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Apport de l'analyse métabolomique par spectrométrie de masse à la détection sans *a priori* de xénobiotiques dans les matrices alimentaires et environnementales

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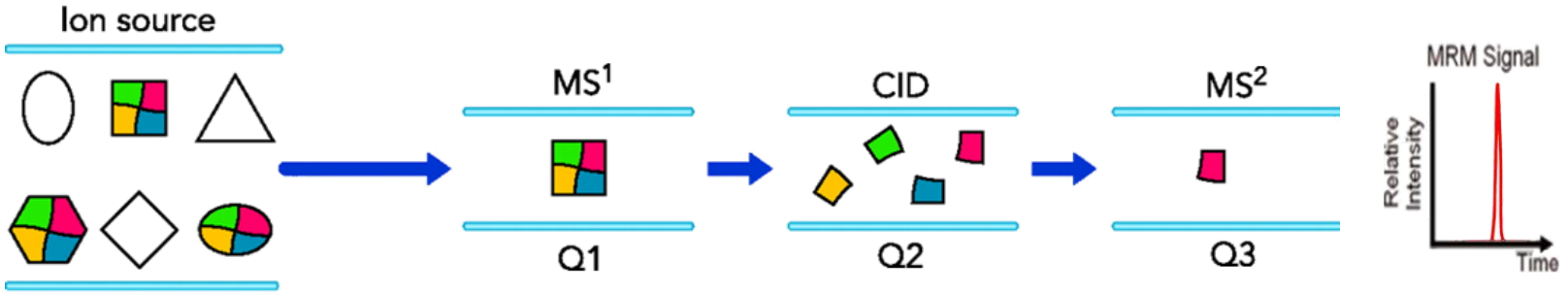
Current regulatory analyses of pollutants

- **GC/MS analyses**
- **LC/ESI-MS/MS analyses in MRM mode (*Multiple Reaction Monitoring*) on triple quadrupole spectrometers**



Advantages :

- Very sensitive
- Specific
- Fast and easy interpretation

Limitations :

- Time consuming development
- **Focused on targeted and known molecules**

Reference methods to date

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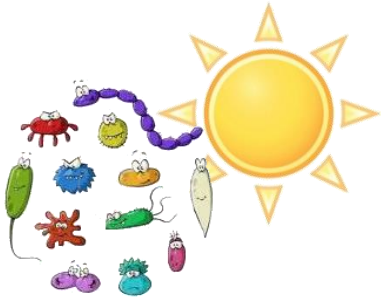
Food safety: unknown or unexpected molecules?

- **Known but unexpected contaminants :**
  - **The case of milk adulteration with melamine :**

Melamine

→ **4 deaths and thousands of intoxications**

- **Metabolism of pollutants :**



In the environment

In water treatment plants

By man or animals

→ **Production of unknown or untargeted xenometabolites with questionable toxicity**

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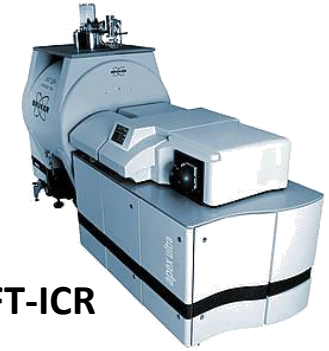
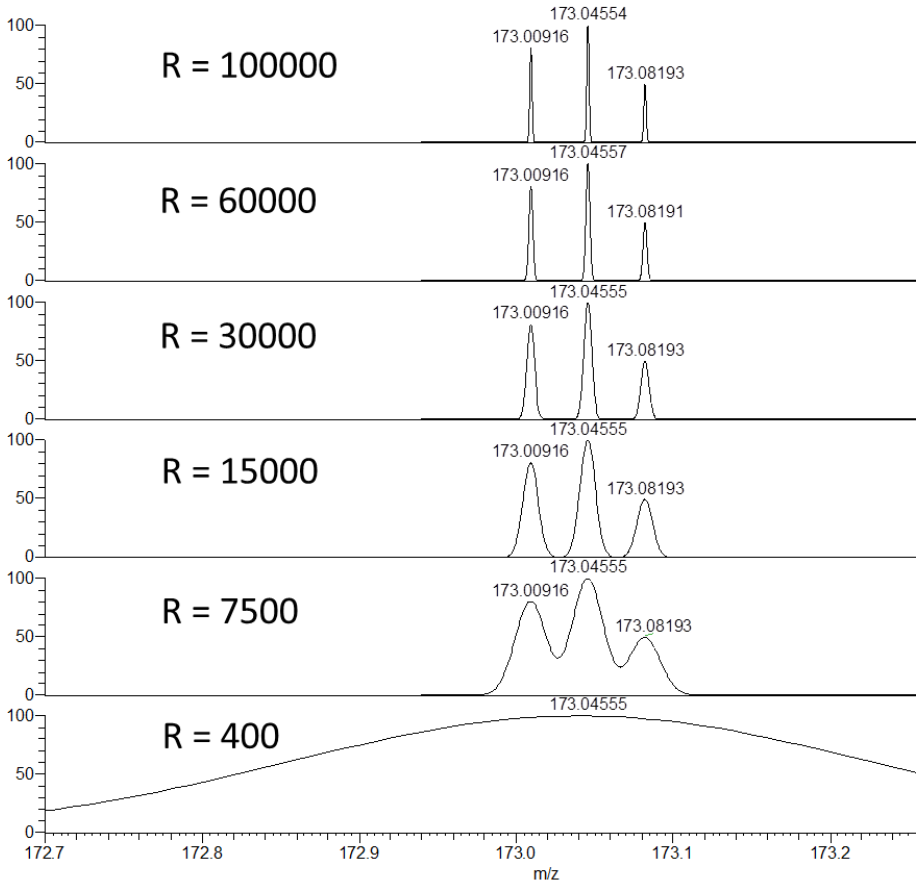
Improvements provided by High Resolution Mass Spectrometry (HRMS)

Orbitrap



FT-ICR

TOF



$R = m/\Delta m$

1 ppm: 100,0001

$C_xH_yN_zO_w$ …

- Aconitic acid (m/z 173.009163)
- Shikimic acid (m/z 173.045548)
- Suberic acid (m/z 173.081933)

- Access to large quantity of information
- High measurement precision : elemental composition

The metabolomic workflow

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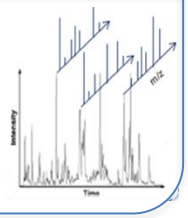
1 Sample preparation

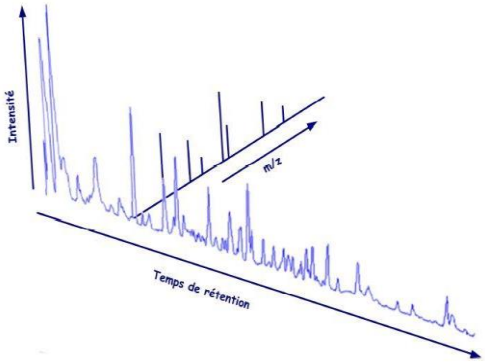
2 Metabolome analysis

GC/MS

LC/MS

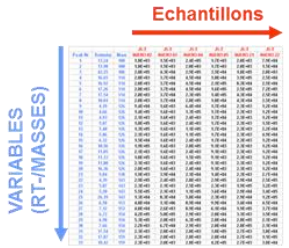
RMN





3 Data processing

Automatic detection of signals

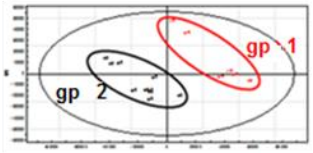


Selection of relevant features

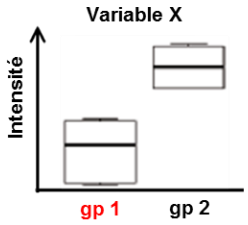
Annotation :
Databases
public / internal

4 Statistical analyses

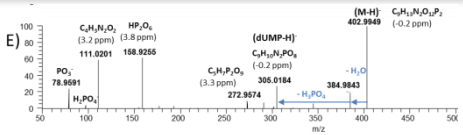
Multivariate

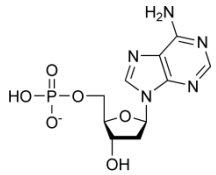


Univariate



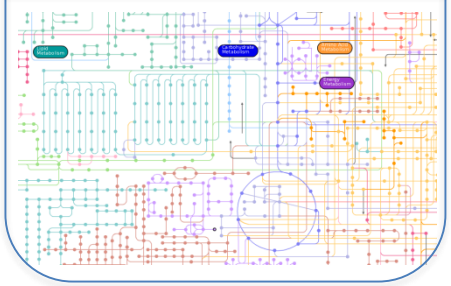
5 Metabolite identification





- To confirm annotations
- To characterize unknowns

6 Data visualization



Cerebrospinal fluid metabolomics highlights dysregulation of energy metabolism in overt hepatic encephalopathy

Nicolas Weiss[1,2], Pierre Barbier Saint Hilaire[3], Benoit Colsch[3], Foucauld Isnard[3], Suleiman Attala[3], Augustin Schaefer[1], Maria del Mar Amador[4], Marika Rudler[1,5], Foudil Lamari[6], Frédéric Sedel[7], Dominique Thabut[1,5,†], Christophe Junot[3,*,†]

