A (non)targeted method for the analysis of the exposome using atmospheric pressure gas chromatography-mass spectrometry

Karl J. Jobst[1,2], Robert Di Lorenzo[2], Alicia Mell[2], Eric J. Reiner[1,3], John Sled[4]

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[2]Ontario Ministry of the Environment, Toronto, ON
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[4]University of Toronto, Toronto, ON

National Environmental Monitoring Conference 2018
New Orleans, Louisiana, USA
August 6, 2018

The *exposome*

Genetic risk factors account for <30% of the risks of cancer, cardiovascular diseases and other non-communicable human diseases.

"The exposome can be defined as the measure of all the exposures of an individual or organism in a lifetime and how those exposures relate to health. An individual's exposure begins before birth and includes insults from environmental and occupational sources."

-National Institute for Occupational Safety and Health (NIOSH)

Strategies to study the exposome

Bottom up: Involves measuring sources of exposure, including water, air, diet and other sources of indoor/outdoor pollution. This is the prevailing approach used by MOECC.

Top down : Involves biological monitoring of exposed individuals and organisms, most appropriately by blood sampling.

S.M. Rappaport et al., Environ. Health Perspect. 122 (2014) 769;
C.P. Wild, Int. J. Epidemiol. 41 (2012) 24.

Ontario

House dust is an important source of environmental exposure

Environmental Science & Technology

Article

pubs.acs.org/est

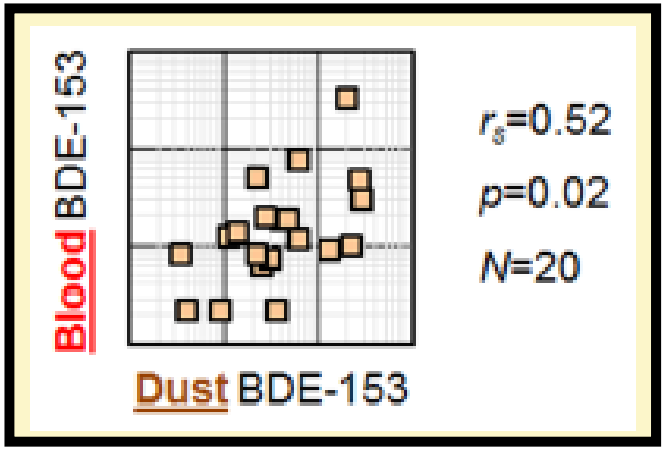
Concentrations of Persistent Organic Pollutants in California Children's Whole Blood and Residential Dust

Todd P. Whitehead,[*,†] Sabrina Crispo Smith,[‡,§] June-Soo Park,[‡] Myrto X. Petreas,[‡] Stephen M. Rappaport,[†] and Catherine Metayer[†]

[†]School of Public Health, University of California, Berkeley, California 94720, United States

[‡]Environmental Chemistry Laboratory, California Department of Toxic Substances Control, Berkeley, California 94710-2721, United States

[§]Sequoia Foundation, La Jolla, California 92037, United States



"Whether dust or diet is the primary source for an individual is tied to loading of PBDE in dust or food items."

"PBDEs have already been replaced with other halogenated and organophosphate compounds…"

ELSEVIER

Environment International

Available online 9 April 2016

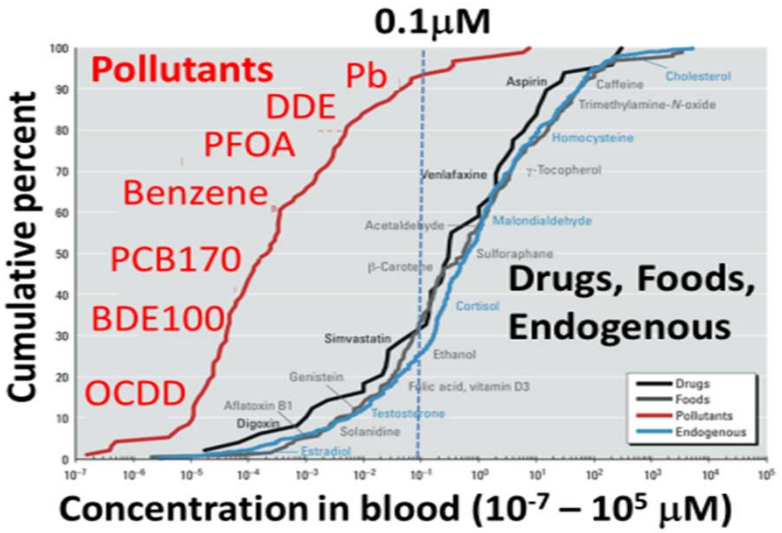
In Press, Corrected Proof— Note to users

Associations between human exposure to polybrominated diphenyl ether flame retardants via diet and indoor dust, and internal dose: A systematic review

Lindsay Bramwell[a], Svetlana V. Glinianaia[a], Judith Rankin[a], Martin Rose[b], Alwyn Fernandes[b], Stuart Harrad[c], Tanja Pless-Mulolli[a]

Non-targeted screening of household dust by GCxGC: D.C. Hilton, R.S. Jones, A. Sjödin, J. Chrom. A, 1217(44), 2010, 6851.

