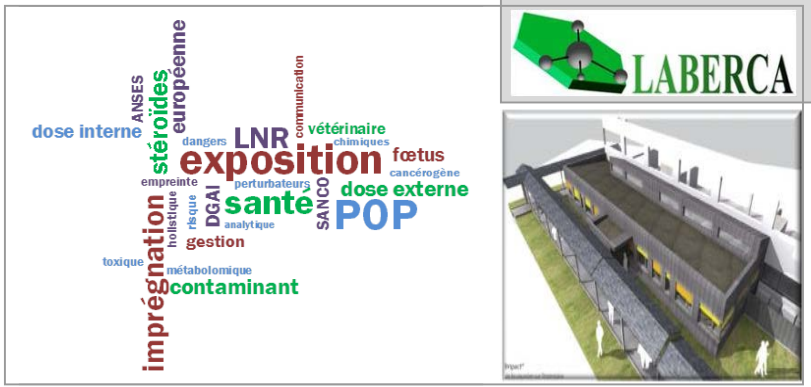
Carrefours de l'innovation agronomique

INRA SCIENCE & IMPACT

# Contaminants alimentaires : approches émergentes pour connaitre et prévenir le risque

**19 décembre 2018 |** APCA, Avenue George V | PARIS

# Promesses et défis des nouvelles approches méthodologiques sans a priori pour la mise en évidence de contaminants émergents et la caractérisation de l'Exposome



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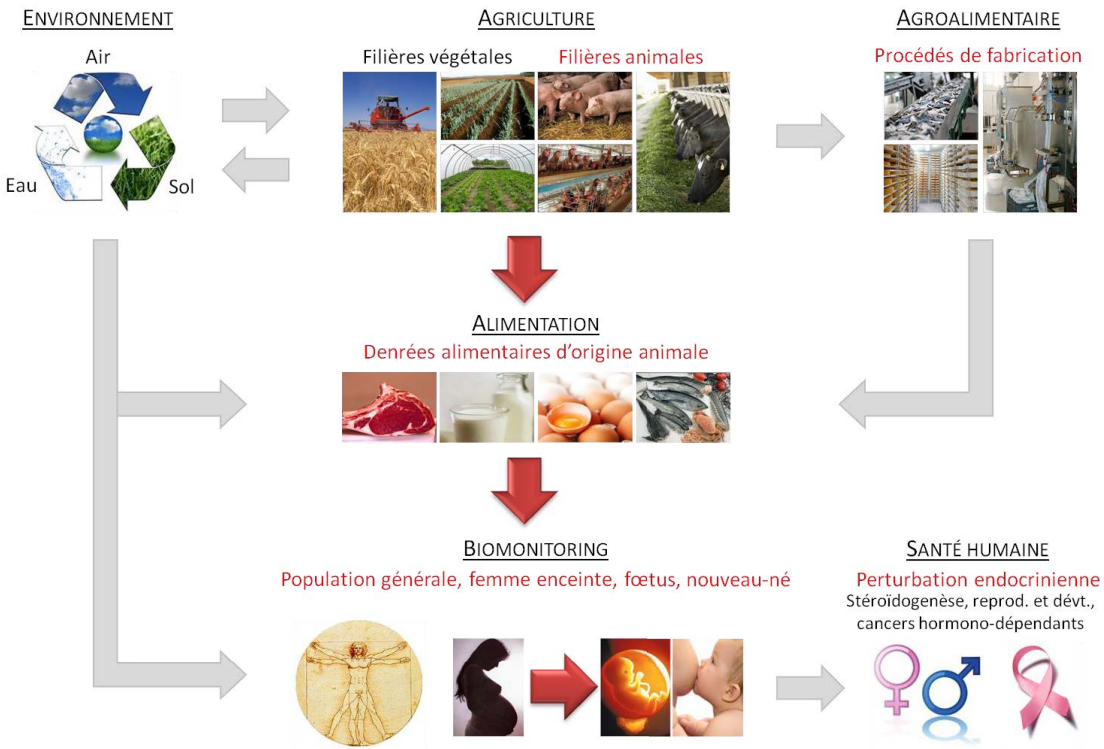
BP 50707, 44307 Nantes Cedex 3, France - www.laberca.org

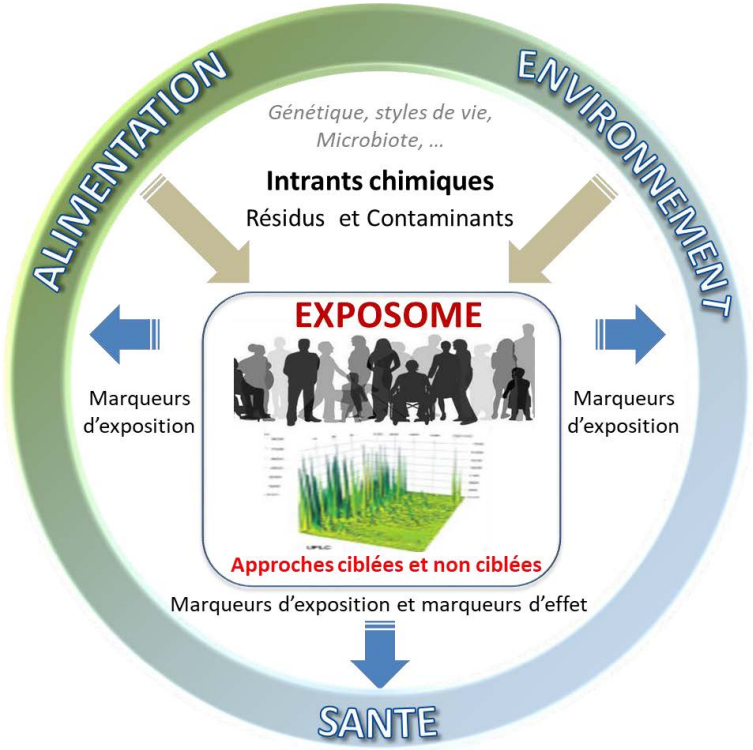
# Plan

- Introduction
- Caractériser l'exposition externe
- Caractériser l'exposition interne
- Conclusion

# Introduction

## L'étude des résidus et contaminants chimiques depuis leurs sources jusqu'à l'Homme

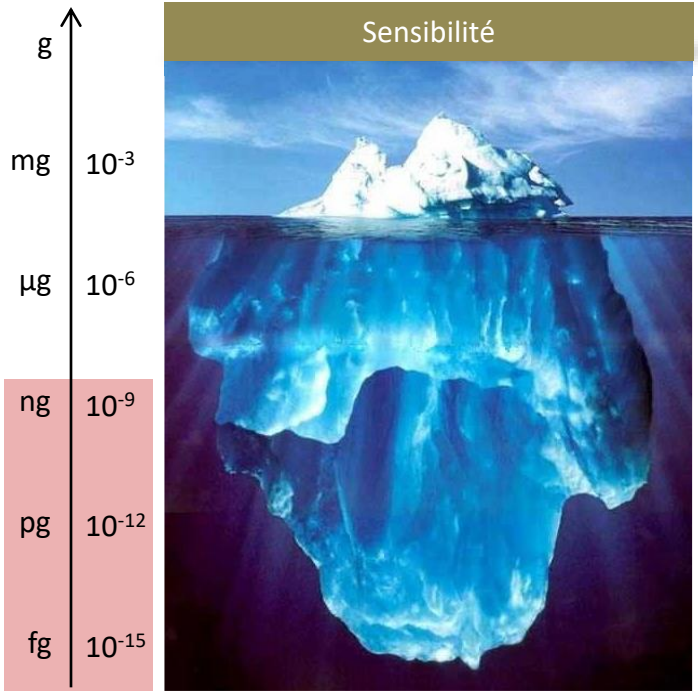


# Introduction

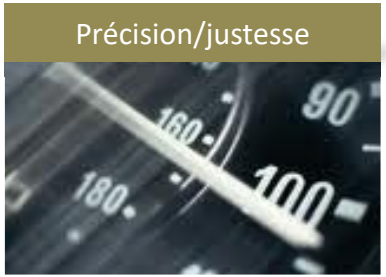
## Plusieurs défis sur le plan analytique

