Implementation of an Advanced Workflow to Enhance the Confidence in Compound Identification for Non-Targeted GC-HR-MS Applications

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Philip Morris International R&D

Reduced-Risk Products (“RRPs”) is the term the company uses to refer to products with the potential to reduce individual risk and population harm in comparison to smoking combustible cigarettes.

PMI’s RRPs are **in various stages of development and commercialization**, and we are conducting **extensive and rigorous scientific studies** to determine whether we can support claims for such products of reduced exposure to harmful and potentially harmful constituents in smoke, and ultimately claims of reduced disease risk, when **compared to smoking combustible cigarettes.**

Before making any such claims, we will **rigorously evaluate the full set of data** from the relevant scientific studies to determine whether they substantiate reduced exposure or risk. Any such claims **may also be subject to government review and approval**, as is the case in the US today.

Outline

- Smoke as complex matrix
- GC-HR-MS instrumentation
- Our workflow for complex matrix characterization
- Modeling of Linear Retention Index
- Creation of library with predicted LRI
- Case study (2 examples)
- Conclusion and next steps

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PMI Science

- PMI is working on various Reduced Risk Products delivering nicotine containing aerosols
- In this context it is important to fully characterize the chemical composition of these aerosols, in particular aerosols produced by heating tobacco compared to smoke from cigarettes
- For analytical method development purpose, we use a reference cigarette (3R4F)

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Generation of complex matrix

Filter is extracted

2 cold impingers in series

- **Reference cigarette: 3R4F***
- **Smoking regimen: Health Canada**
  - 2 sticks
  - Puff volume: 55mL
  - Puff duration: 2 sec
  - Puff interval: 30 sec
  - Puff count (butt length)

* University of Kentucky (Kentucky Tobacco R&D Center). http://www2.ca.uky.edu/refcig/

GVP - Gas Vapor Phase

TPM - Total Particulate Matter → Whole smoke

- **Smoke sample generated on a linear smoking machine**
- **The cambridge filter is combined with the impingers** ⇒ **Whole smoke**

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Analytical Technique: GC-High Resolution (GC-HR-MS)

GC-HR-MS_1
(7200A Agilent Q-TOF-MS)

Volatile and semi-volatiles
LRI from 500 to 1,900

GC-HR-MS_2
(7200B Agilent Q-TOF-MS)

Apolar and polar
LRI from 1,000 to 3,000

Goal is to screen the broadest range of smoke constituents.
Non-Targeted Screening

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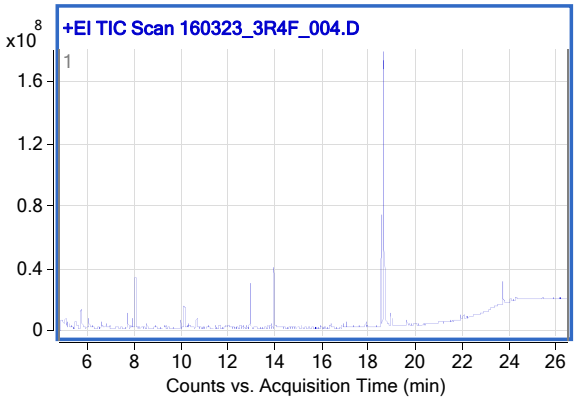
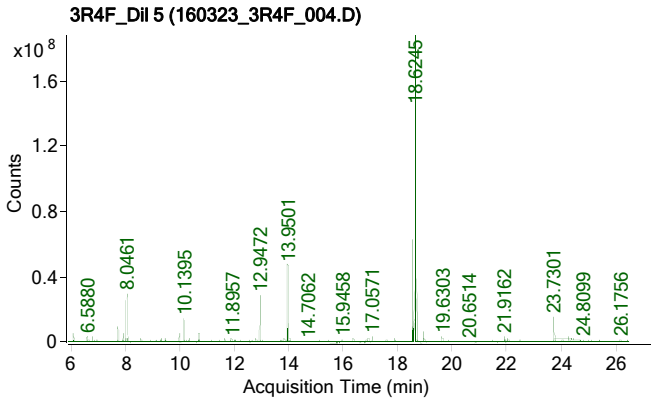
Automated Workflow for Identification in Complex Matrices





	Compound Name	Formula	CAS#	Component RI	Library RI	Delta RI	Match Factor	Library File	Component Area
353	Cyclopropa[a]indene, 1,1a,6,6a-tetrah	C10H10	15677-15-3	1204.02			92.1	NIST14.L	1776138
354	Naphthalene, 1,2-dihydro-	C10H10	447-53-0	1214.03			82.6	NIST14.L	1365794
355	3-Hexanone, 2,2-dimethyl-	C8H16O	5405-79-8	1218.05			71.1	NIST14.L	270040
356	3-Buten-2-ol	C4H8O	598-32-3	1220.75			65.4	NIST14.L	391516
357	Naphthalene, 1,2-dihydro-	C10H10	447-53-0	1222.51			62.9	NIST14.L	183093
358	glycerine monoacetate	C5H10O4	106-61-6	1226.70	1232.96	6.26	46.9	Fingerprinting_DB624.xml	1163960
359	1H-Indene, 1,1-dimethyl-	C11H12	18636-55-0	1230.64			74.6	NIST14.L	142832
360	4H-Pyran-4-one, 2,3-dihydro-3,5-dih	C6H8O4	28564-83-2	1237.20			73.5	NIST14.L	3220141
361	(2S,6R,7S,8E)-(+)-2,7-Epoxy-4,8-mega	C13H20O	100342-25-2	1246.27			86.0	NIST14.L	023013
362	naphthalene	C10H8	91-20-3	1255.06	1257.68	2.62	70.9	Fingerprinting_DB624.xml	582905
363	2(1H)-Pyridinone, 3-methyl-	C6H7NO	1003-56-1	1256.71			64.6	NIST14.L	304134
364	Cyclohexylamine	C6H13N	108-91-8	1260.70			66.2	NIST14.L	471352
365	3-Hydroxypyridine	C5H5NO	109-00-2	1264.45	1272.07	7.62	52.0	Fingerprinting_DB624.xml	3969362
366	4-Ethylphenol	C8H10O	123-07-9	1275.38	1279.99	4.61	76.4	Fingerprinting_DB624.xml	1584474
367	3-ethyl phenol	C8H10O	620-17-7	1279.84	1282.00	2.16	66.3	Fingerprinting_DB624.xml	143776
368	5-Acetyl-6-hydroxy-3,7,7-trimethylbi	C13H14O4	52183-01-4	1289.82			62.0	NIST14.L	598673
369	Butanoic acid, 3-methyl-, 3-methyl-3	C10H18O2	54410-94-5	1296.49			65.5	NIST14.L	2090746
370	Phenol, 3-amino-	C6H7NO	591-27-5	1298.61			60.7	NIST14.L	207103
371	Sarcosylsarcosine, N-methoxycarbor	C15H28N2O5	1000314-83-0	1299.86			66.4	NIST14.L	263351
372	**tridecane**	**C13H28**	**629-50-5**	**1300.00**	**1300.00**	**0.00**	**74.0**	**Fingerprinting_DB624.xml**	**4821309**
373	3,4-dimethylphenol	C8H10O	95-65-8	1301.95	1302.07	0.71	60.3	Fingerprinting_DB624.xml	254565

MassHunter Data Acquisition (EI mode)

Deconvolution

MassHunter Unknown Analysis

Identification

- Stop when identified:
  - ➔ DB-624 Accurate Mass Library
  - ➔ **Compound library**
  - ➔ NIST 14 or Wiley
- Export .cef and review
- Purchase of ref std if available

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Purpose

The present work focuses on building a relevant library containing LRI prediction.

- To predict LRI we used two softwares:
  1. RapidMiner-Dragon
  2. ACD/Labs ChromGenius

- To build a relevant LRI prediction system 552 molecules were used:
  1. Experimental LRI
  2. Quantitative Structure-Property Relationship (QSPR) and structure similarities

The experimental linear retention indices were randomly split as training (n=401) and test (n=151) sets.
Validation set (n=23) confirmed the great performance of both prediction models.