The blood *exposome*

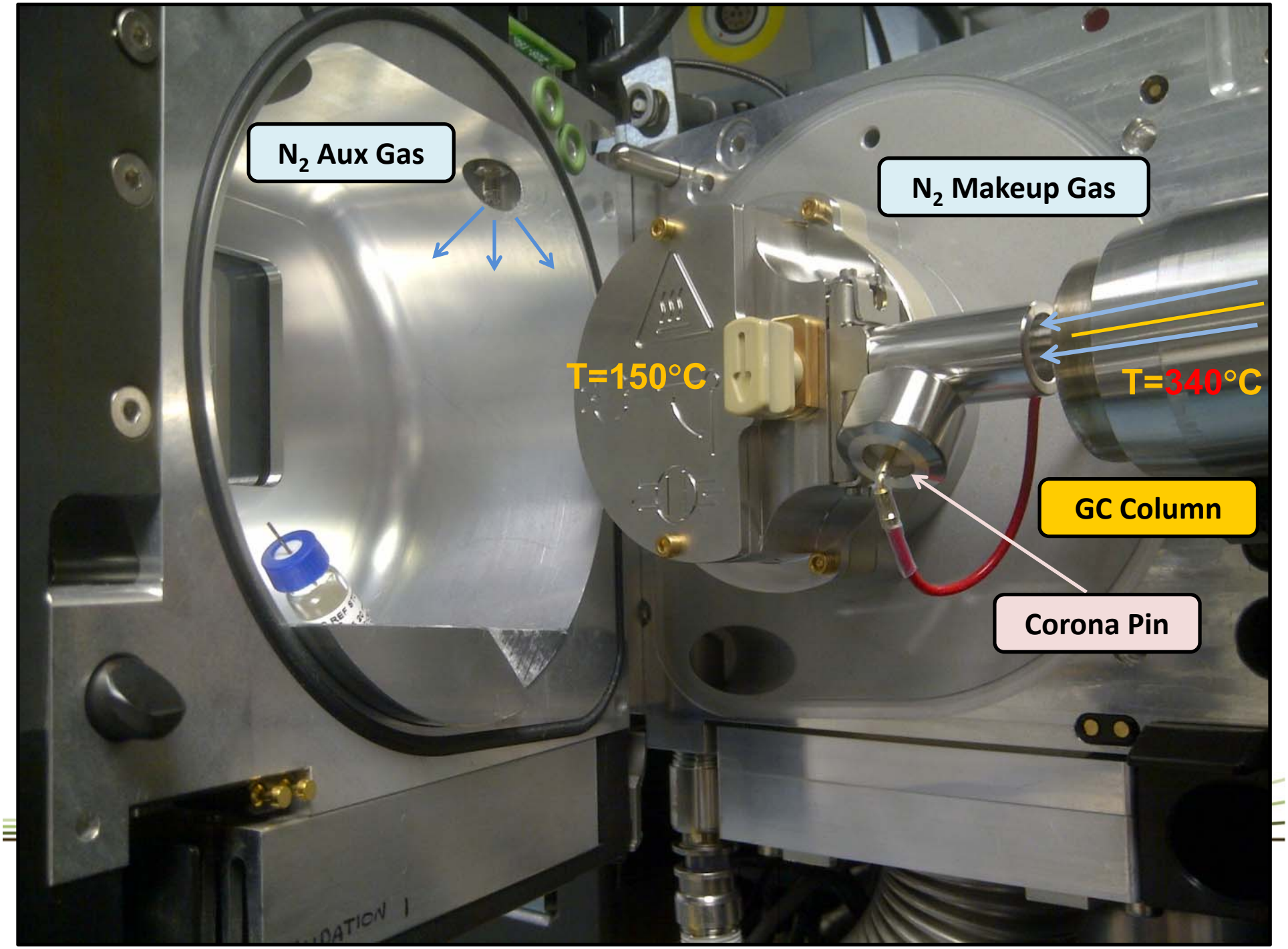


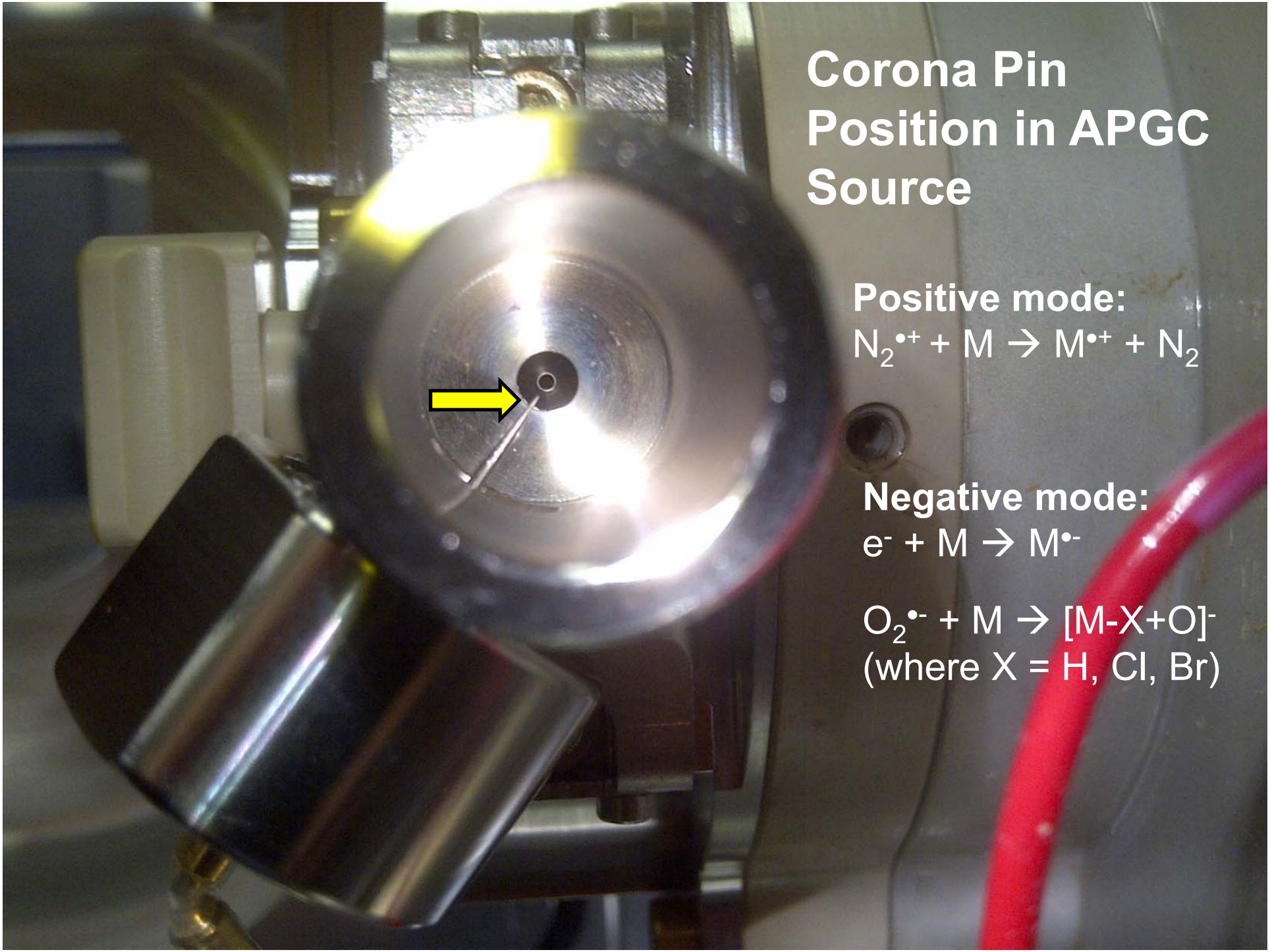
Rappaport et al., Environ. Health Perspect. 122 (2014) 769.