### Des niveaux de concentration extrêmement bas




### Des matrices biologiques complexes


### Un besoin d'identification non ambigüe et de quantification juste et précise



# Introduction

## Plusieurs défis sur le plan analytique

Fonds Européen de Développement Régional

Région PAYS DE LA LOIRE

Biogenouest

Corsaire
plate-forme de métabolomique du Grand Ouest

UPLC-MS/MS (x 2)

HPLC (x 2)

GC-MS (x 3)

LC-HRMS$^n$ (x 3)

GC-MS/MS (x 2)

LC-MS/MS (x 2)

UPLC-IM-HRMS (x 1)

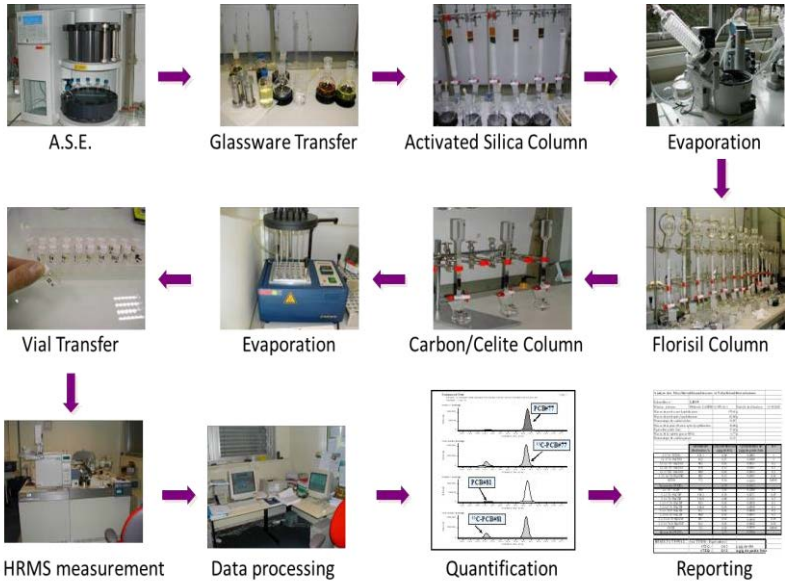
GC-HRMS (x 3)

GC-C-IRMS (x 3)

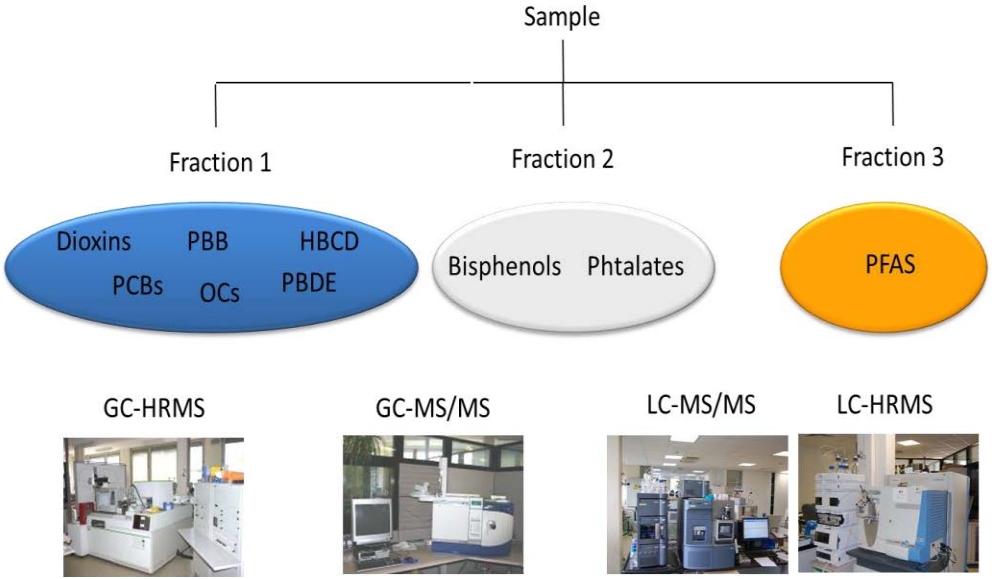
# Introduction

## Plusieurs défis sur le plan analytique

### Isoler (extraire et purifier) pour mieux caractériser



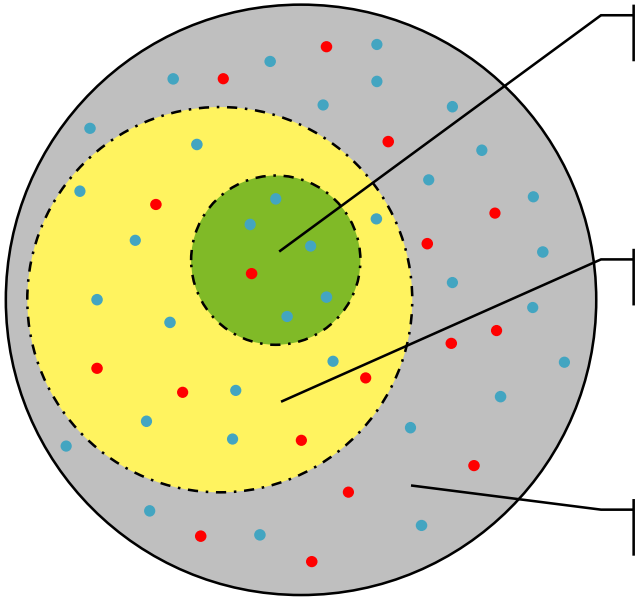

### Fractionner pour optimiser le prélèvement



# Introduction

## Les nouvelles approches méthodologiques

### Un exposome chimique très étendu

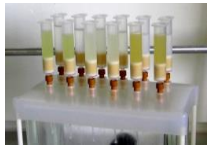


| | | Approche analytique | Exemples |
|---|---|---|---|
| Known | *Méthode quantitative disponible et validée* | Mesure ciblée (Targeted) | PFOS, PBDE47, DEHP, BPA, … |
| Known unknown | *Structure connue mais pas (encore) de méthode ciblée quantitative bien établie* | Mesure semi-ciblée (Suspect screening) | Panel étendu de pesticides, nouveaux retardateurs de flamme, halogénophénols, … |
| Unknown unknown | *Marqueur d'exposition encore inconnu* | Profilage non ciblé (Non-targeted screening - NTS/NTA) | Marqueur d'exposition non encore identifié |