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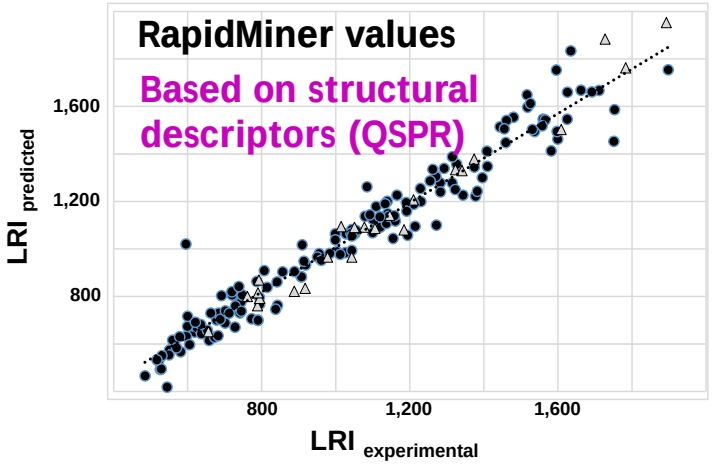
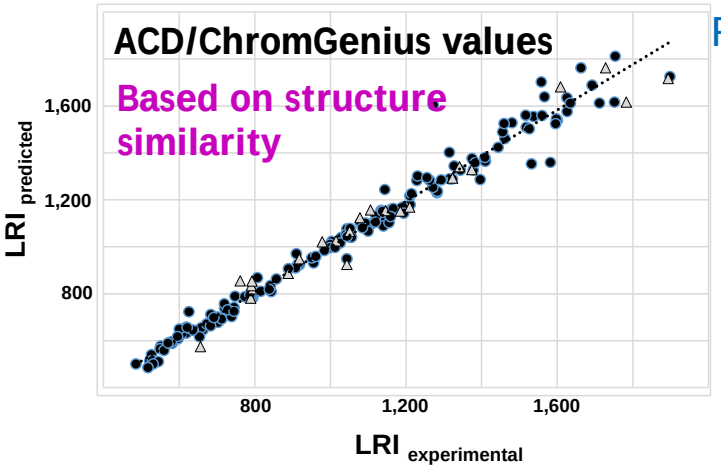
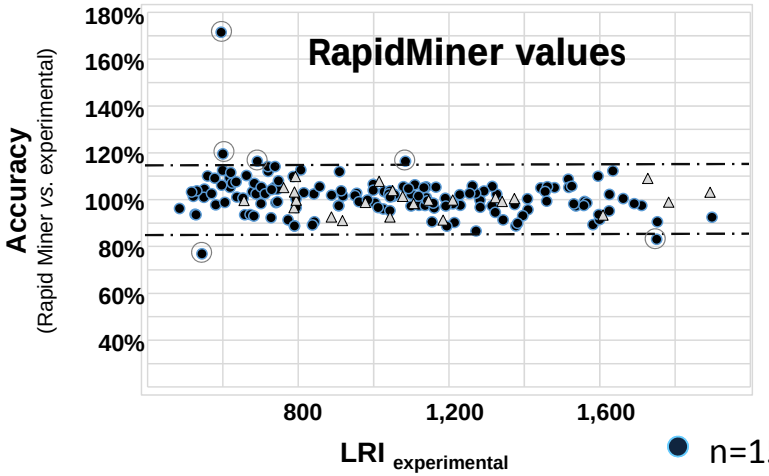
Assessment of the Prediction Models (Test Set and Validation Set)

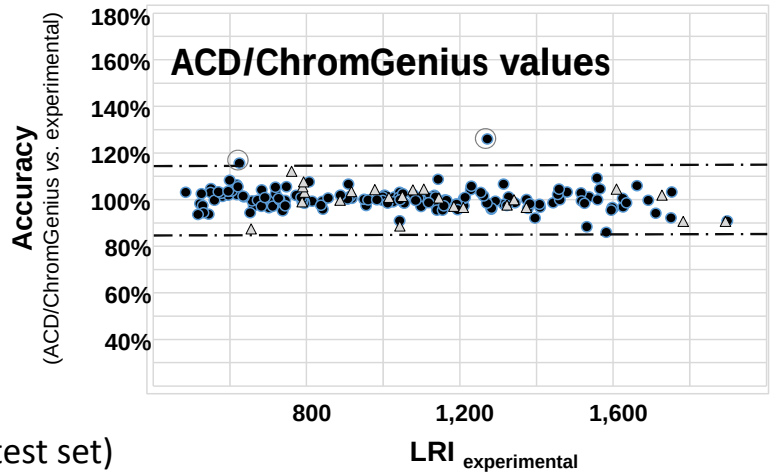


R^2 : 0.949



R^2 : 0.976





● n=151 reference standards (test set)

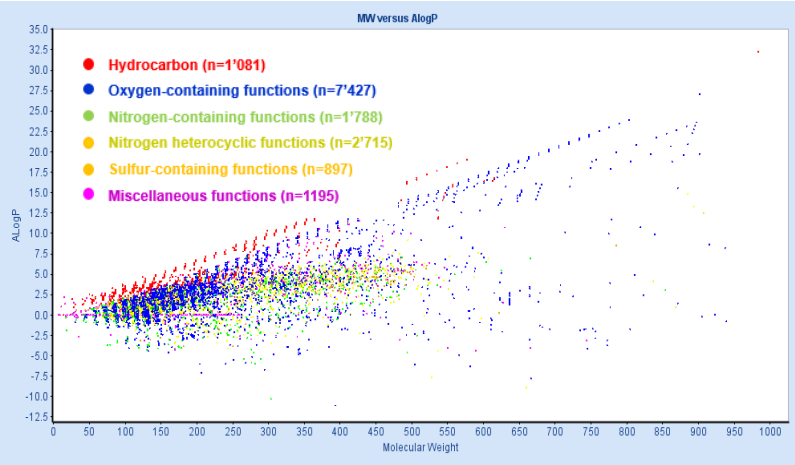
△ n=23 reference standards (validation set)

Unique Compounds & Spectra Database

UCSD is our in-house database that contains 11567 molecules:

- 7000 chemicals reported as present in tobacco plant and smoke[1]
- 3000 molecules associated with flavor properties[2,3]

1013 accurate mass spectra and LRI are registered in UCSD



[1] The Chemical Components of Tobacco and Tobacco Smoke, A. Rodgman, T.A. Perfetti, 2013, *2nd Ed. CRC press*.
[2] Leffingwell, J. C.; Young, H. J.; Bernasek, E. Tobacco flavoring for Smoking Products, *R. J. Reynolds Tobacco Company, Winston-Salem,* **1972**.
[3] EFSA flavoring substances database

