right) using hydrogen carrier gas for o-xylene. Note: RSA_EL.L is a custom library created from the NIST 23 library for ease of analysis in MassHunter Unknowns Analysis. Spectral scale is relative and out of 100%.

Conclusion

This application demonstrates that hydrogen carrier gas, when paired with the Agilent HydroInert source, is a viable option for the analysis of residual solvents in cannabis products. The HydroInert source, with the 9 mm extractor lens and smaller diameter (0.18 mm) columns, delivers acceptable performance similar to GC/MS analysis using helium carrier gas. In most cases, both LOD and LOQ values from the current study are well below the regulatory values published in states where cannabis is currently legal.

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7. The Agilent GC custom columns are available for ordering at https:// explore.agilent.com/individual-column

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