PMI RESEARCH & DEVELOPMENT

‘Next Generation Fingerprinting’

A GC-HR-TOF-MS Method to Semi-Quantify Constituents in Aerosols and Aerosol Fractions

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Outline

1. Description of the existing GC-MS fingerprinting method
   - Pros & cons of the current fingerprinting method
   - Why switching to a 7200 Agilent high resolution MS instrument?
2. How to tackle semi-quantification of the smoke constituents with the help of chemoinformatics tools
   - Curation step for smoke constituents to be monitored
   - Analysis of reference standards
   - Retention time prediction model (QSPR approach)
   - Selection of appropriate internal standards (clustering approach)
3. Semi-quantification from calibration curve of reference standards
   - Linearity
   - Assessment of silylation
4. What about other smoke constituents?
5. Conclusion

Existing Fingerprinting Method

- Aerosol sample generated from a smoking machine (ISO)
  - Whole smoke
  - Gas Vapor Phase (GVP)
  - Total Particulate Matter (TPM)

} sbPBS

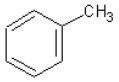
- Compounds list

- GC columns (HP6890 GC)
  - DB-624: HS-SPME-GC-MS — Volatile Chemicals
  - DB-FFAP: GC-MS — Non Polar Chemicals
  - DB-5-MS: HT-GC-MS — Polar Chemicals (TMS)

- Detection (MSD5973 MS)
  - Electron ionization mode
  - Full scan (low resolution) — Semi-quantification (d_6-phenol)

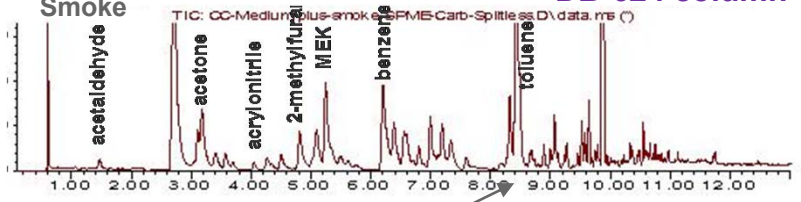
Description of the Former GC-MS Fingerprinting Method (HP6890 GC - MSD5973 MS)

- **Headspace(HS)-SPME-GC-MS**
  high volatile compounds

e.g.:  acetaldehyde up to  toluene

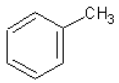
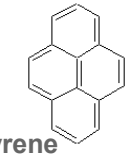
Cell culture Medium plus Cigarette Smoke

DB-624 column



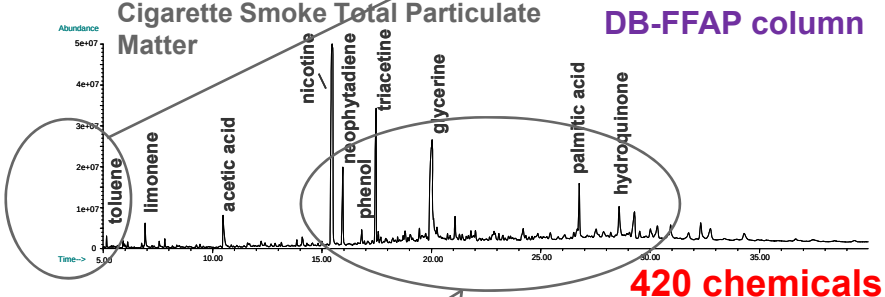
51 chemicals

- **GC-MS Fingerprint (Standard Method)**
  nonpolar compounds

e.g.:  toluene up to  pyrene

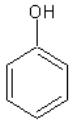
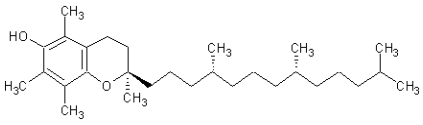
Cigarette Smoke Total Particulate Matter

DB-FFAP column



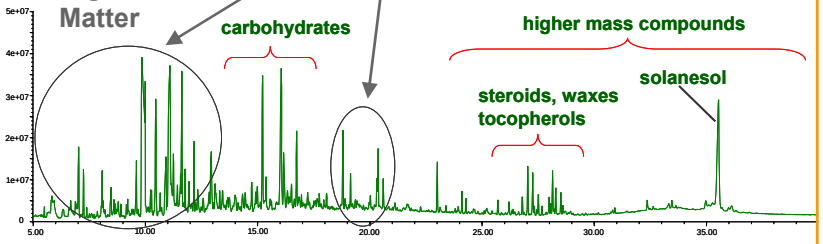
420 chemicals

- **High Temperature(HT)-GC-MS**
  derivatized, polar compounds

e.g.:  phenol up to  (±)-α-tocopherol

Cigarette Smoke Total Particulate Matter

DB-5-MS column



155 chemicals

A total of ~607 smoke constituents are monitored using 3 distinct GC columns but not all were unambiguously identified

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Smoke Constituents Targeted in the Previous Method

aliph. Hydrocarbons	aliphatic hydrocarbon-isom.4	propylbenzene	methyl-fluorene	anethol	benzoic acid	isovaleramide-isom.2
1,3-butadiene	unsaturated hydrocarbon-isom.4	C3-alkyl.benzene-isom.1	phenanthrene	methylanisole-isom.1	2-furanecarboxolic acid	4-methyl-pentaneamide
isoprene	unsaturated hydrocarbon-isom.5	C3-alkyl.benzene-isom.2	fluoranthene	**alcoholes (without glycerine)**	phenylacetic acid	picolinamide
1,3,5-heptatriene	4,4'-dimethylbiphenyl	C3-alkyl.benzene-isom.3	pyrene	2-methoxyethanol	phenylpropionic acid	glykolamide
1,3,5-cycloheptatriene	aliphatic hydrocarbon-isom.5	styrene	**o-heterocycles**	2-methoxypropanol	niacine	phenylacetamide
dimethyl-methylenecyclohexene	unsaturated hydrocarbon-isom.6	C3-alkyl.benzene-isom.4	furan	propylenglykole	**long-chained acids (>=C8)**	N-methyl-nicotinamide
terpene (type:limonene)	unsaturated hydrocarbon-isom.7	2-propenylbenzene	2,5-dimethylfuran	2-furanmethanole	caprylic acid (C8:0)	pyrrole-2-carboxamide
2,7-dimethyl-1,6-octadiene	aliphatic hydrocarbon-isom.6	C4-alkyl.benzene-isom.1	2,4-dimethylfuran	beta-citronellol	decanoic acid(C10:0)	niacinamide
2,6-dimethyl-2,6-octadiene	unsaturated diterpen	C3-alkyl.benzene-isom.5	2,3,5-trimethylfuran	benzylalcohol	dodecanoic acid(C12:0)	hexadecaneamide
p-menthene (hydrocarbon-terpene)	unsaturated hydrocarbon (ca. C25)	C4-alkyl.benzene-isom.2	vinylfurane	beta-ionol	myristic acid (C14:0)	O-methyl-N-methylcarbamate
1-undecene	unsaturated hydrocarbon-isom.8	C4-alkyl.benzene-isom.3	2-vinyl-5-methylfurane	farnesol-s		
trimethylheptatriene	unsaturated hydrocarbon-isom.9	C4-alkyl.benzene-isom.4	benzofuran	glycerine-		
methyl-methyleneoctadiene	heptacosane (C27H56)	methyl-styrene-isom.1	methylbenzofuran	**glycerine**		
beta-myrcene	aliphatic hydrocarbon-isom.7	C3-alkyl.benzene-isom.6	1,3-dihydroisobenzofurane	farnesol-is		
limonene	2-methyloctacosane(C29H60)	C4-alkyl.benzene-isom.5	2,3-dihydrobenzofurane	geranyllina		
dodecane	aliphatic hydrocarbon-isom.8	methyl-styrene-isom.2	**steroids derivatives**	cis-phytol		
dodecene	aliphatic hydrocarbon-isom.9	ethinylbenzene	stigmasterolacetate	trans-phyt		
2,7-dimethyl-1,3,6-octatriene	aliphatic hydrocarbon (ca. C30H62)	C4-alkyl.benzene-isom.6	beta-sitosterolacetate	farnesol s		
tridecane	triacontane(C30H62)	propenylbenzene	**esters + ethers (without triacetine)**	isomentho		
aliphatic hydrocarbon-isom.1	2-methyltriacontane(C31H64)	propenyltoluene-isom.1	3-butenoic acid methylester	phytubero		
1,3,8-p-menthatriene	unsaturated hydrocarbon-isom.11	propenyltoluene-isom.2	2-propenylformiate	**sugars,**		
aliphatic hydrocarbon-isom.2	unsaturated hydrocarbon-isom.12	indene	isoamylbutyrate	dianhydro		
aliphatic hydrocarbon-isom.3	hentriacontane(C31H64)	methyl-indene-isom.1	glycoldiacetate	3,4-anhyd		
copaene	aliphatic hydrocarbon-isom.10	methyl-indene-isom.2	geranylacetate	levoglucos		
pentadecane	aliphatic hydrocarbon (C32H66)	methyl-indene-isom.3	benzylacetate	**short-ch. + ar. Acids**	3-methylbutanenitrile	3-methyl-2-butenal
1-pentadecene	aliphatic hydrocarbon-isom.11	dimethylindene-isom.1	dimethylsuccinate	acetic acid	crotonnitrile	2-hexenal
1-methylcyclooctene	2-methyldotriacontane(C33H68)	azulene	**triacetine**	formic acid	4-methyl-pentanenitrile	2,4-hexadienal
unsaturated hydrocarbon-isom.1	aliphatic hydrocarbon (C33H68)	dimethylindene-isom.2	methylpalmitate	propionic acid	2-ethylideneamino-propionnitrile	furfural
1-hexadecene	unsaturated hydrocarbon-isom.13	ethylindene	glycerin-diacetate	2-methyl-propionic acid	benzonitrile	1-(2-furanyl)-ethanone
sesquiterpene(unsaturated KW)	beta-caryophyllene	naphthalene	ethylpalmitate	butyric acid	tolunitrile-isom.1	benzaldehyde
heptadecane	alpha-caryophyllene	trimethylindene	methylstearate	acrylic acid	tolunitrile-isom.2	methylimidazole-carboxaldehyde
farnesene	**arom. Hydrocarbons**	2-methylnaphthalene	6-acetoxy-2,7,11-cembratriene	2-/3-methylbutyric acid	nicotinonitrile	5-methyl-2-furfural
unsaturated hydrocarbon-isom.2	toluene	1-methylnaphthalene	methyl-pyroglutamate	isocrotonic acid	benzylnitrile	tolualdehyde
delta-cadinene	ethylbenzene	dimethylnaphthalene	benzyl benzoate	crotonic acid	**amides**	cinnamaldehyde
3,7,11,15-tetramethyl-2-hexadecene	xylene-isom.1	biphenyl	muskalactone	3-methyl-valeric acid	acetamide	p-ethylbenzaldehyde
neophytadiene	xylene-isom.2	methyl-biphenyl	methyl-salicylate	capronic acid (C6:0)	propionamide	acetaldehyde
unsaturated hydrocarbon-isom.3	isopropylbenzene	trimethylnaphthalene	1,1-dimethyl-2-phenylethylbutyrate	2-methyl-crotonic acid	isovaleramide-isom.1	trimethoxy-acetophenone(Ga
1,4-eicosadiene	xylene-isom.3	fluorene	triethylcitrate	sorbic acid	acrylamide	