Cirrhosis

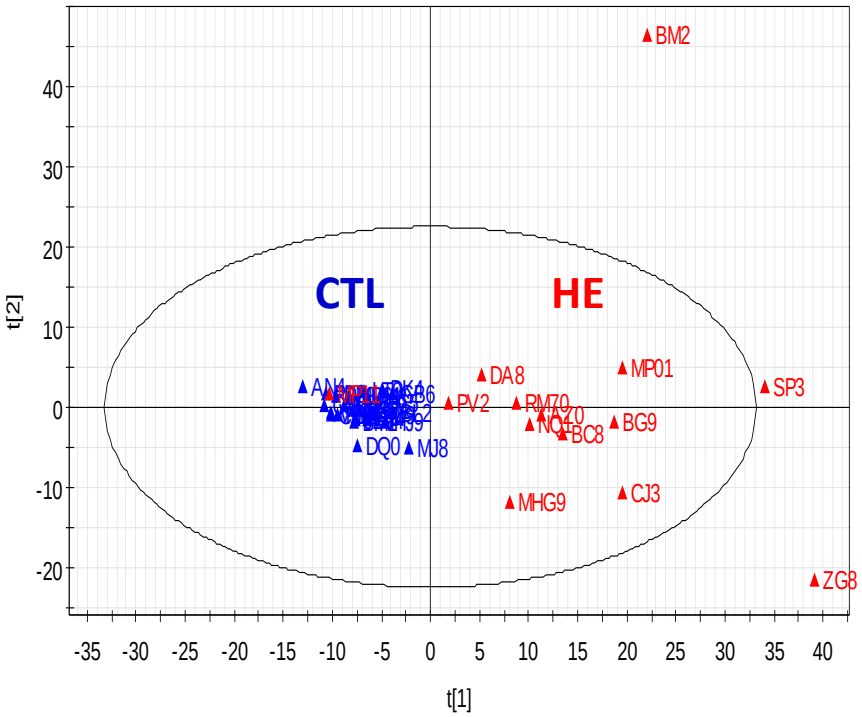
EASL JOURNAL OF HEPATOLOGY

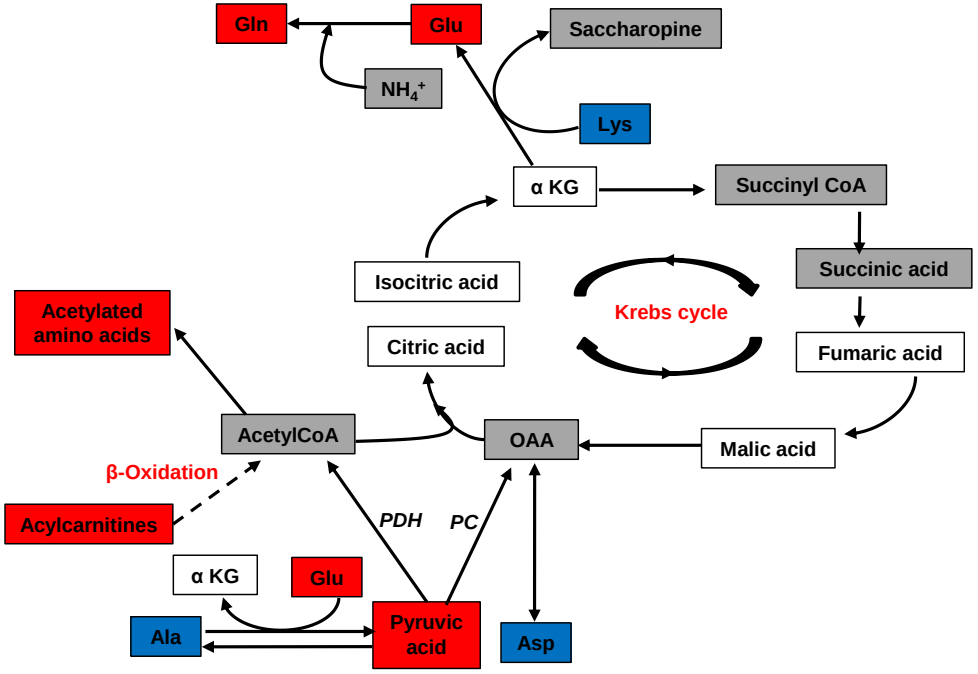
HE is a neurological complication of acute or chronic liver disease.

60 to 80 % of cirrhotic patients exhibit cognitive disorders potentially related to minimal HE.

The aim of the study: to highlight altered metabolic pathways in HE patients by using CSF metabolomics.

- **patient stratification**
- **pharmacological targets**





~ 500 signaux LC/MS annotés, 120 identifiés et sélectionnés, 73 métabolites dont les concentrations sont modifiées par la pathologie

- Altération du métabolisme énergétique cérébral: potentielles nouvelles cibles pharmacologiques

- Possibilité de stratifier les patients selon la gravité des atteintes hépatique et neurologique

High intensity features related to drugs and metabolites have been detected in 7 out of the 14 HE patients

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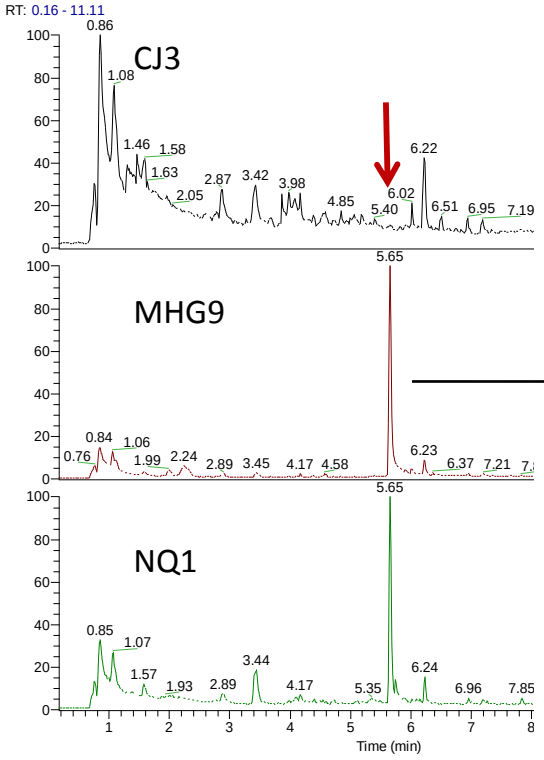
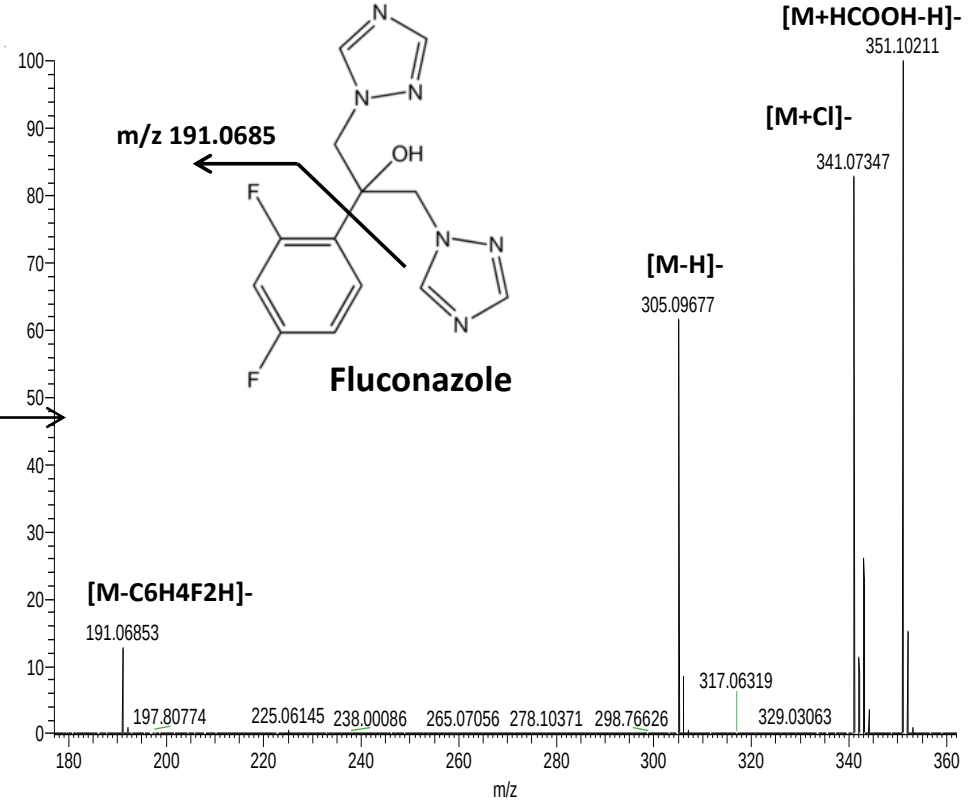
Putative annotation	HMDB	Metlin	KEGG	Samples
Levetiracetam	HMDB15333	66750	C07841	BM2
Metronidazole	HMDB15052	573	C07203	BG9
Fluconazole	HMDB14342	2708		MGH9, NQ1, ZG8, AZ0
diazepam	HMDB14967	3521	C06948	BC8, MHG9, MP01, NQ1, ZG8
N-Desmethyldiazepam	HMDB60538	896	C07486	BC8, MHG9, MP01, NQ1, ZG8
Tazobactam	HMDB15544	581	D00660	BG9, NQ1, ZG8
Piperacillin	HMDB14464	1964	D08380	BG9, NQ1, ZG8

Could explain PCA outliers

Drug induced HE???