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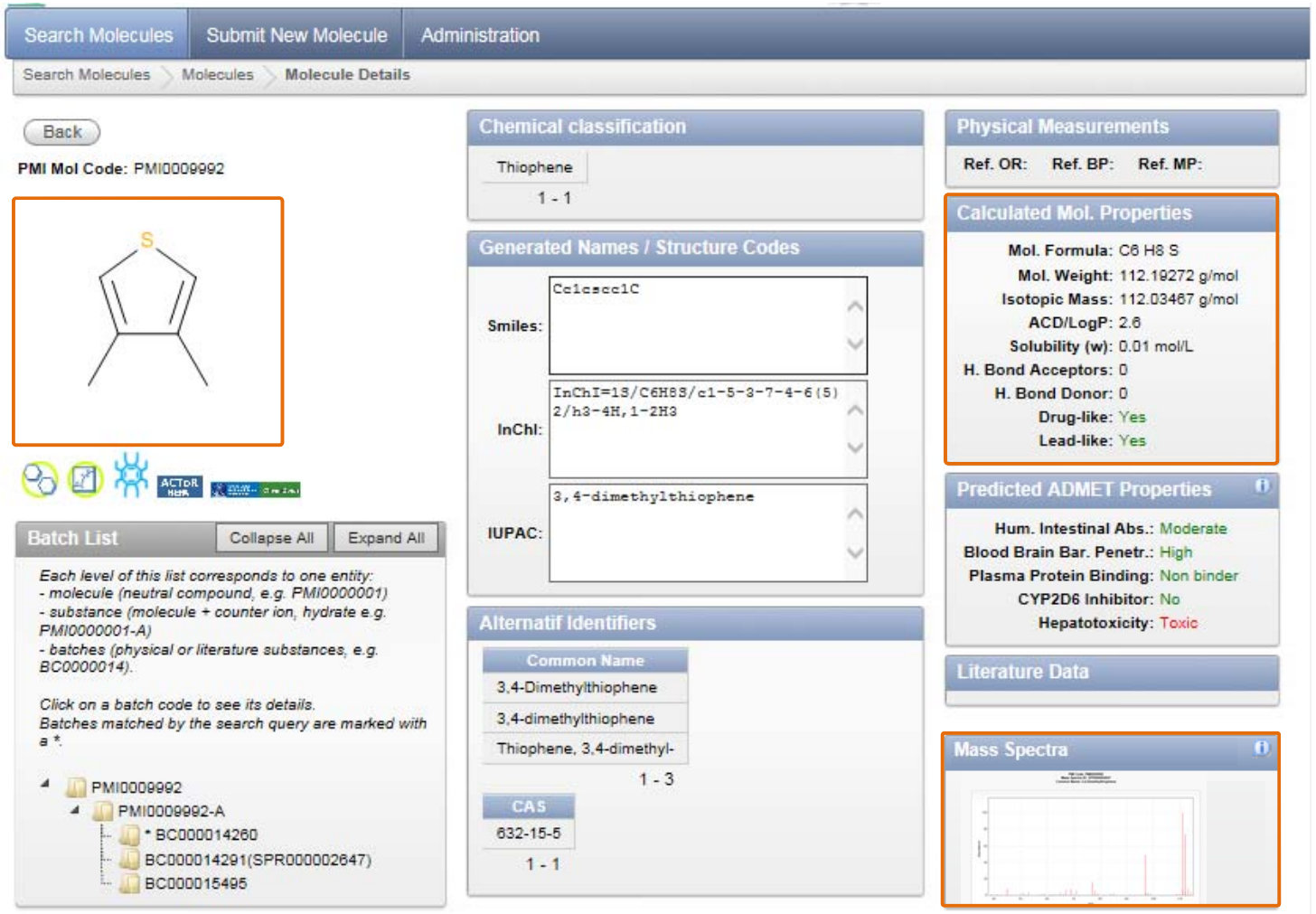
UCSD Web Interface



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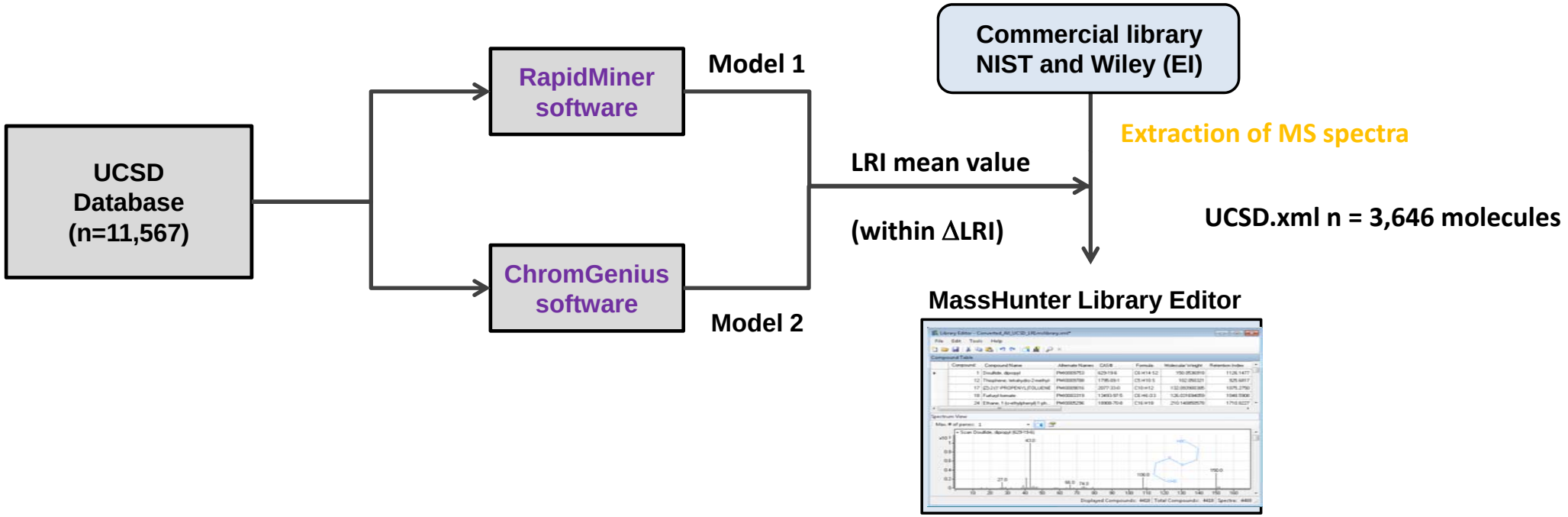
Creation of the UCSD Compound Library



- Predicted LRI of flavors and tobacco-related compounds database when there implemented in our current identification workflow.
- 6,053 molecules were predicted with LRI values between 500 and 1,900
- **3,646** molecules have an available nominal EI Mass Spectra (NIST or Wiley)

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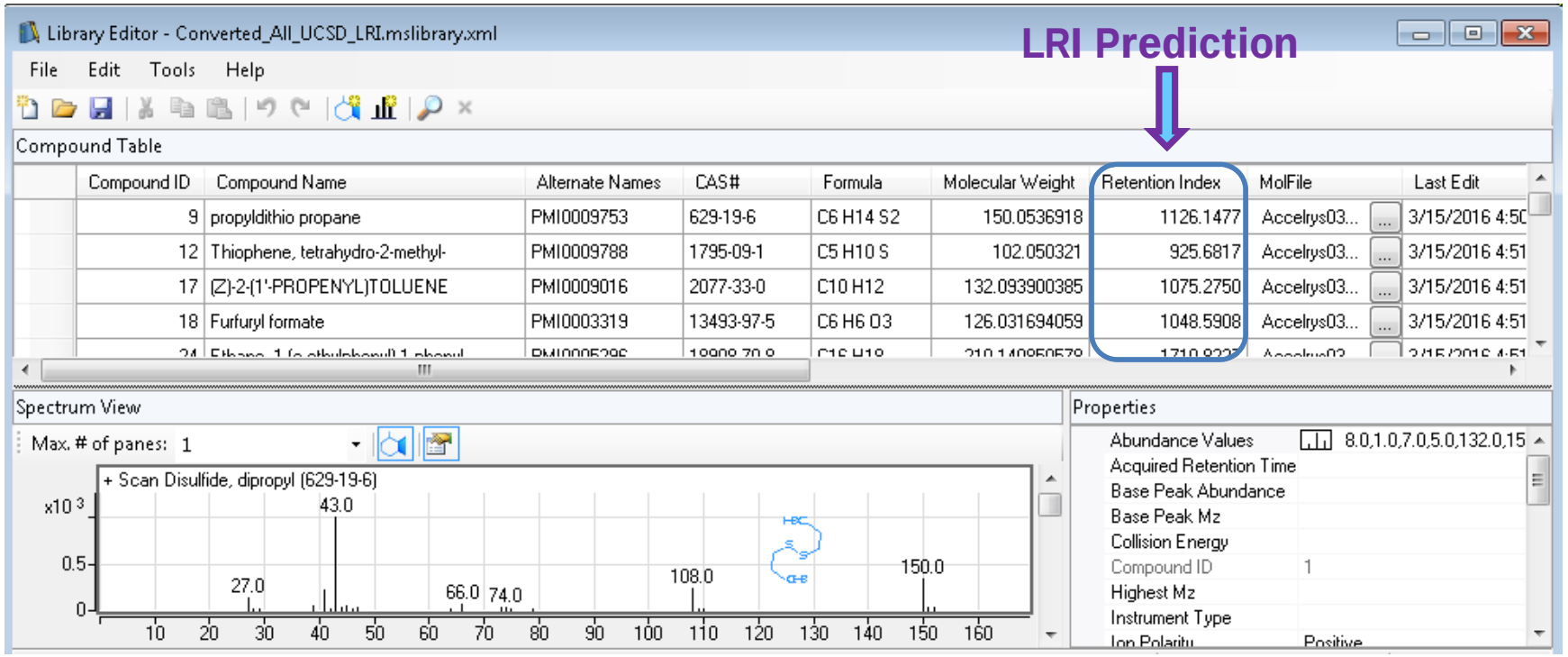
UCSD Compound Library



LRI predictions were associated with the 3,646 nominal EI mass spectra extracted from commercial libraries.

