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Application News

No.M268

Gas Chromatography Mass Spectrometry

Analysis of Residual Solvents – Class 1, Class 2A, Class 2B – in Pharmaceuticals Using Headspace-GC/MS

Residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. Residual solvents are classified and managed as Class 1 to Class 3 substances, depending on the risk they pose to human health.
According to the USP, "General Chapter <467> Residual Solvents" method, analysis of these residual solvents is to be conducted by the headspace GC-FID method (HS-GC). However in this application, we investigated using headspace-GC/MS (HS-GC/MS) according to Procedure A. Using the HS-GC method, measurement is to be performed as three separate analyses, which are required to achieve chromatographic separation within the three different classes of compounds, Class 1, Class 2A, and Class 2B. However, using HS-GC/MS, complete chromatographic separation is not necessary, so all the compounds can be analyzed in a single run. In addition, compound confirmation and qualitative information of unknown peaks can also be obtained.

■ Sample Preparation

The Class 1, Class 2A, and Class 2B aqueous standard solutions were prepared so that the concentrations become the same as standard solution designated in the "USP <467> Residual Solvents" method.

■ Analytical Conditions

Headspace Sampler	: HS-20
Gas Chromatograph Mass Spectrometer	: GCMS-QP2010 Ultra
HS	
Mode	: Loop (Volume: 1 mL)
Oven Temperature	: 80 °C
Sample Line Temperature	: 150 °C
Transfer Line Temperature	: 150 °C
Gas Pressure for Vial Pressurization	: 100 kPa
Vial Equilibrating Time	: 60 min
Vial Pressurizing Time	: 2.0 min
Pressure Equilibrating Time	: 0.1 min
Load Time	: 0.1 min
Load Equilibrating Time	: 0.1 min
Injection Time	: 0.5 min
Needle Flush Time	: 5.0 min
GC	
Column	: Rxi-624sil MS (30 m × 0.25 I.D.,1.4 µm)
Injection Mode	: Split
Split Ratio	: 1:30
Control Mode	: Constant linear velocity (35 cm/sec)
Oven Temperature	: 40 °C (20 min) → 10 °C/min → 240 °C (20 min)
MS	
Ion Source Temperature	: 200 °C
Interface Temperature	: 250 °C
SCAN Range	: m/z 29 ~ 200
SIM Conditions	: Table 1
Event Time	: SIM 0.2 sec, SCAN 0.3 sec

Table 1 SIM Monitoring Ions

	Compound Name	Target	Ident 1	Ident 2
Class 1	1,1-Dichloroethene	61	96	
	1,1,1-Trichloroethane	97	99	
	Carbon Tetrachloride	117	119	
	Benzene	78	77	51
	1,2-Dichloroethane	62	64	
Class 2A	Methanol	31	29	
	Acetonitrile	40	39	
	Methylene chloride	84	86	
	trans-1,2-Dichloroethene	96	61	
	cis-1,2-Dichloroethene	96	61	
	Tetrahydrofuran	72	42	
	Cyclohexane	84	56	
	Methylcyclohexane	98	83	
	1,4-Dioxane	88	58	
	Toluene	91	92	
	Chlorobenzene	112	77	
	Ethylbenzene	91	106	
	m,p-Xylene	91	106	
	o-Xylene	91	106	
Class 2B	*n*-Hexane	86	56	
	Nitromethane	30	46	
	Chloroform	83	85	
	1,2-Dimethoxyethane	45	29	
	Trichloroethene	130	132	
	Pyridine	79	52	
	2-Hexanone	58	100	
	Tetralin	104	132	

■ Results

Fig. 1 shows Total Ion Chromatogram (TIC) for the USP Class 1 compounds. Fig. 2 and 3 are the TICs for Class 2A and 2B compounds, respectively. Peaks that cannot be identified in the TIC and peaks that completely or partially co-elute are shown in the extracted ion chromatogram (EIC). Due to the selectivity of the GC/MS, good separation was obtained by using the SIM acquisition mode. Fig. 4, 5 and 6 show the EIC/SIM chromatograms of the individual components. Good peak shapes were obtained for most of the compounds. In addition, an improved signal-to-noise ratio (S/N) was obtained for CCl_4 using the HS-GC/MS method, compared to that obtained by the HS-GC method.
Repeatability using the HS-GC/MS SIM mode yielded an RSD of 1.3 to 3.9 % (Tables 2, 3, and 4).