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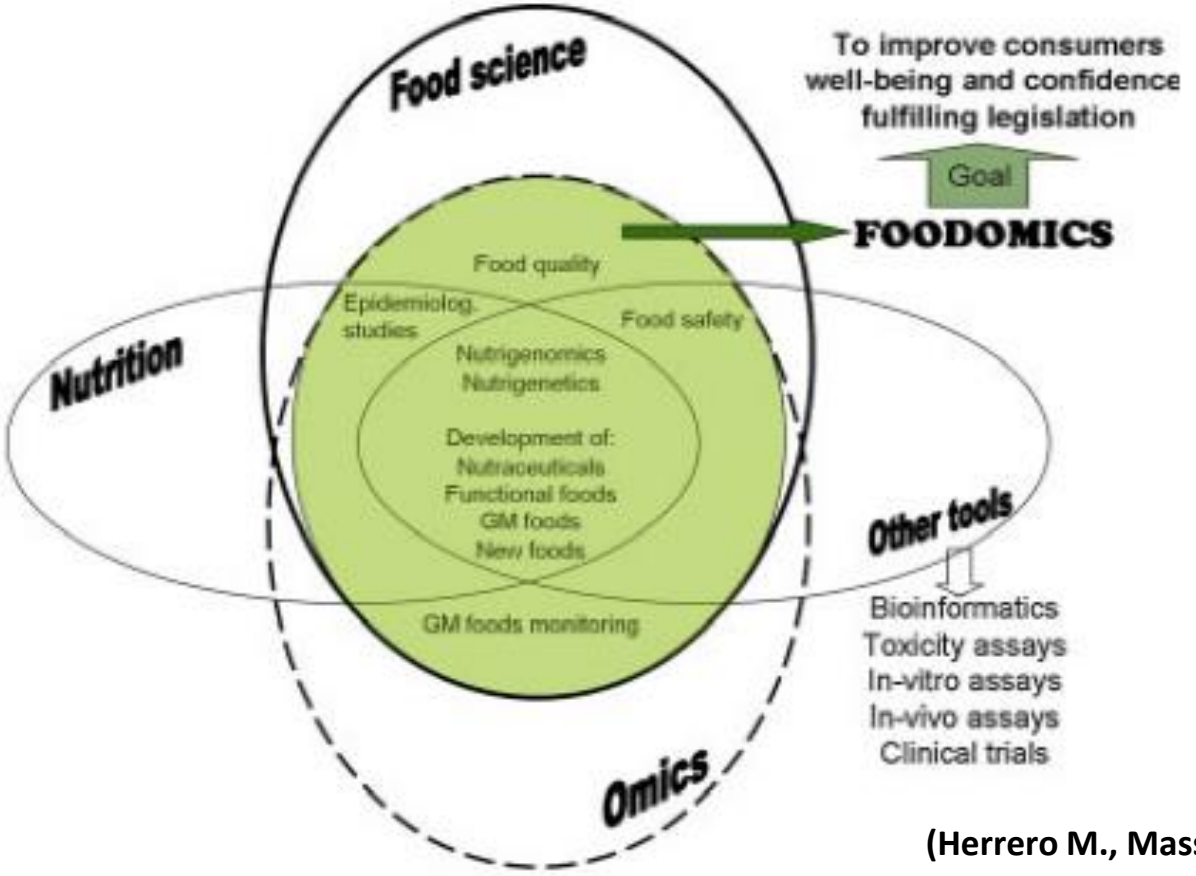
Foodomics

The study of food and nutrition through advanced omics technologies to improve consumer's well-being, health and confidence.



(Herrero M., Mass Spectrom. Rev., 2012)

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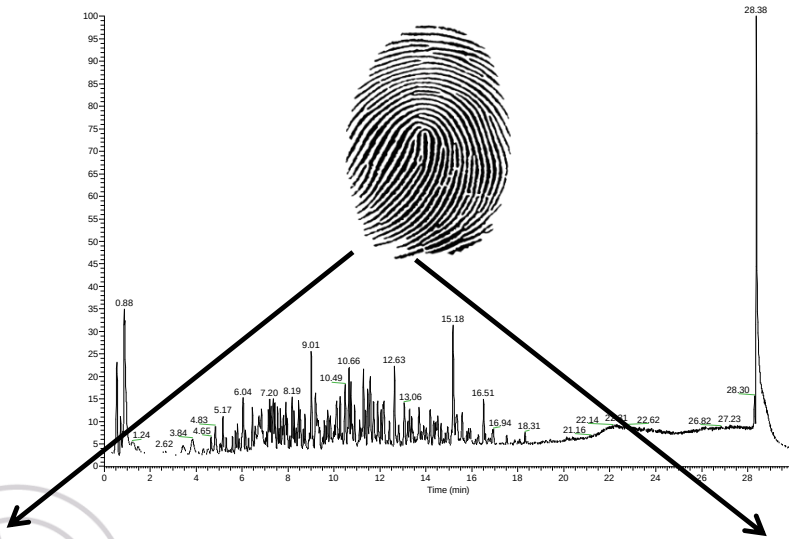
HRMS: all in one approach

Orbitrap

FT-ICR

TOF



Targeted approach

- Based on a large spectral database of hundreds of pollutants

Metabolomic based approach

- Unknown or untargeted contaminants
- Adulteration markers

✓ **Advantages :**

- High resolution
- High versatility
- Retrospective analyses
- Structural analysis

✓ **Limitations** :

- Data complexity
- Sensitivity
- Time consuming interpretation

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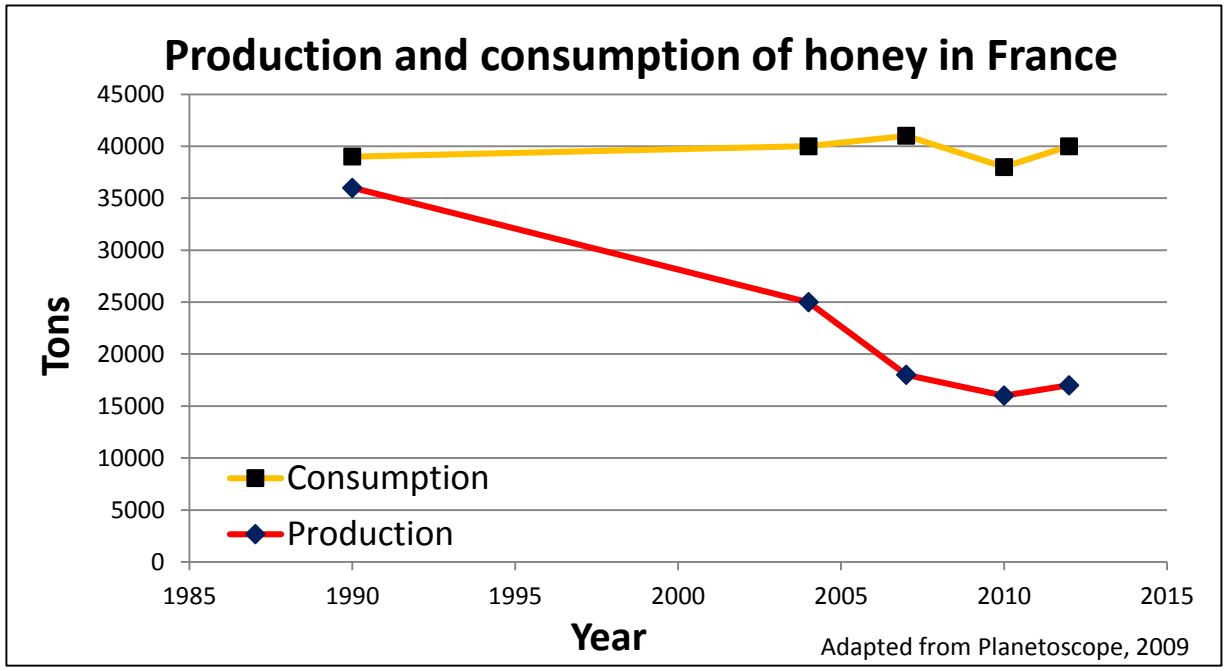
Proof of concept study on honey



- Decline of bees population: exposition to pesticides
- Significant imports of honey: increased risks of adulteration
- Presence of antibiotics: human health concern

Evaluation of the quality of honey

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Material and Methods

Pollutants:

- 55 pesticides
- 28 antibiotics

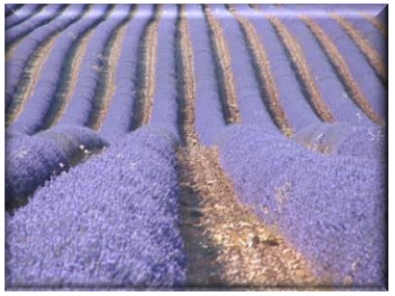
} 83 targeted pollutants

Spectral database:

Injection of individual standard
Implementation of pertinent information

Samples:

- 76 honeys regrouping 6 floral origins :
  - Multi flower
  - Acacia
  - Orange tree
  - Lavender
  - Mountain
  - Eucalyptus