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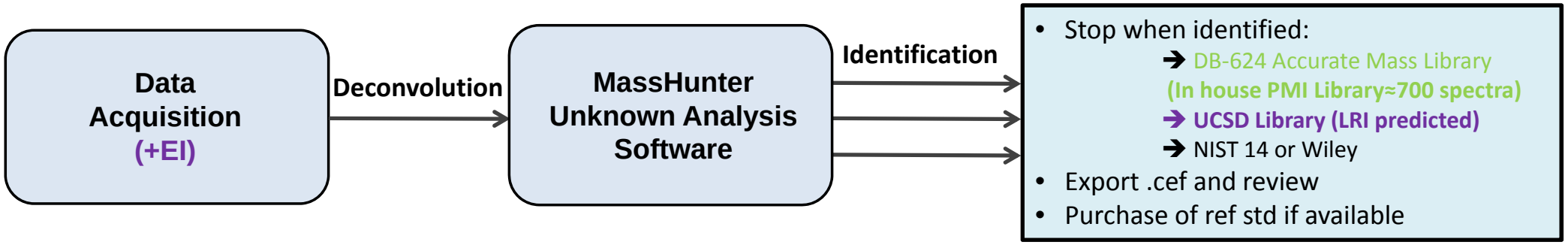
Different Output With the New Workflow



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355	3-Hexanone, 2,2-dimethy	C8H16O	5405-79-8	1218.05			71.1	NIST14.L	270040
356	3-Buten-2-ol	C4H8O	598-32-3	1220.75			65.4	NIST14.L	391516
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358	glycerine-monoacetate	C5H10O4	106-61-6	1226.70	1232.96	6.26	46.9	Fingerprinting_DB624.xml	1163960
359	1H-Indene, 1,1-dimethyl-	C11H12	18636-55-0	1230.64			74.6	NIST14.L	142832
360	4H-Pyran-4-one, 2,3-dihyc	C6H8O4	28564-83-2	1237.20			73.5	NIST14.L	3220141
361	(2S,6R,7S,8E)-(+)-2,7-Epox	C13H20O	108342-25-	1246.27			86.8	NIST14.L	823013
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363	2(1H)-Pyridinone, 3-meth	C6H7NO	1003-56-1	1256.71			64.6	NIST14.L	304134
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366	4-Ethylphenol	C8H10O	123-07-9	1275.38	1279.99	4.61	76.4	Fingerprinting_DB624.xml	1584474
367	3-ethyl phenol	C8H10O	620-17-7	1279.84	1282.00	2.16	66.3	Fingerprinting_DB624.xml	143776
368	5-Acetyl-6-hydroxy-3,7,7-	C13H14O4	52183-01-4	1289.82			62.0	NIST14.L	598673
369	Butanoic acid, 3-methyl-,	C10H18O2	54410-94-5	1296.49			65.5	NIST14.L	2898746
370	Phenol, 3-amino-	C6H7NO	591-27-5	1298.61			60.7	NIST14.L	287183
371	Sarcosylsarcosine, N-meth	C15H28N2	1000314-83	1299.86			66.4	NIST14.L	263351
372	**tridecane**	**C13H28**	**629-50-5**	**1300.00**	**1300.00**	**0.00**	**74.0**	**Fingerprinting_DB624.xml**	**4821309**
373	3,4-dimethylphenol	C8H10O	95-65-8	1301.35	1302.07	0.71	60.3	Fingerprinting_DB624.xml	254565

1	Compound Name	Formula	CAS#	Component RI	Library RI	Delta RI	Match Factor	Library File	Component Area
353	**1H-Indene, 3-methyl-**	**C10 H10**	**767-60-2**	**1204.02**	**1211.71**	**7.69**	**89.2**	**UCSD.mslibrary.xml**	**1776138**
354	**1H-Indene, 3-methyl-**	**C10 H10**	**767-60-2**	**1214.03**	**1211.71**	**-2.33**	**82.1**	**UCSD.mslibrary.xml**	**1365794**
355	**UNDECANE, 2,6-DIMETHY**	**C13 H28**	**17301-23-4**	**1218.05**	**1211.13**	**-6.92**	**63.4**	**UCSD.mslibrary.xml**	**270040**
356	3-Buten-2-ol	C4H8O	598-32-3	1220.75			65.4	NIST14.L	391516
357	1H-Indene, 3-methyl-	C10 H10	767-60-2	1222.51	1211.71	-10.80	54.3	UCSD.mslibrary.xml	183093
358	glycerine-monoacetate	C5H10O4	106-61-6	1226.70	1232.96	6.26	46.9	Fingerprinting_DB624.xml	1163960
359	1H-Indene, 1,1-dimethyl-	C11 H12	18636-55-0	1230.64	1251.28	20.64	56.5	UCSD.mslibrary.xml	142832
360	4H-Pyran-4-one, 2,3-dihyc	C6H8O4	28564-83-2	1237.20			73.5	NIST14.L	3220141
361	**Phenol, 2-ethyl-**	**C8 H10 O**	**90-00-6**	**1246.27**	**1236.11**	**-10.16**	**79.8**	**UCSD.mslibrary.xml**	**823013**
362	naphthalene	C10H8	91-20-3	1255.06	1257.68	2.62	70.9	Fingerprinting_DB624.xml	582905
363	2(1H)-Pyridone, 6-methyl-	C6 H7 N O	3279-76-3	1256.71	1287.94	31.23	51.7	UCSD.mslibrary.xml	304134
364	**2,5-Pyrrolidinedione**	**C4 H5 N O**	**123-56-8**	**1260.70**	**1249.71**	**-10.99**	**67.5**	**UCSD.mslibrary.xml**	**471352**
365	3-Hydroxypyridine	C5H5NO	109-00-2	1264.45	1272.07	7.62	52.8	Fingerprinting_DB624.xml	3969362
366	4-Ethylphenol	C8H10O	123-07-9	1275.38	1279.99	4.61	76.4	Fingerprinting_DB624.xml	1584474
367	3-ethyl phenol	C8H10O	620-17-7	1279.84	1282.00	2.16	66.3	Fingerprinting_DB624.xml	143776
368	5-Acetyl-6-hydroxy-3,7,7-t	C13H14O4	52183-01-4	1289.82			62.0	NIST14.L	598673
369	Butanoic acid, 3-methyl-,	C10H18O2	54410-94-5	1296.49			65.5	NIST14.L	2898746
370	2(1H)-Pyridone, 6-methyl-	C6 H7 N O	3279-76-3	1298.61	1287.94	-10.67	59.6	UCSD.mslibrary.xml	287183
371	Sarcosylsarcosine, N-meth	C15H28N2	1000314-83-(	1299.86			66.4	NIST14.L	263351
372	**tridecane**	**C13H28**	**629-50-5**	**1300.00**	**1300.00**	**0.00**	**74.0**	**Fingerprinting_DB624.xml**	**4821309**
373	3,4-dimethylphenol	C8H10O	95-65-8	1301.35	1302.07	0.71	60.3	Fingerprinting_DB624.xml	254565

Implementation of predicted LRI allows alternative proposals.

