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GC Applications Engineer

July 19, 2007

USP <467> Residual Solvents

Adapting to the New Requirements

USP Chapter <467> Delayed…

General Chapter <467> Organic Volatile Impurities/Residual Solvents—Implementation Date Delayed to July 2008

In accordance with the Rules and Procedures of the Council of Experts, this Revision Bulletin changes the implementation date of the General Notices statement on Residual Solvents from July 1, 2007, **to July 1, 2008**. This Revision Bulletin is effective as of this date and will be published as an IRA in Pharmacopeial Forum 33(5). Official text for the change also will appear in USP 31-NF 26, as follows:

Residual solvents – The requirements are stated in Residual Solvents <467> together with information in Impurities in Official Articles <1086>. Thus all drug substances, excipients, and products are subject to relevant control of residual solvents, even when no test is specified in the individual monograph. The requirements have been aligned with the ICH guideline on this topic. If solvents are used during production, they are of suitable quality. In addition, the toxicity and residual level of each solvent are taken into consideration, and the solvents are limited according to the principles defined and the requirements specified in Residual Solvents <467>, using the general methods presented therein or other suitable methods. (Official July 1, 2007) (Official July 1, 2008).

http://www.usp.org/USPNF/notices/generalChapter467Revision.html

USP

Some Main Points from the USP

Testing is to be performed **only** for solvents “likely to be present”

used or produced in the final manufacturing step

used in previous steps and not removed by a validated procedure

The limits for acceptable concentrations listed in the Chapter are for ***drug products***, not for its components.

If all raw materials pass specs., you don’t have to test the drug product.

USP

Some Main Points from the USP continued…..

The amount in the drug product may be:

A. calculated from the contributions of components
B. determined experimentally; mandatory if
    1. solvents are used in its manufacture
    2. cumulative calculation exceeds limits

Manufacturers of drug products may rely on data provided by the suppliers of components

Provides unambiguous identification and quantification methods

USP

Some Main Points from the USP continued…..

Includes options to allow use of materials that exceed the limits established

*When a manufacturer has received approval from a competent regulatory authority for a higher level of residual solvent, it is the responsibility of that manufacturer to notify the USP regarding the identity of that solvent and the approved residual solvent limit in the article. USP will address the matter with the individual mongraph.

If you have your own validated method, you do not need to show equivalence to <467>

Wording in current PF will change

Submission of alternative methods is not required.

Determining Concentrations

Option 1 For doses less than 10 g per day

Residual Solvent: Acetonitrile PDE 4.1

5 g of a drug

$$Concentration(ppm) = \frac{1000xPDE}{dose}$$

Concentration Limits are used.
ACN 410 ppm

Component	Amount in Formulation (g)	Acetonitrile Content (ppm)	Daily Exposure (mg)
Drug Substance	0.3	800	0.24
Excipient 1	0.9	400	0.36
Excipient 2	3.8	800	3.04
Drug product	**5.0**	**728**	**3.64**

Option 2 Limit is on Daily Exposure. The Drug product meets the Option 2 requirement for the level of Acetonitrile

Determining Concentrations

Option 2 May be applied by adding the amounts of a residual solvent present in each of the components of the drug. Should be less than the PDE.

Component	Amount in Formulation (g)	Acetonitrile Content (ppm)	Daily Exposure (mg)
Drug Substance	0.3	800	0.24
Excipient 1	0.9	2000	1.80
Excipient 2	3.8	800	3.04
Drug product	**5.0**	**1016**	**5.08**

The product did not meet either Option 1 or Option 2 limits. This product fails the requirement of the test.

Three additional changes relating to General Chapter <467> Residual Solvents are affected by this Revision Bulletin. These are:

Title Change: On July 1, 2008, the title of General Chapter <467> will change from Organic Volatile Impurities to Residual Solvents.

Other Analytical Procedures: The section in General Chapter <467> titled Other Analytical Procedures will be retained as official text until July 1, 2008.

Monographs that contain the Test for Organic Volatile Impurities will keep this test as an official requirement until July 1, 2008. After that date, the General Notices statement will apply to all monographs.

Pharmaceutical manufacturers that adopt the requirements of General Chapter <467> Residual Solvents prior to July 1, 2008 are considered to meet the monograph requirements for Organic Volatile Impurities. This approach also is suitable for other official articles.

Please direct any questions to Horacio Pappa, Ph.D., Senior Scientist (+1-301-816-8319 or hp@usp.org) or Joy Chacon, Senior Project Manager (+1-301-816-8298 or jlc@usp.org).

Working within USP <467>

3 “Classes” of solvents

Possibility of running 3 successive chromatographic analyses for 1 sample. ~3+ hours

2-3 Different chromatographic configurations to use

System suitability Requirements

Validation Requirements

Water Soluble, and Water Insoluble sample preparations

*Solvents may be moved from one class to another

*Limits may be changed based on new safety data

Classification of Residual Solvents

Class 1	Residual Solvents: Solvents to be Avoided Known human carcinogens Strongly suspected human carcinogens Environmental hazards.
Class 2	Residual Solvents: Solvents to be Limited Nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or teratogenicity. Solvents suspected of other dignificant but reversible toxicities.
Class 3	Residual Solvents: Solvents with Low Toxic Potential Solvents with low toxic potential to humans; no health-based exposure limit is needed. [NOTE-Class 3 residual solvents may have PDE's of up to 50 mg or more per day.]*

Limit of Residual Solvents: Class 1

"Class 1 solvents should not be used in the manufacturing of drug substances, excipients or drug products because of unaccceptable toxicities or deleterious environmental effects of the residual solvent."

However if their use is unavoidable, their levels should be restricted to the levels posted in the table to follow..

US Pharmacopeia

Class 1 Residual Solvents
"Solvents to be Avoided"

Solvent	CAS Number	Concentration Limit (ppm)	Concern
Benzene	[71-43-2]	2	Carcinogen
Carbon Tetrachloride	[56-23-5]	4	Toxic and environmental hazard
1,2-Dichloroethane	[107-06-2]	5	Toxic
1,1-Dichloroethene	[75-35-4]	8	Toxic
1,1,1-Trichloroethane	[71-55-6]	1500	Environmental Hazard

Class 2 Residual Solvents

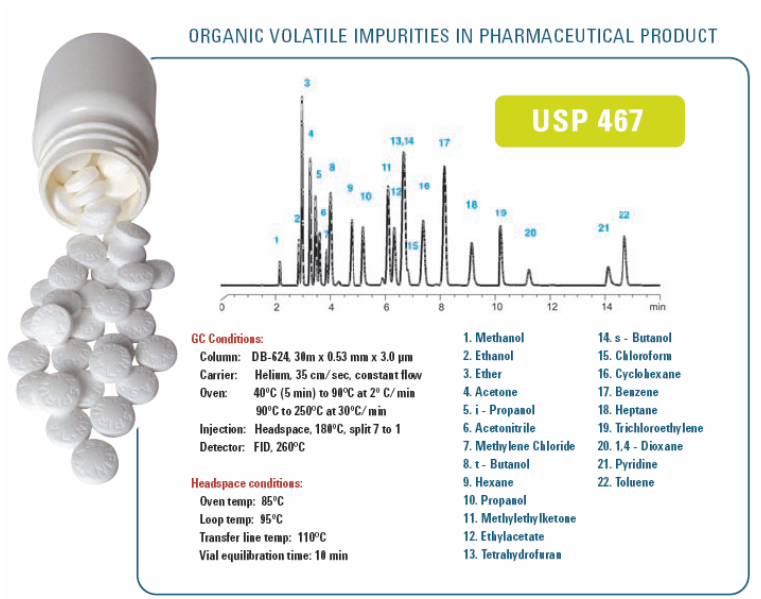
Solvent	[CAS]	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	[75-05-8]	4.1	410
Chlorobenzene	[108-90-7]	3.6	360
Chloroform	[67-66-3]	0.6	60
Cyclohexane	[110-82-7]	38.8	3880
1,2-Dichloroethene	[156-59-2]	18.7	1870
1,2-Dimethoxyethane	[110-71-4]	1.0	100
N,N-Dimethylacetamide	[127-19-5]	10.9	1090
N,N-Dimethylformamide	[68-12-2]	8.8	880
1,4-Dioxane	[123-91-1]	3.8	380
2-Ethoxyethanol	[110-80-5]	1.6	160
Ethylene glycol	[107-21-1]	6.2	620
Formamide	[75-12-7]	2.2	220
Hexane	[110-54-3]	2.9	290
Methanol	[67-56-1]	30.0	3000
2-Methoxyethanol	[109-86-4]	0.5	50
Methylbutylketone	[591-78-6]	0.5	50
Methylcyclohexane	[108-87-2]	11.8	1180
Methylene chloride	[75-09-2]	6.0	600
N-Methylpyrrolidone	[872-50-4]	5.3	530
Nitromethane	[75-52-5]	0.5	50
Pyridine	[110-86-1]	2.0	200
Sulfolane	[126-33-0]	1.6	160
Tetrahydrofuran	[109-99-9]	7.2	720
Tetralin	[119-64-2]	1.0	100
Toluene	[108-88-3]	8.9	890
Trichloroethylene	[79-01-6]	0.8	80
Xylene*		21.7	2170