# Introduction

## Du ciblé vers le non-ciblé : un continuum

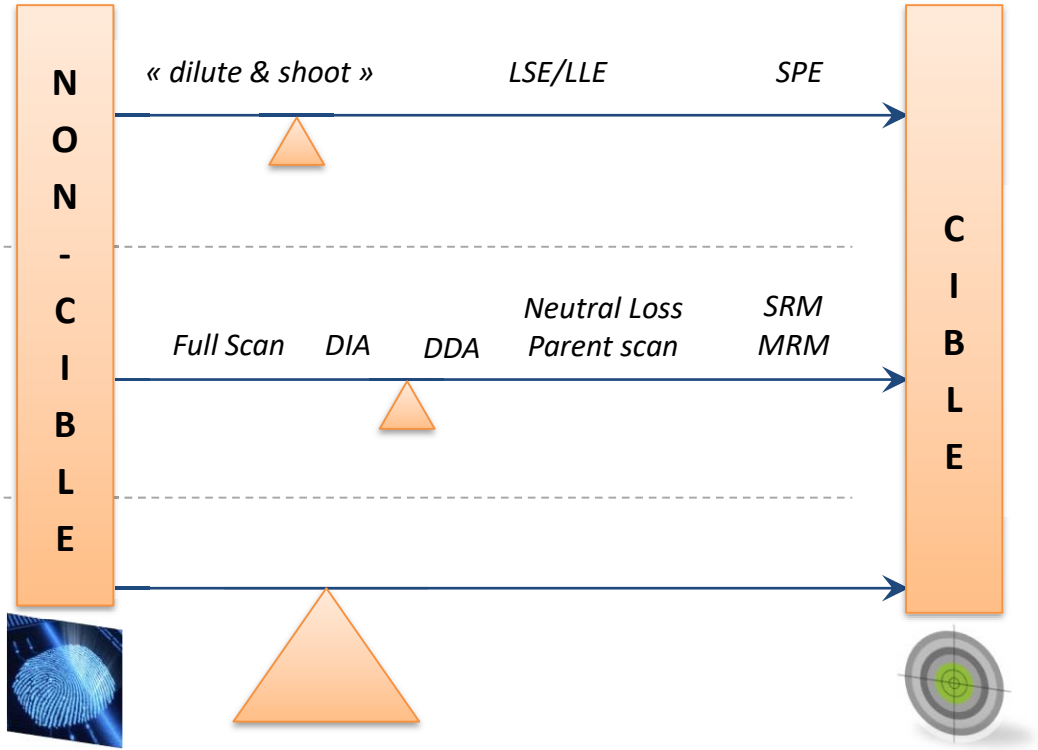
### Préparation de l'échantillon



### Acquisition spectrométrique

### Stratégie globale



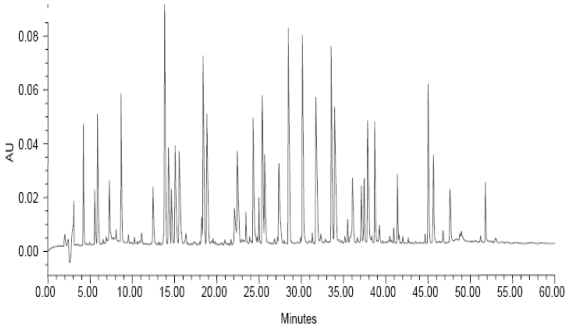


# Introduction

## Le principe général du suspect screening

Matrices environnementales
Matrices alimentaires
Matrices humaine

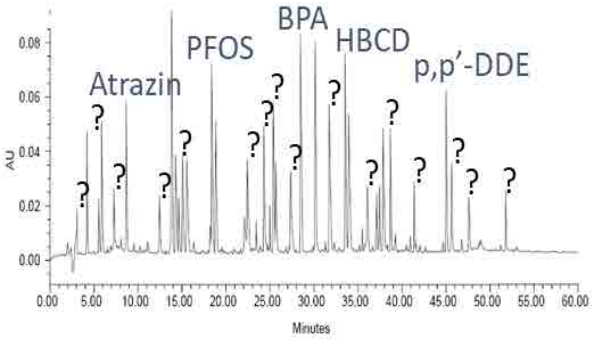
Profilage par chromatographie-spectrométrie de masse haute résolution
*(LC-HRMS, GC-HRMS)*




*Suspect screening predefined list of target markers*

*Accurate mass*
*Retention time*
*MS spectrum*
*MS/MS spectrum*

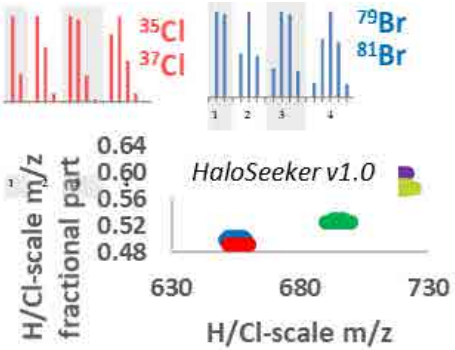
Annotation des descripteurs obtenus via l'interrogation de spectres de référence
*(Quel niveau de confiance / identification ?)*



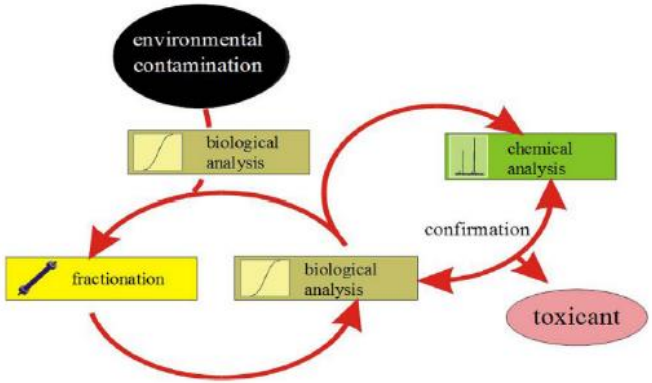
# Introduction

## Le principe général du non-targeted screening

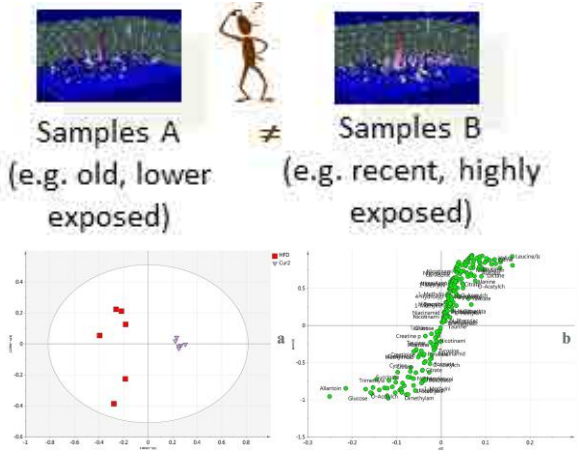
### Chemistry driven approach
(look for particular signatures, e.g. halogens)




### Biology driven approach
(look for biological activity / toxicity, e.g. EDA, adducts)




### Statistic driven approach
(look for temporal trends, differential patterns)



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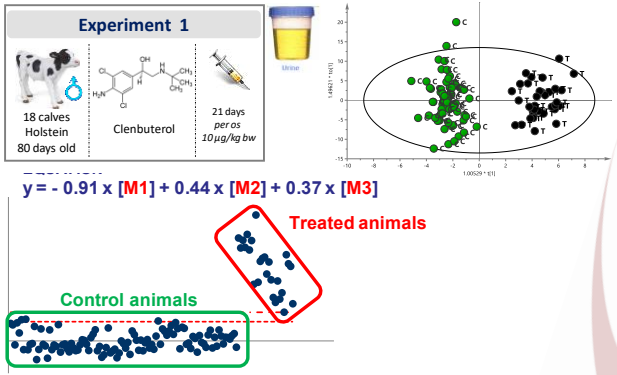
# Caractériser l'exposition externe