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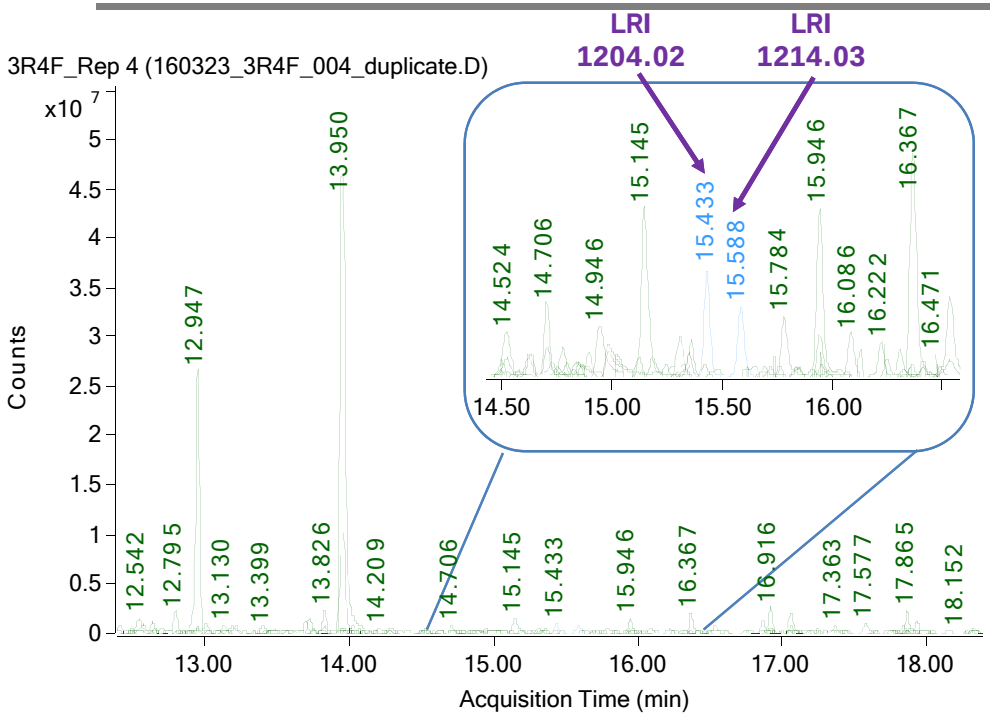
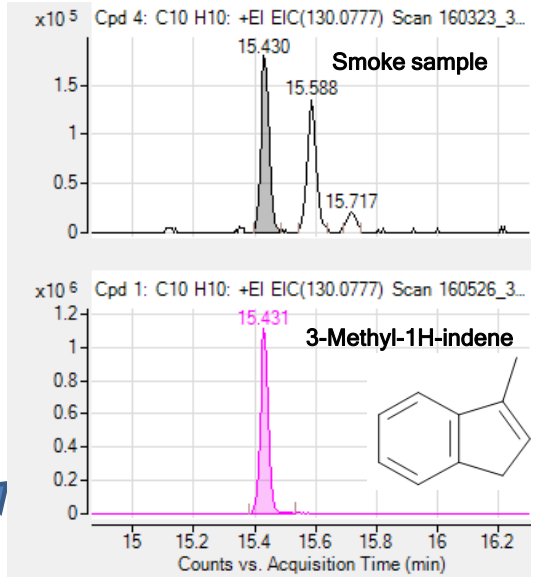
1st Example / Evaluation





Confirmation

1	Compound Name	Formula	CAS#	Component RI	Library RI	Delta RI	Match Factor	Library File	Component Area
353	1H-Indene, 3-methyl-	C10 H10	767-60-2	1204.02	1211.71	7.69	89.2	UCSD.mslibrary.xml	1776138
354	1H-Indene, 3-methyl-	C10 H10	767-60-2	1214.03	1211.71	-2.33	82.1	UCSD.mslibrary.xml	1365794
355	UNDECANE, 2,6-DIMETHYI	C13 H28	17301-23-4	1218.05	1211.13	-6.92	63.4	UCSD.mslibrary.xml	270040
356	3-Buten-2-ol	C4H8O	598-32-3	1220.75			65.4	NIST14.L	391516

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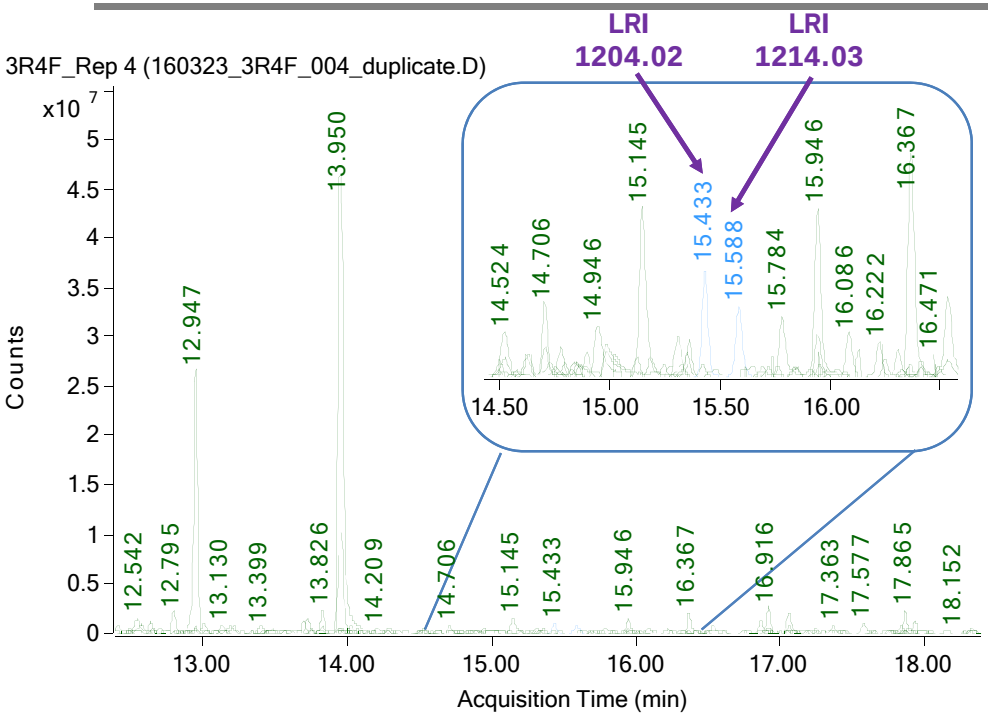
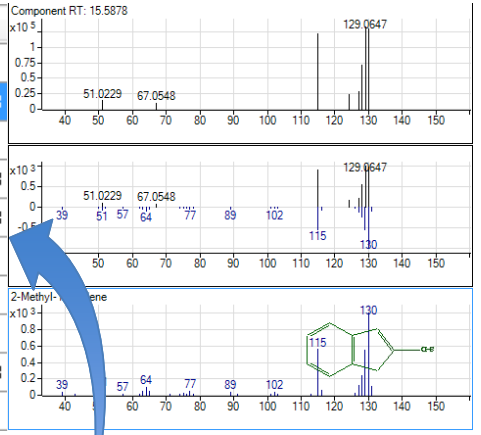
1st Example / Evaluation



LRI Prediction

Compound Name	Match	CAS#	Library Retention
1H-Indene, 3-methyl- (CAS)	82.07	767-60-2	1211.708430938...
2-Methyl-1H-indene	81.29	2177-47-1	1214.3176031238
1H-Indene, 3-methyl- (CAS)	80.99	767-60-2	1211.708430938...
2-Methylindene	79.56	2177-47-1	1214.3176031238
2-Methyl-1H-indene	79.54	2177-47-1	1214.3176031238
1H-Indene, 3-methyl- (CAS)	77.88	767-60-2	1211.708430938...
1H-Indene, 3-methyl-	73.41	767-60-2	1211.708430938...
1H-Indene, 3-methyl- (CAS)	73.38	767-60-2	1211.708430938...
2-Methyl-1H-indene	57.38	2177-47-1	1214.3176031238
1H-Indene, 3-methyl- (CAS)	54.89	767-60-2	1211.708430938...