- Xylenes are typcically broken up as:
- 60% m-Xylene
- 14% p-Xylene
- 9% 0-Xylene
- 17% Ethyl benzene

Pharmaceutical Quality Control of Residual Solvents

Gas chromatograph equipped with

- Headspace Sampler
- Flame Ionization Detector (FID)
- Mass-selective Detector (MSD) *(optionally)* for identification & confirmation



Procedure A Requirements:

Headspace

G43 capillary GC column： 6% cyanopropylphenyl-dimethyl polysiloxane

DB-624

0.32 mm X 30 m X 1.8 um * Agilent p/n 123-1334

0.53 mm X 30 m X 3.0 um Agilent p/n 125-1334

Split ratio 1:5

Oven 40^{o}C hold 20 mins

10^{o}C 20 240^{o}C hold 20 mins

Inlet temp: 140^{o}C

FID temp: 250^{o}C

Total run time: 1hour.

Head Space Operating Parameters

	1	2	3
Equilibration Temperature (°C)	80	105	80
Equilibration Time (min)	60	45	45
Transfer-line Temperature (°C)	85	110	105
Carrier Gas (35 cm/sec)	Nitrogen or Helium		
Pressurization Time (sec)	30	30	30
Injection Volume (mL)	1	1	1

Some parameters may be left out!

Procedure A Requirements:

Headspace

G16 capillary GC column： Poly

DB-624

0.32 mm X 30 m X 1.8 um * Agilent p/n 123-1334

0.53 mm X 30 m X 3.0 um Agilent p/n 125-1334

Split ratio 1:5

Oven 40^{o}C hold 20 mins

10^{o}C 20 240^{o}C hold 20 mins

Inlet temp: 140^{o}C

FID temp: 250^{o}C

Total run time: 1hour.

System Suitability: Procedure A

Class 1 Standard Solution

Signal-to-Noise (S/N): 1,1,1-trichloroethane NLT 5

Class 1 System Suitability Solution

S/N: All peaks NLT 3

Class 2 Mixture A Standard Solution

Resolution: Acetonitrile and Methylene Chloride

NLT 1.0

Procedure B Requirements:

Headspace

G16 capillary GC column: Poyethylene Glycol compound 20M

0.32 mm X 30 m X 0.25 um	Agilent p/n 123-7032
0.53 mm X 30 m X 0.25 um	Agilent p/n 125-7031