Broad chemical diversity categorized in chemical families … but smoke constituents were not well defined

A time consuming curation of smoke constituents was required to register every compound as Unique Compound Spectral Database (UCSD)

Martin et al. Building an R&D chemical registration system, J. Cheminformatics 2012, *4*:11.

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Next Generation Fingerprinting: Practical Considerations

- Smoke constituents (SC) to monitor:
  - Unique identified compounds
  - List of chemicals & chemical compounds identified by FDA* as Harmful & Potential Harmful Constituents (HPHCs) in tobacco products & tobacco smoke (n=72 out of 93)
  - Reported compounds in tobacco plant and tobacco smoke
  - Flavor compounds

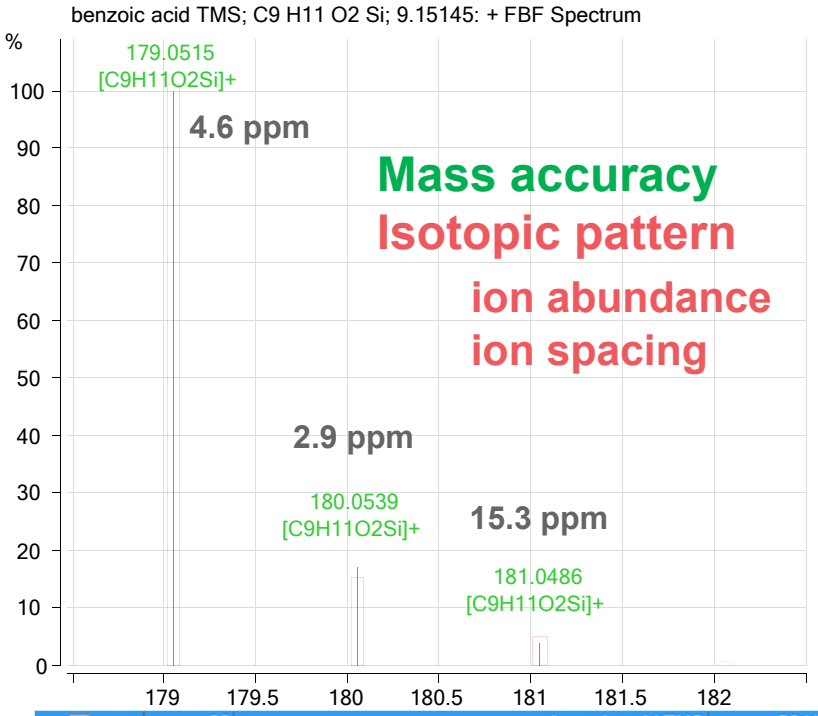
- GC (7890A)
  - DB-624: HS-SPME-GC-MS — Volatile chemicals
  - DB-5-MS: GC-MS — Non-polar and Polar chemicals (TMS)
  - DB-FFAP: HT-GC-MS

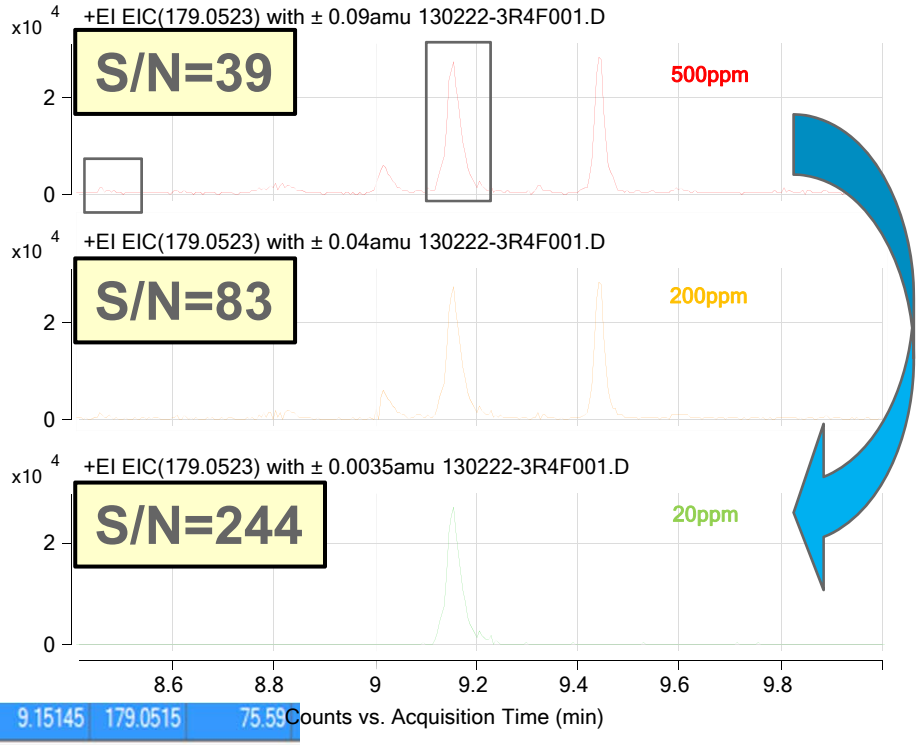
- MS detection (7200 Agilent Q-TOF)
  - Electron ionization mode
  - Full scan - Low resolution ➔ High Resolution, Mass Accuracy

Semi-quantification (several ISs)

**FDA: Federal Register / Vol. 77, No. 64 / Tuesday, April 3, 2012 / Notices, 20034-20037*

The Impact of use of High Resolution MS Instrument





☑	28		benzoic acid TMS	C9 H11 O2 Si	9.15145	179.0515	75.59

Best	ID Source	Name	Formula	Score	Score (RT)	RT Diff	Diff (ppm)
◉	FBF	benzoic acid TMS	C9 H11 O2 Si	75.59	0.27	0.279	4.72

m/z	Species	Score (MS)	Score (mass)	Score (iso. abund)	Score (iso. spacing)	Height
179.0515	M+	94.42	92.39	94.65	96.9	12673.8

m/z (Calc)	m/z	Diff (ppm)	Height	Height (Calc)	Height %	Height % (Calc)	Height Sum
179.0523	179.0515	4.62	12550.7	12673.8	100	100	
180.0544	180.0539	2.85	2134.9	1903.2	17	15	
181.0514	181.0486	15.26	488.2	596.9	3.9	4.7	

Sensitivity ☝

Confidence level ☝

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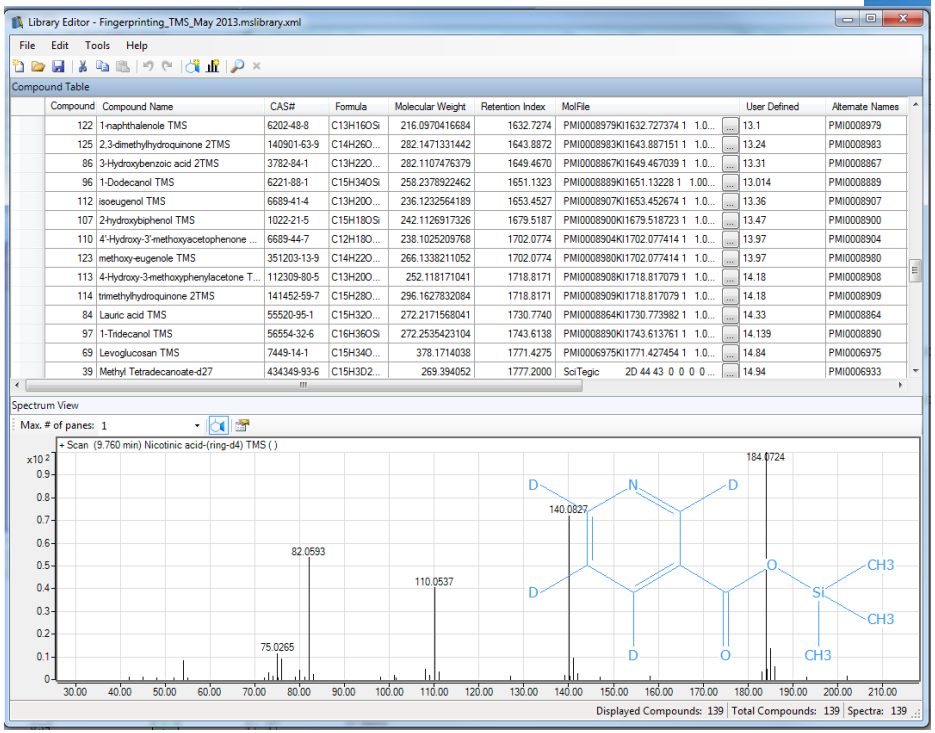
Analysis of Reference Compounds