Alternative hits proposal

1	Compound Name	Formula	CAS#	Component RI	Library RI	Delta RI	Match Factor	Library File	Component Area
353	1H-Indene, 3-methyl-	C10 H10	767-60-2	1204.02	1211.71	7.69	89.2	UCSD.mslibrary.xml	1776138
354	1H-Indene, 3-methyl-	C10 H10	767-60-2	1214.03	1211.71	-2.33	82.1	UCSD.mslibrary.xml	1365794
355	UNDECANE, 2,6-DIMETHYL	C13 H28	17301-23-4	1218.05	1211.13	-6.92	63.4	UCSD.mslibrary.xml	270040
356	3-Buten-2-ol	C4H8O	598-32-3	1220.75			65.4	NIST14.L	391516

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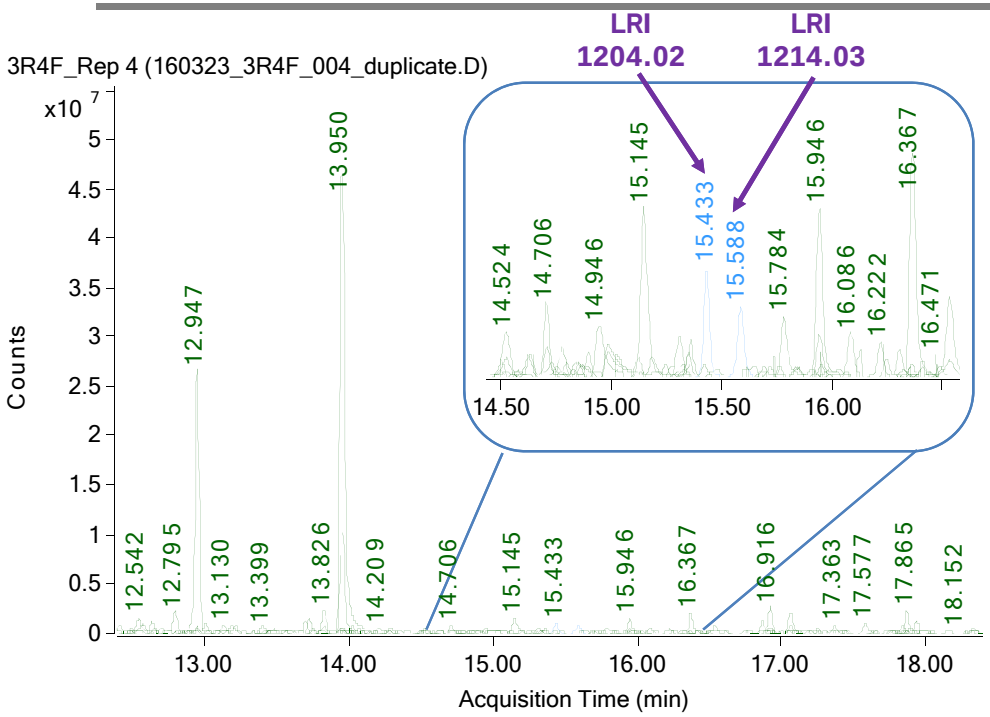
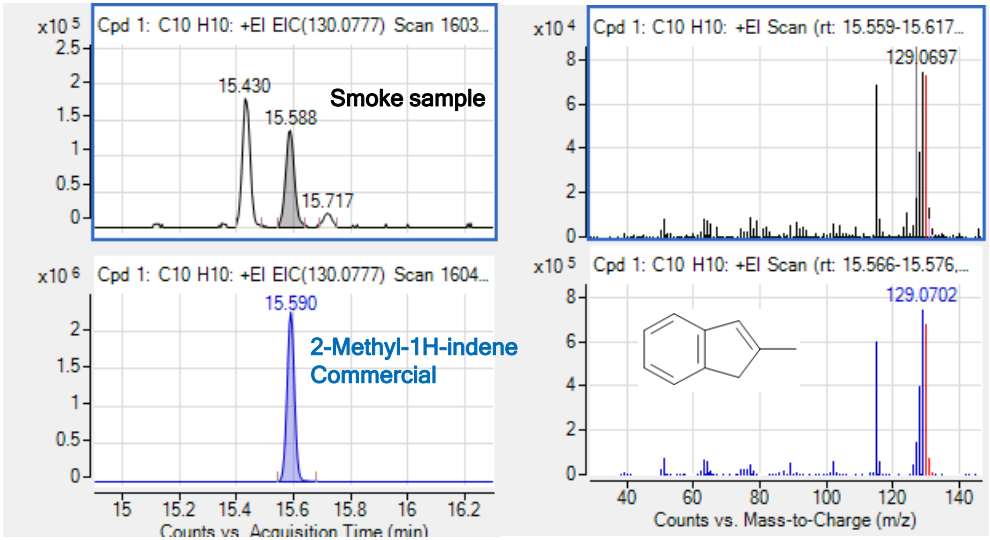
1st Example / Confirmation





Same RT **Similar EI Mass Spectra**

1	Compound Name	Formula	CAS#	Component RI	Library RI	Delta RI	Match Factor	Library File	Component Area
353	1H-Indene, 3-methyl-	C10 H10	767-60-2	1204.02	1211.71	7.69	89.2	UCSD.mslibrary.xml	1776138
354	1H-Indene, 2-methyl-	C10 H10	2177-47-1	1214.03	1214.31	0.28	81.3	UCSD.mslibrary.xml	1365794
355	UNDECANE, 2,6-DIMETHYL	C13 H28	17301-23-4	1218.05	1211.13	-6.92	63.4	UCSD.mslibrary.xml	270040
356	3-Buten-2-ol	C4H8O	598-32-3	1220.75			65.4	NIST14.L	391516

3-Methyl-1H-indene is confirmed

2-Methyl-1H-indene is confirmed

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Evaluation of NIST Proposals

1	Compound Name	Formula	CAS#	Component RI	Library RI	Delta RI	Match Factor	Library File	Component Area
353	Cycloprop[a]indene, 1,1a,	C10H10	15677-15-3	1204.02			92.1	NIST14.L	1776138
354	Naphthalene, 1,2-dihydro	C10H10	447-53-0	1214.03			82.6	NIST14.L	1365794
355	3-Hexanone, 2,2-dimethy	C8H16O	5405-79-8	1218.05			71.1	NIST14.L	270040
356	3-Buten-2-ol	C4H8O	598-32-3	1220.75			65.4	NIST14.L	391516

Compound Name	Mach Factor	CAS#	Library	LRI_EXP	LRI_Prediction	LRI score	Rank
Naphthalene, 1,2-dihydro-	82.6	447-53-0	NIST14.L	1214.034	1237.17	57%	3rd
Cycloprop[a]indene, 1,1a,6,6a-tetrahydro-	82.3	15677-15-3	NIST14.L		1172.88	34%	5th
1H-Indene, 3-methyl-	81.8	767-60-2	NIST14.L		1211.71	81%	1st
2-Methylindene	81.4	2177-47-1	NIST14.L		1214.32	81%	1st
Benzene, 1-methyl-4-(1-propynyl)-	80.0	2749-93-1	NIST14.L		1136.45	13%	7th
1,4-Dihydronaphthalene	79.9	612-17-9	NIST14.L		1246.90	42%	4th
Benzene, (1-methyl-2-cyclopropen-1-yl)-	79.7	65051-83-4	NIST14.L		1114.95	9%	8th
1H-Indene, 1-methyl-	79.0	767-59-9	NIST14.L		1167.63	28%	6th

Alternative ranking using the LRI model!!!

The combination of mass spectral similarity and LRI modeling enhances the confidence in compound identification.

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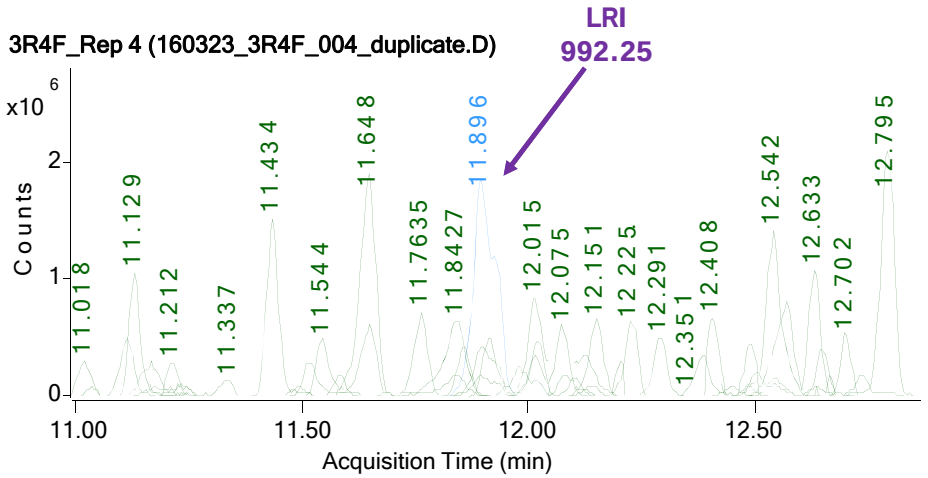
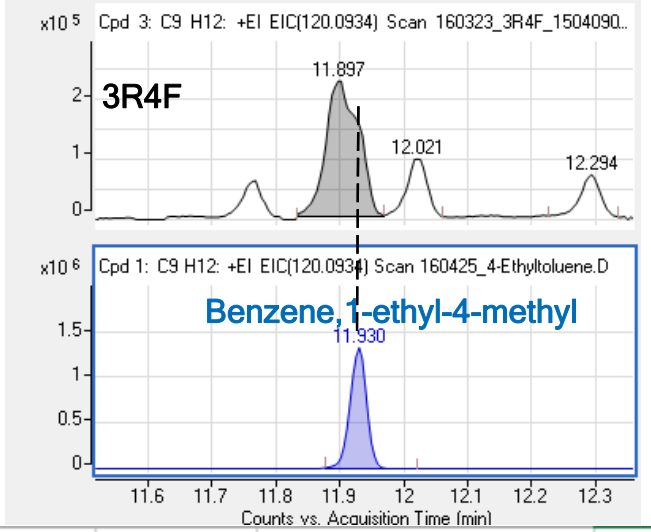
2nd Example / Evaluation