■ Conclusion

Using the HS-GC/MS method, simultaneous analysis of USP <467> Class 1, Class 2A, and Class 2B compounds was demonstrated without compromising separation, repeatability, or analysis accuracy.

Note: Measurement of residual solvents in pharmaceuticals using HS-GC/MS has not been adopted as an official method.
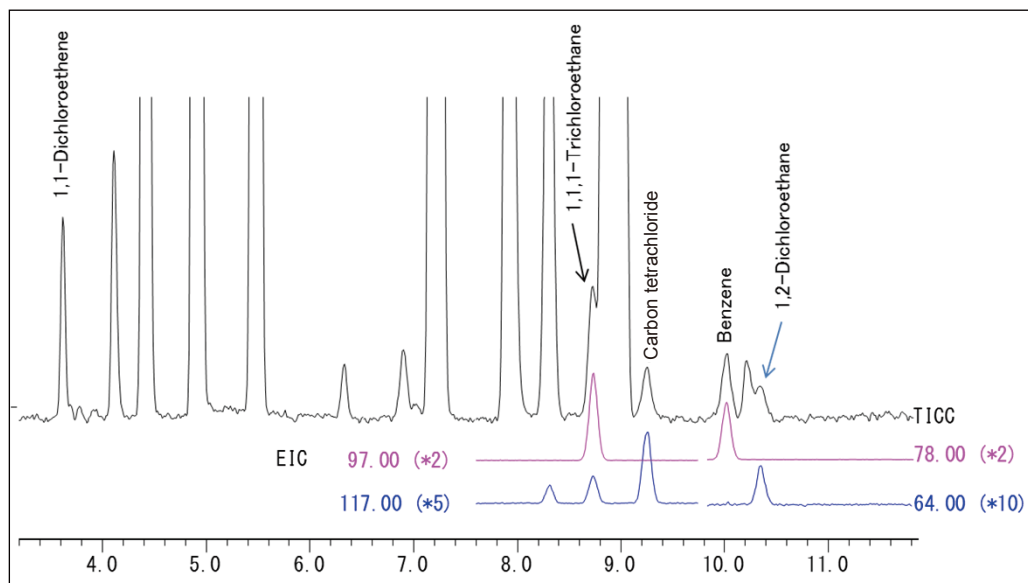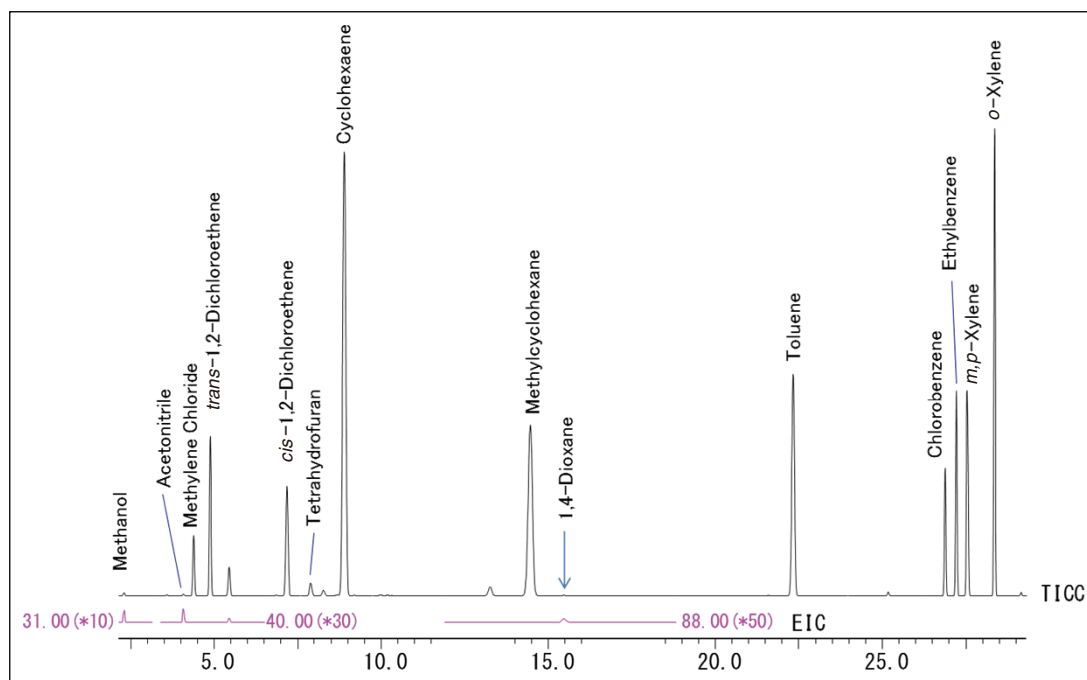
Fig. 1 TIC Chromatogram of Class 1 Solvents