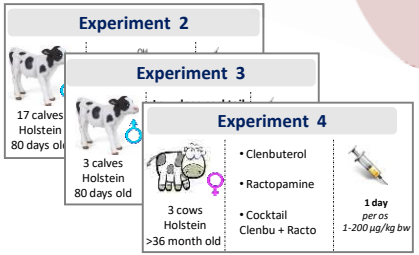
## Application à la sécurité chimique des aliments

### 1 Model Generation




### 2 Model Validation

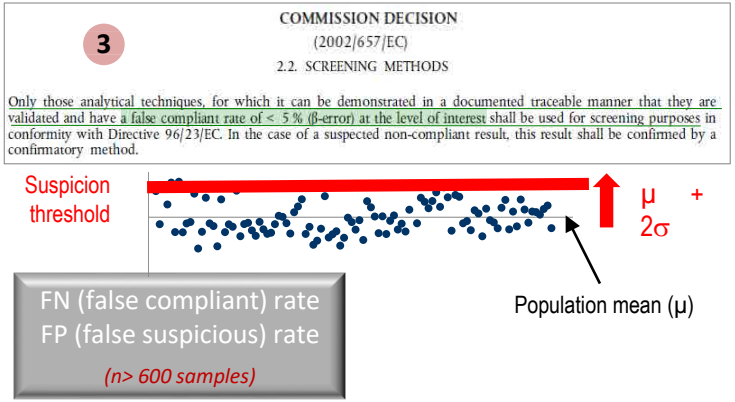
- ❑SELECTIVITY
- ❑SENSITIVITY
- ❑ROBUSTNESS
- ❑PERFORMANCES




Traitement aux promoteurs de croissances anabolisants (β-agonistes)?

### 4 Practical implementation


### Threshold Definition

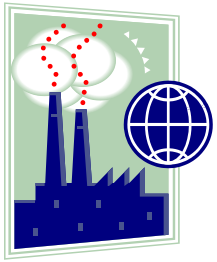


# Caractériser l'exposition externe

## Application à l'étude de l'impact du traitement des eaux

Eaux de surface

Présence de résidus et contaminants chimiques "parents"
Ex : Ethinylestradiol (EE2)



Procédés de traitement (ozonation, chloration,...)

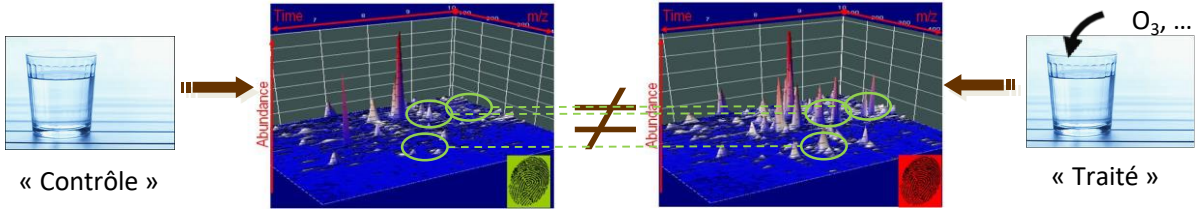
Eau potable

Elimination de certains poluants natifs...
mais... génération de certains sous produits ?

Projet PEVEO
Collab. LABERCA-VEOLIA (V Ingrand)

VEOLIA ENVIRONNEMENT
Recherche & Innovation

Génération puis comparaison de profils chimiques globaux avant et après traitement



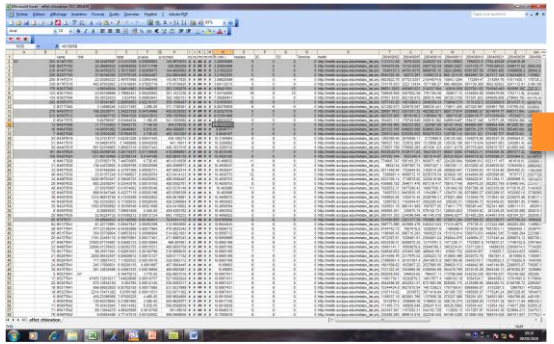

« Contrôle »

« Traité »

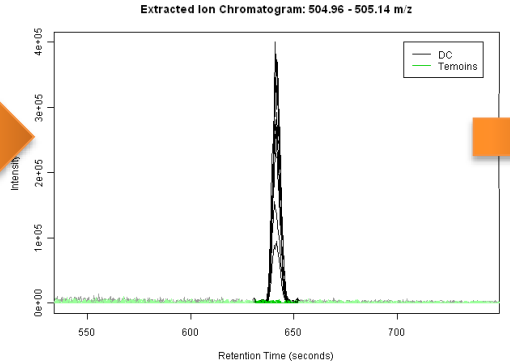
# Caractériser l'exposition externe

## Application à l'étude de l'impact du traitement des eaux

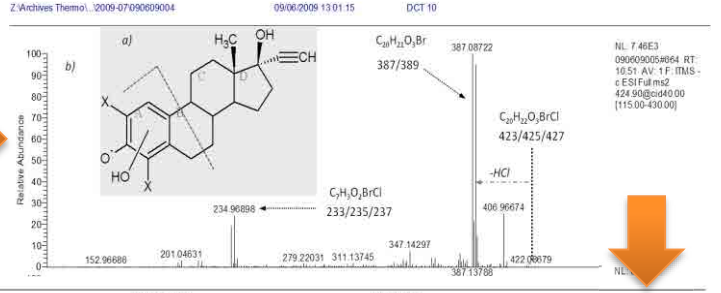
1. Détection des composés constituant les profils



2. Extraction des signaux différentiels avant/après traitement




3. Elucidation structurale des sous-produits de dégradation de l'EE2




| Compose | Temps de rétention (min.) | m/z observé pour l'ion le plus intense (amu) | m/z et rapport des intensités | Hypothèse de formule brute | m/z calculé pour l'ion le plus intense (amu) | Précision en masse (Δmmu) | Correlation isotopique (R) | Structures proposées |
|---|---|---|---|---|---|---|---|---|
| EE2 | 10.20 | 295.1704 | 295 | $C_{20}H_{24}O_2$ | 295.1704 | | | |
| M1 | 10.32 | 379.0881 | 379/381/383 9:6:1 | $C_{20}H_{22}O_2Cl_2$ | 379.0873 | 0.8 | 0.99900 | |
| M2 | 10.50 | 425.0350 | 423/425/427 3:4:1 | $C_{20}H_{22}O_2BrCl$ | 425.0347 | 0.3 | 0.99795 | |
| M3 | 10.70 | 468.9846 | 467/469/471 1:2:1 | $C_{20}H_{22}O_2Br_2$ | 468.9842 | 0.4 | 0.99977 | |
| M4 | 10.85 | 545.0002 | 543/545/547 1:2:1 | $C_{22}H_{28}O_4Br_2$ (adduit) | 545.0004 | 0.2 | 0.99706 | |
| M5 | 11.62 | 502.9461 | 501/503/505/507 3:7:5:1 | $C_{20}H_{21}O_2ClBr_2$ | 502.9452 | 0.9 | 0.99717 | |
| M6 | 11.74 | 546.8941 | 545/547/549/551 1:3:3:1 | $C_{20}H_{21}O_2Br_3$ | 546.8947 | 0.6 | 0.99886 | |
| M7 | 12.15 | 409.0401 | 407/409/411 3:4:1 | $C_{20}H_{22}O_2BrCl$ | 409.0398 | 0.3 | 0.99909 | |
| M8 | 12.42 | 452.9901 | 451/453/455 1:2:1 | $C_{20}H_{22}O_2Br_2$ | 452.9893 | 0.8 | 0.99937 | |