Reference standards ordered (n~600 + 63 ISs)

- Chemical registration within UCSD ➔ unique PMI code
- GC-EI-HR-MS (DB-5) with silylation (BSTFA) ➔ **n=360 standards**
- GC-EI-HR-MS (DB-5) without silylation ➔ **n=182 standards**
- HS-GC-EI-HR-MS (DB-624) ➔ **n= 60 standards**
- Assignment of EI HR mass spectrum – reference chemical
- Uploading of HR EI mass spectra in UCSD (unique SpecID)
- Building MS library specific to experimental conditions
  - Absolute Retention Time
  - Retention Index
  - EI mass spectrum
  - Mol file,…



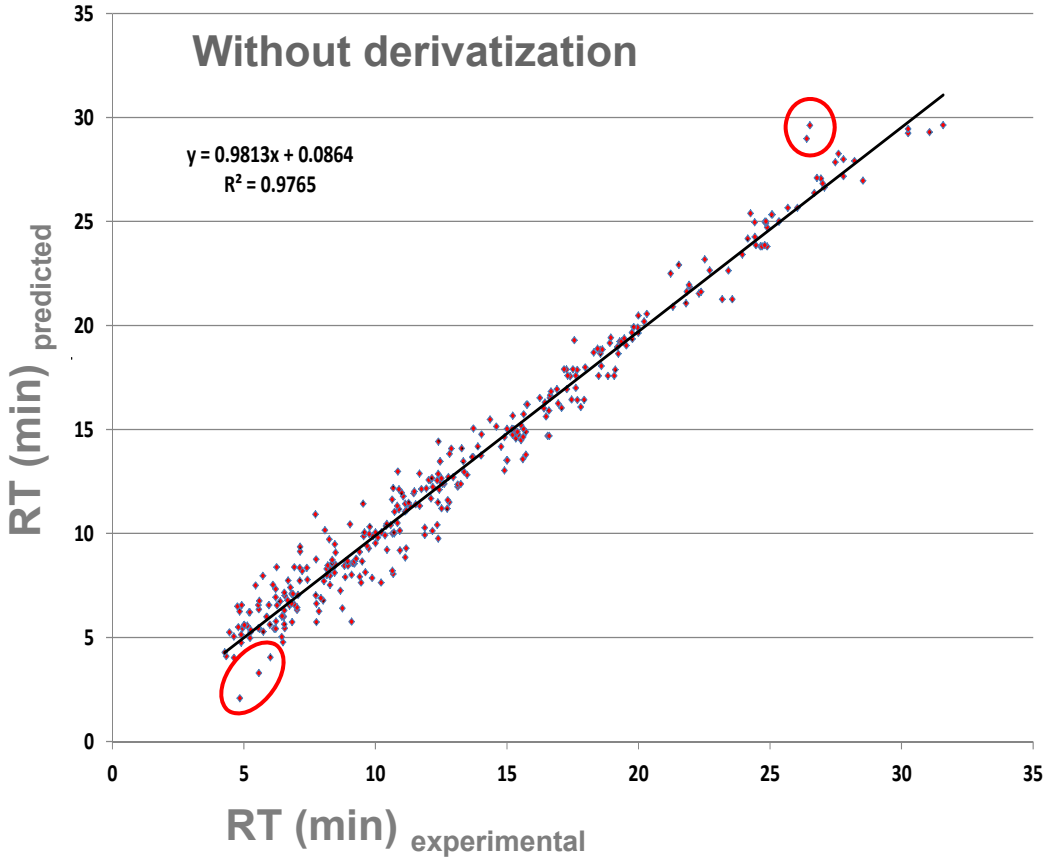
Building Statistical Prediction Model of Retention Time from Reference compounds on a DB-5-MS GC column

QSPR (structure-based) modeling was used to predict RT of compounds (Dragon)

- Training set:
  n=116 reference compounds
  10 chemical descriptors
  $r^2 = 0.986$

- Test set:
  n=56 reference compounds
  $r^2 = 0.979$

- Total external Validation set:
  n=346 reference compounds
  $r^2 = 0.9765$
  Median dev. = -8 sec
  Min = -3.3 min
  Max = +3.2 min



Very good prediction model was obtained from a set of broadly diverse reference compounds. Same model was used to predict over 900 components.

Clustering approaches to select appropriate internal standards

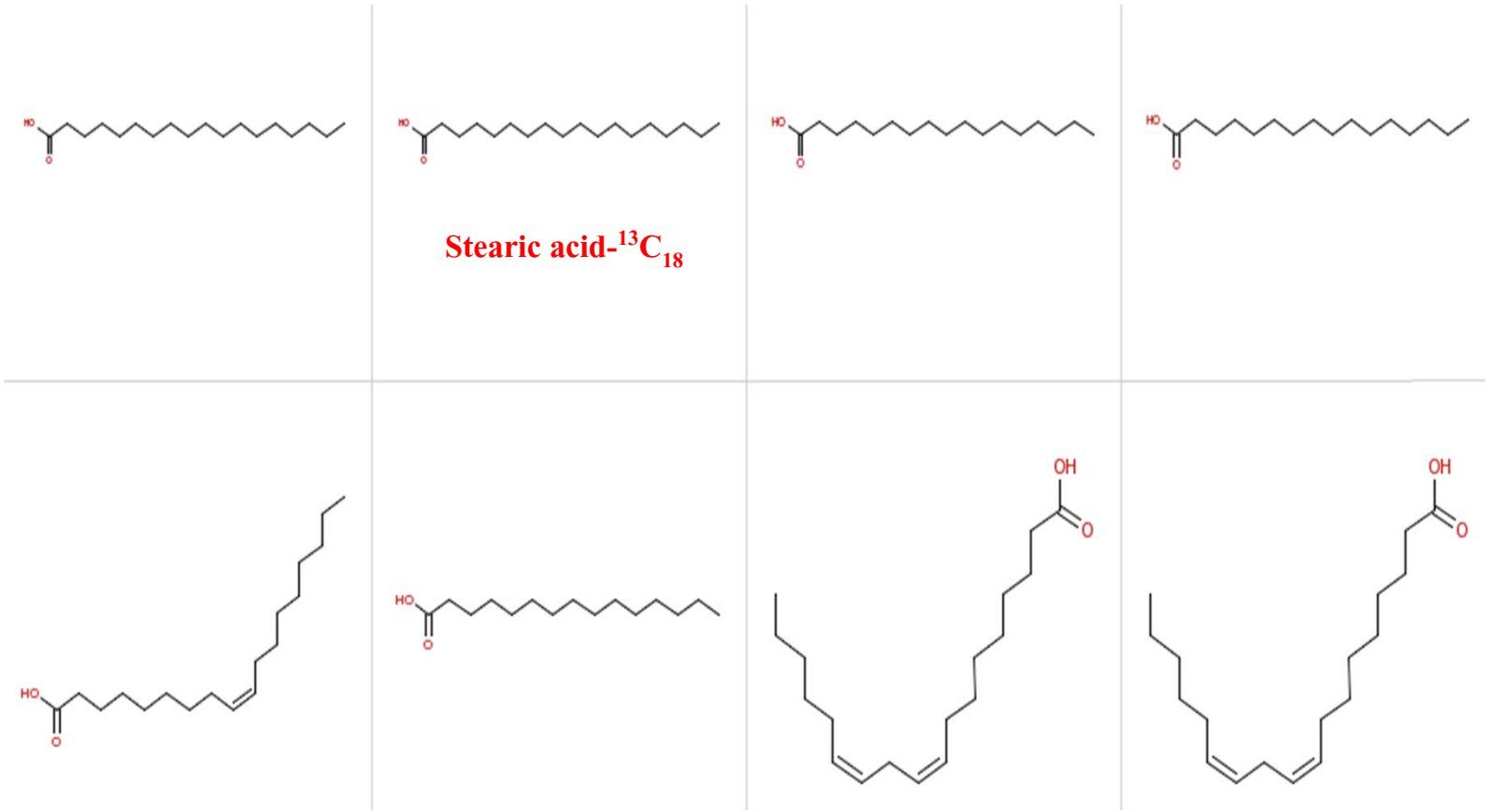
- Fingerprinting method should be high throughput
  - No calibration curve
  - Concentration estimated from an adequate IS (spiking addition)

- Clustering approach was used to select appropriate internal standards (Accelrys Pipeline Pilot 8.5)

- Adequate selection of IS is based on:
  - Similar physicochemical properties (i.e., logP, number of rotational bonds, polar surface area, volatility…)

- Smoke constituents were clustered into chemical families so that
  - At least one isotopically labeled IS (cluster center) was purchased for each cluster

Example: Cluster of Long Chain Fatty Acids



Selection of isotopically labeled internal standard was made from Central Euclidian distance value & commercial availability

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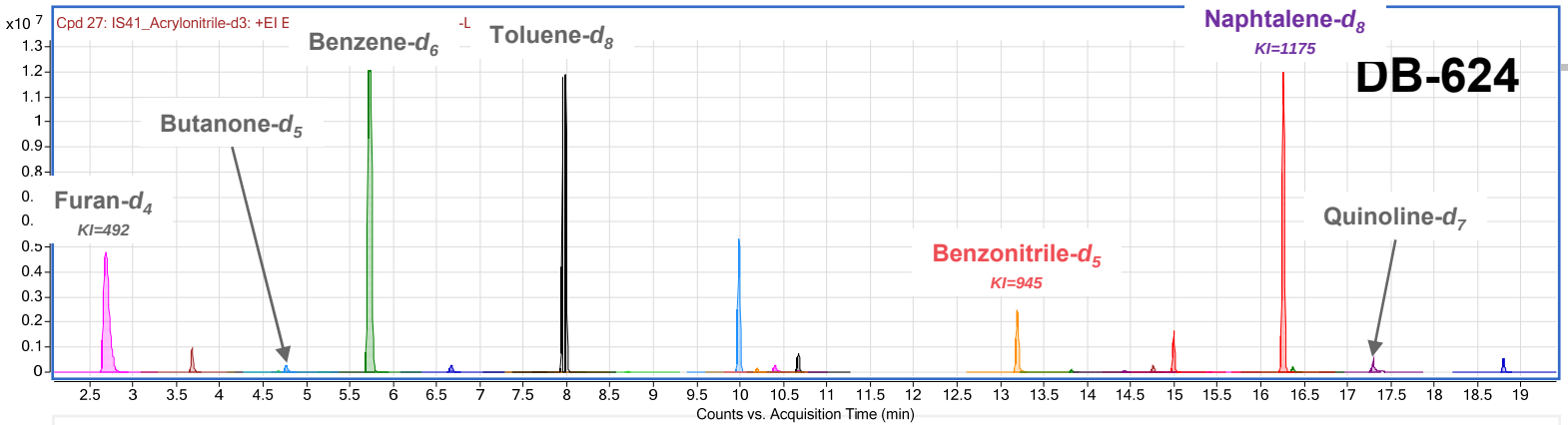
Clustering approach to improve semi-quantification