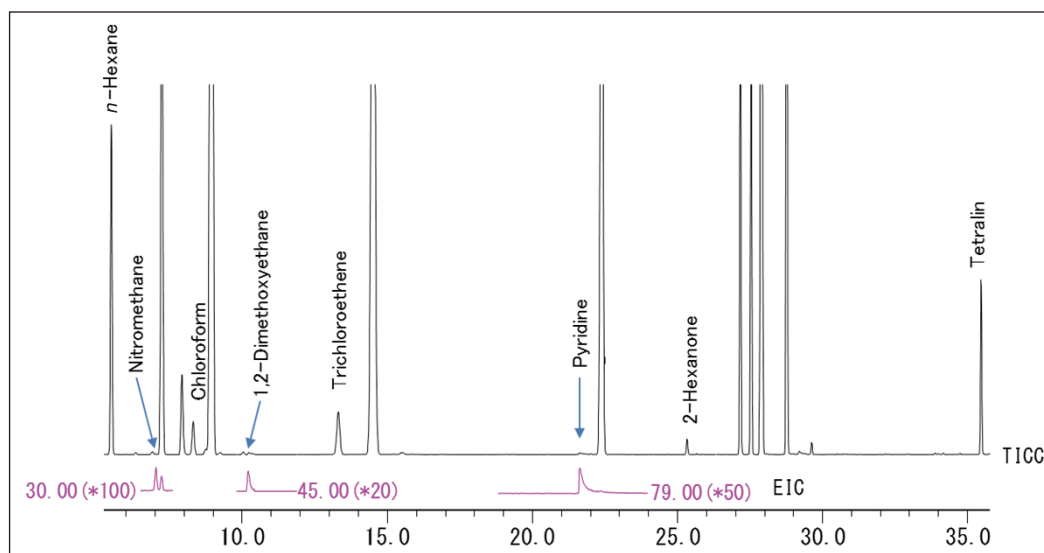Fig. 2 TIC Chromatogram of Class 2A Solvents
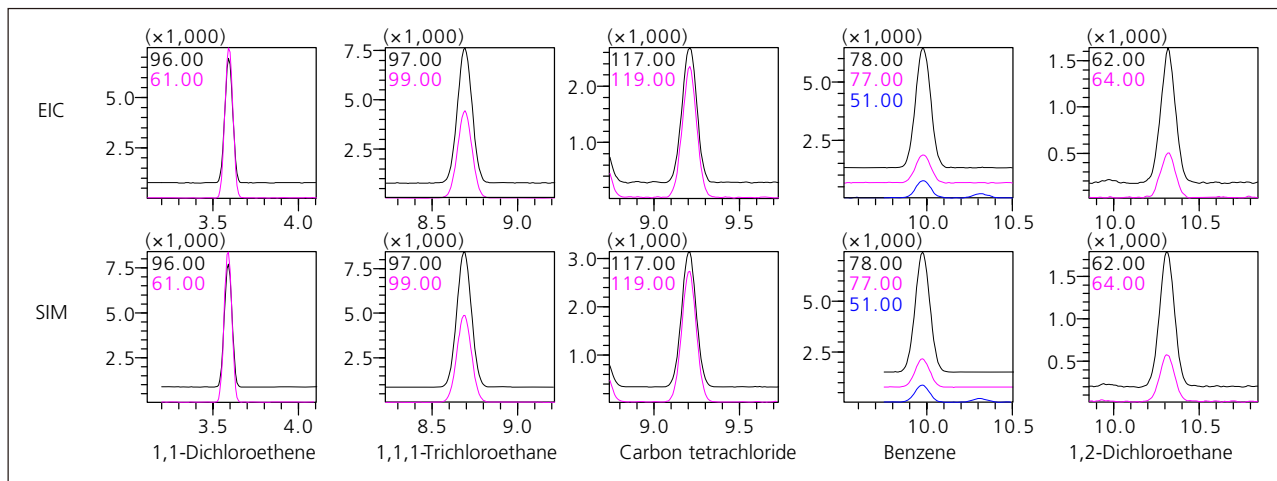