*Gervais et al., Chemosphere, 2011:83,1553-1559.*
*Bourgin et al. Chemosphere 2013; 93:2814–2822.*
*Bourgin et al. Water Research 2013;47:3791-3802*

# Caractériser l'exposition externe

## Application à la détection de contaminants émergents


Contents lists available at ScienceDirect

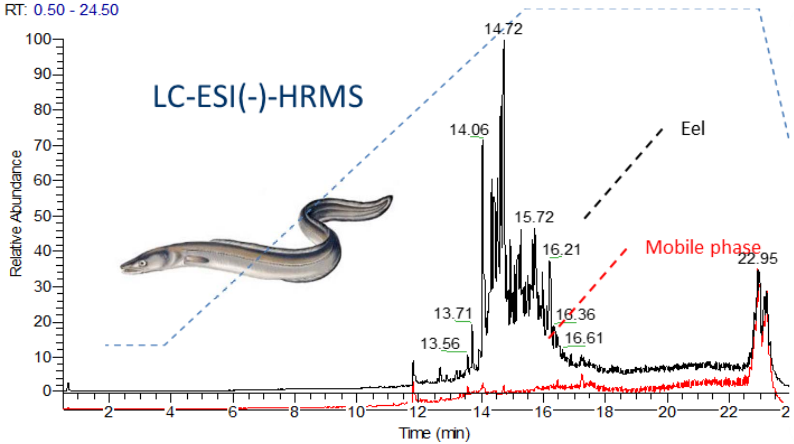
Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

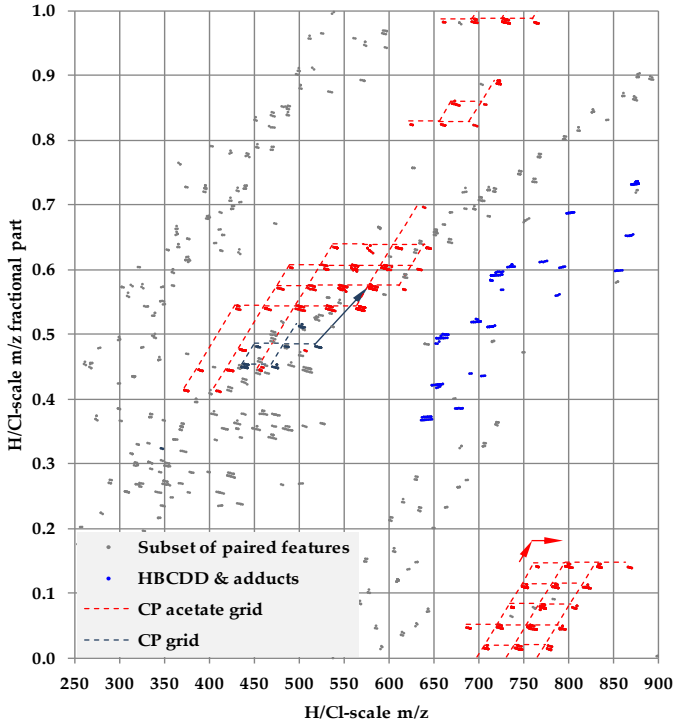
Screening halogenated environmental contaminants in biota based on isotopic pattern and mass defect provided by high resolution mass spectrometry profiling

Ronan Cariou*, Elsa Omer, Alexis Léon, Gaud Dervilly-Pinel, Bruno Le Bizec

LUNAM Université, ONIRIS, Laboratoire d'Etude des Résidus et Contaminants dans les Aliments (LABERCA), Nantes, F-44307, France


Possible application to screen for not yet known novels flame retardants, pesticides metabolites, Br/Cl phenols, BR+Cl POPs



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- Conclusion

# Caractériser l'exposition interne

## Application à la détection de contaminants émergents

Great Lakes Water Quality
AGREEMENT
PRIORITIES 2007-09 SERIES
**Work Group Report on Chemicals of Emerging Concern**

Network of reference laboratories for monitoring of emerging environmental pollutants

DISCUSSION Open Access

**Emerging pollutants in the EU: 10 years of NORMAN in support of environmental policies and regulations**

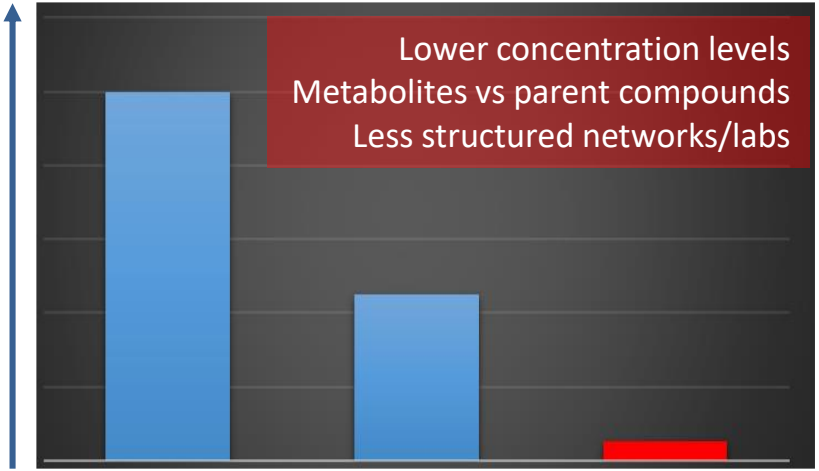
Valeria Dulio[1*], Bert van Bavel[2], Eva Brorström-Lundén[3], Joop Harmsen[4], Juliane Hollender[5], Martin Schlabach[6], Jaroslav Slobodnik[7], Kevin Thomas[7] and Jan Koschorreck[8]

efsa
European Food Safety Authority
**EFSA's Work on Contaminants and Emerging Risks**
*EEA Workshop on Emerging Contaminants*
*4-5 Dec 2011, Copenhagen*

*Andrea Altieri – Emerging Risk Unit*

DEPARTMENT OF ENVIRONMENTAL PROTECTION
FLORIDA
Emerging Substances of Concern

Level of maturity




Environnent Food HBM

http://orcid.org/0000-0003-1423-330X
EPA
**Using the US EPA's CompTox Chemistry Dashboard to support identification and screening of emerging contaminants in the environment**
*Andrew D. McEachran*, Seth Newton, Mark Strynar, Rebecca McMahen, Melanie Hedgespeth, Damian Shea, Jon R. Sobus, Elizabeth G. Nichols, Antony J. Williams*
ENVR 136

FoodSafety magazine
How to Assess the Risk of Emerging Chemical Contaminants in Foods

# Caractériser l'exposition interne

## Application à la détection de contaminants émergents

HBM4EU

science and policy for a healthy future

Call: H2020-SC1-2016-RTD
Project nb. : 733032
"Human Biomonitoring for EU"

- European Joint Programme (EJP) – Cofund
DG RTD, DG SANTE, DG ENV, DG GROWTH, JRC

- 28 countries, 41 Grant Signatories + 68 "linked third parties" (LTPs)

- Total cost: 70 M€
EU subvention: 50 M€
INRA budget : 763 k€

Coord.