Split ratio: 1:5

Oven 50^{o}C hold for 20 mins

6^{o}C/min to 165^{o}C hold for 20 mins

Inlet temp: 140^{o}C

FID temp: 250^{o}C

System Suitability Requirements: Procedure B

Class 1 Standard Solution

S/N: Benzene NLT 5

Class 1 System Suitability Solution

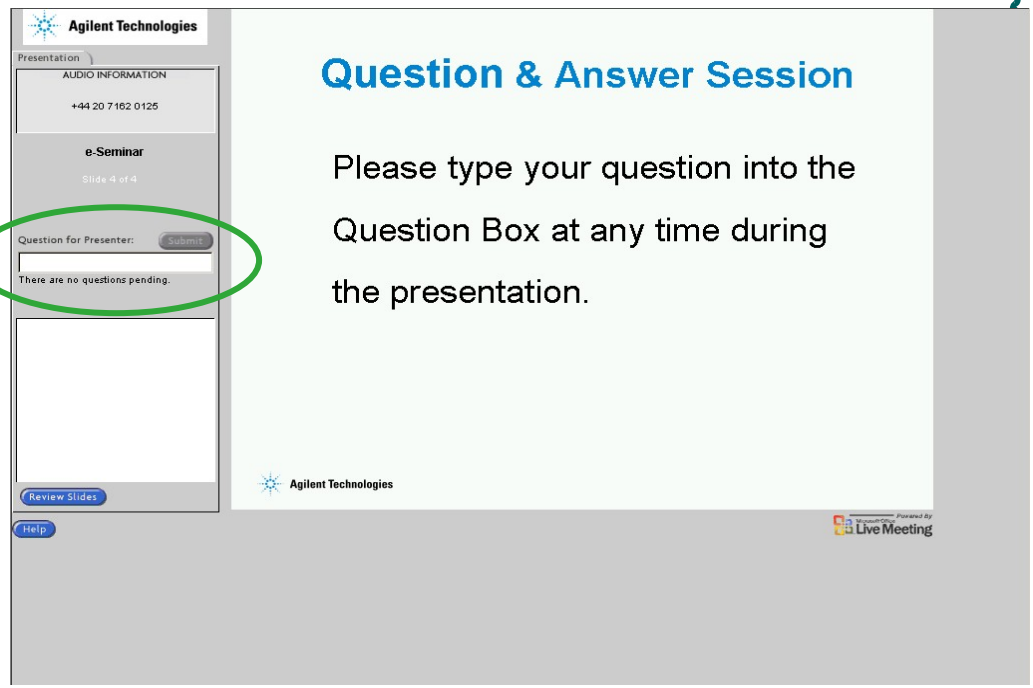
S/N: All peaks NLT 3

Class 2 System Suitability Solution

Resolution: Acetonitrile and trichloroethylene NLT 1.0

Break Number 1

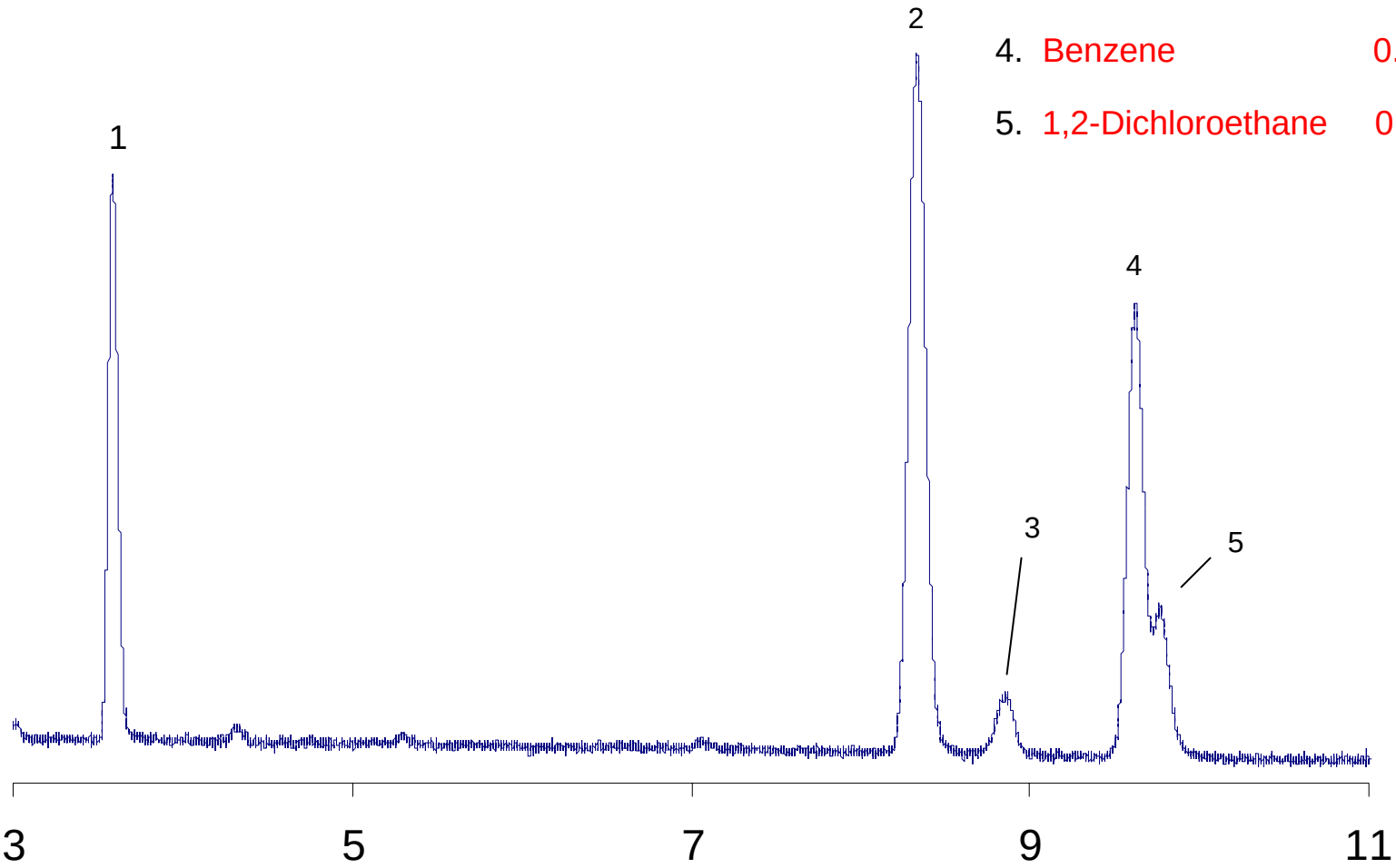
For questions, at break please dial 1 on your phone, or type in the Question Box at any time during the presentation.



Procedure A Class 1 Solvents

Agilent DB-624 p/n 123-1334
30m X 0.32mm X 1.8um

1. 1,1-Dichloroethylene 0.4 ppm
2. 1,1,1-Trichloroethane 75 ppm
3. Carbon Tetrachloride 0.2 ppm
4. Benzene 0.1 ppm
5. 1,2-Dichloroethane 0.25 ppm



System Suitability Results: Procedure A

Class 1 Solvents @ concentrations @ 1/20th Limit

S/N ratio:	Dichloroethylene	36
	Trichloroethane	41
	Carbon Tetrachloride	4
	Benzene	27
	Dichloroethane	7.9

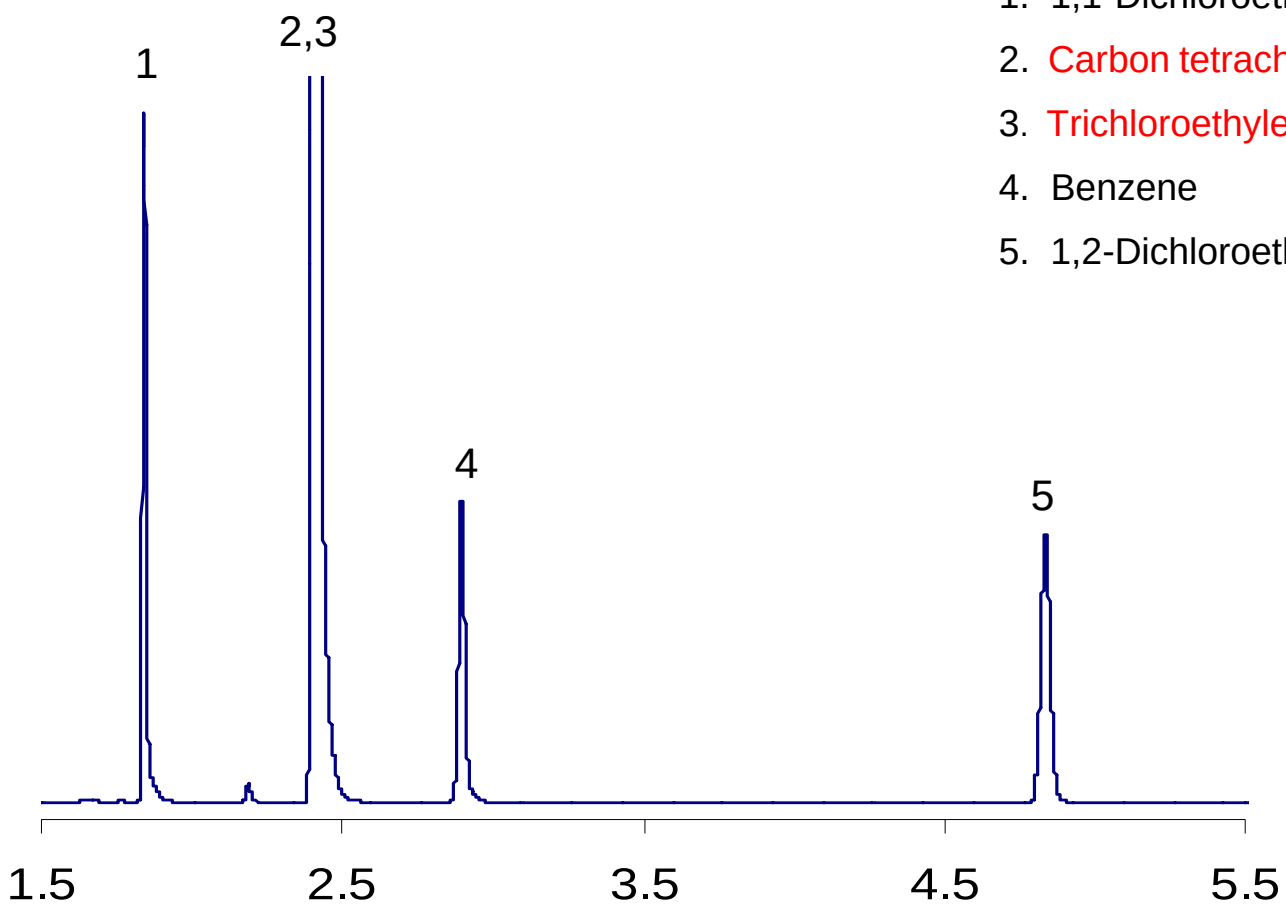
Class 2 Solvents @ Conentrations at Limit