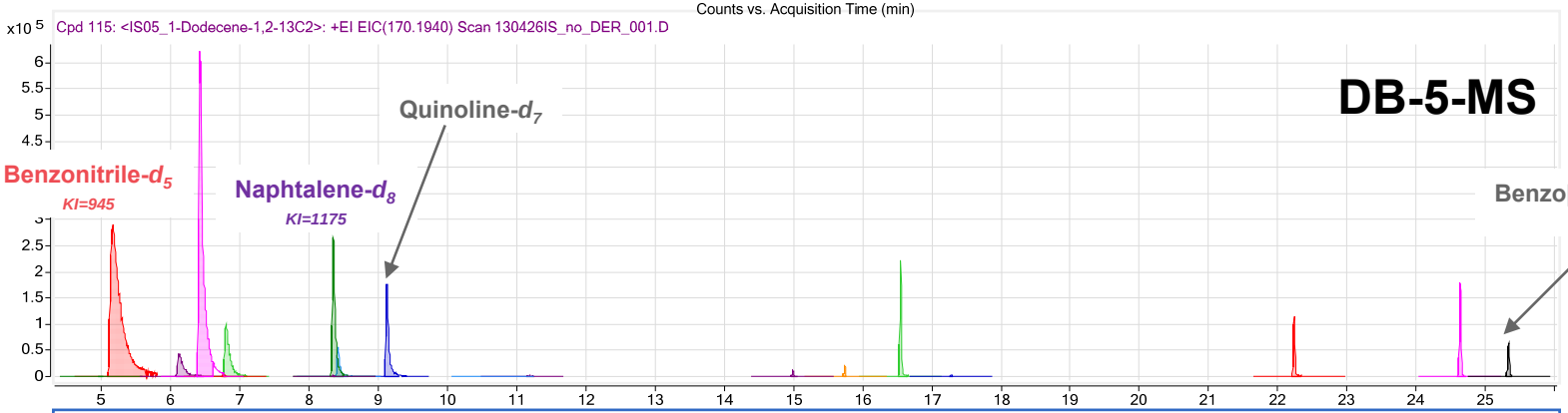
- Selection of 1 or 2 internal standards (IS) per cluster : **63** IS were purchased (from which **19** IS are present in the FDA list)
- Determination of semi-quantitative compound concentrations in relation to their respective internal standard
- Compensation for compound degradation issues (stability, partial silylation,…) was best by selecting adequate IS from the same cluster

	A	B	C	D	E	F	G	H	I	J	K
1	1	Name	Class	PMICODE	SMILES	MOLFORMULA	Cluster	DistanceToClosest	ClusterCenter	Predicted RT (min)	ClusterSize
38	38	1,4-eicosadiene	aliph. Hydrocarbons	PMI0000005	CCCCCCCCCCCCCCC/C=C/CC=C	C20 H38	3	0.598632979	0	17.72	12
39	31	heptadecane	aliph. Hydrocarbons	PMI0000067	CCCCCCCCCCCCCCCCC	C17 H36	3	0.611239758	0	14.62	12
40	36	neophytadiene	aliph. Hydrocarbons	PMI0000070	CC(C)CCCC(C)CCCC(C)CCCC(=C)C=C	C20 H38	3	0.630227377	0	15.22	12
1	645	**eicosanoic acid**	long chain Fatty Acids (>=C15)	PMI0000329	CCCCCCCCCCCCCCCCCCCC(=O)O	C20 H40 O2	5	0	5	20.9	8
2	197	stearic acid (C18:0)	long chain Fatty Acids (>=C15)	PMI0000166	CCCCCCCCCCCCCCCCCC(=O)O	C18 H36 O2	5	0.144818919	0	19.4	8
3	196	heptadecanoic acid (C17:0)	long chain Fatty Acids (>=C15)	PMI0000165	CCCCCCCCCCCCCCCCC(=O)O	C17 H34 O2	5	0.217228378	0	18.04	8
4	195	palmitic acid (C16:0)	long chain Fatty Acids (>=C15)	PMI0000164	CCCCCCCCCCCCCCCC(=O)O	C16 H32 O2	5	0.289637837	0	17	8
5	198	oleic acid (C18:1)	long chain Fatty Acids (>=C15)	PMI0000167	CCCCCCCC/C=C\CCCCCCCC(=O)O	C18 H34 O2	5	0.316505227	0	19.16	8
6	194	pentadecanoic acid (C15:0)	long chain Fatty Acids (>=C15)	PMI0000163	CCCCCCCCCCCCCCC(=O)O	C15 H30 O2	5	0.362113201	0	15.9	8
7	199	linolic acid(C18:2)	long chain Fatty Acids (>=C15)	PMI0000168	CCCCC/C=C\C/C=C\CCCCCCCC(=O)O	C18 H32 O2	5	0.388127838	0	19.23	8
8	200	linolenic acid (C18:3)	long chain Fatty Acids (>=C15)	PMI0000169	CC/C=C\C/C=C\C/C=C\CCCCCCCC(=O)O	C18 H30 O2	5	0.51606665	0	19.23	8
49	117	**pyrene**	arom. Hydrocarbons	PMI0000098	c1cc2ccc3cccc4c3c2c(c1)cc4	C16 H10	12	0	12	7.65	54

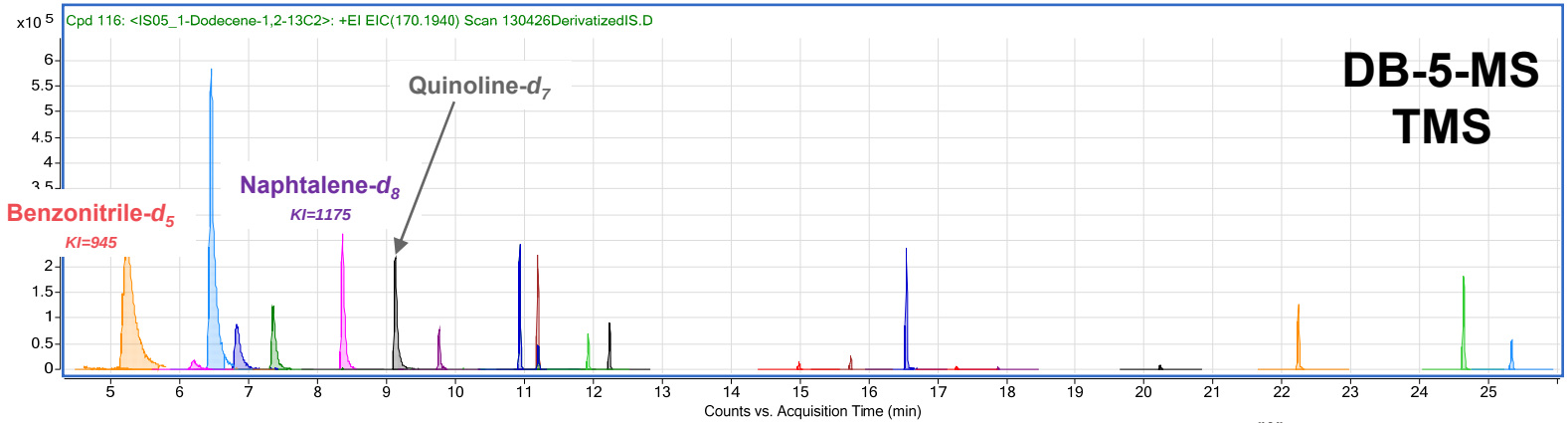
GC-EI-HR-MS of Internal Standards (n=63)