Fig. 3 TIC Chromatogram of Class 2B Solvents
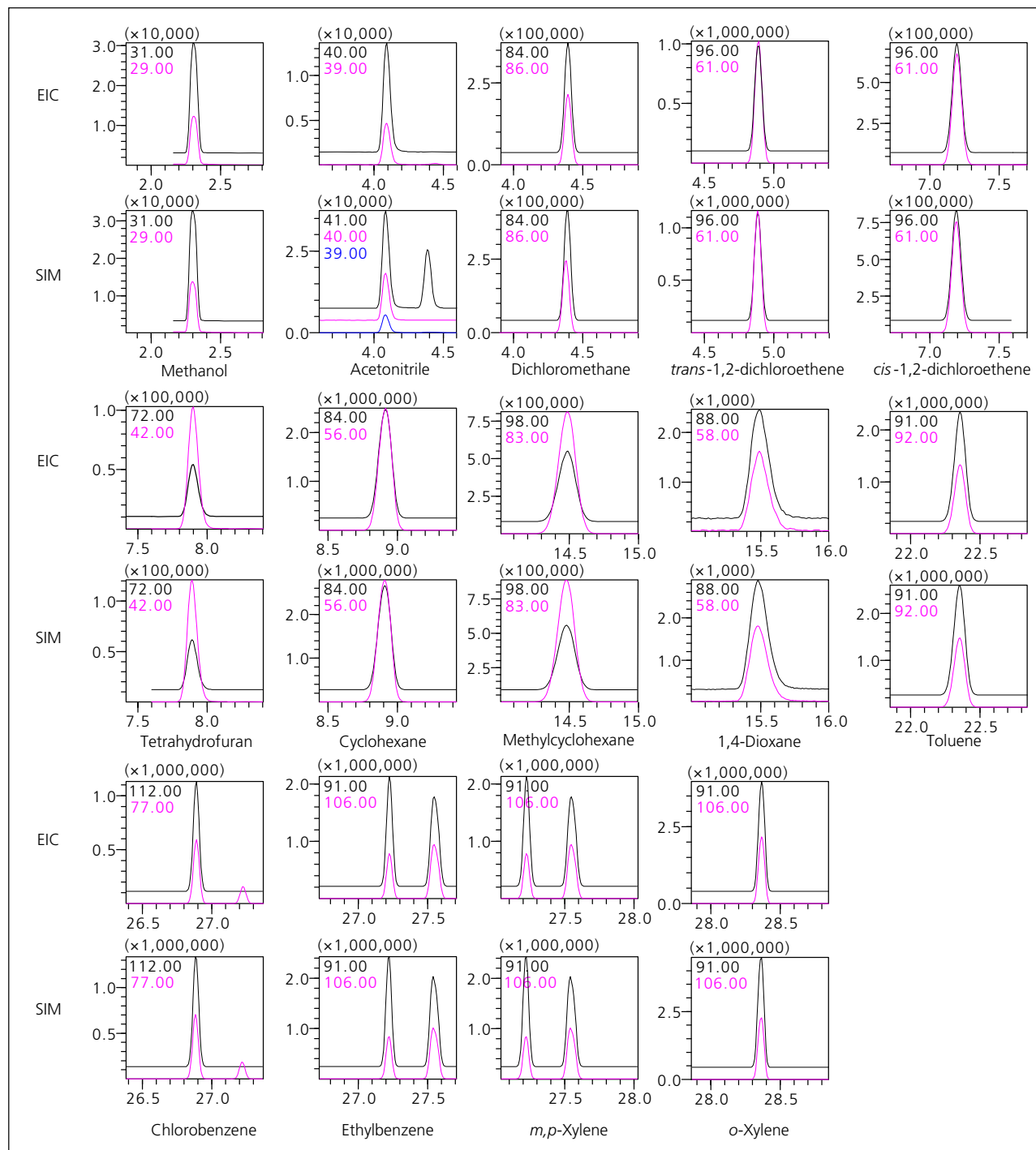
Fig. 4 EIC/SIM Chromatograms of Class 1 Solvents