Class 2 Resolution: Acetonitrile and Methylene Chloride 3.3

Class 1 Solvents: Procedure B

1

Agilent DB-WAX (G16 phase) p/n 122-7032
30m X 0.25mm X 0.25um



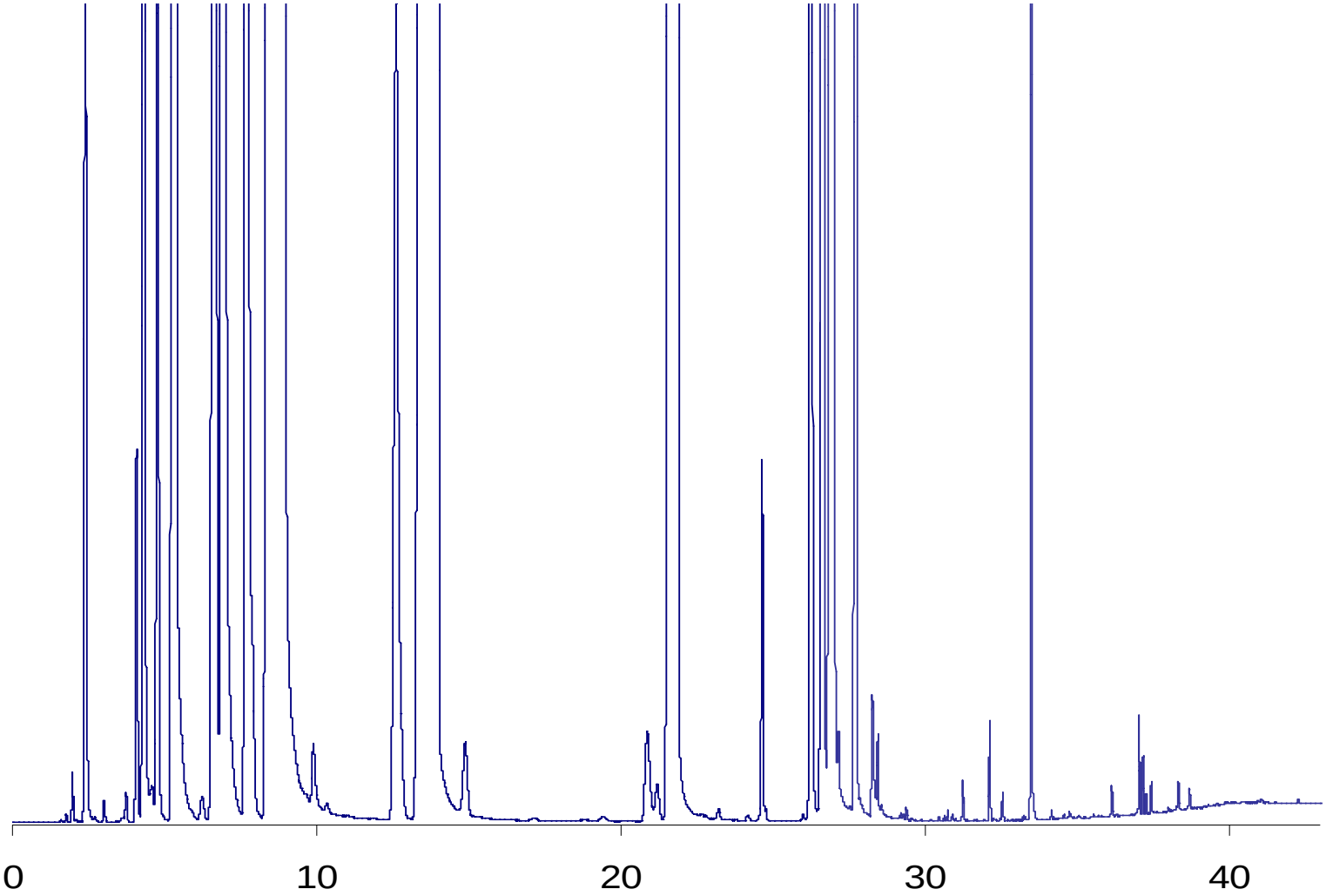
1. 1,1-Dichloroethylene
2. Carbon tetrachloride
3. Trichloroethylene
4. Benzene
5. 1,2-Dichloroethane

Class 2 Peak Identifiers

Peak #	Solvent		
1	Acetonitrile		
2	Chlorobenzene		
3	Chloroform		
4	Cyclohexane		
5	1,2-Dichloroethene		
6	1,2-Dimethoxyethane		
7	N,N-Dimethylacetamide		
8	N,N-Dimethylformamide		
9	1,4-Dioxane		
10	2-Ethoxyethanol		
11	Ethylene glycol		
12	Formamide		
13	Hexane		
14	Methanol		
15	2-Methoxyethanol		
16	Methylbutylketone		
17	Methylcyclohexane		
18	Methylene chloride		
19	N-Methylpyrrolidone		
20	Nitromethane		
21	Pyridine		
22	Sulfolane		
23	Tetrahydrofuran		
24	Tetralin		
25	Toluene		
26	Trichloroethylene		
27	Ethyl Benzene		
28	o-Xylene		
29	m-Xylene		
30	p-Xylene		

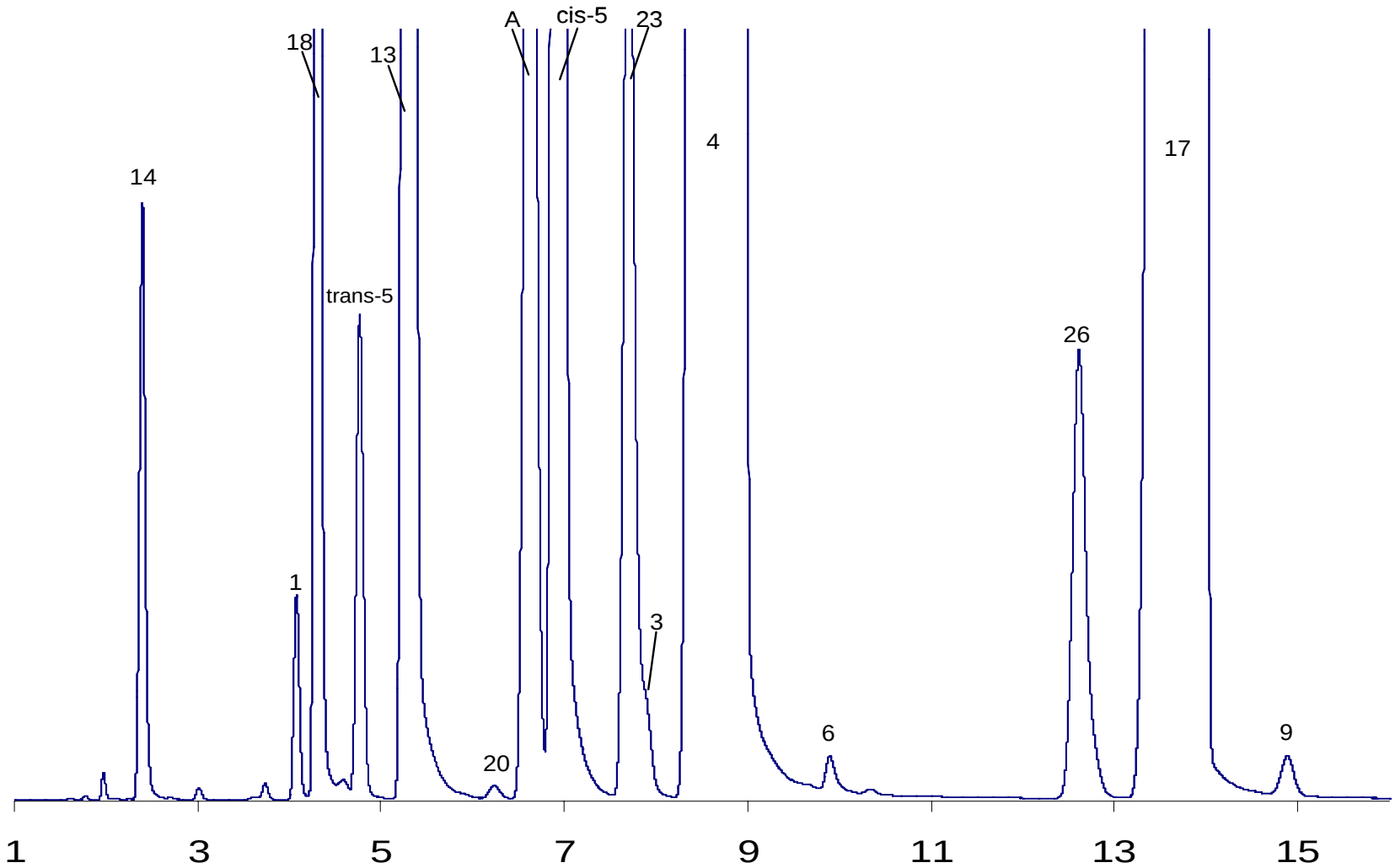
Prodecure A: Class 2 Solvents

DB-624 (G43 phase)