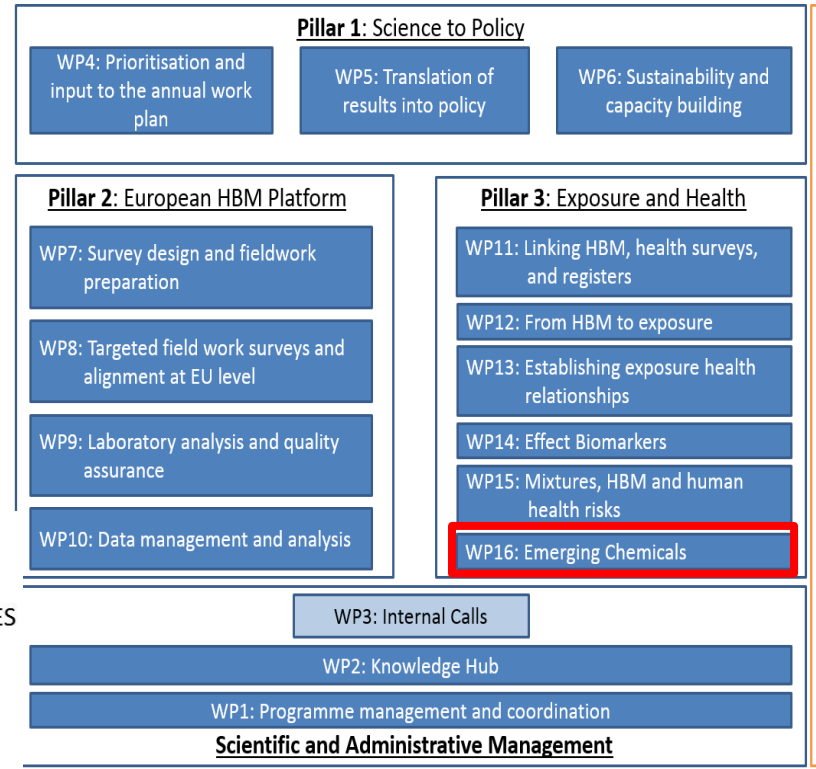
Umwelt Bundesamt

Marike Kolossa-Gehring, DE

Pillar 2

Instituto de Salud Carlos III

Argelia Castaño, ES




Pillar 1

vito

Greet Schoeters, BE

Pillar 3

Inserm

Robert Barouki, FR

# Caractériser l'exposition interne

## The HBM4EU WP16 action plan

### 1. Capitalize on existing suspect screening capabilities

**2017**

Selection/exchange of samples from existing EU cohorts/biocollections
- General population
- Occupational populations

**2018**

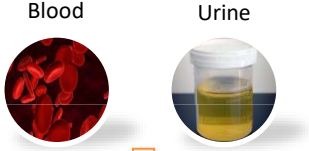
LC-HRMS and GC-HRMS profiling after complementary procedures and technologies
(6 countries/labs and various instrumental platforms incl. (Q)-Orbitrap and (Q)-TOF)

**2019**

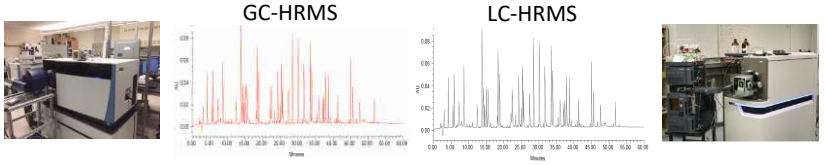
Data processing and analysis through complementary procedures and tools


## Application à la détection de contaminants émergents

Conventional HBM circulating / excretion compartments




Semi-targeted high resolution MS profiling



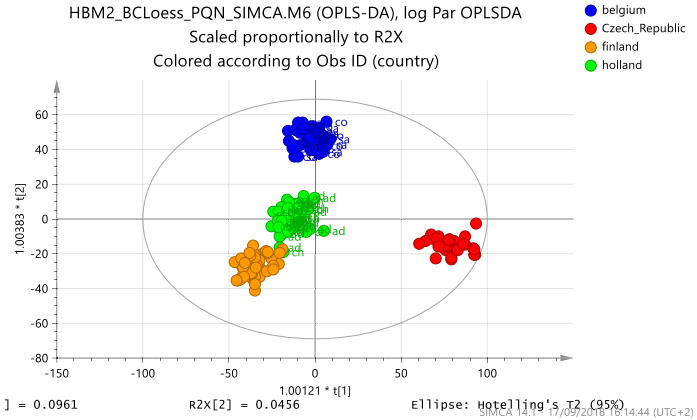

Annotation through reference MS libraries

# Caractériser l'exposition interne

## Application à la détection de contaminants émergents

## The HBM4EU WP16 action plan

### 1. Capitalize on existing suspect screening capabilities




HELMHOLTZ CENTRE FOR ENVIRONMENTAL RESEARCH – UFZ

INRA SCIENCE & IMPACT

MEDIZINISCHE UNIVERSITÄT INNSBRUCK

Examples of detected compounds in urine samples based on MS1 Verification & confirmation pending:

| Compound | MDL (µg/L) | # of samples (159 total) |
|---|---|---|
| 1-Butyl-3-methyl-imidazolium (+) | 0.08 | 76 |
| DEET (+) | - | 48 |
| Benzothiazole (+) | 0.92 | 31 |
| Propamocarb (+) | 3.5 | 23 |
| Benzophenone (-) | 5.1 | >100 |
| 2-Naphtalene sulfonic acid (-) | 2.3 | 37 |
| Bentazone (-) | 0.70 | 30 |
| 2-Hydroxybezothiazole (-) | 2.40 | 24 |
| Butylparaben (-) | 2.80 | >100 |
| Propylparaben (-) | 2.30 | 27 |

| Compound | Occurrences children | Occurrences mothers | Total occurrences |
|---|---|---|---|
| 2-phenyl-1H-benzo[d]imidazole-6-sulfonic acid | 29 | 30 | 59 |
| phthalic acid dibutyl ester | 28 | 30 | 58 |
| tributylphosphate | 19 | 23 | 42 |
| triphenylphosphate | 4 | 1 | 5 |
| benzothiazole | 0 | 6 | 6 |
| butylparaben | 1 | 0 | 1 |
| dibenzothiazyldisulfide | 2 | 0 | 2 |
| diphenylguanidine | 0 | 1 | 1 |
| ethylparaben | 9 | 12 | 21 |
| oxyquinoline | 30 | 30 | 60 |
| phthalimide | 11 | 9 | 20 |
| tri(butoxyethyl)phosphate | 6 | 1 | 7 |

# Caractériser l'exposition interne

## The HBM4EU WP16 action plan

### 2. Expand the current suspect screening capabilities

**2018**

- Crossed sample preparation procedures
- Harmonized data acquisition guidelines
- Consolidated QA/QC dispositions
- Interlab assay for QA/QC consolidation

**2019**

- Aggregation of already existing data
- Modelling new data
- Generation of new experimental data

WHAT'S TO DO

**2020**

**2021**

Common and consolidated annotation framework and related reference library, e.g. MassBank format

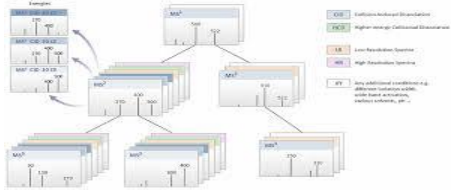
WHAT'S TO DO



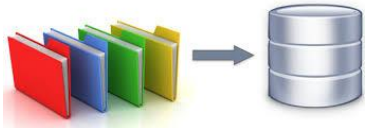
Harmonization of mass spectral annotation strategies for untargeted chemical profiles

Sample prep, LC/GC, and HRMS procedures

MS and dependent scan MS/MS reference data



Consolidated framework for MS profiles annotation



# Caractériser l'exposition interne

## The HBM4EU WP16 action plan

### 2. Expand the current suspect screening capabilities

2017 - Aggregated list of ECs (n ≈70 000) (Norman, AFSA, ECHA, EPA, REACH, OECD, TEDX,…)