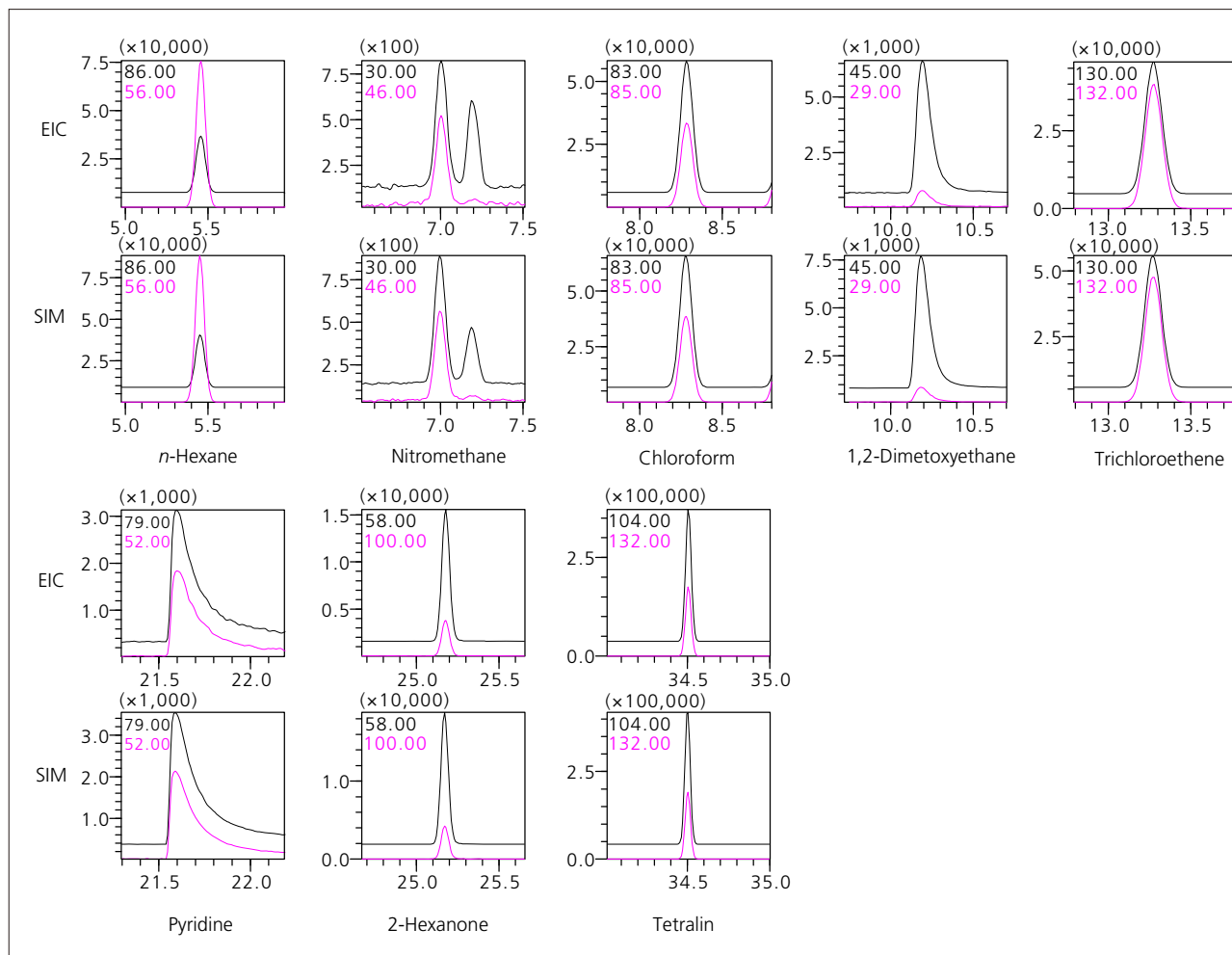**Fig. 5 EIC/SIM Chromatograms of Class 2A Solvents**