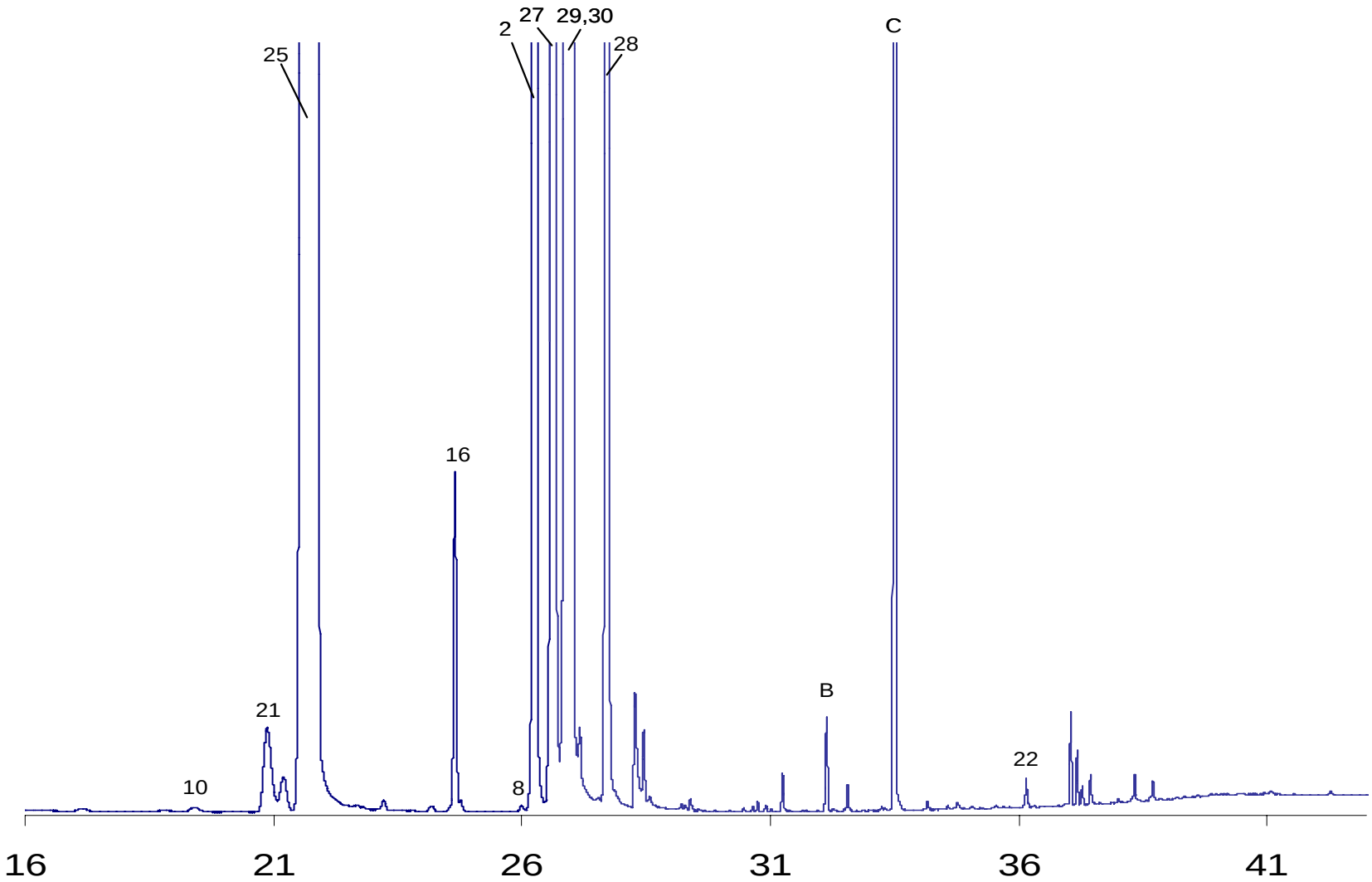
Class 2 Solvents Procedure A

DB-624 (G43 phase)



Procedure A Class 2

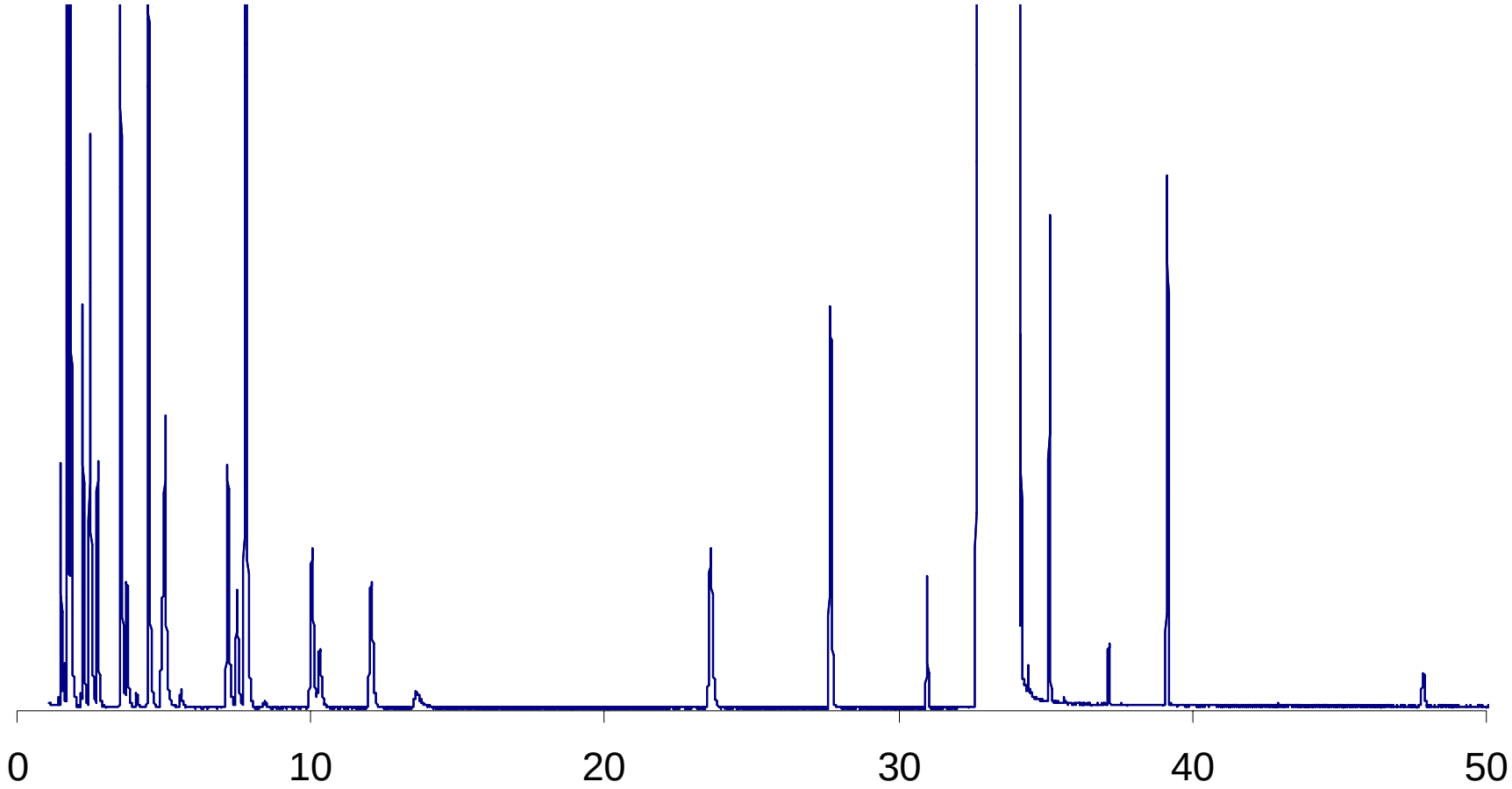
DB-624 (G43 phase)