1	Compound Name	Formula	CAS#	Component RI	Library RI	Delta RI	Match Factor	Library File	Component Area
221	Benzamide, O-[(phenylamin	C14H13N3	1000112-26-	992.14			58.7	NIST14.L	606404
222	**Benzene, 1-ethyl-4-methyl-**	**C9 H12**	**622-96-8**	**992.25**	**992.19**	**-0.06**	**90.1**	**UCSD.mslibrary.xml**	6329363
223	Benzene, 1-ethyl-4-methyl-	C9 H12	622-96-8	992.47	992.19	-0.28	47.8	UCSD.mslibrary.xml	1452721
224	**1,6-Octadiene, 2,7-dimethyl-**	**C10 H18**	**40195-09-3**	**993.29**	**991.19**	**-2.10**	**62.1**	**UCSD.mslibrary.xml**	1051796

As Match Factor > 90%, the confidence in identification is very high.
Let's go further to identify this co-eluting compound!!!

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Evaluation of NIST Proposals

1	Compound Name	Formula	CAS#	Component RI	Library RI	Delta RI	Match Factor	Library File	Component Area
221	Benzamide, O-[(phenylamino)carbor	C14H13N3O2	1000112-26-3	992.14			58.7	NIST14.L	606404
222	Benzene, 1-ethyl-2-methyl-	C9H12	611-14-3	992.25			91.0	NIST14.L	6329363
223	Benzene, [(methylsulfinyl)methyl]-	C8H10OS	824-86-2	992.52			88.8	NIST14.L	696399
224	2-Heptyne-4-one	C7H10O	71932-98-4	993.29			69.5	NIST14.L	1051796

Compound Name	Mach Factor	CAS#	Library	LRI_EXP	LRI_Prediction	LRI score	Rank
Benzene, 1-ethyl-2-methyl-	91.0	611-14-3	NIST14.L		966.98	55%	5th
Benzene, 1-ethyl-4-methyl-	90.1	622-96-8	NIST14.L		992.19	90%	1st
Benzene, 1-ethyl-3-methyl-	89.4	620-14-4	NIST14.L	992.2521	971.37	62%	4th
~~Benzene, (1-methylethyl)-~~	~~89.0~~	~~98-82-8~~	~~NIST14.L~~		~~974.74~~	~~68%~~	~~3rd~~
~~Mesitylene~~	~~87.8~~	~~108-67-8~~	~~NIST14.L~~		~~980.59~~	~~77%~~	~~2nd~~

Alternative ranking using the LRI model !!!

Already parts of our accurate mass library

Again, the combination of mass spectral similarity and LRI modeling improves the identification process

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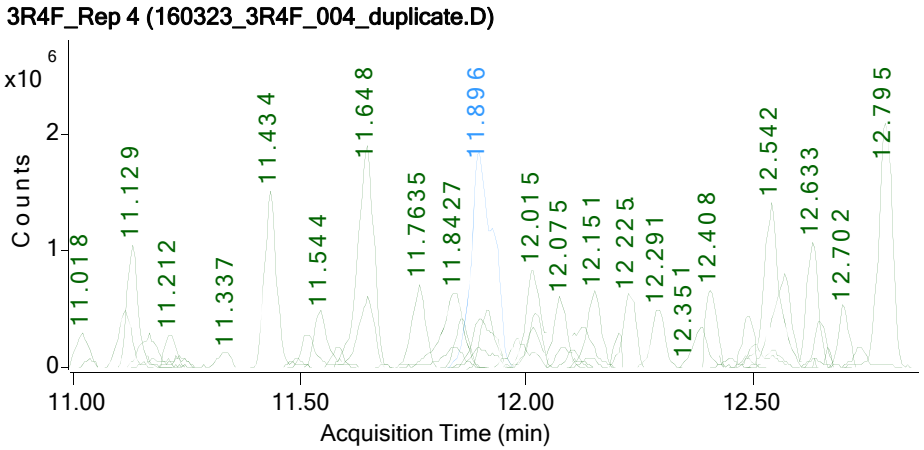
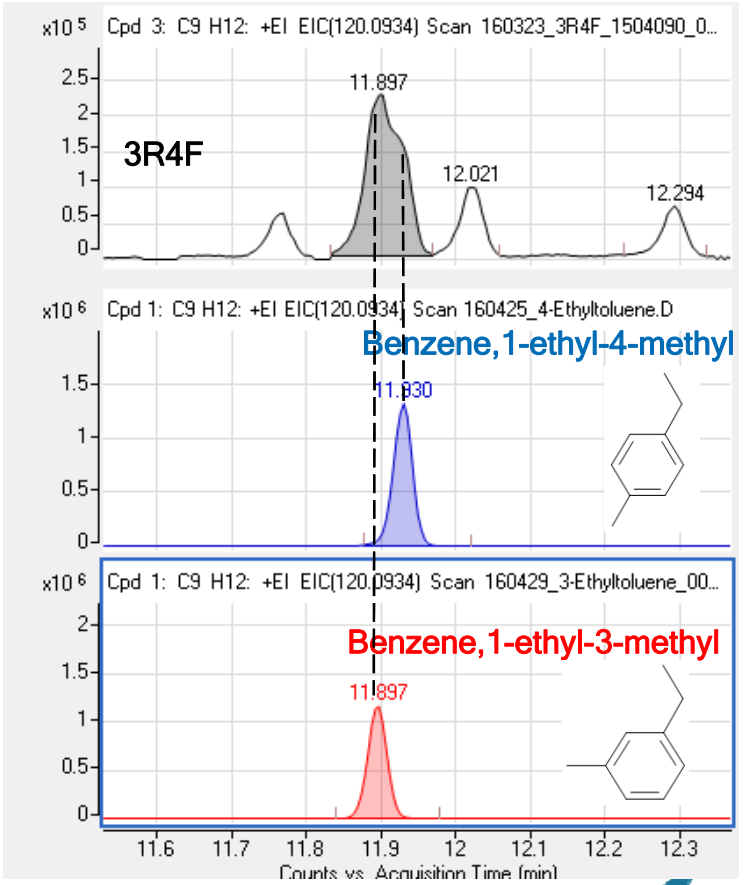
Final Confirmation





Both ethyl-toluene isomers were confirmed in the smoke sample explaining the co-eluting peaks.