Fig. 6 EIC/SIM Chromatograms of Class 2B Solvents

Table 2 Repeatability of Peak Area of Class 1 Solvents (n = 6)

Compound Name	Conc. (μg/mL)	Area RSD (%) EIC	SIM
Class 1 1,1-Dichloroethene	0.018	2.42	2.79
1,1,1-Trichloroethane	0.033	1.86	2.61
Carbon tetrachloride	0.045	1.64	1.62
Benzene	0.064	1.52	2.01
1,2-Dichloroethane	0.085	2.21	2.30

Table 3 Repeatability of Peak Area of Class 2A Solvents (n = 6)

Compound Name	Conc. (μg/mL)	Area RSD (%) EIC	SIM
Class 2A Methanol	3.03	4.26	3.83
Acetonitrile	2.85	2.74	3.29
Methylene Chloride	27.0	2.24	2.78
trans-1,2-Dichloroethene	14.6	1.91	2.60
cis-1,2-Dichloroethene	5.05	1.93	2.49
Tetrahydrofuran	3.12	1.87	2.12
Cyclohexane	24.1	1.67	2.27
Methylcyclohexane	8.72	1.33	1.69
1,4-Dioxane	6.15	3.13	2.54
Toluene	7.00	1.17	1.56
Chlorobenzene	2.92	1.30	1.28
Ethylbenzene	1.47	1.32	1.41
m,p-Xylene	2.48	1.07	1.41
o-Xylene	10.3	1.23	1.66

Table 4 Repeatability of Peak Area of Class 2B Solvents (n = 6)

Compound Name	Conc. (μg/mL)	Area RSD (%) EIC	SIM
Class 2B n-Hexane	0.52	3.46	3.38
Nitromethane	0.82	3.72	2.44
Chloroform	1.97	2.48	2.67
1,2-Dimethoxyethane	0.42	2.62	2.74
Trichloroethene	0.42	1.23	1.56
Pyridine	1.67	2.94	3.29
2-Hexanone	0.83	0.83	1.34
Tetralin	0.65	1.87	1.77

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