Procedure B Class 2

DB-WAX (G16 phase)

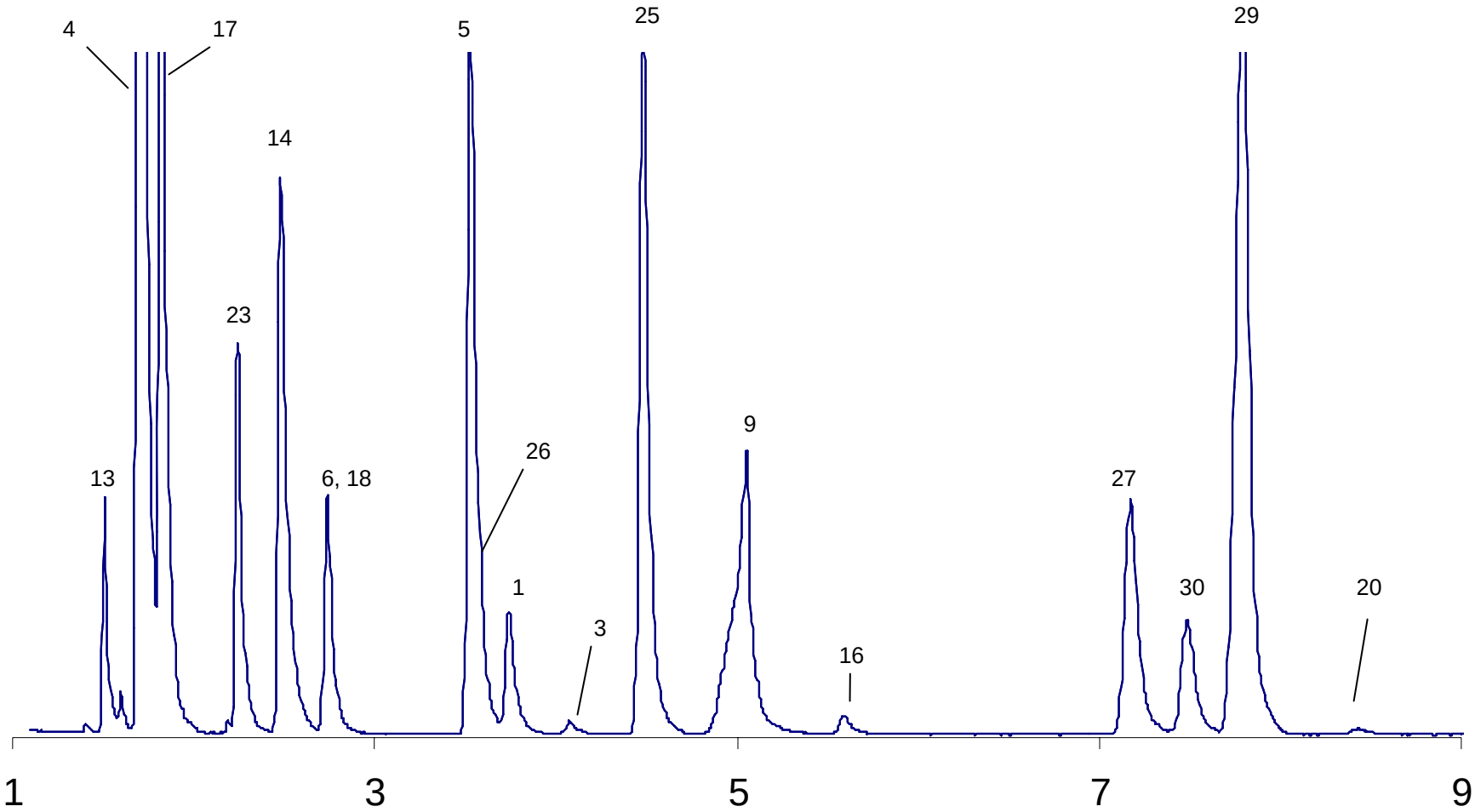
30m X 0.25mm X 0.25um



Procedure B Class 2

DB-WAX (G16 phase)

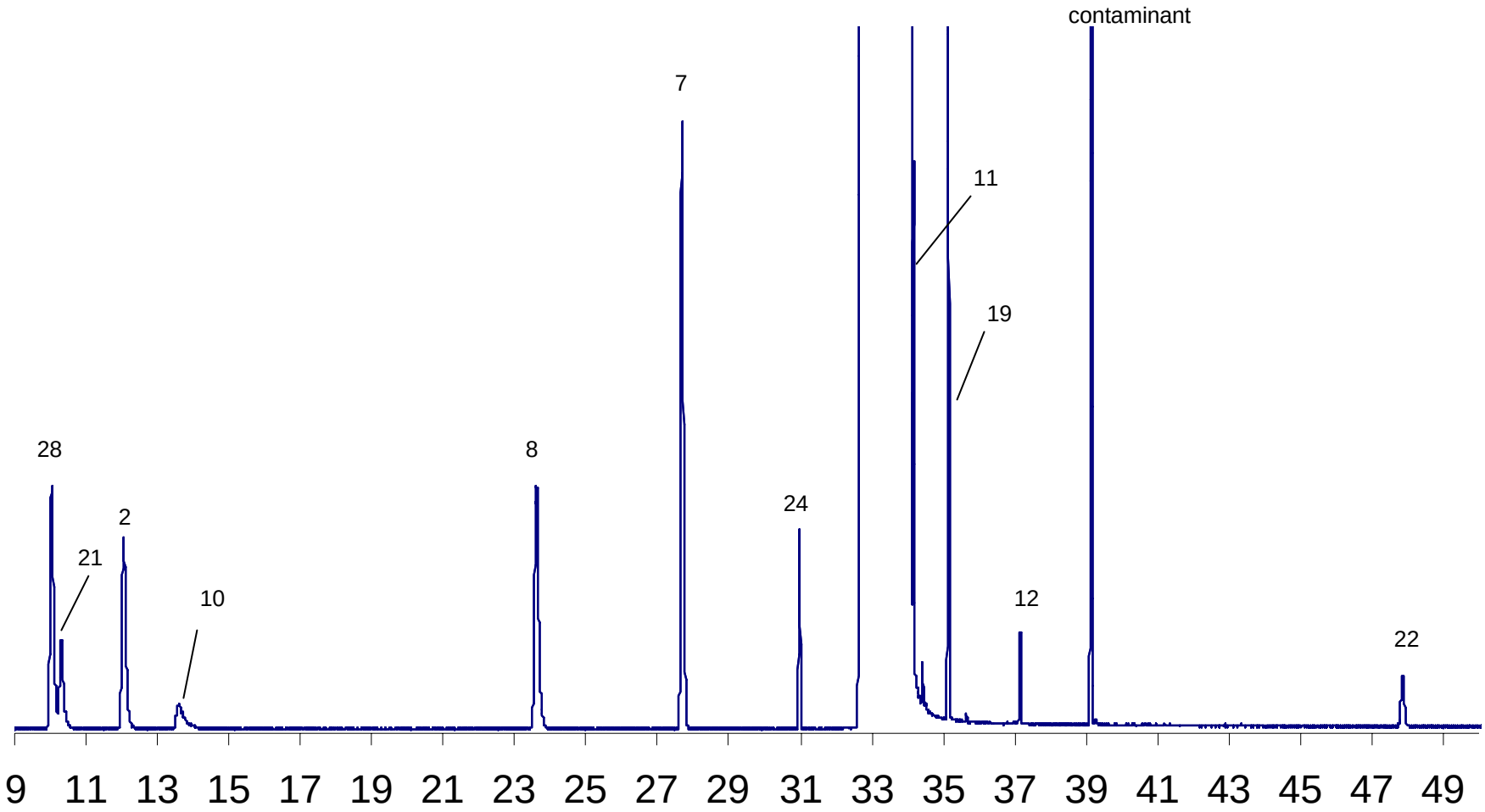
30m X 0.25mm X 0.25um



Procedure B Class 2

DB-WAX (G16 phase)