- With few exceptions, the identities of most environmental pollutants and their roles in causing chronic diseases are not known.
- Current (predominantly LC/MS) platforms used for non-target analysis cannot detect more than 90% of environmental pollutants!

Ontario

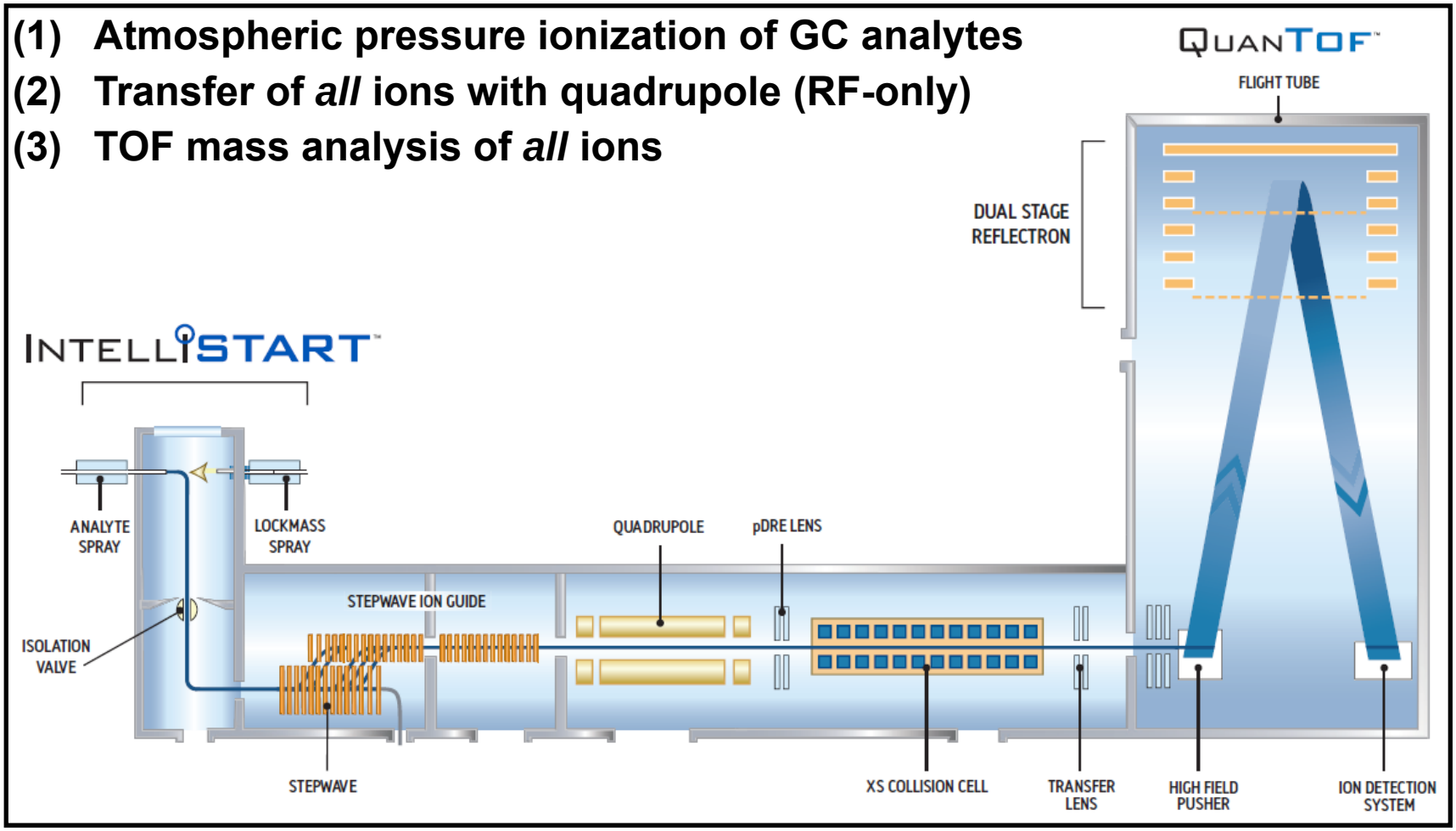
Waters Xevo G2-XS QTOF with APGC and Zoex ZX2 modulator


N_2 Aux Gas
N_2 Makeup Gas
T=150°C
T=340°C
GC Column
Corona Pin


Corona Pin Position in APGC Source
Positive mode:
$N_2^{\bullet+} + M \rightarrow M^{\bullet+} + N_2$
Negative mode:
$e^- + M \rightarrow M^{\bullet-}$
$O_2^{\bullet-} + M \rightarrow [M\text{-}X+O]^-$
(where X = H, Cl, Br)