2018 - First level curation (overlaps, unambiguous compound ID, QA consolidation)
- MS ready data calculations

2019 - Second level curation (delete environmental markers, include HBM biotransformation products & QSAR/QSURs data)
- Collect existing and reliable MS/MS data
- Generate/modelling new MS/MS data

2020 Operational MS reference library for unambiguous annotation of a wide range of exposure markers in HBM matrices

WHAT'S TO DO

# Application à la détection de contaminants émergents

One extended and QA/QC consolidated annotation MS reference library

| 1 | X__1 | INCHIKEY | cas.no | CAS_PubMed | IUPAC_Name_PUBMED | OtherNames_PUBMED | smiles | Monoisotopic_Mass | MolecularFormula_PUBMED | [M+H]+ |
|---|---|---|---|---|---|---|---|---|---|---|
| 37598 | 37597 | NZGWDASTMWD | 15932-80-6 | 15932-80-6 | 5-methyl-2-propa | Pulegone, p-Men | CC1CCC(=C(C)C)C | 152.1201151 | C10H16O | 153.1273916 |
| 37599 | 37598 | NZHAUOLVIWXXE | 87848-97-3 | 87848-97-3 | 6-[2-(4-methylph | 87848-97-3, EINEC | Cc1ccc(cc1)C2(OC | 269.1051934 | C16H15NO3 | 270.1124698 |
| 37600 | 37599 | NZHGWWWHIYH | 53902-12-8;53902 | 53902-12-8 | 2-[[(E)-3-(3,4-dim | tranilast, Rizaben | COC1=CC=C(\C=C' | 327.1106727 | C18H17NO5 | 328.1179491 |
| 37601 | 37600 | NZHMAQSCHUSS | 1248-42-6;1248-4 | 54063-52-4 | methyl 2-[4-(2-pi | Pitofenone, 5406 | [H+].[Cl-].COC(=C | 367.1783583 | C22H25NO4 | 368.1856347 |
| 37602 | 37601 | NZHUXMZTSSZXS | 42399-40-6;42399 | 42399-40-6 | (2S,3S)-5-[2-(dim | Deacetyldiltiazen | [H][C@]1(SC2=C(( | 372.1507634 | C20H24N2O3S | 373.1580398 |
| 37603 | 37602 | NZHXEWZGTQSYJ | 596-43-0;596-43-0 | 596-43-0 | [bromo(diphenyl | Bromotriphenylm | BrC(C1=CC=CC=C1 | 322.0357134 | C19H15Br | 323.0429898 |
| 37604 | 37603 | NZIACPHCVAFJBF | 69844-33-3;69844 | 69844-33-3 | (5-methyl-2-prop | 69844-33-3, 5-Me | CC(C)CC(=O)OC1= | 234.1619799 | C15H22O2 | 235.1692564 |
| 37605 | 37604 | NZIDBRBFGPQCR | 93878 | 93878 | octyl 2-methylpro | Octyl methacrylat | CCCCCCCCOC(=O) | 198.1619799 | C12H22O2 | 199.1692564 |
| 37606 | 37605 | NZIDEIRWYRJYAI | 68692-77-3;68692 | 68692-77-3 | (1-phenylcyclohe | (1-phenylcyclohe | OCC1(CCCCC1)C1 | 190.1357652 | C13H18O | 191.1430416 |
| 37607 | 37606 | NZIOTNYOYJRBSN | 54746-52-0 | 54746-52-0 | (2S)-2-(butanoyla | N-(1-Oxobutyl)-L- | CCCC(=O)N[C@@ | 219.0929141 | C9H17NO3S | 220.1001906 |
| 37608 | 37607 | NZIUUYVTBDHFPI | 12225-88-6;20262 | 109603-48-7 | (3Z)-6-acetamido | Reactive Orange : | [Na+].[Na+].CC(=( | 573.0181706 | C20H19N3O11S3 | 574.0254471 |
| 37609 | 37608 | NZIJSYLOGZGJHU | 71216-01-8 | 71216-01-8 | 1-[3-(2-ethylhexc | 71216-01-8, N,N"- | CCCCC(CC)COCCC | 584.4301563 | C34H56N4O4 | 585.4374328 |
| 37610 | 37609 | NZIJSGBXNOJOCJI | 37794-15-3 | 37794-15-3 | 4-methylsulfinylt | 4-(methylsulfinyl | C[S](=O)c1ccc(C=( | 168.0245002 | C8H8O2S | 169.0317767 |
| 37611 | 37610 | NZJWITSLFKTATC | 71510-64-0;7544-9 | 71510-64-0 | 4-(benzylamino)t | 4-(benzylamino)t | N#CCCCNCc1cccc | 174.1156985 | C11H14N2 | 175.1229749 |
| 37612 | 37611 | NZJXADCEESMBP | 3079-28-5 | 3079-28-5 | 1-methylsulfinylc | Decyl methyl sulf | CCCCCCCCCC[S](( | 204.1547861 | C11H24OS | 205.1620626 |
| 37613 | 37612 | NZKIRHFOLVYKFT | 4466-14-2;4466-14 | 5777-73-1 | [2-methyl-4-oxo- | Jasmoline I, AC1N | CC/C=C/CC1=C(C) | 330.2194948 | C21H30O3 | 331.2267713 |
| 37614 | 37613 | NZKIRHFOLVYKFT | 4466-14-2;4466-14 | #N/A | (2-methyl-4-oxo- | CTK8J4295, Cyclo | CCC=CCC1=C(C(C( | 330.2194948 | C21H30O3 | 331.2267713 |
| 37615 | 37614 | NZKIRHFOLVYKFT | 4466-14-2 | 4466-14-2 | [(1S)-2-methyl-4- | Jasmolin I, 4466-1 | CC\C=C/CC1=C(C) | 330.2194948 | C21H30O3 | 331.2267713 |
| 37616 | 37615 | NZKNHIQZWSVJG | 81428-04-8 | 81428-04-8 | 2-(1,3-dioxoisoin | Taltrimide, UNII-1 | CC(C)N[S](=O)(=C | 296.0830777 | C13H16N2O4S | 297.0903542 |
| 37617 | 37616 | NZKRYJGNYPYXJZ | 51317-41-0 | #N/A | [5-(2-azaniumyle | 5-(2-aminoethyl) | NCCc1ccc(O)c(O[S | 233.0357932 | C8H11NO5S | 234.0430696 |
| 37618 | 37617 | NZKTVPCPQIEVQ | 20721-50-0;20721 | 12222-69-4 | 2-[4-[(4-aminoph | Disperse black 9, | NC1=CC=C(C=C1)I | 300.1586259 | C16H20N4O2 | 301.1659024 |
| 37619 | 37618 | NZLBHDRPUJLHCE | 33237-74-0;37640 | 37640-71-4 | N'-(2,3-dihydro-1 | APRINDINE, Aprir | [H+].[Cl-].CCN(CC | 322.240899 | C22H30N2 | 323.2481754 |
| 37620 | 37619 | NZLJDTKLZIMONF | 1129-69-7;1129-6 | 1129-69-7 | 2-hexylpyridine | 2-Hexylpyridine, | CCCCCCC1=CC=CC | 163.1360996 | C11H17N | 164.143376 |
| 37621 | 37620 | NZLJLZVXWBEGCE | 31010-60-3;31010 | 31010-60-3 | 2-amino-4-oxo-1H | 31010-60-3, 7-Car | NC1=NC(=O)C2=N | 207.0392391 | C7H5N5O3 | 208.0465155 |
| 37622 | 37621 | NZLPWFTXPYJYSS | 193901-90-5;1939 | 193901-91-6 | 2-[[(2R)-2-[bis(ca | Fosveset, UNII-5V | O.[Na+].[Na+].[N | 737.2560896 | C33H44N3O14P | 738.2633661 |
| 37623 | 37622 | NZLVRVYNQYGMJ | 13187-06-9;314-0 | 314-03-4 | 1-methyl-4-thiox | pimethixene, Me | CN1CCC(CC1)=C2( | 293.1238203 | C19H19NS | 294.1310968 |
| 37624 | 37623 | NZMAJUHVSZBJH | 761-65-9 | 761-65-9 | N,N-dibutylforma | N,N-DIBUTYLFORI | CCCCN(CCCC)C=C | 157.1466642 | C9H19NO | 158.1539407 |