30m X 0.25mm X 0.25um

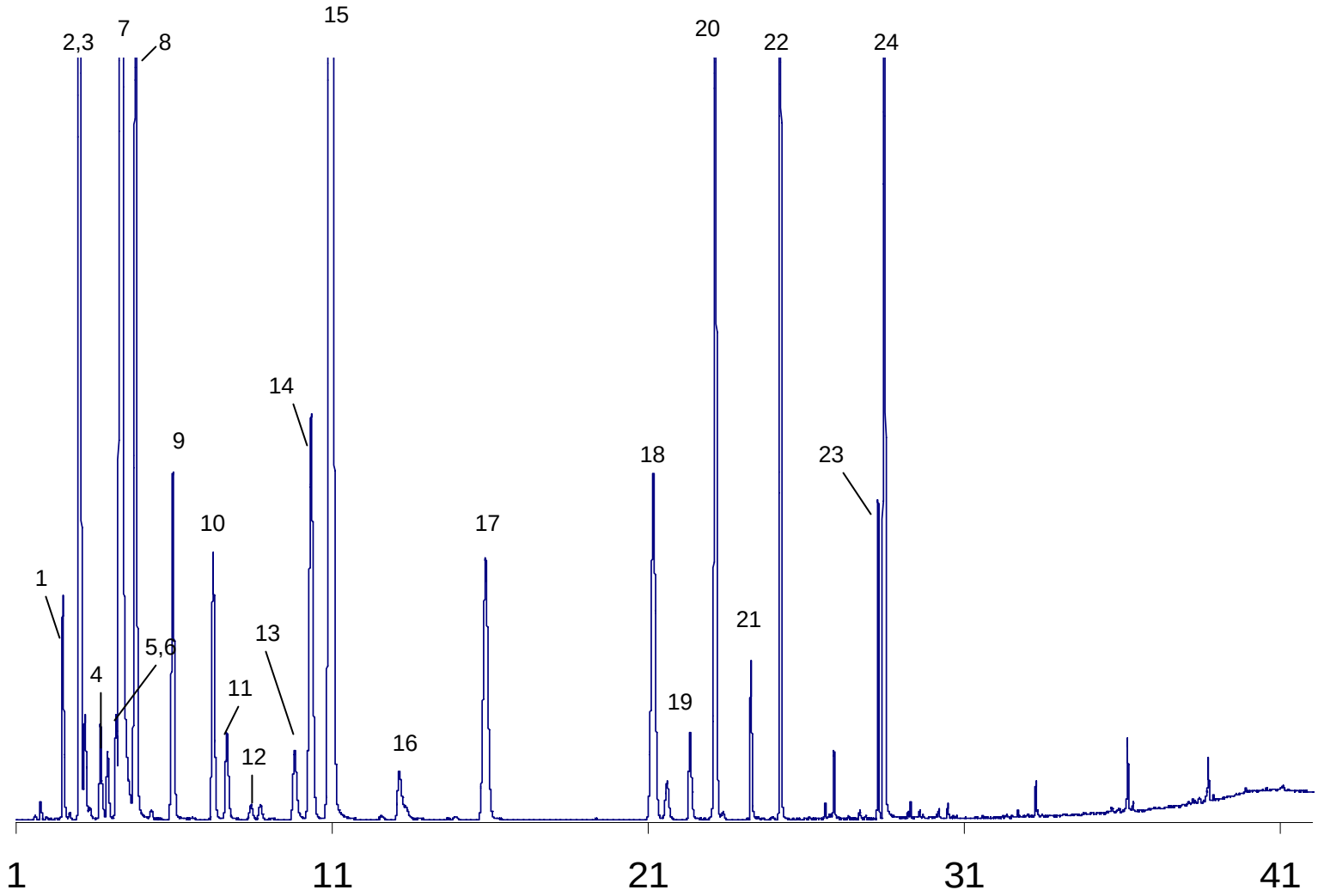


Class 3 Residual Solvents: Low Toxic Potential

Peak #	Solvent	CAS #	Concentration Limit (ppm)
1	Pentane	109-66-0	5000 for daily doses not greater than 10 g.
2	Ethanol	64-17-5	
3	Ethyl ether	60-29-7	
4	Acetone	67-54-1	
5	Ethyl formate	109-94-4	
6	2-Propanol	67-63-0	
7	Methyl acetate	79-20-9	
8	Methyl –tert-Butyl ether	1634-04-4	
9	1-Propanol	71-23-8	
10	Methyl ethyl ketone	78-93-3	
11	Ethyl acetate	141-78-6	
12	2-Butanol	98-92-2	
13	2-Methyl-1-propanol	78-83-1	
14	Isopropyl acetate	108-21-4	
15	Heptane	142-82-5	
16	1-Butanol	71-36-3	
17	Propyl acetate	109-60-4	
18	Methyl isobutyl ketone	108-10-1	
19	3-Methyl-1-butanol	123-51-3	
20	Isobutyl acetate	110-19-0	
21	1-Pentanol	71-41-0	
22	Butyl acetate	123-86-4	
23	Cumene	98-82-8	
24	Anisole	100-66-3	
25 Not shown	Dimethyl sulphoxide	67-68-5	
26 Not shown	Formic acid	64-18-6	
27 Not shown	Acetic acid	64-19-7	