n=21



n=19



n=24

Good coverage of retention times

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   - Curation step for smoke constituents to be monitored
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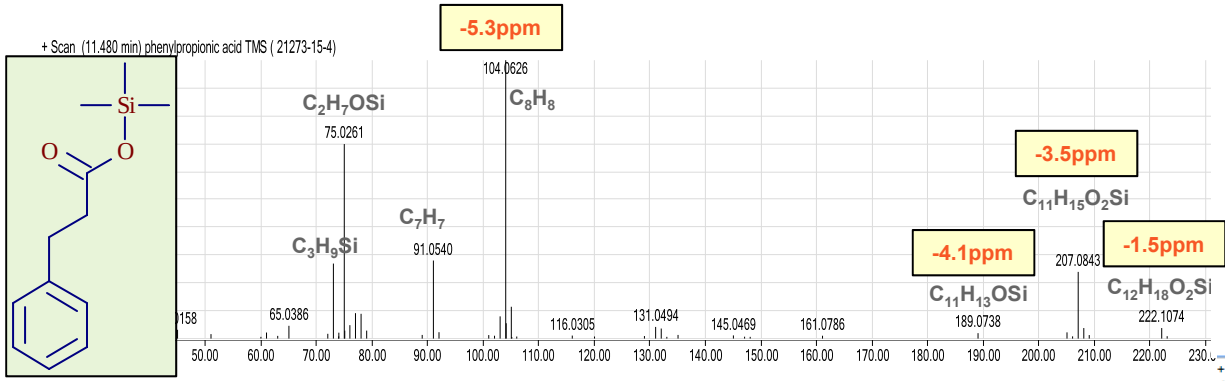
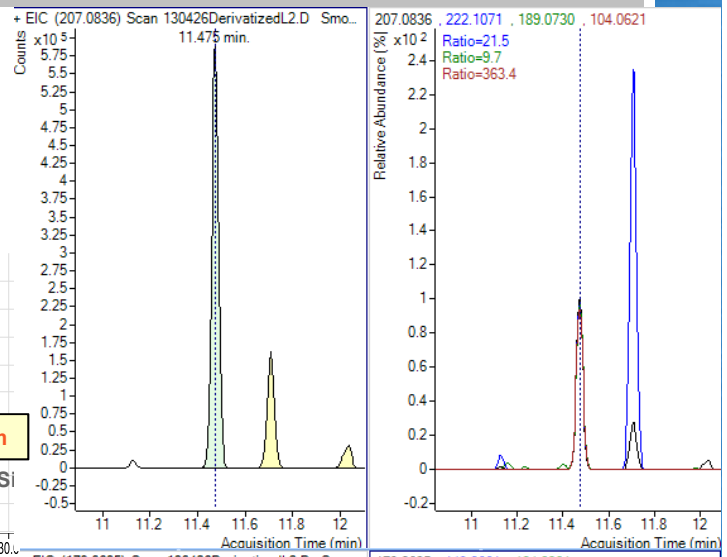
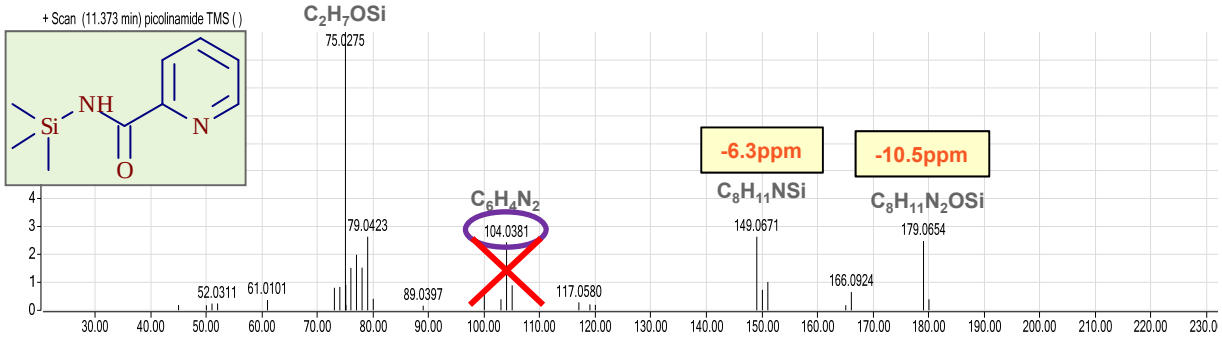
Quantitative Aspect: Importance of Qualifier ions

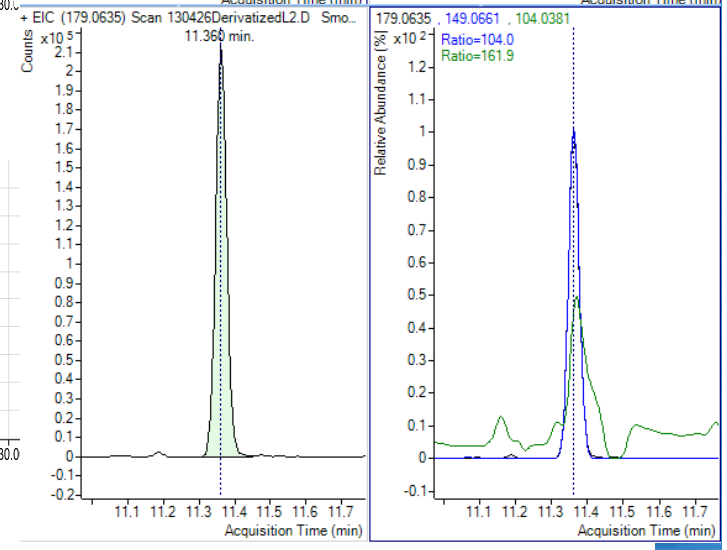
Phenylpropionic acid-TMS





Picolinamide-TMS





Ions highlighted in yellow were extracted for the semi-quantification

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Case Study: Cresol Isomers *o*-Cresol

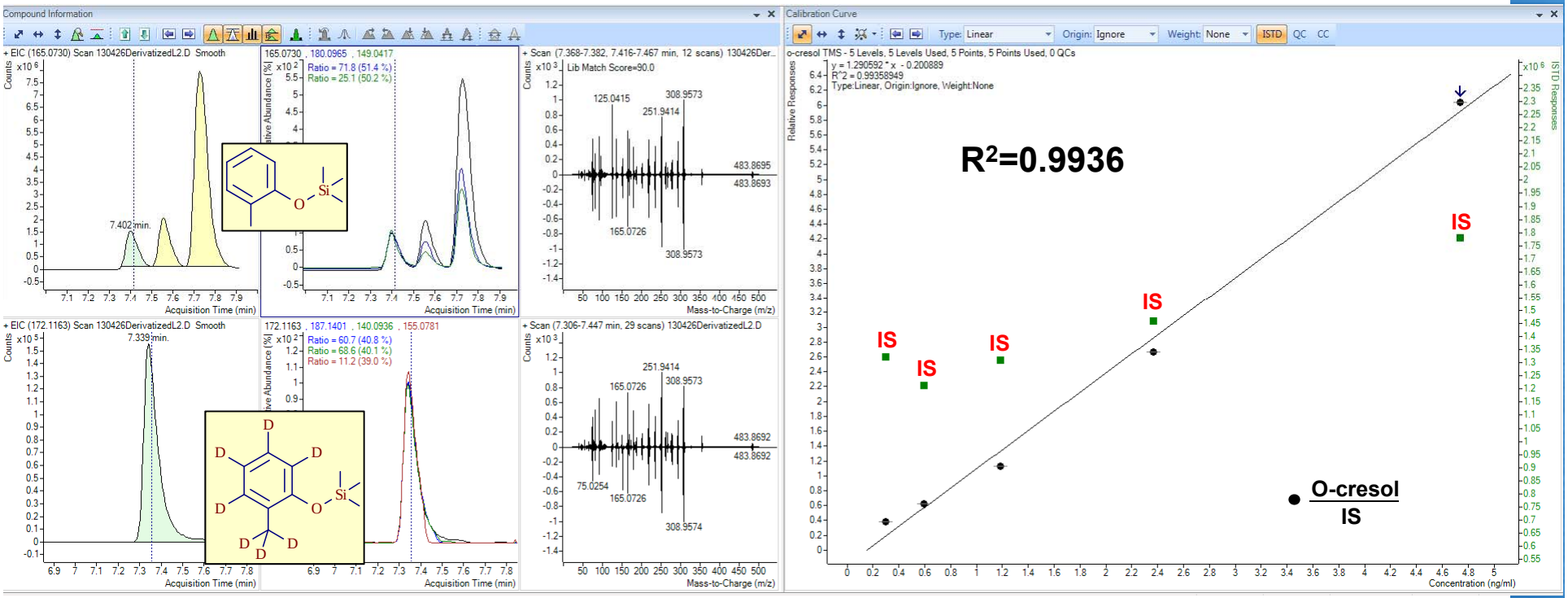
RT shift 0.11%

Library Match Score Average: 78%

Mass Accuracy o-cresol **5.2ppm** **-4.9ppm** **-2.8ppm**

Mass Accuracy *o*-cresol-d_8 **-4.8ppm** **-4.4ppm** **+0.6ppm**

	o-cresol TMS Results						Qualifier (180.0965) Res...		Qualifier (149.0417) Res...		Qualifier (187.1401) Re...		Qualifier (140.0936) Re...		Qualifier (155.0781) R...	
y	RT	Accuracy	Area	Calc. Conc.	Library Match Score	Mass Accuracy	Area	Mass Accuracy	Area	Mass Accuracy	Area	Mass Accuracy	Area	Mass Accuracy	Area	Mass Accuracy
1	7.399	153.9	272920	0.4559	66.9	-4.9840	171194	-5.3805	68214	-0.8435	331537	-4.6461	386800	-4.5267	66785	1.2703
5	7.409	108.1	373585	0.6408	71.3	-5.5543	281220	-5.0604	105179	-3.1423	304238	-4.7049	353165	-4.7734	59152	1.3921
5	7.395	86.9	716723	1.0302	78.7	-4.0376	558650	-4.2589	201484	-2.5614	322816	-4.7313	380060	-4.6442	65369	2.8279
9	7.416	93.6	2380645	2.2193	87.1	-7.2401	1055578	-4.0991	448316	-4.1611	380325	-5.5089	426430	-4.5011	71464	0.2721
6	7.402	102.1	5463737	4.8390	90.0	-4.0990	3923058	-5.5639	1371337	-3.2790	449155	-4.6438	507820	-3.6561	82651	-2.7396