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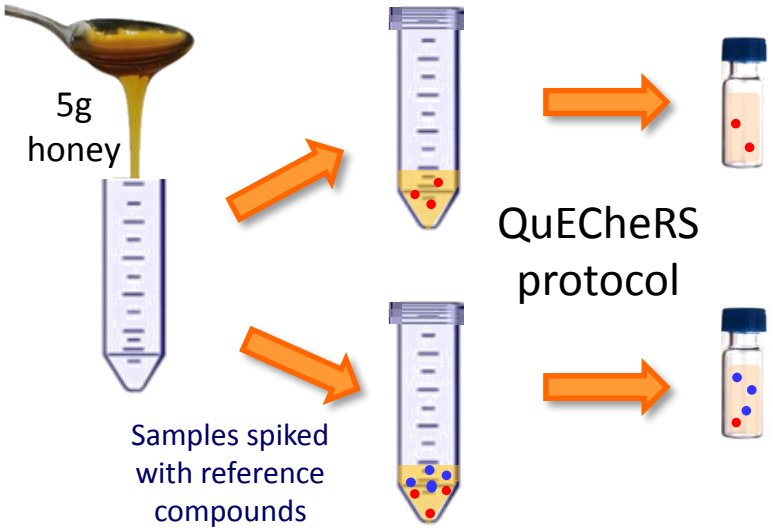
Material and Methods

❖ Sample preparation: liquid-liquid extraction



- Semi-quantification
- 80% < extraction yields < 100%
- 3 replicates of each condition
- All molecules spiked at 10ng/g = MRLs

❖ Honeys samples analyses:

Nexera (Shimadzu)

Q-Exactive (Thermo Fisher scientifics)

POS
R = 50 000
< 5ppm

C18 column

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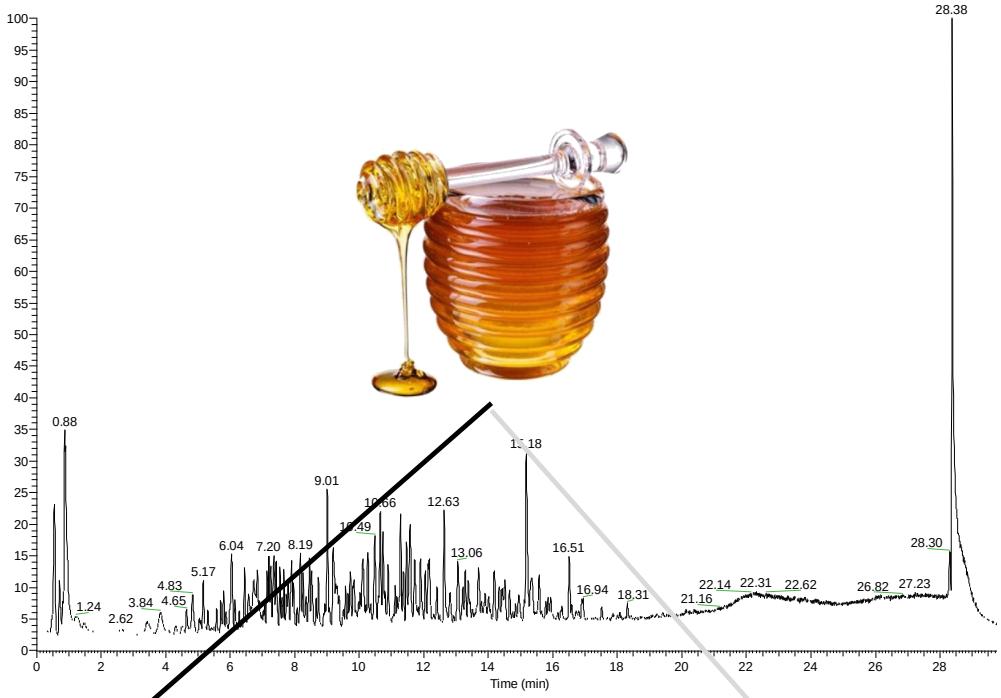
First data mining



Targeted approach

- 83 molecules in the chemical library

Metabolomic based approach

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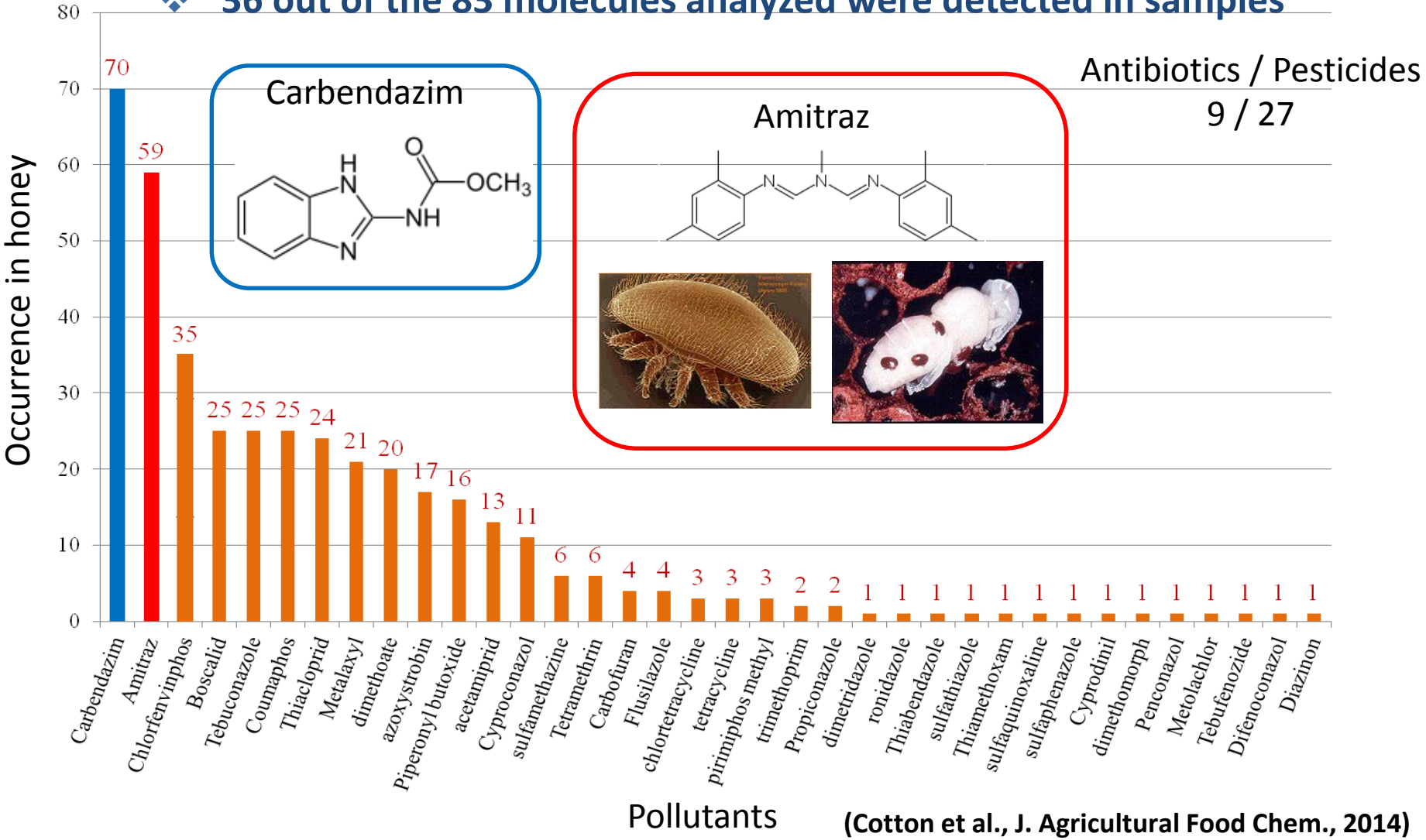
Targeted analysis results

- 74 out of 76 honey samples are polluted by at least one molecule
- 36 out of the 83 molecules analyzed were detected in samples

Antibiotics / Pesticides
9 / 27



(Cotton et al., J. Agricultural Food Chem., 2014)

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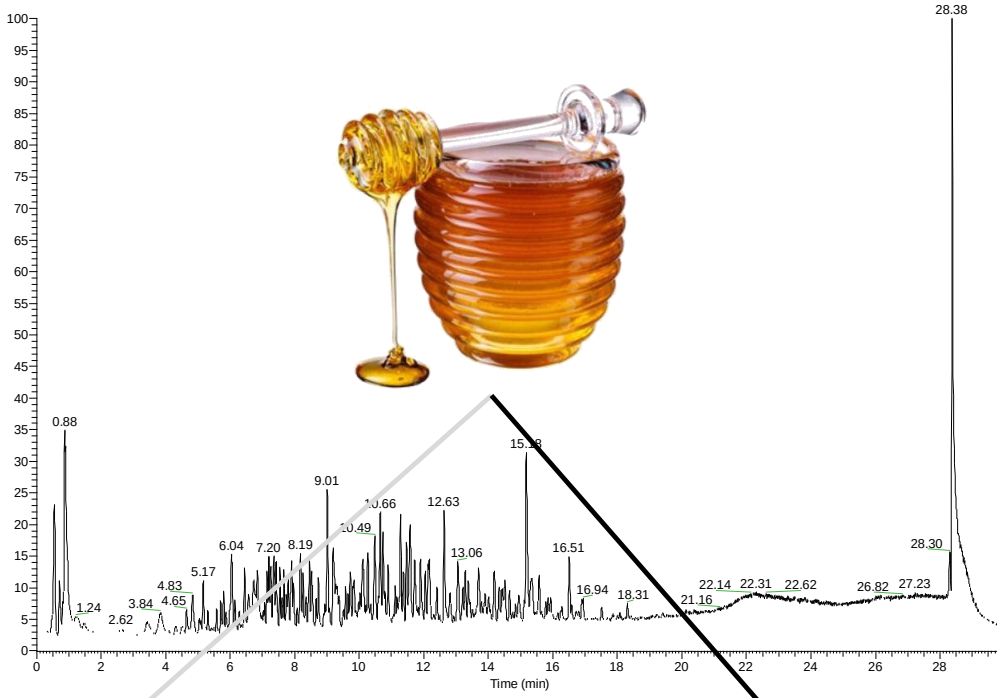
Second data mining