The Waters Xevo G2-XS Q-TOF mass spectrometer

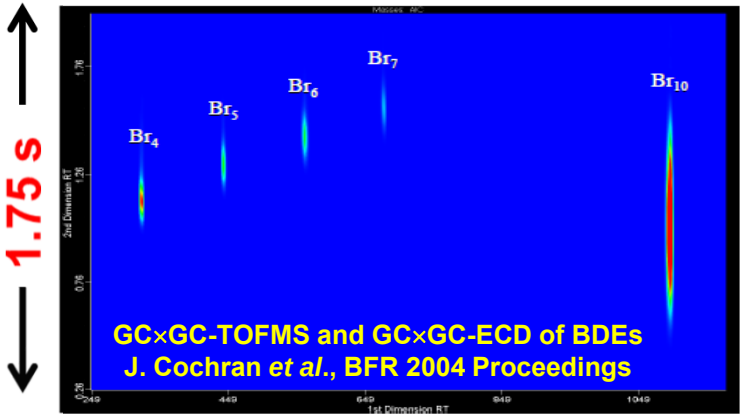
(1) Atmospheric pressure ionization of GC analytes
(2) Transfer of *all* ions with quadrupole (RF-only)
(3) TOF mass analysis of *all* ions



Ontario

Comprehensive two-dimensional gas chromatography (GCxGC)

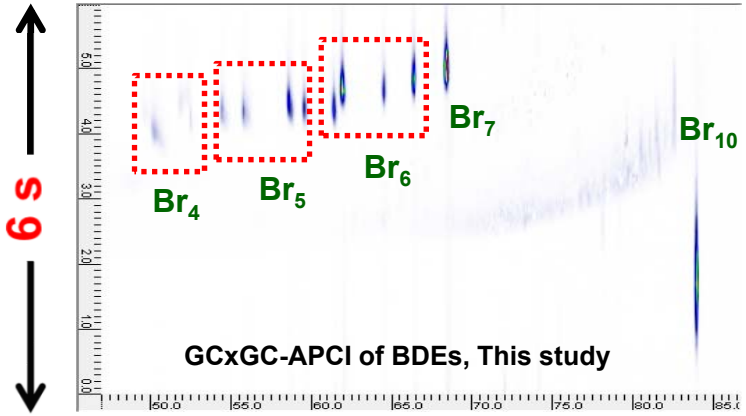
"…most GCxGC peaks are on the order of 100ms to 500 ms wide."
"Unfortunately, the 2D peak width of BDE 209 became extremely broad (>1s)"



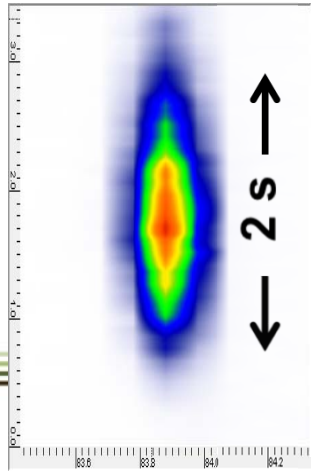
Cochran *et al.* 1D : Rtx-5 10mx0.18mmx0.2µm
2D : Stx-500 0.75m x 0.25mm x 0.15µm
Flow : **7.5**mL/min 2nd Oven offset +30

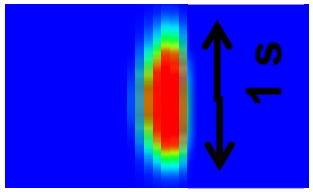
This study, 1D : DB-5 15m x 0.25mm x 0.1µm
2D : Rtx-17SIL 0.5m x 0.15mm x 0.15µm
Flow: **3**mL/min 2nd Oven offset +30

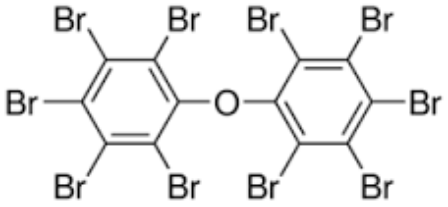
Trans. Line: Restek sulfinert metal tubing (0.18mm) ID)