Case Study: Cresol Isomers *m*-Cresol

RT shift 0.11%

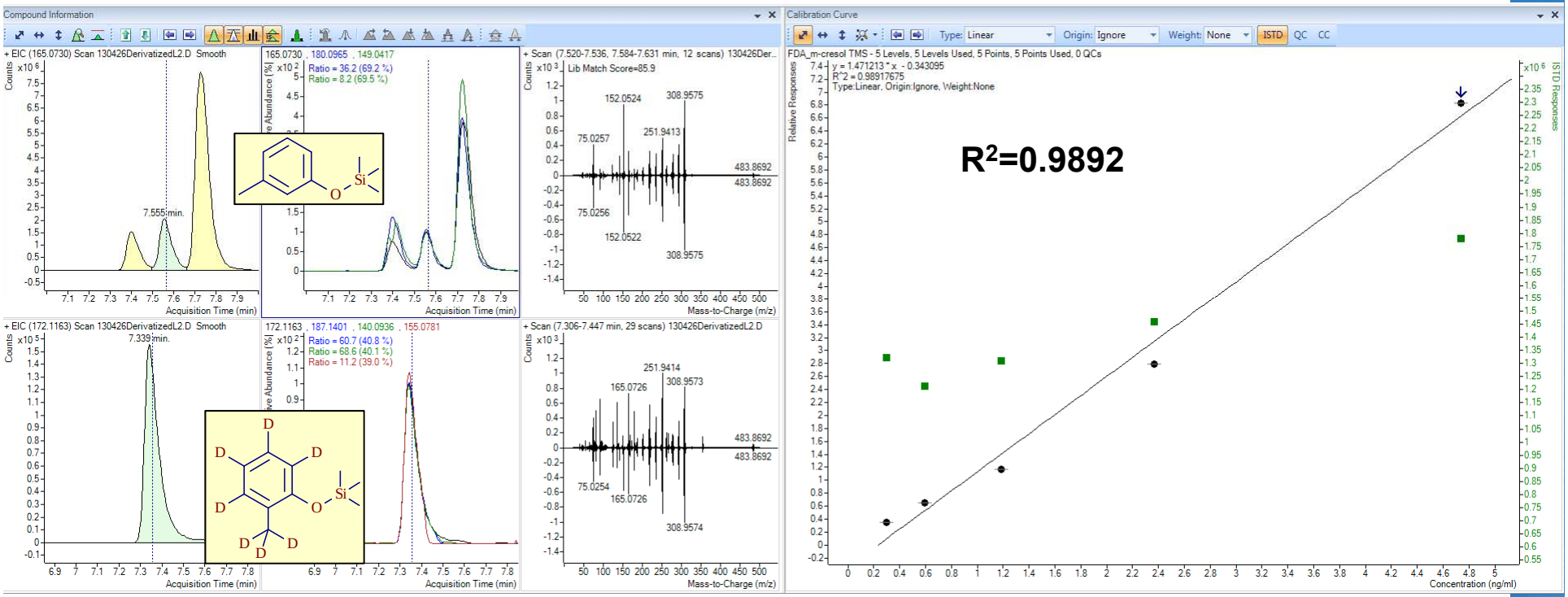
Library Match Score Average: 70%

Mass Accuracy -4.8ppm

m-Cresol -4.6ppm

o-Cresol-d_8 -8.2ppm

FDA_m-cresol TMS Results						Qualifier (180.0965) Res...		Qualifier (149.0417) Re...		Qualifier (187.1401) Re...		Qualifier (140.0936) Re...		Qualifier (155.0781) R...	
RT	Accuracy	Area	Calc. Conc.	Library Match Score	Mass Accuracy	Area	Mass Accuracy	Area	Mass Accuracy	Area	Mass Accuracy	Area	Mass Accuracy	Area	Mass Accuracy
7.552	160.5	339547	0.4757	57.7	-5.2242	114394	-5.2844	17729		331537	-4.6461	386800	-4.5267	66785	1.2703
7.567	114.2	563434	0.6767	60.6	-4.7209	190705	-4.5788	37914		304238	-4.7049	353165	-4.7734	59152	1.3921
7.548	86.4	1079822	1.0236	70.1	-3.5166	368591	-4.3676	73235	14.7864	322816	-4.7313	380060	-4.6442	65369	2.8279
7.564	89.8	3032648	2.1291	76.5	-5.5059	832621	-4.2079	203001	5.0035	380325	-5.5089	426430	-4.5011	71464	0.2721
7.555	102.9	8427563	4.8800	85.9	-5.1211	3046810	-4.5390	693679	4.7681	449155	-4.6438	507820	-3.6561	82651	-2.7396



Very good chromatography separation

Reliable automatic peak integration

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Case Study: Cresol Isomers *p*-Cresol

RT shift 0.11%

Library Match Score Average: 57%

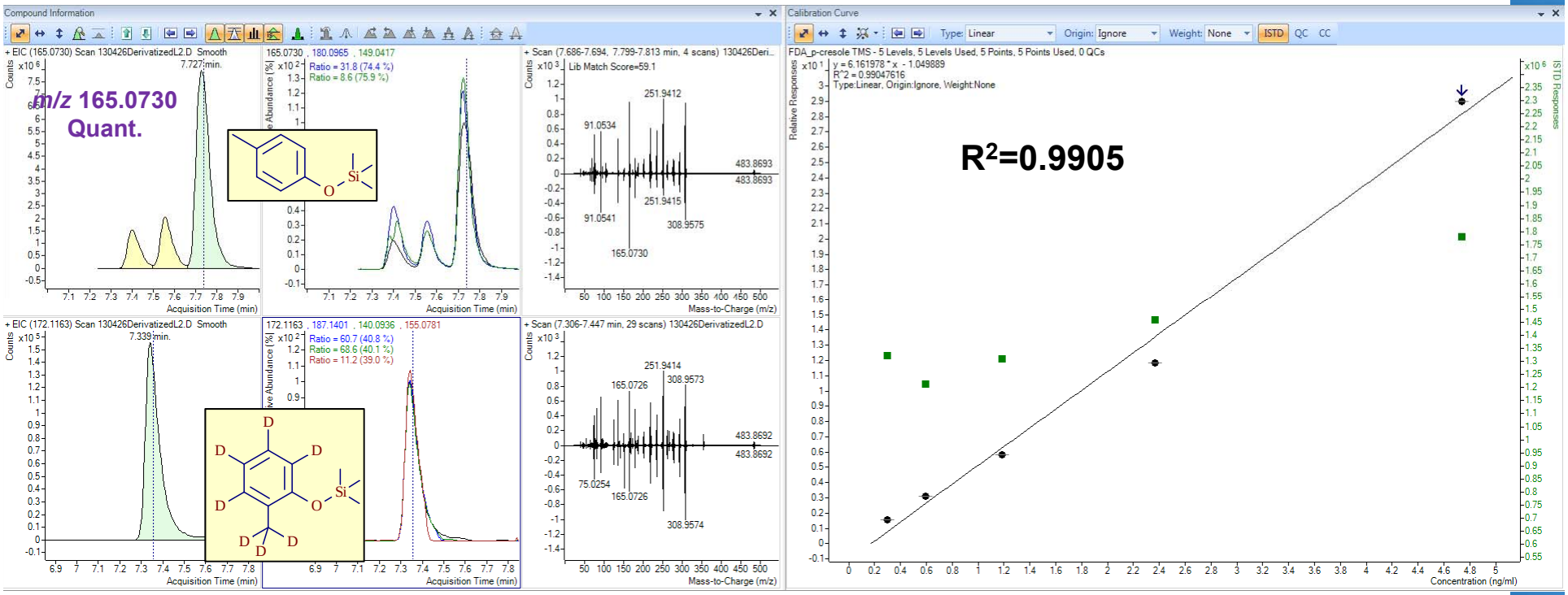
Mass Accuracy 5.1ppm

p-cresol -4.6ppm

o-cresol-d_8 -3.2ppm

FDA_p-cresole TMS Results

RT	Accuracy	Area	Calc. Conc.	Library Match Score	Mass Accuracy	Qualifier (180.0965) Resul... Area	Qualifier (180.0965) Resul... Mass Accuracy	Qualifier (149.0417) Res... Area	Qualifier (149.0417) Res... Mass Accuracy	Qualifier (187.1401) Re... Area	Qualifier (187.1401) Re... Mass Accuracy	Qualifier (140.0936) Re... Area	Qualifier (140.0936) Re... Mass Accuracy	Qualifier (155.0781) R... Area	Qualifier (155.0781) R... Mass Accuracy
7.720	144.5	1598784	0.4281	50.9	-6.3749	393860	-5.1960	107200	-2.6073	331537	-4.6461	386800	-4.5267	66785	1.2703
7.734	113.1	2905709	0.6702	56.1	-6.2962	657830	-4.5495	175185	-2.1371	304238	-4.7049	353165	-4.7734	59152	1.3921
7.720	94.2	5715028	1.1162	60.7	-3.7175	1557736	-4.5404	353181	-3.7319	322816	-4.7313	380060	-4.6442	65369	2.8279
7.737	88.2	12508184	2.0909	61.3	-5.0819	3921429	-4.3371	830498	-2.9071	380325	-5.5089	426430	-4.5011	71464	0.2721
7.727	102.9	36785631	4.8798	59.1	-3.9370	11711031	-4.1451	3154194	-4.6172	449155	-4.6438	507820	-3.6561	82651	-2.7396