Targeted approach

Metabolomic based approach

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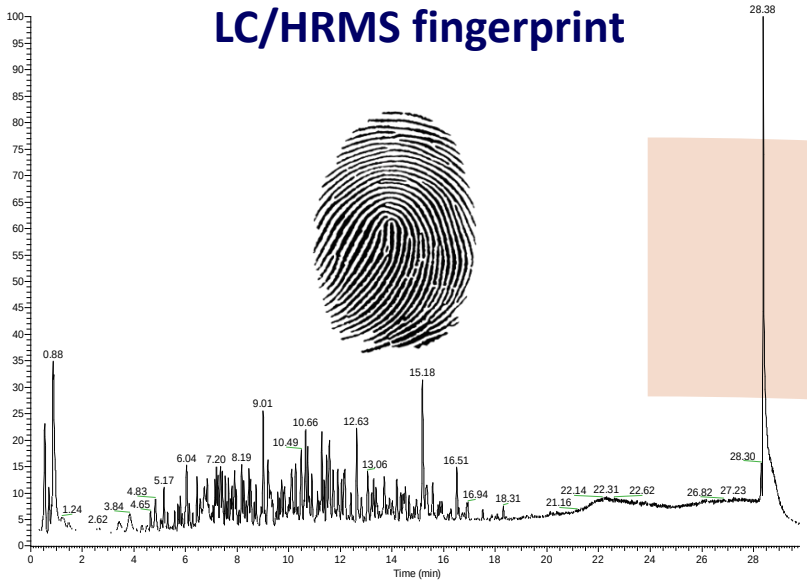
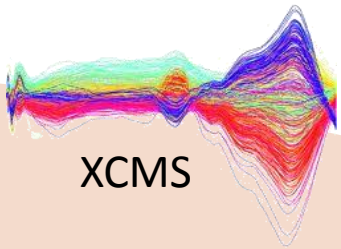
LC/HRMS fingerprint



Automatic peak detection and alignment



XCMS

Samples

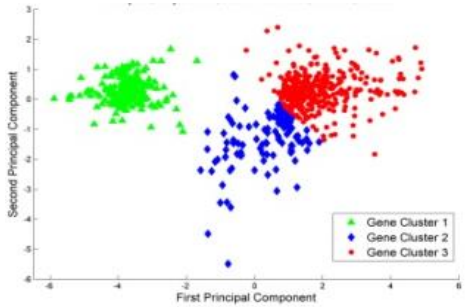
Features (rt-m/z)

Peaktable

Peak Nr	Ret(min)	Mass	J5-T 060303-02	J5-T 060303-03	J5-T 060303-04	J5-T 060303-05	J5-T 060303-21	J5-T 060303-22
1	13.24	100	1.8E+03	1.5E+03	2.4E+05	1.7E+03	2.0E+03	7.9E+04
2	13.98	100	1.8E+03	1.5E+03	2.0E+03	1.7E+03	2.0E+03	1.5E+04
3	42.25	106	2.0E+05	4.3E+04	2.9E+05	3.5E+04	1.8E+05	2.0E+03
4	16.65	114	2.0E+03	3.7E+04	4.5E+04	1.0E+04	3.9E+05	2.5E+04
5	16.92	114	2.0E+03	3.7E+04	4.5E+04	2.1E+05	8.3E+04	2.5E+04
6	17.26	114	2.0E+03	3.7E+04	4.5E+04	1.6E+05	2.5E+05	7.2E+05
7	17.54	114	2.0E+03	3.7E+04	2.3E+05	1.4E+05	4.3E+04	2.5E+04
8	18.01	114	2.0E+03	3.7E+04	2.8E+05	1.0E+04	4.3E+04	2.5E+04
9	4.19	126	9.4E+04	1.6E+03	6.4E+04	1.7E+04	2.3E+03	1.2E+04
10	4.66	126	1.4E+05	1.6E+03	1.3E+05	1.7E+04	2.3E+03	1.2E+04
11	4.93	126	2.1E+03	1.6E+03	2.4E+03	1.7E+04	2.3E+03	1.2E+04
12	5.07	126	1.8E+05	1.6E+03	2.4E+03	1.7E+04	2.3E+03	1.5E+05
13	5.40	126	1.3E+05	1.6E+03	1.1E+05	1.7E+04	2.3E+03	2.2E+04
14	5.86	126	2.1E+03	1.6E+03	1.1E+05	1.7E+04	2.3E+03	4.9E+04
15	6.32	126	1.5E+04	1.6E+03	2.4E+03	1.7E+04	2.3E+03	1.2E+04
16	10.56	126	1.9E+05	1.6E+03	2.0E+05	9.1E+03	2.3E+03	1.2E+04
17	11.05	126	2.1E+03	1.6E+03	2.4E+03	9.1E+03	2.3E+03	1.2E+04
18	11.33	126	1.0E+05	1.6E+03	1.5E+05	9.1E+03	2.3E+03	1.2E+04
19	11.80	126	2.1E+03	1.6E+03	2.4E+03	9.1E+03	2.3E+03	1.2E+04
20	16.36	126	2.0E+03	1.6E+03	2.4E+04	9.1E+03	2.3E+03	1.2E+04
21	9.04	138	1.9E+03	3.9E+04	2.1E+04	1.4E+04	2.3E+03	2.7E+04
22	4.39	143	2.9E+05	2.4E+05	2.8E+03	2.9E+05	2.9E+04	2.5E+05
23	5.07	143	2.3E+03	2.1E+03	2.5E+05	2.3E+03	1.9E+05	3.2E+05
24	5.20	143	5.5E+05	2.1E+03	1.1E+05	3.6E+04	2.9E+04	3.4E+05
25	26.39	143	1.3E+04	8.3E+04	5.8E+04	2.3E+03	2.9E+04	1.2E+05
26	6.58	153	4.0E+04	1.1E+06	8.9E+04	9.9E+04	3.4E+04	4.5E+04
27	7.12	153	4.0E+04	2.6E+03	8.9E+04	6.1E+04	1.9E+05	3.7E+04
28	6.72	154	4.2E+05	5.0E+05	2.9E+03	2.0E+04	3.1E+03	3.9E+04
29	6.98	154	5.3E+05	2.0E+03	6.3E+05	2.0E+04	2.8E+05	2.1E+05
30	7.66	154	2.2E+03	6.7E+04	2.9E+03	2.0E+04	2.8E+05	2.1E+04
31	17.54	159	2.3E+03	2.0E+03	2.8E+03	3.0E+05	2.7E+03	3.8E+04
32	17.87	159	2.3E+03	2.0E+03	2.8E+03	2.8E+04	2.7E+03	1.1E+05
33	18.42	159	2.3E+03	2.0E+03	2.8E+03	4.2E+05	2.7E+03	3.8E+04

1. Identification of new xenobiotics

2. Chemical characterization of honey samples



Statistical analyses and data mining

Detection of new xenobiotics

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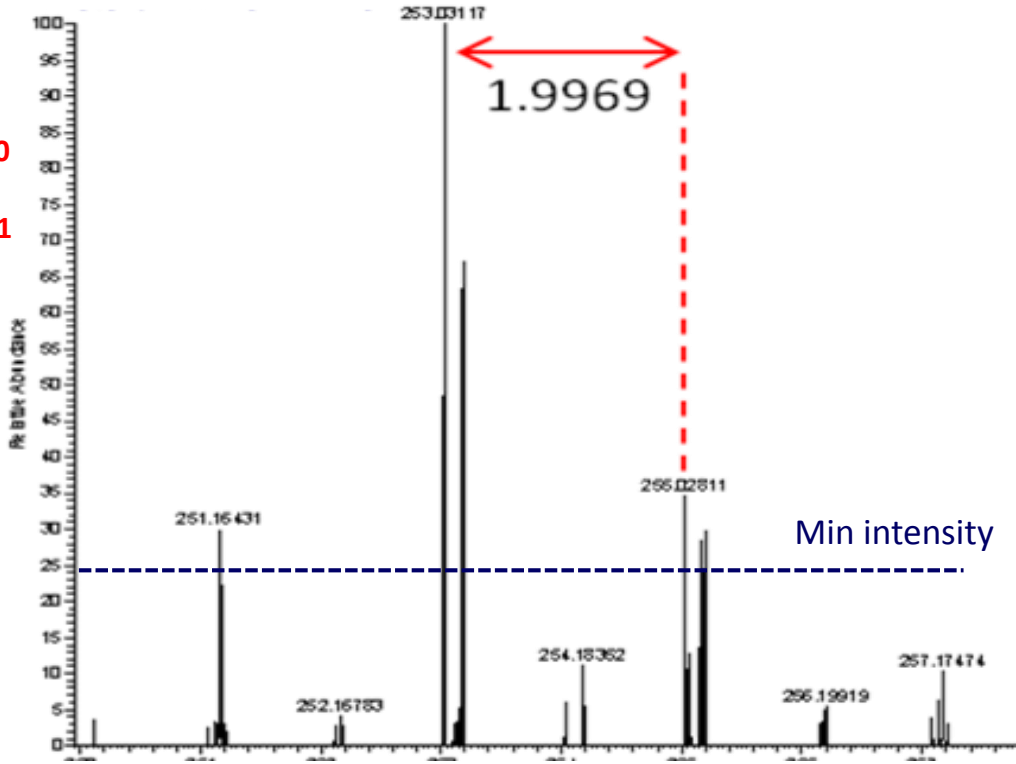
- Use of chlorine isotope contribution: ^{35}Cl and ^{37}Cl $\Delta m/z\ (^{37}Cl - ^{35}Cl) = 1.9970$
- Implementation of an algorithm for the automatic detection of chlorinated compounds from XCMS peaktables