GC×GC-APCI vs. GC×GC-EI

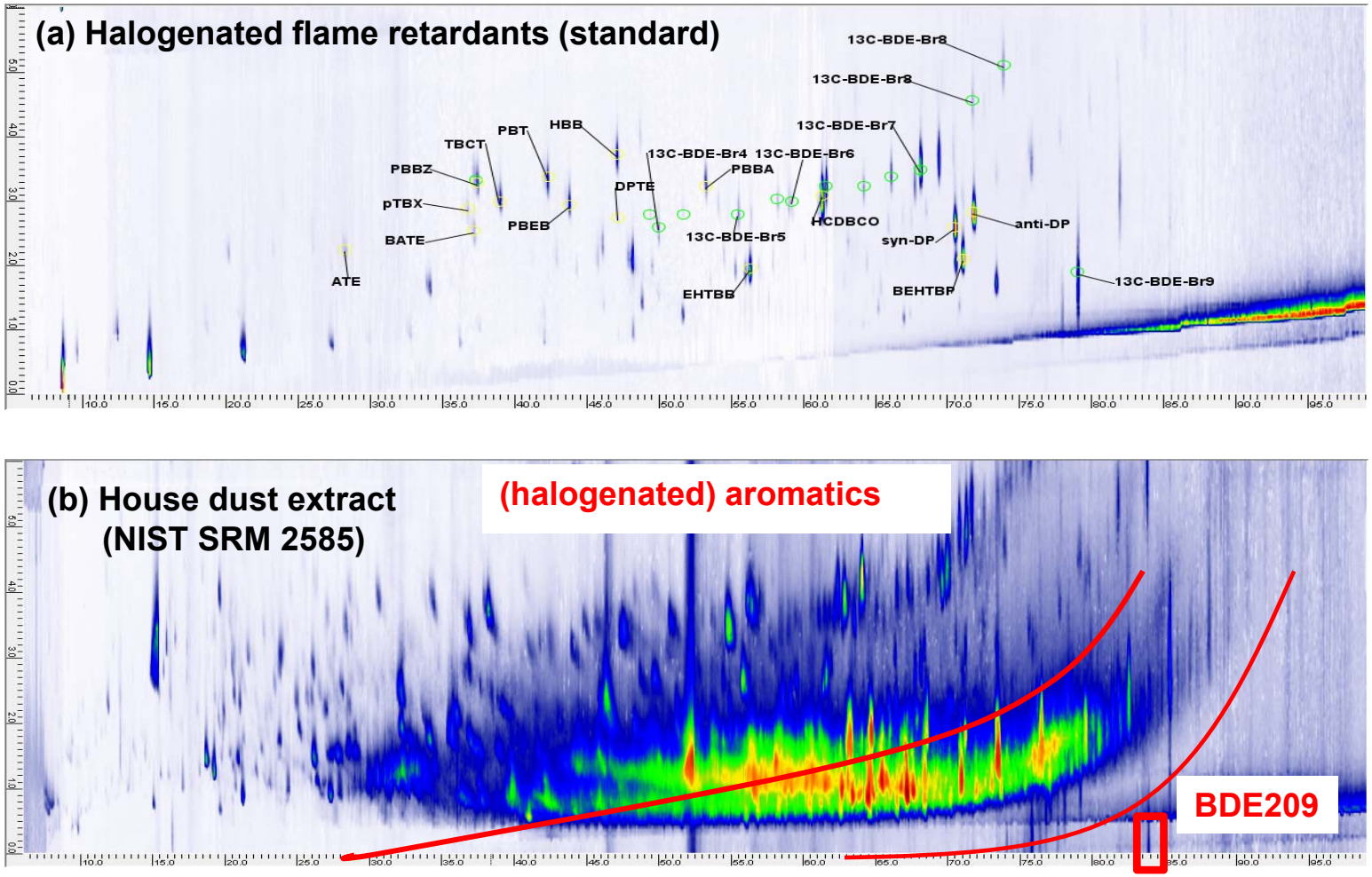






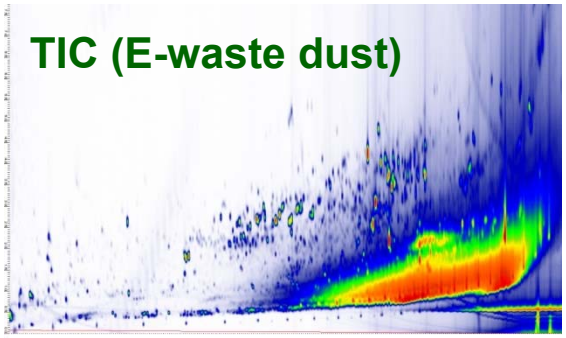
Ontario

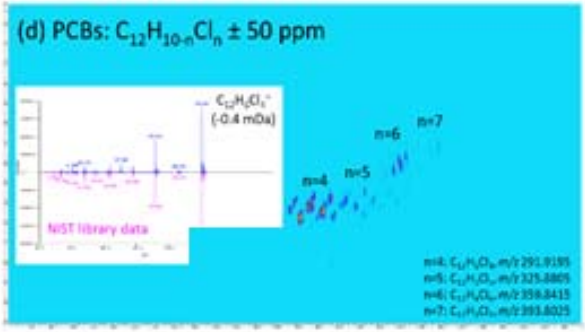
GCxGC enables separation of BFRs from matrix interference

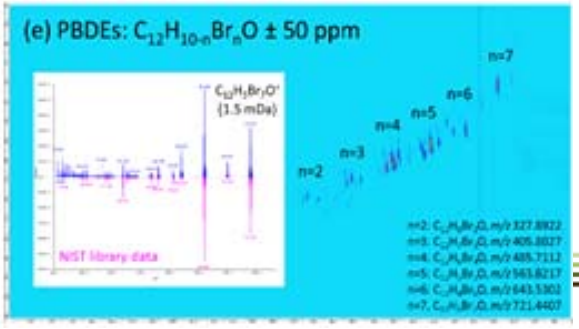


Ontario

“Orthogonal” accurate mass measurements







Recent GCImage version incorporates mass defect plots

Contents lists available at ScienceDirect

Journal of Chromatography A

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

Non-targeted analysis of electronics waste by comprehensive two-dimensional gas chromatography combined with high-resolution mass spectrometry: Using accurate mass information and mass defect analysis to explore the data

Masaaki Ubukata[a], Karl J. Jobst[b], Eric J. Reiner[b], Stephen E. Reichenbach[c], Qingping Tao[d], Jiliang Hang[d], Zhanpin Wu[e], A. John Dane[a], Robert B. Cody[a,*]