HBM4EU_EmergScreenDB_v1.0 → v2.0

# Caractériser l'exposition interne

## The HBM4EU WP16 action plan

### 3. First proof of concept for untargeted screening

2017 — Selection/exchange of samples from existing EU cohorts / biocollections
- General population

2018 — LC-HRMS and GC-HRMS profiling after complementary procedures and technologies
(5 countries/labs and various instrumental platforms incl. (Q)-Orbitrap and (Q)-TOF)

2019 — Data processing and analysis for particular screening of halogenated substances

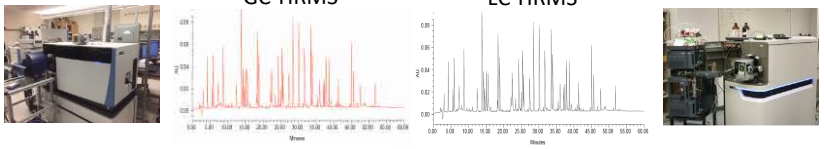
WORK IN PROGRESS

## Application à la détection de contaminants émergents

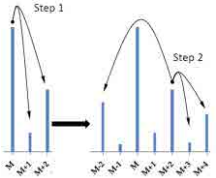
Storage / excretion "fatty" compartments

Adipose tissue | Milk | Meconium

Semi-targeted high resolution MS profiling




Biocomputing tools for revealing halogenated chemical species



# Caractériser l'exposition interne



## The HBM4EU WP16 action plan

### 3. First proof of concept for untargeted screening

2017

Development of a user friendly application for untargeted screening of halogenated features from HRMS chemical profiles

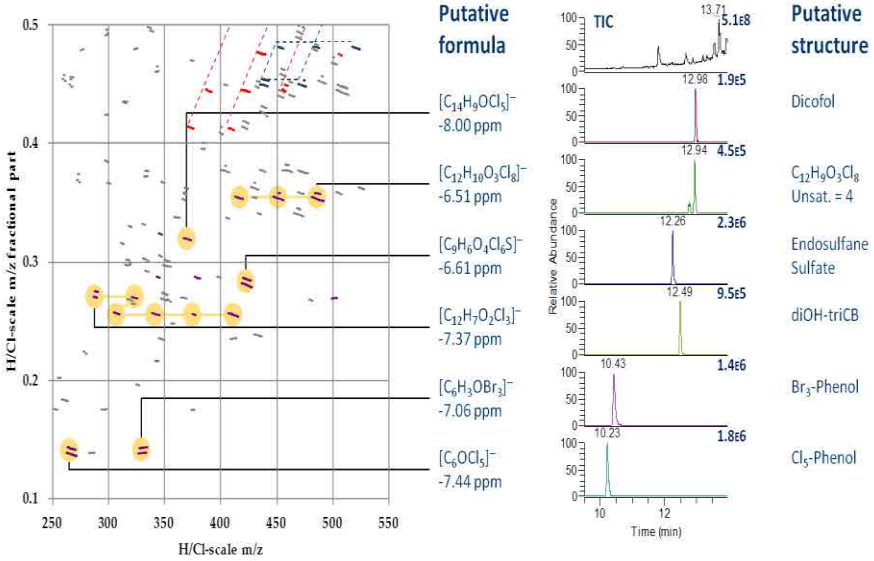
2018


Possible application to screen for not yet known novels flame retardants, pesticides metabolites, Br/Cl phenols, BR+Cl POPs

Application on real human samples


2019

Global chemical profile -> M/D plot -> putative formulae -> > Putative structures




Leon A, Cariou R et al. Anal Chem, submitted

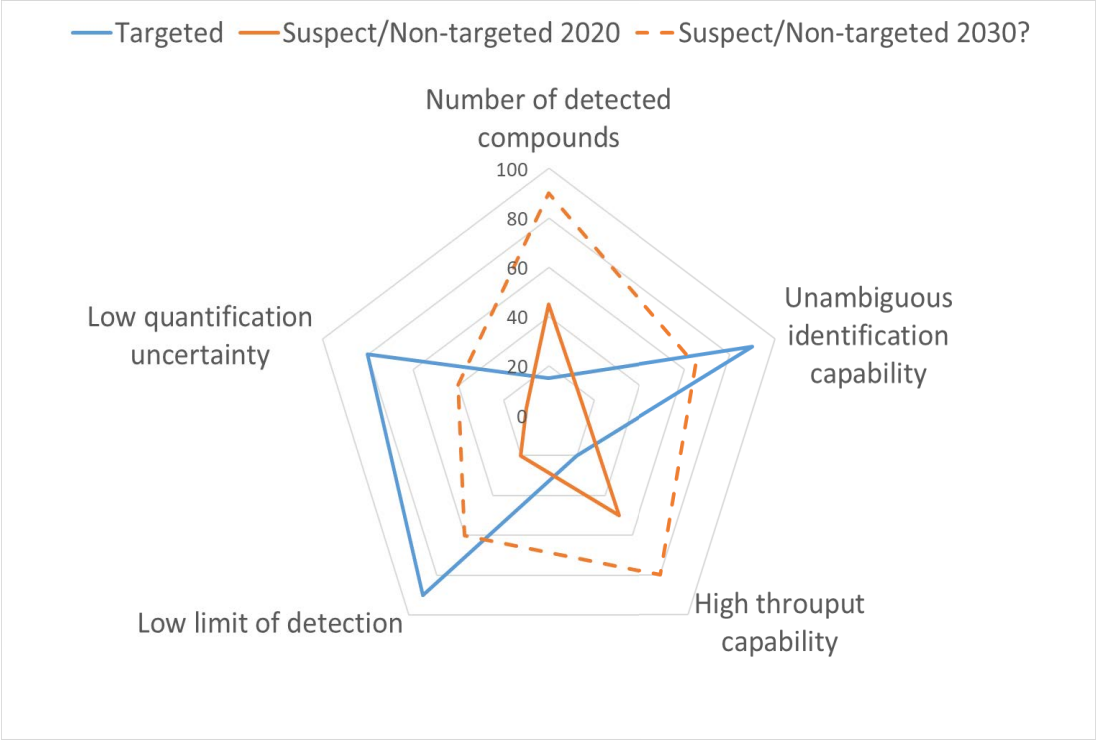
# Plan

- Introduction
- Caractériser l'exposition externe
- Caractériser l'exposition interne
- Conclusion

# Conclusion

## Où en sommes nous (vraiment) ?

- Un fort potentiel et un effet d'opportunité
- Une réelle tendance sur le plan analytique
- Un défi majeur au plan analytique et structurel
- La qualité des données avant l'harmonisation
- Des attentes au plan de la recherche et du support aux politiques publiques



# Conclusion

## Remerciements

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