	A		E		M	N
1	mzmed		rtmed (min)		Var Isotope	
2837	253.02861		2.74			
2838	253.03067		11.15		2892	
2839	253.07000		6.57			
2840	253.07003		7.06			
2841	253.07021		7.88			
2842	...		...			
2856	253.25216		17.51			
2857	253.26674		15.21			
2858	253.55378		16.20			
2859	254.03392	✗	11.16	✓		
2860	254.06612		14.72			
2861	254.06634		6.63			
2862	254.07295		6.56			
2863	254.07950		12.39			
2867	...		...			
2889	254.25591		17.51			
2890	254.54324		14.16			
2891	255.02757	✓	13.13	✗		
2892	255.02770	✓	11.15	✓		
2893	255.04335		6.98			
2894	255.07699		12.95			

$\Delta m/z\ (^{37}Cl - ^{35}Cl) = 1.9970$
Same RT
0.25 < Intensity ratio < 1.1

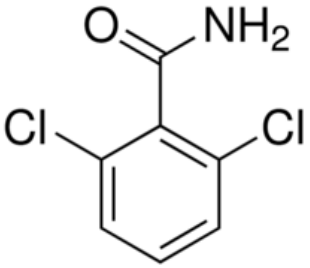


(Cotton et al., J. Agricultural Food Chem., 2014)

✓ Validation:

- All chlorinated pollutants detected previously were found

✓ Formal identification of 2,6-dichlorobenzamide



- Metabolite of dichlobenil, an herbicide used in lavender culture
- **Only found in lavender honey**
- Banned in France in 2010

✓ Characterization of 10 unknown xenobiotics (present in 1 to 70 honey samples):

- Elemental composition (MS/MS experiments often not informative)
- **Not found in databases** (HMDB, KEGG, METLIN)
- Unknown metabolites or abiotic degradation products ?

(Cotton et al., J. Agricultural Food Chem., 2014)

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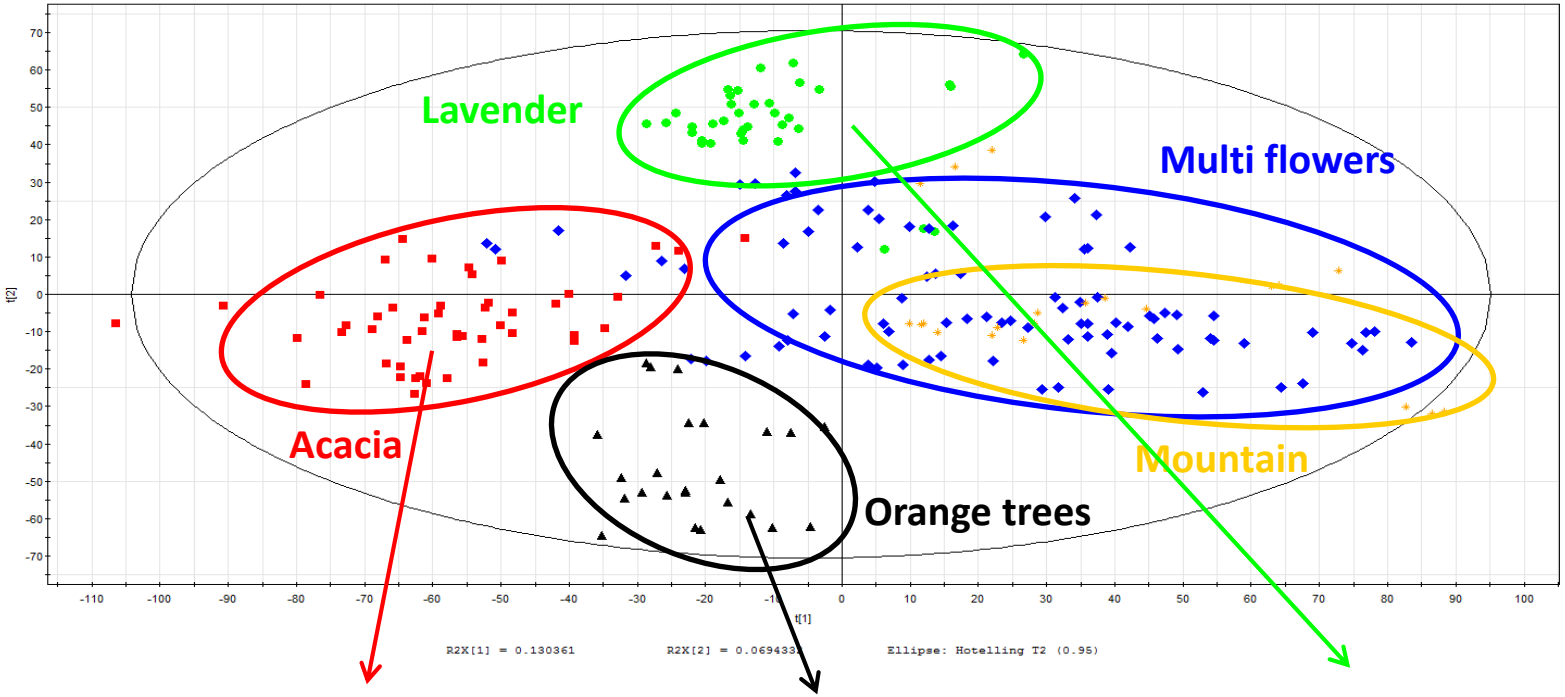
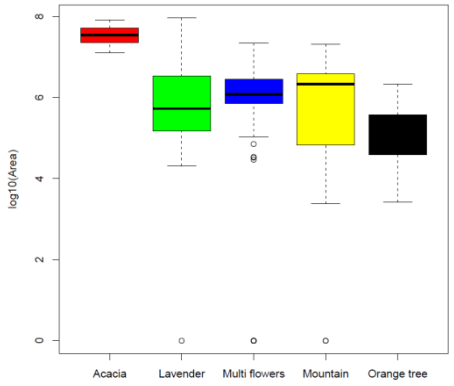
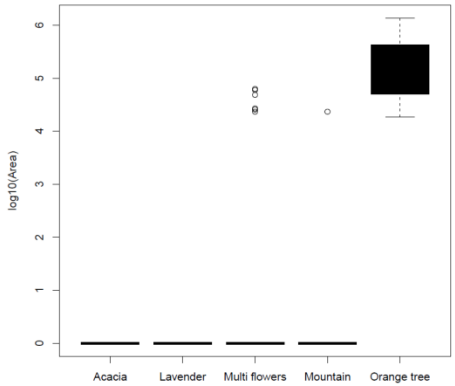
Discrimination of honeys according to their floral origin



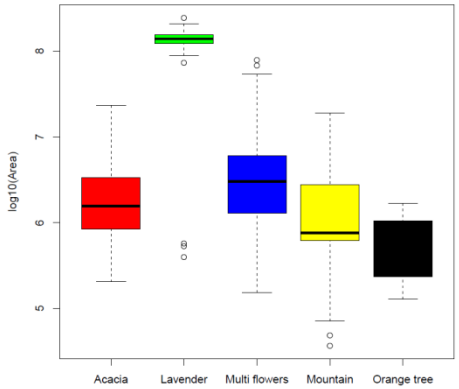
Hypoxanthine



Naringin



Phenylalanine



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Future safety analyses?

- ✓ Screening of hundreds of contaminants (regulatory assessments)
- ✓ Warnings based on chemical profile databases

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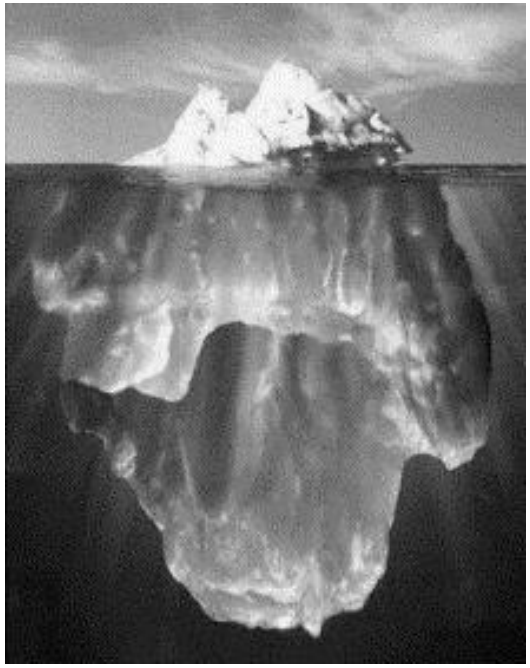
The main challenges:
Xenobiotic detection and identification

There is no universal method to detect, identify and quantify metabolites and xenobiotics