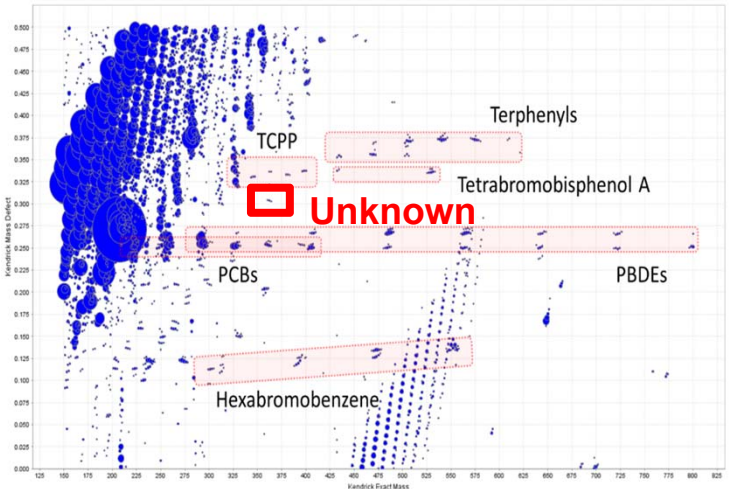
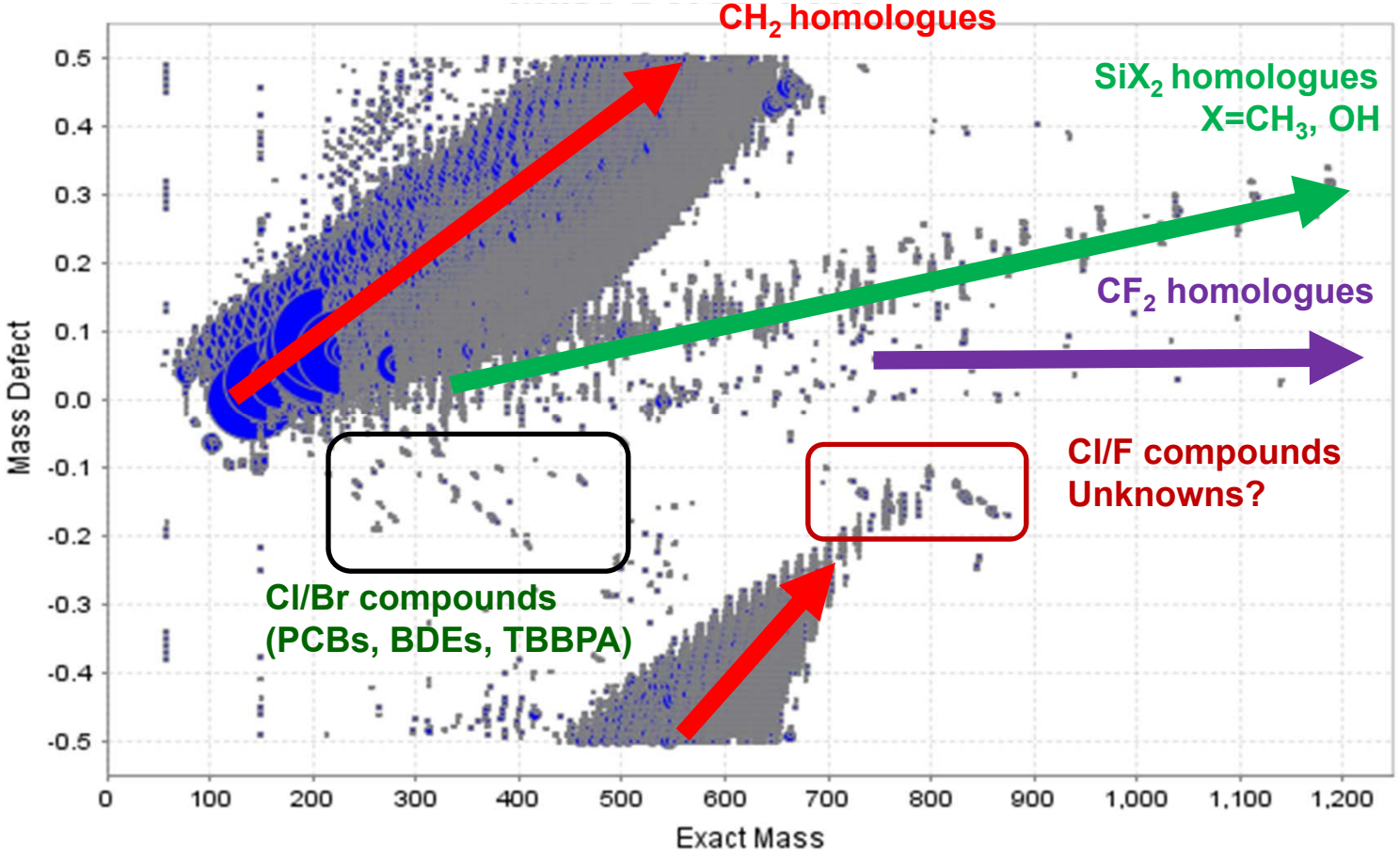


Fig. 2 H/Cl mass defect plot for the average mass spectrum

Ontario

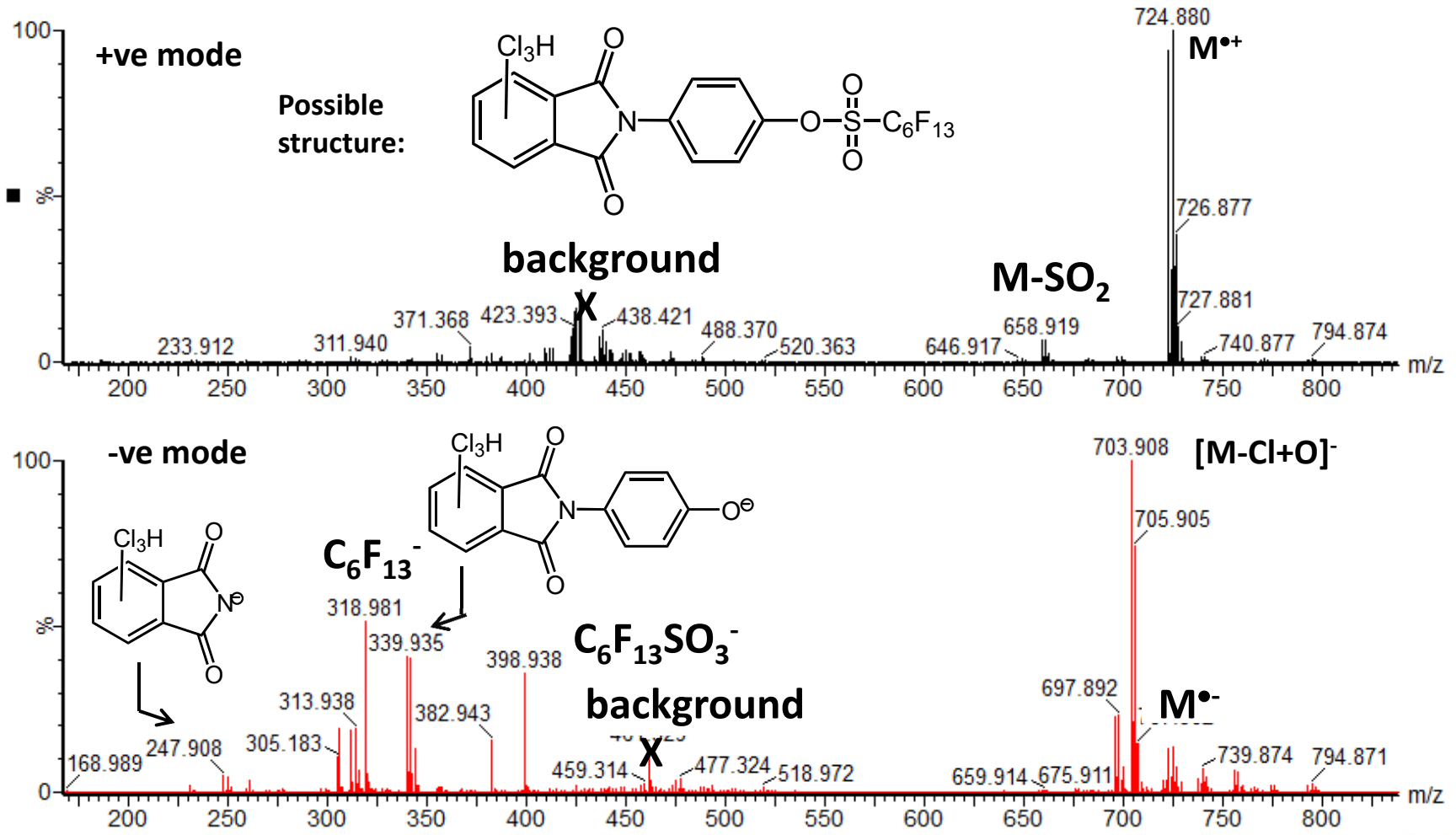
The mass defect plot of SRM 2585 reveals mixed Cl/F compounds