Very good chromatography separation

Reliable automatic peak integration using MassHunter software

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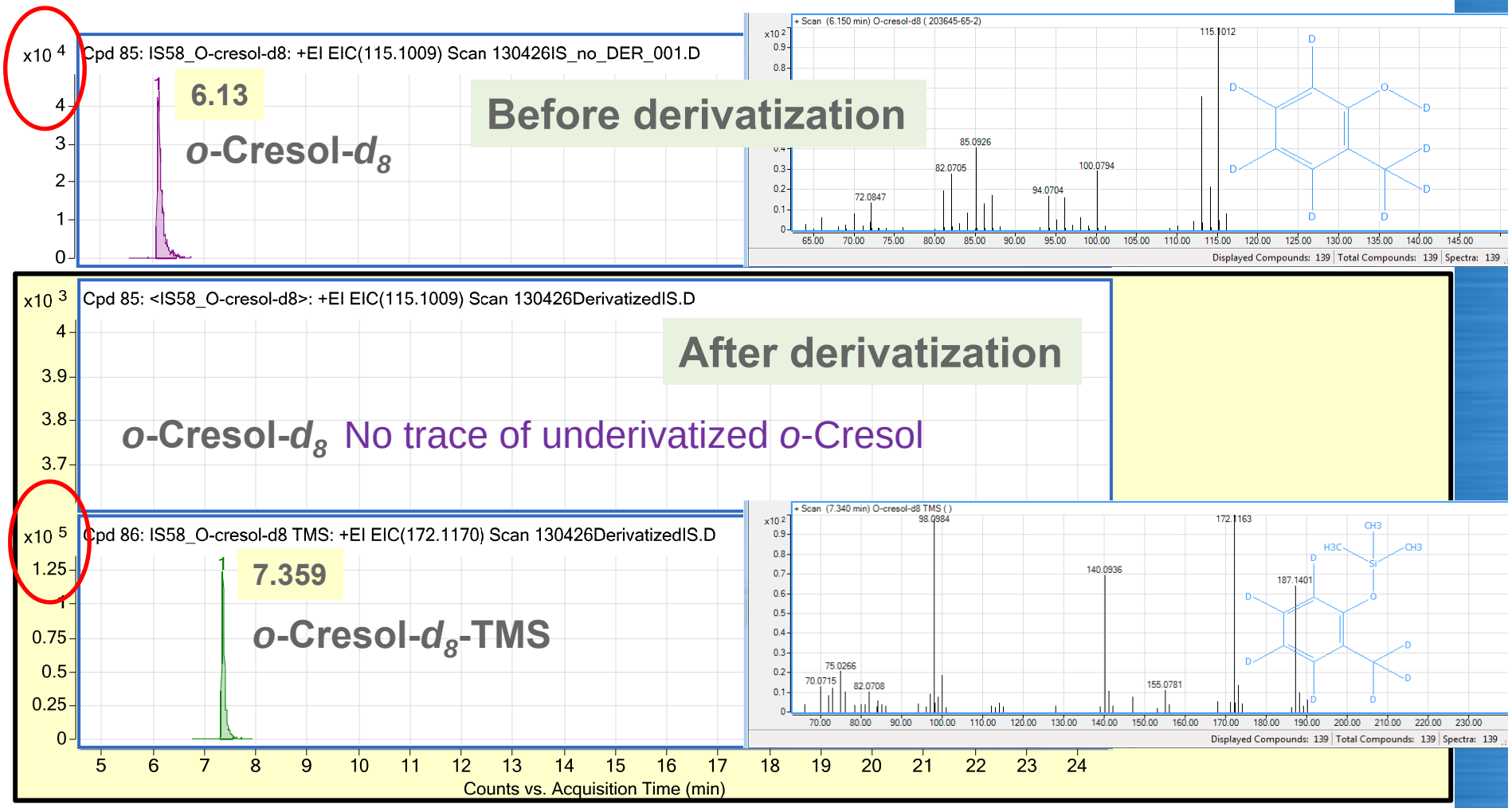
Key Consideration for Semi-Quantification

- Need to have a good chromatographic separation to resolve:
  - Isomers issue
  - Peak deconvolution
- Selection of characteristic for Quantifier & Qualifier ions
- Robustness due to usage of both Retention Times & Retention Index
- Assessment of linearity:
  - Using a 5-points calibration curves [0.29 – 4.8 ng/µL]
  - Analysis with and without silylation
  - Average of R^2=0.9694 (n=71 compounds)
  - R^2 < 0.9 only for 3 standards (due to sensitivity)

After silylation

Silylation Efficiency – example of o-cresol



Less fragmentation occurred after TMS derivatization

Higher sensitivity

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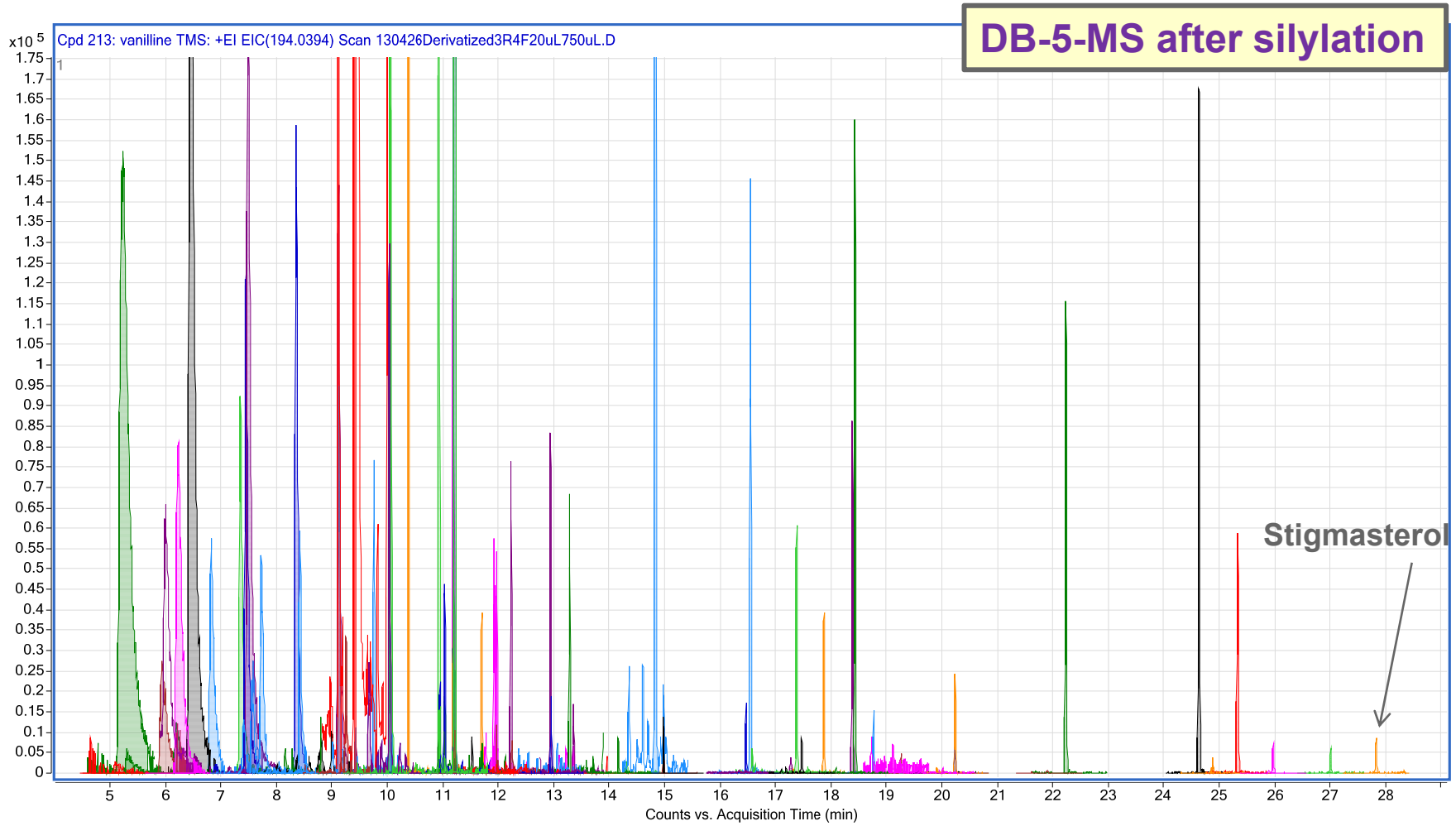
Sample of reference cigarette (3R4F TPM)
GC-EI-HR-MS after TMS derivatization



The *csv* file is used for an automatic and systematic search of smoke constituents

Fast data processing

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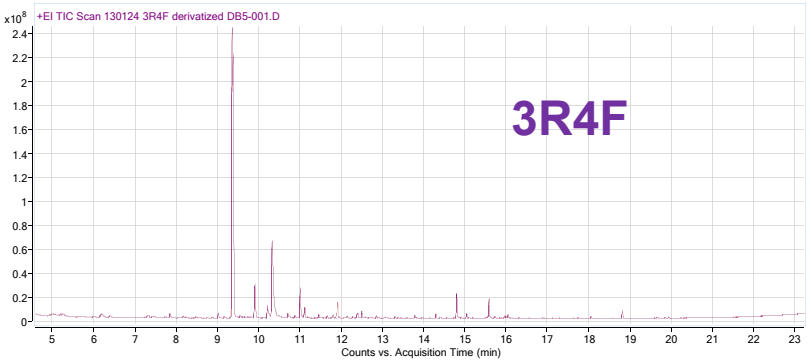
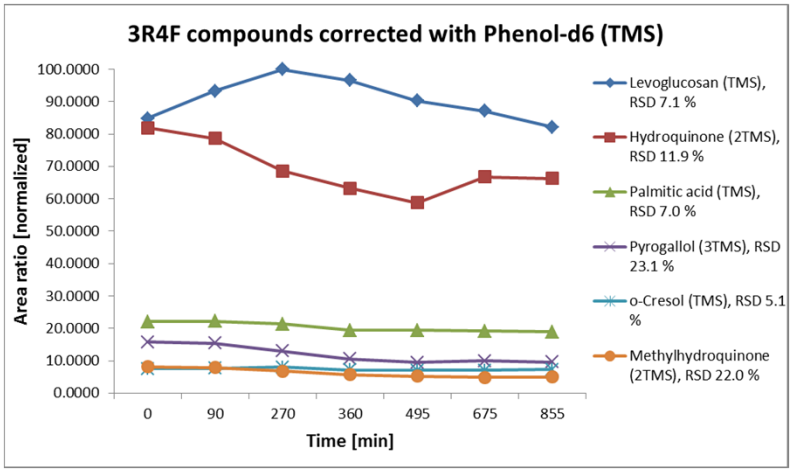
Sample Stability After Chemical Derivatization (Silylation)

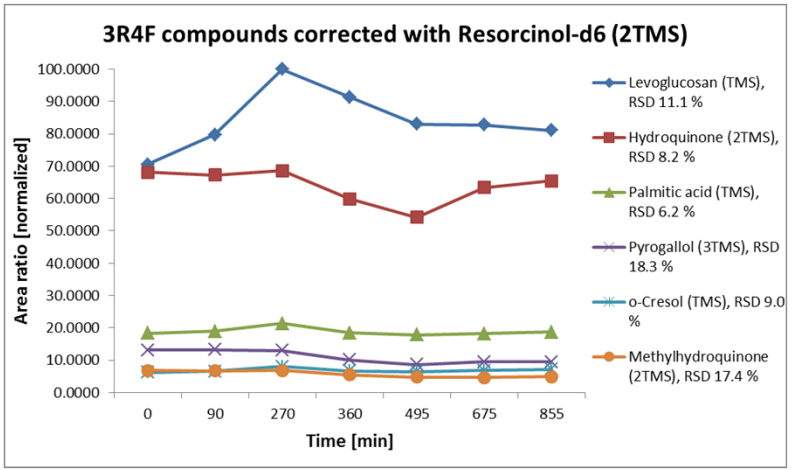
10µL 3R4F TPM extract (ethanolic) evaporated under nitrogen

Add 100 µL of IS mix + RI-markers
Add 800 µL CH_2Cl_2 / Acetone 80:20 v/v
Add 50 µL of BSTFA and 50 µL of pyridine
Incubate @ 80°C for different time period



Samples stability was monitored over a period of approximately 15 hours.
The analyzed smoke constituents do not show any significant differences.