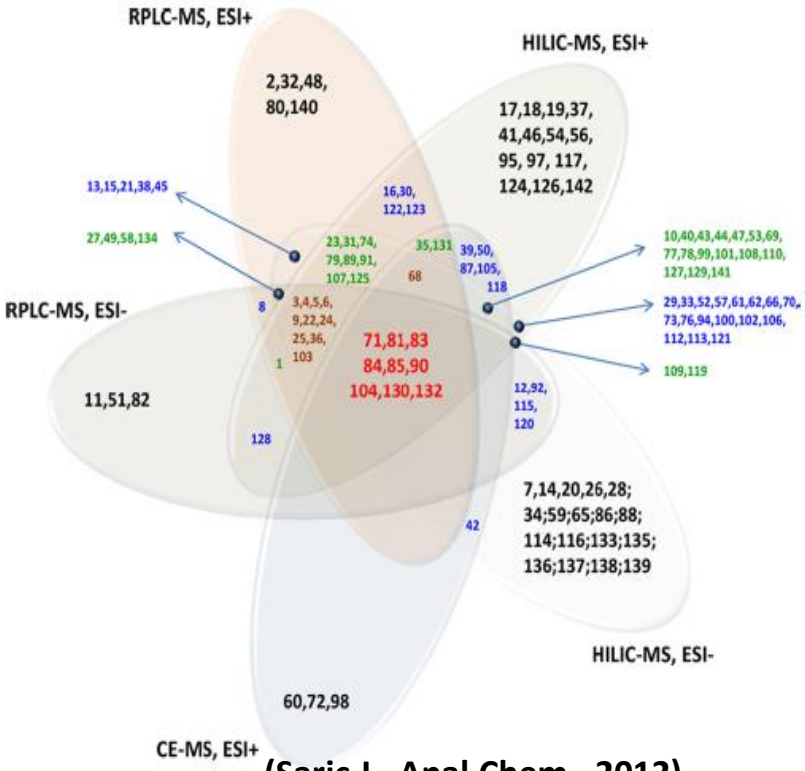
Global approaches are less sensitive than targeted ones



(Adapted from Sumner L.W. et al., 2003)

Concentration range

mM	NMR
µM	GC/MS
nM	LC/MS
pM	LC/Fluo



(Saric J., Anal.Chem., 2012)

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Metabolite identification

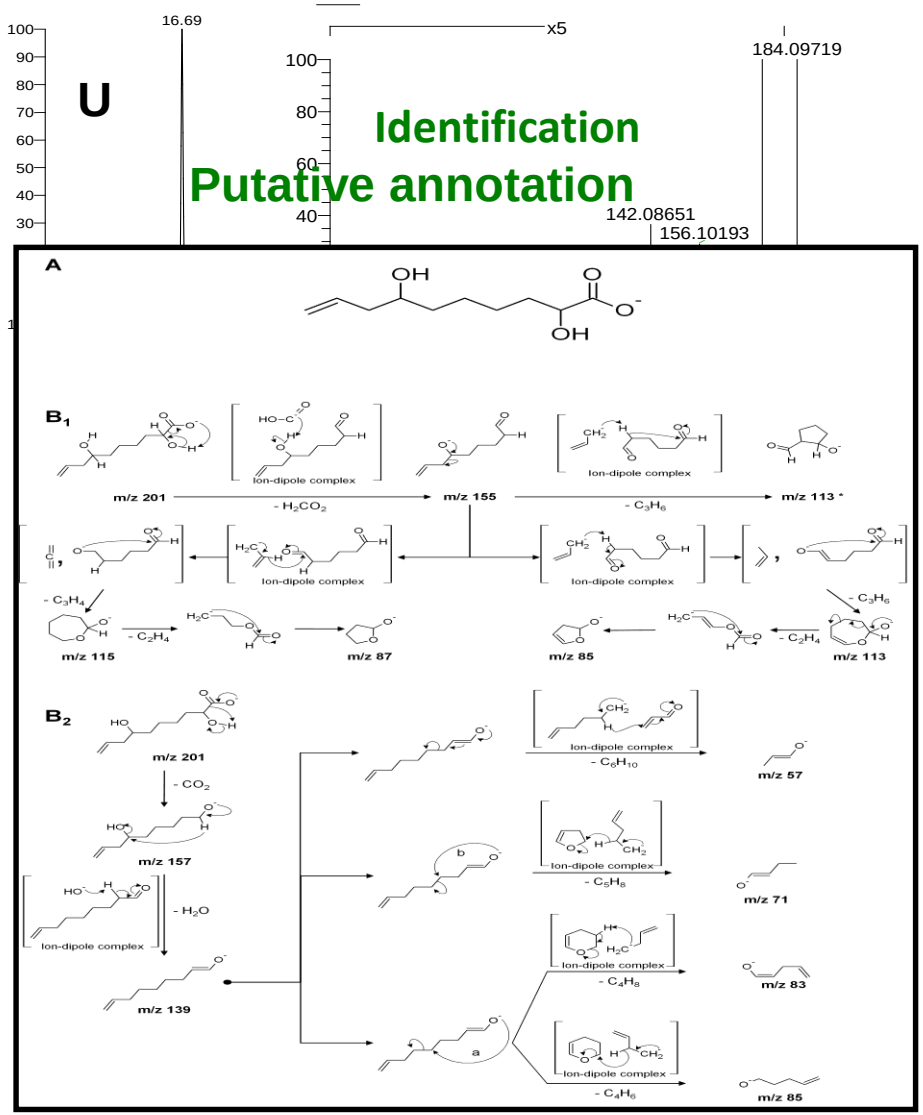
Metabolomics (2007) 3:211–221
DOI 10.1007/s11306-007-0082-2

ORIGINAL ARTICLE

Proposed minimum reporting standards for chemical analysis

Chemical Analysis Working Group (CAWG) Metabolomics Standards Initiative (MSI)

1. Identified compounds (see below).
2. Putatively annotated compounds (e.g. without chemical reference standards, based upon physicochemical properties and/or spectral similarity with public/commercial spectral libraries).
3. Putatively characterized compound classes (e.g. based upon characteristic physicochemical properties of a chemical class of compounds, or by spectral similarity to known compounds of a chemical class).
4. Unknown compounds—although unidentified or unclassified these metabolites can still be differentiated and quantified based upon spectral data.



As only few authentic references are available, most of the compounds will be putatively annotated

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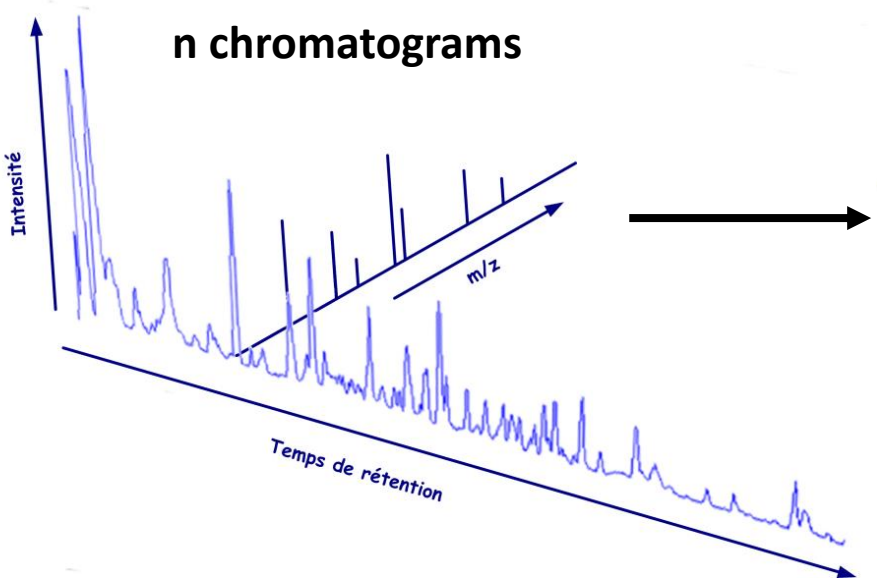
The main challenges: automatic detection and alignment of signals



Samples

Variables (Rt-masse)