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Conclusion & Next Steps

- **Combination of state-of-the-art instrumentation with advanced chemoinformatic tools (Predicted LRIs using QSPR methods) enhance the confidence level in compound identification**
- **This combined approach reduces the list of putative compounds to purchase for final confirmation, leading to**
  - Shortened time for compound identification
  - Reduced total cost for ordering chemicals
  - Reduced rate of false positive compound identification
- **Automation of the workflow reduces the time for complex matrix characterization**

Implement the LRI prediction in the MassHunter Unknown Analysis software

Dossin, E. *et al*. Prediction Models of Retention Indices for Increased Confidence in Structural Elucidation during Complex Matrix Analysis: Application to Gas Chromatography Coupled with High Resolution Mass Spectrometry coming in *Anal. Chem.* in 2016

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THANK YOU

eric.dossin@pmi.com

Implementation of an Advanced Workflow to Enhance the Confidence in Compound Identification for Non-Targeted GC-HR-MS Applications

40th ISCC Symposium, May 29 - June 04, 2016

Eric Dossin, Antonio Castellon, Pierrick Diana, Pavel Pospisil, Mark Bentley, Philippe Guy
Philip Morris International R&D

Analytical Technique: GC-High Resolution (GC-HR-MS)

GC-HR-MS_2
(7200B Agilent Q-TOF-MS)

Apolar & Polar
LRI from 1000 to 3000

Column HP-5MS (30m, Ø=0.25mm)
5% phenyl-arylene
95% dimethyl-polysiloxane

Carrier gas: He

Injection volume: 0.5 µL

Injection mode split 5:1

Sample spiked with several deuterated IS

Full scan acquisition mode (*m/z* 40-620 amu)

BFTSA derivatization (labile hydrogens, alcohols, carboxylic acids, amides…)

GC-HR-MS_1
(7200A Agilent Q-TOF-MS)

Volatile and semi-volatiles
LRI from 500 to 1900

Column DB-624 (30m, Ø=0.25mm)
6% cyanopropyl-phenyl
94% dimethyl-polysiloxane

Carrier gas: He

Injection volume: 250 µL (headspace)
1 µL (liquid)

Injection mode split 5:1

Full scan acquisition mode (*m/z* 20-500 amu)

Goal is to screen the broadest range of smoke constituents

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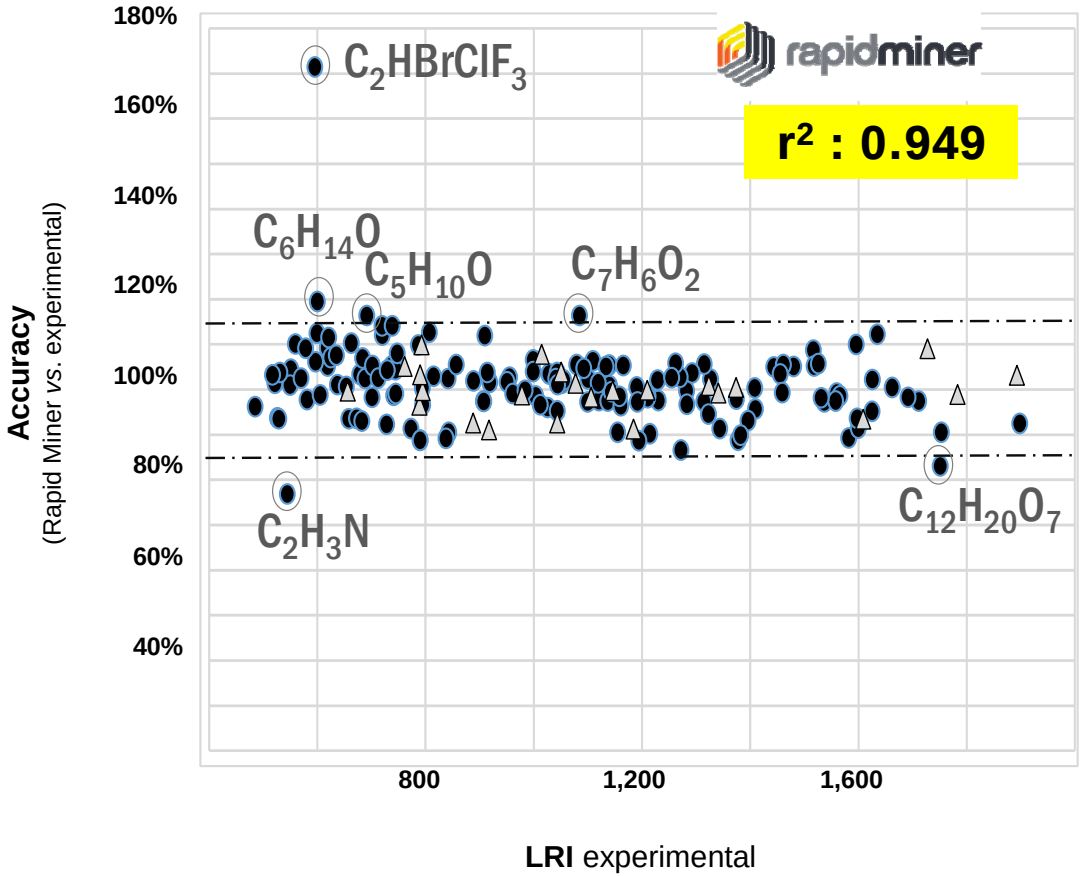
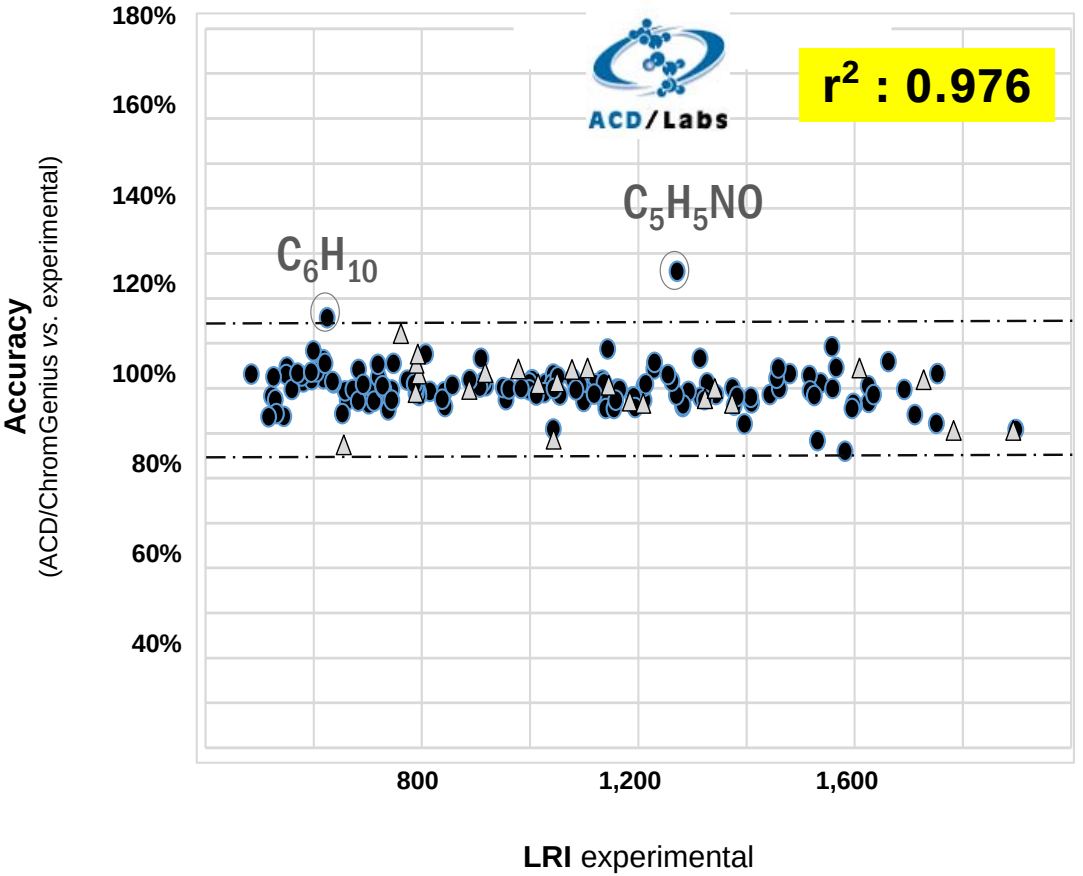
Accuracy Data of Predicted vs Experimental LRI Values





- n=151 reference standards (test set)
- n=23 reference standards (validation set)

Manuscript in revision

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Mathematical Formula

$$LRI\ Score = \frac{Match\ Factor \times LRI_{Exp}}{LRI_{Exp} + (LRI_{Pred} - LRI_{Exp})^2}$$

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