Orthogonal "separation" of CF_2, Cl, Br and Cl/F compounds from "matrix"



Ontario

Mass spectral interpretation is still a bottleneck!



"Negative ions can give higher sensitivity for electronegative molecules; **however, their fragmentations (Budzikiewicz 1981; Bowie 1989; Hites 1988) are not used much for structure determination**." p. 5 Interpretation of mass spectra by McLafferty and Turecek

Ontario

F/Cl/Br phthalimides in-use since 1980s

United States Patent [19]

Schmidt et al.

[11] **4,208,489**

[45] **Jun. 17, 1980**

[54] **POLYCARBONATE MOLDING COMPOSITIONS WITH IMPROVED FLAME-REPELLENCY**

[75] Inventors: **Manfred Schmidt**, Krefeld; **Wolfgang Cohnen**, Leverkusen; **Frank Kleiner**, Cologne; **Dieter Freitag**; **Karsten Idel**, both of Krefeld, all of Fed. Rep. of Germany

[73] Assignee: **Bayer Aktiengesellschaft**, Leverkusen, Fed. Rep. of Germany

[21] Appl. No.: **868,145**

[22] Filed: **Jan. 9, 1978**

[30] **Foreign Application Priority Data**

Jan. 29, 1977 [DE] Fed. Rep. of Germany 2703710
Feb. 24, 1977 [DE] Fed. Rep. of Germany 2707928
Sep. 10, 1977 [DE] Fed. Rep. of Germany 2740850

[51] **Int. Cl.**[2] **C08K 5/34**; C08K 5/42; C08K 5/53

[52] **U.S. Cl.** ..... **525/146**; 260/45.7 P; 260/45.7 R; 260/45.7 S; 260/45.75 F; 260/45.8 N

[58] **Field of Search** ..... 260/45.8 NB, 45.7 SF, 260/45.75 F, 37 PC; 525/146

[56] **References Cited**

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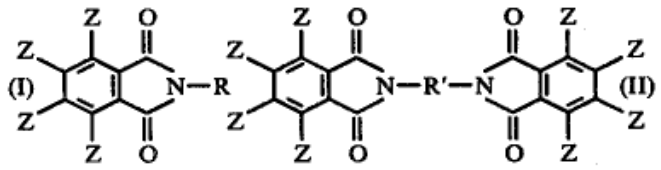
4,113,695	9/1978	Mark	260/45.8 N

FOREIGN PATENT DOCUMENTS

[57] **ABSTRACT**

Thermoplastic aromatic polycarbonate molding compositions with improved flame retardancy which contain an alkali metal salt of an organic or inorganic acid and optionally a perfluoroethylene, characterized in that they contain a tetrahalogenophthalimide of the general formulae (I) or (II) or mixtures thereof



wherein

R denotes a hydrogen atom or a C_1 toC_4 alkyl C_6H_5, $C_{10}H_7$, C_6H_4X, $C_6H_3X_2$ or $C_6H_2X_3$ group, in which X denotes a fluorine, chlorine or bromine atom, R′ denotes a single bond or a C_2 to C_4 alkylene, C_6H_4 or p-diphenylene radical, and Z denotes a chlorine or bromine atom,

are provided.

Polycarbonate composition having improved flame resistance for extrusion applications

US 20120244359 A1

ABSTRACT

tes to compositions containing flame retardant
suitable for producing flame-resistant milk-white

US20120244359 A1
Application
US 13/505,590
PCT/EP2010/066736
Sep 27, 2012
Nov 3, 2010
Nov 5, 2009

CN102725341A, 5 More »