Peak Nr	Ret(min)	Mass	J5-T 060303-02	J5-T 060303-03	J5-T 060303-04	J5-T 060303-05	J5-T 060303-21	J5-T 060303-22
1	13.24	100	1.8E+03	1.5E+03	2.4E+05	1.7E+03	2.0E+03	7.9E+04
2	13.98	100	1.8E+03	1.5E+03	2.0E+03	1.7E+03	2.0E+03	1.5E+04
3	42.25	106	2.0E+05	4.3E+04	2.9E+05	3.5E+04	1.8E+05	2.0E+03
4	16.65	114	2.0E+03	3.7E+04	4.5E+04	1.0E+04	3.9E+05	2.5E+04
5	16.92	114	2.0E+03	3.7E+04	4.5E+04	2.1E+05	8.3E+04	2.5E+04
6	17.26	114	2.0E+03	3.7E+04	4.5E+04	1.6E+05	2.5E+05	7.2E+05
7	17.54	114	2.0E+03	3.7E+04	2.3E+05	1.4E+05	4.3E+04	2.5E+04
8	18.01	114	2.0E+03	3.7E+04	2.8E+05	1.0E+04	4.3E+04	2.5E+04
9	4.19	126	9.4E+04	1.6E+03	6.4E+04	1.7E+04	2.3E+03	1.2E+04
10	4.66	126	1.4E+05	1.6E+03	1.3E+05	1.7E+04	2.3E+03	1.2E+04
11	4.93	126	2.1E+03	1.6E+03	2.4E+03	1.7E+04	2.3E+03	1.2E+04
12	5.07	126	1.8E+05	1.6E+03	2.4E+03	1.7E+04	2.3E+03	1.5E+05
13	5.40	126	1.3E+05	1.6E+03	1.1E+05	1.7E+04	2.3E+03	2.2E+04
14	5.86	126	2.1E+03	1.6E+03	1.1E+05	1.7E+04	2.3E+03	4.9E+04
15	6.32	126	1.5E+04	1.6E+03	2.4E+03	1.7E+04	2.3E+03	1.2E+04
16	10.56	126	1.9E+05	1.6E+03	2.0E+05	9.1E+03	2.3E+03	1.2E+04
17	11.05	126	2.1E+03	1.6E+03	2.4E+03	9.1E+03	2.3E+03	1.2E+04
18	11.33	126	1.0E+05	1.6E+03	1.5E+05	9.1E+03	2.3E+03	1.2E+04
19	11.80	126	2.1E+03	1.6E+03	2.4E+03	9.1E+03	2.3E+03	1.2E+04
20	16.36	126	2.0E+03	1.6E+03	2.4E+04	9.1E+03	2.3E+03	1.2E+04
21	9.04	138	1.9E+03	3.9E+04	2.1E+04	1.4E+04	2.3E+03	2.7E+04
22	4.39	143	2.9E+05	2.4E+05	2.8E+03	2.9E+05	2.9E+04	2.5E+05
23	5.07	143	2.3E+03	2.1E+03	2.5E+05	2.3E+03	1.9E+05	3.2E+05
24	5.20	143	5.5E+05	2.1E+03	1.1E+05	3.6E+04	2.9E+04	3.4E+05
25	26.39	143	1.3E+04	8.3E+04	5.8E+04	2.3E+03	2.9E+04	1.2E+05
26	6.58	153	4.0E+04	1.1E+06	8.9E+04	9.9E+04	3.4E+04	4.5E+04
27	7.12	153	4.0E+04	2.6E+03	8.9E+04	6.1E+04	1.9E+05	3.7E+04
28	6.72	154	4.2E+05	5.0E+05	2.9E+03	2.0E+04	3.1E+03	3.9E+04
29	6.98	154	5.3E+05	2.0E+03	6.3E+05	2.0E+04	2.8E+05	2.1E+05
30	7.66	154	2.2E+03	6.7E+04	2.9E+03	2.0E+04	2.8E+05	2.1E+04
31	17.54	159	2.3E+03	2.0E+03	2.8E+03	3.0E+05	2.7E+03	3.8E+04
32	17.87	159	2.3E+03	2.0E+03	2.8E+03	2.8E+04	2.7E+03	1.1E+05
33	18.42	159	2.3E+03	2.0E+03	2.8E+03	4.2E+05	2.7E+03	3.8E+04

~ 80% of features are detected

Many artifacts are generated (~ 400 for 100 reliable features)

Data matrices have to be filtered/cleaned

(Tautenhahn R, 2008)

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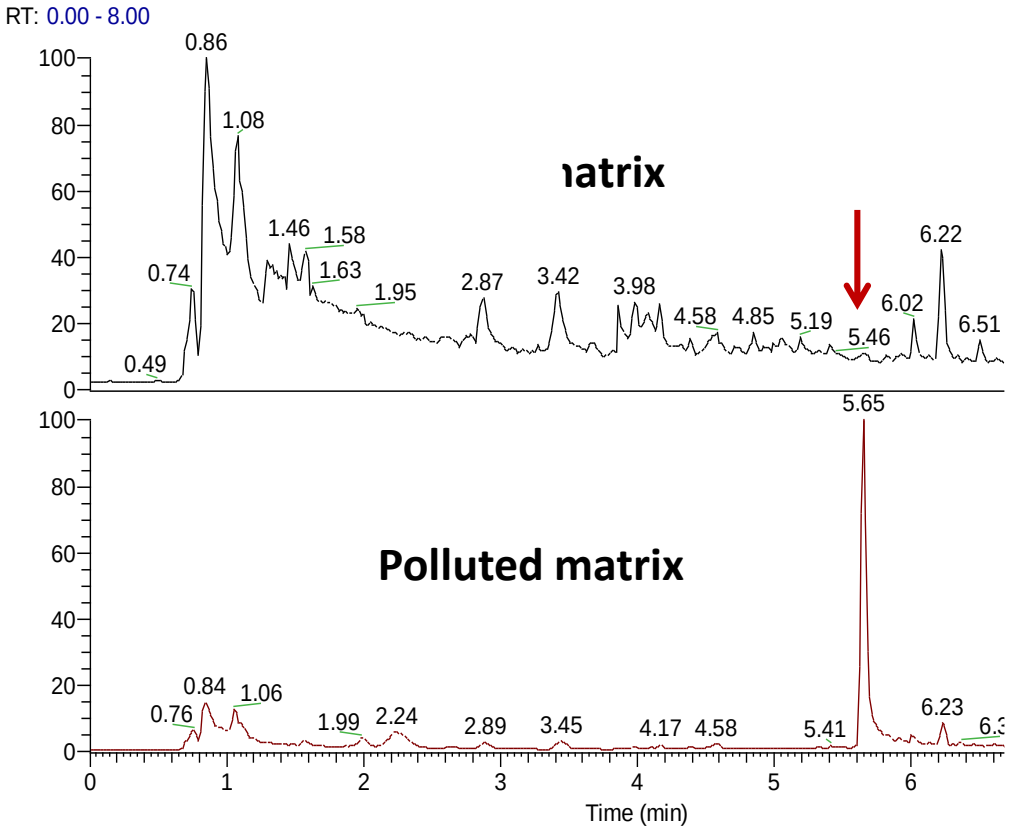
The main challenges: How to select signals of interest among thousands of features?



Which kinds of statistical tools?

A huge variability is observed in the chemical composition of matrices. «Control/normal matrices» have to be extensively characterized

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The main challenges: how to build databases?

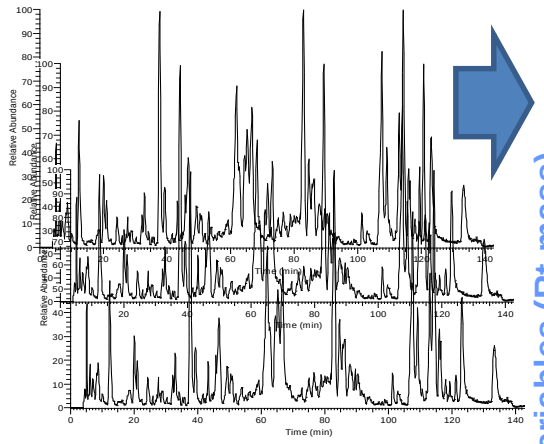
Biochemical/chemical DB

annotation

Spectral DB

ESI/MS: annotation

MS/MS: identification



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16	10.56	126	1.9E+05	1.6E+03	2.0E+05	9.1E+03	2.3E+03	1.2E+04
17	11.05	126	2.1E+03	1.6E+03	2.4E+03	9.1E+03	2.3E+03	1.2E+04
18	11.33	126	1.0E+05	1.6E+03	1.5E+05	9.1E+03	2.3E+03	1.2E+04
19	11.80	126	2.1E+03	1.6E+03	2.4E+03	9.1E+03	2.3E+03	1.2E+04
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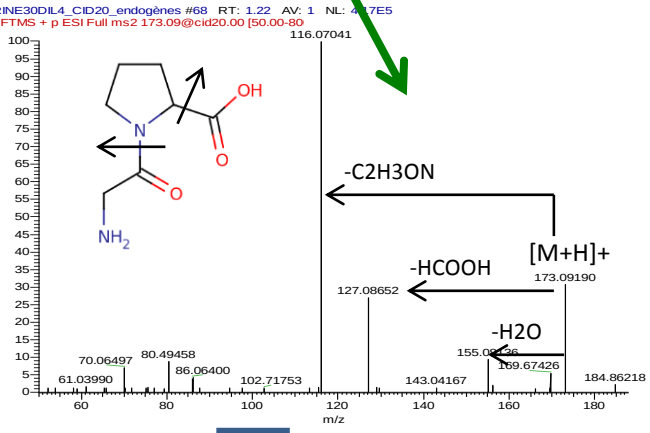
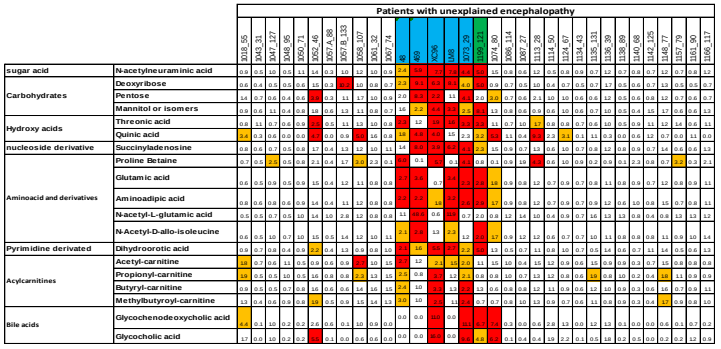


Chemical/metabolic profile DB



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Conclusion : Analyses beyond regulatory concerns for better food safety

- High Resolution Mass Spectrometry can be successfully applied to different food matrices for large screening of xenobiotics.

- Unexpected pollutant determination or quality assessment can be simultaneously performed on the same food samples by comparison with reference spectral fingerprint databases

- Implementation of global approaches for highlighting unexpected contaminants in food matrices will require advanced statistical tools and the development of spectral and chemical profile databases.

Acknowledgement

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And thank you for your attention!!!