Procedure A Class 3 Solvents

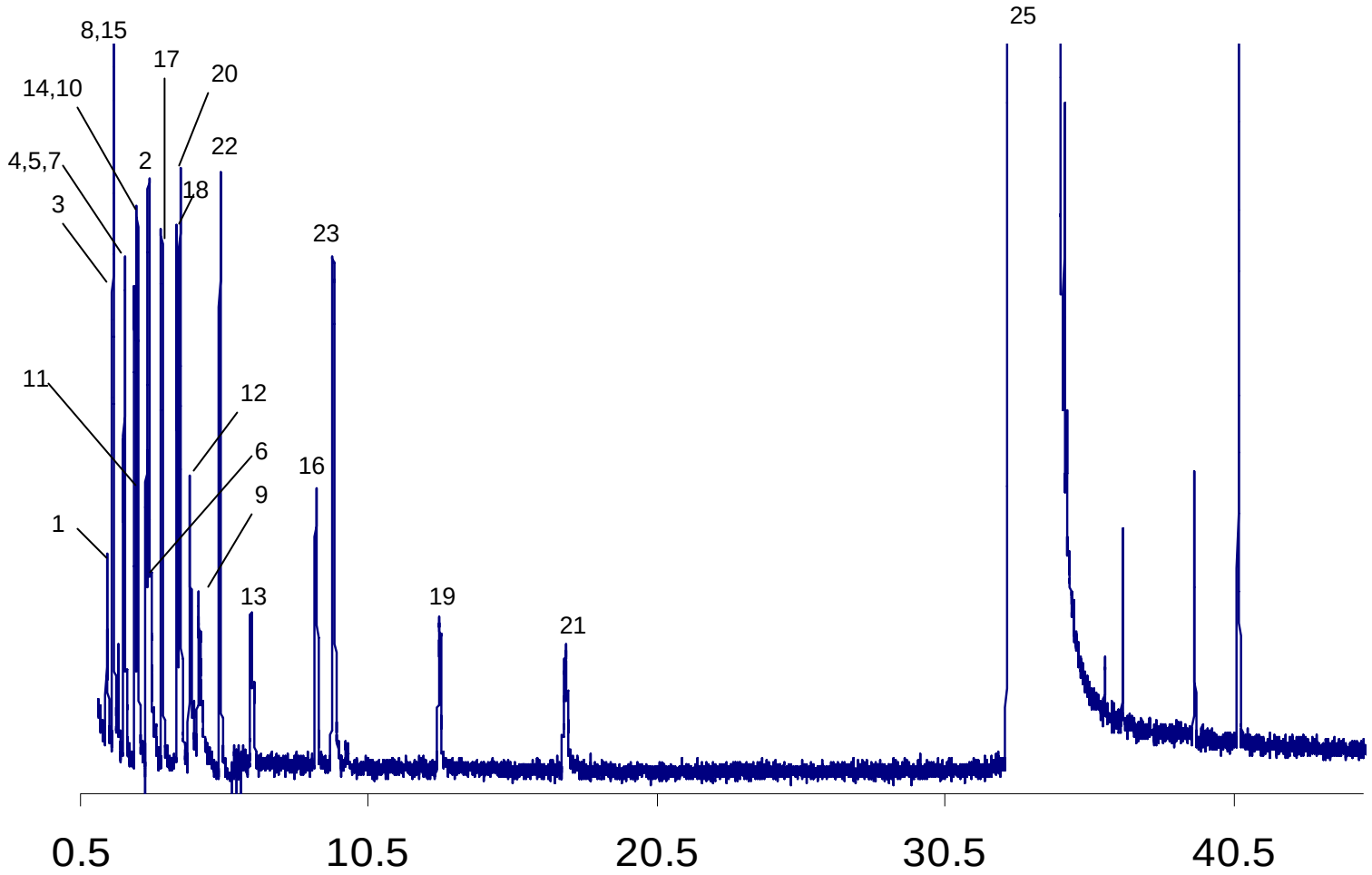
DB-624 (G43 phase)



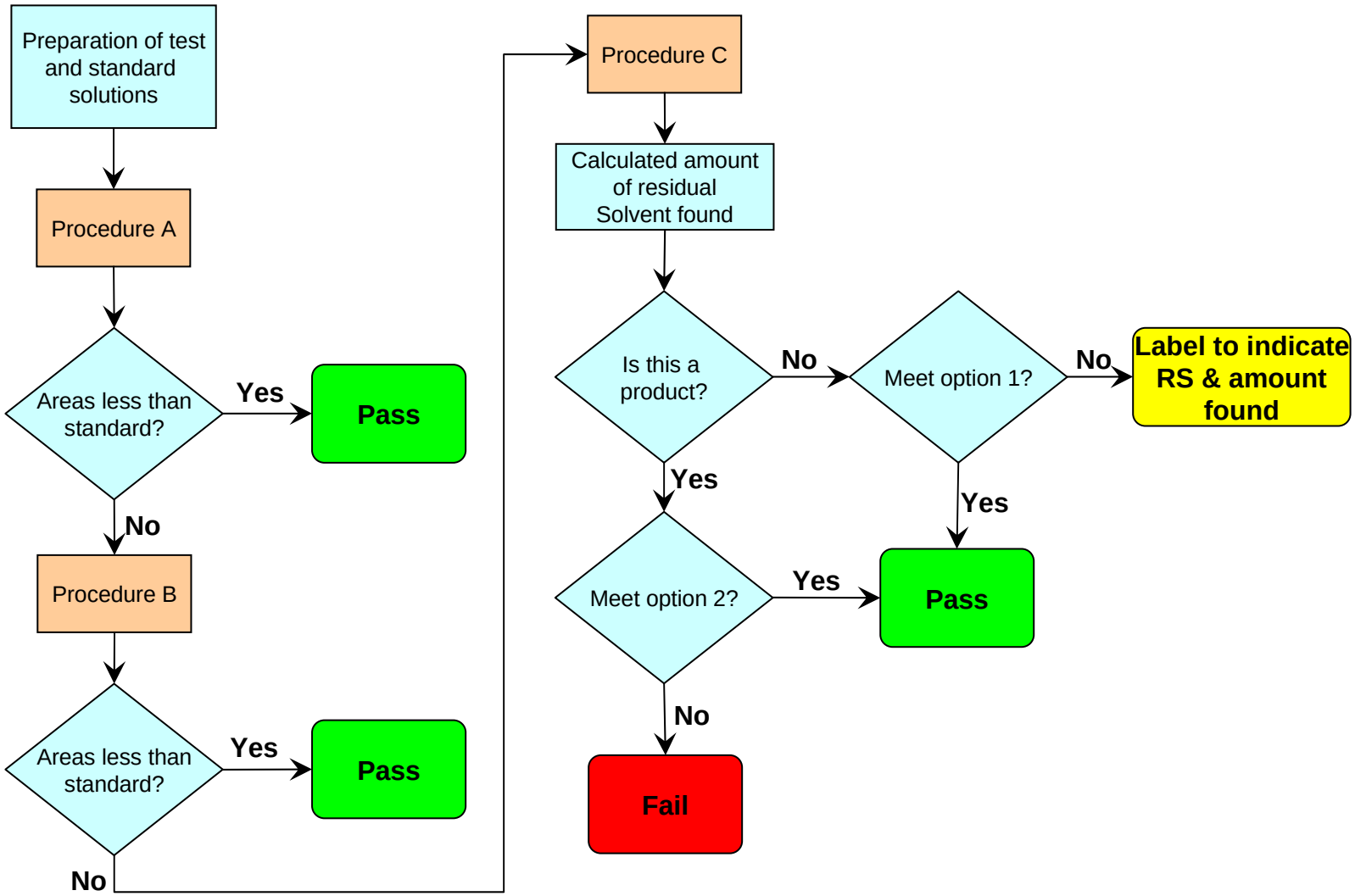
Procedure B Class 3

DB-WAX (G16 phase)

30m X 0.25mm X 0.25um



Navigating the Decision Tree:



Procedure C

Same as for Procedure A*…….Plus

Standard solution(s) – for each peak identified and verified by Prodecures A & B by dilution of the respective USP Residual Solvent Reference Standard

Spiked Test solution

*If the results from Procedure B are superior, use procedure B conditions

Procedure C continued…

Same System Suitability Applies

Calculate the ppm of each residual solvent:

$$= 5\left(\frac{C}{W}\right)\left(\frac{r_u}{(r_{st} - r_u)}\right)$$

C = Concentration in ppm of USP Standard

W = Weight in g of test article

Ru = peak response of the RS in the Test Solution

Rst = peak response of RS in the Spiked Test Solution

What Changes “May” be Acceptible

Permit a change in split ratio

Permit the addition of Water to the vial for Water-Insoluble Articles

Permit the use of DMI, DMF, or DMSO as the aprotic solvent for Water-Insoluble Articles

Proposed Limits for Adjustments

Column length +/- 70%

Column Inner Diameter: +/- 50%

Film thickness: -50 to 100%

Flow rate: +/- 50%

Injection volume: can be reduced provided LOD and RSD are OK

Oven temperature: +/- 10%

Oven temperature program: temperature +/- 10% - plateau temperature or “change temperature” +/- 20%

What Can Agilent Help You With?

Faster analyses?

- Backflushing
- Smaller ID columns?

Reproducibility?

- Back pressure regulation for Headspace.

Worried about updating your GC?

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