After derivatization, aerosol components are stable over time
Appropriate selection of IS needed

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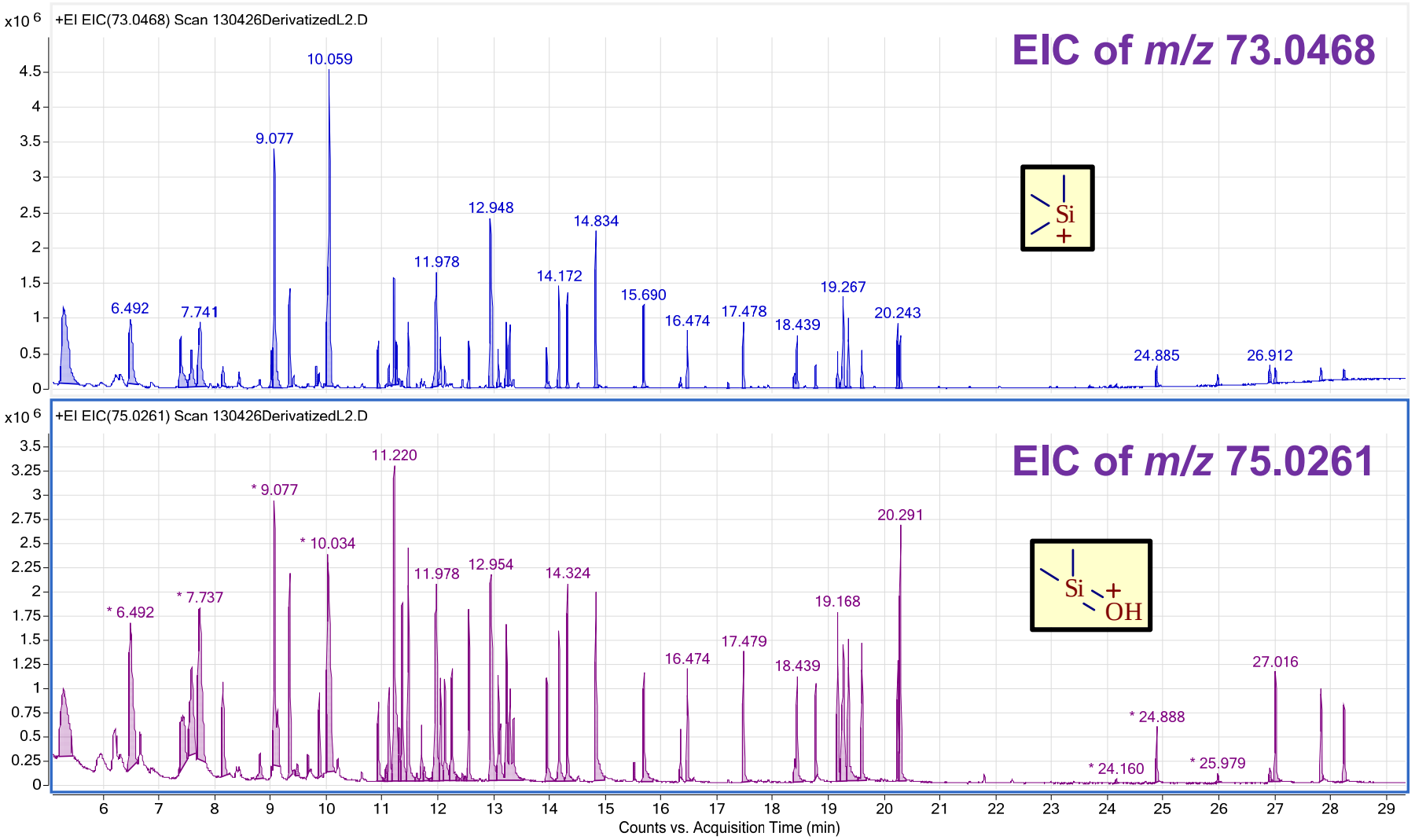
What about other Smoke Constituents?

Updating the Fingerprinting Method with New Compounds

Extraction of Silylated compounds can be of great help to identify additional smoke constituents



Mass accuracy AND predicted RT are of great interest to postulate new compounds

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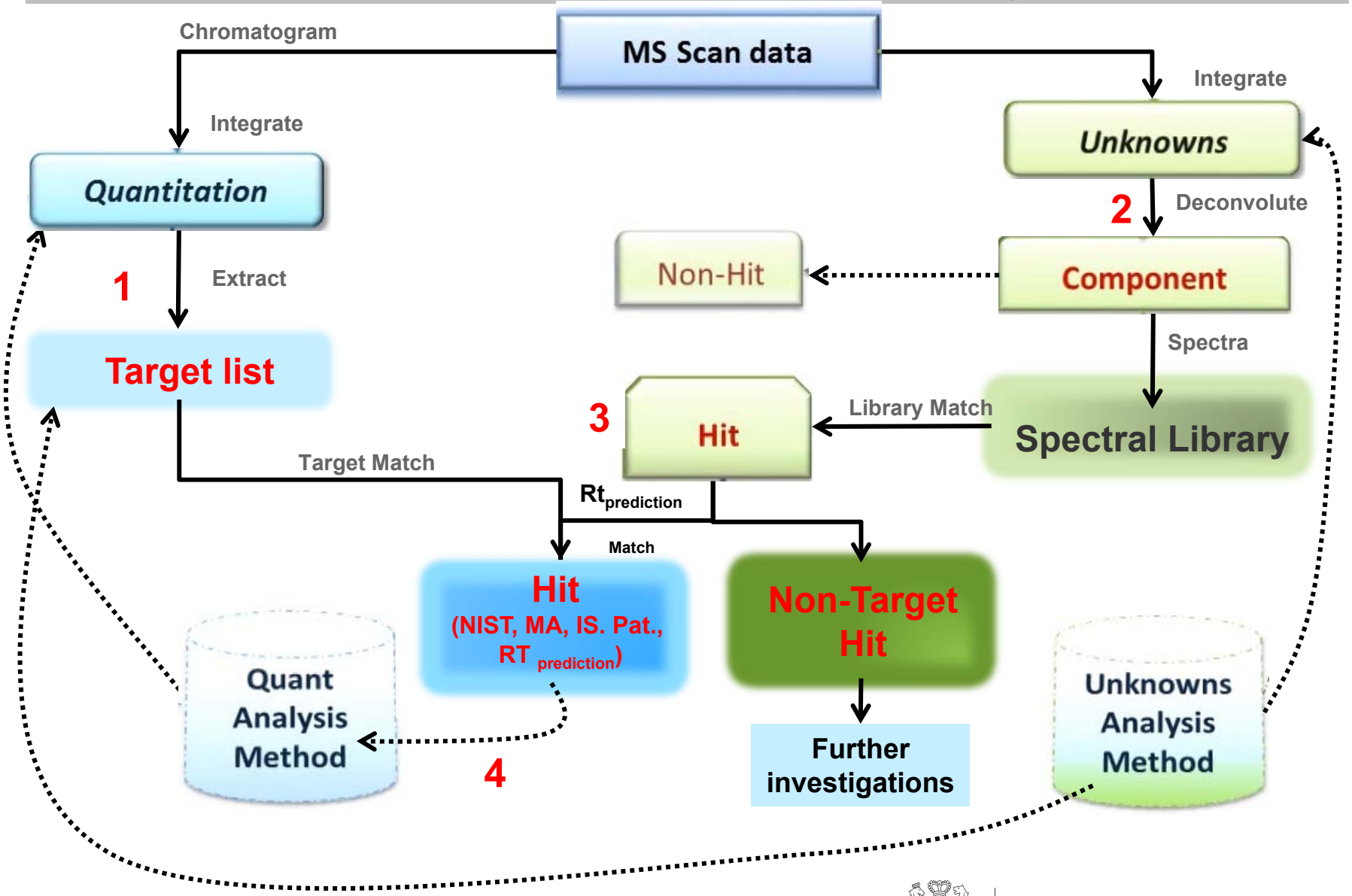
Analytical Workflow for Unknowns: Advantage of Full Scan / High Resolution analysis



Conclusion

- A GC-EI-HR-MS method has been established to semi-quantify smoke constituents in aerosol and aerosol fractions.
- The method has been simplified with:
  - ✓ Two GC columns instead of three,
  - ✓ Removal of Solid Phase MicroExtraction (SPME)
- We have demonstrated the great advantage of high resolution _ mass accuracy:
  - ✓ Improved S/N
  - ✓ Specificity and selectivity
  - ✓ Enhanced sensitivity
- Improved semi-quantification with:
  - ✓ Clustering approach to select adequate internal standards (n=63)
  - ✓ Compensate for compound degradation issues
  - ✓ Very good automatic peak integration (MassHunter software)
  - ✓ Very good linearity: averaged R^2 = 0.9694 (n=71)
- Monitoring of compounds can be expanded thanks to:
  - ✓ Full scan analysis at high mass accuracy (< 10 ppm)
  - ✓ Very good prediction model of retention time (median RT_{shift} = 8 sec, n=346)

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Quentin Dutertre


Daniel Arndt

Thank you for your attention.

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