Alexander Meyer, Berit Krauter, Claus Rüdiger, Ulrich Blaschke, Peter Schwarz

Bayer Intellectual Property Gmbh

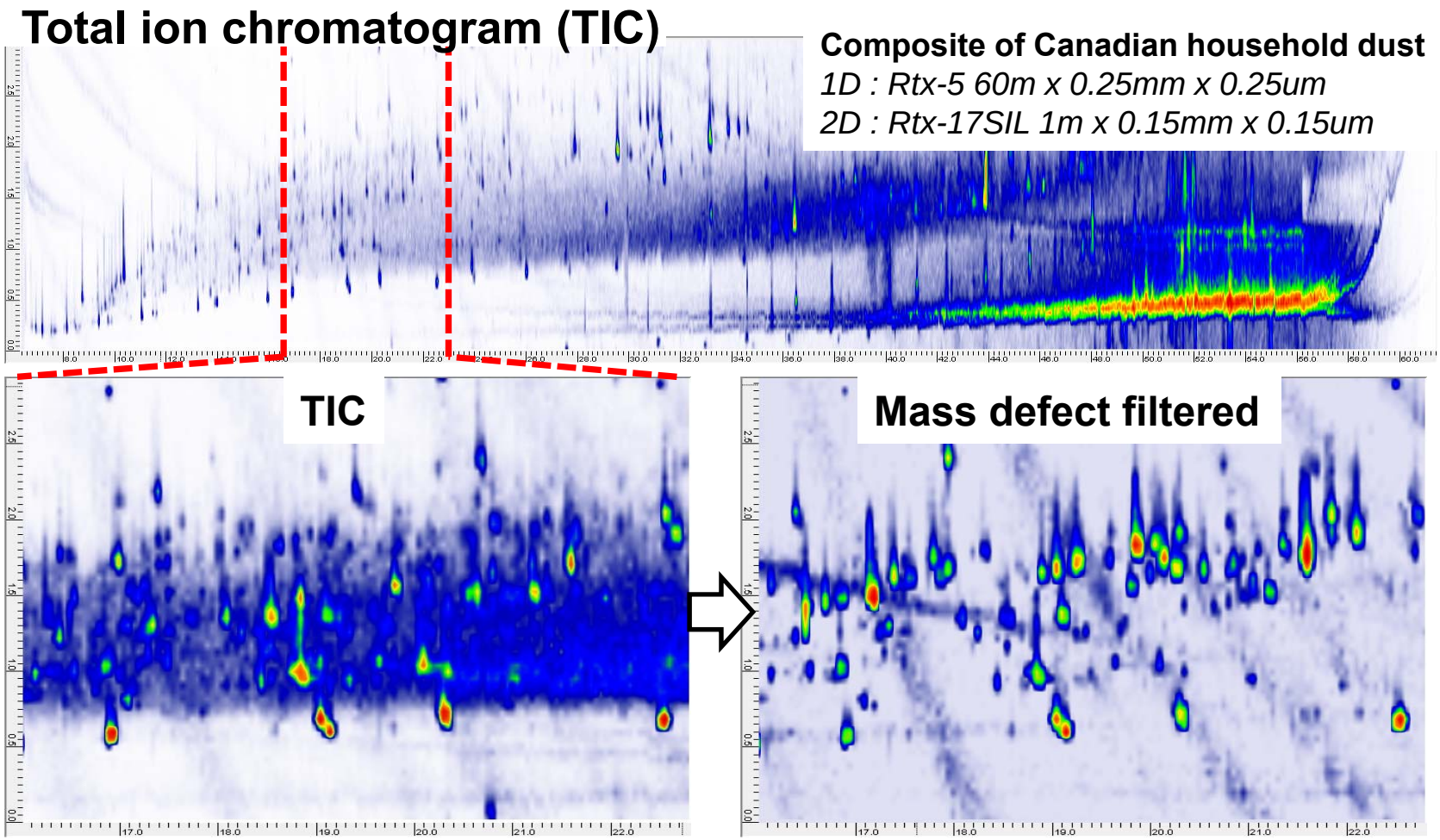
BiBTeX, EndNote, RefMan

ssifications (22), Legal Events (2)

, USPTO Assignment, Espacenet

Ontario

Mass defect filtered GC×GC chromatogram – +ve ion mode

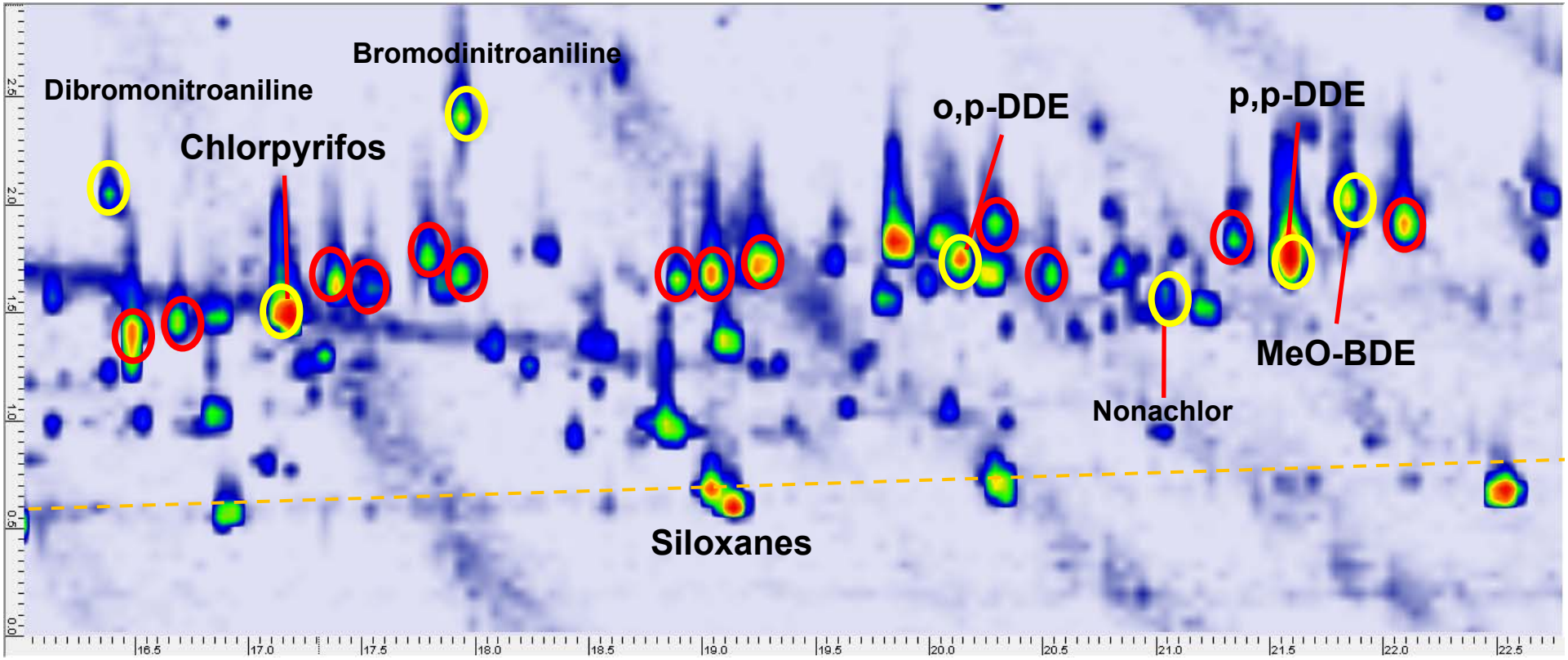


Ontario

Peak picking, library searching and accurate mass confirmation

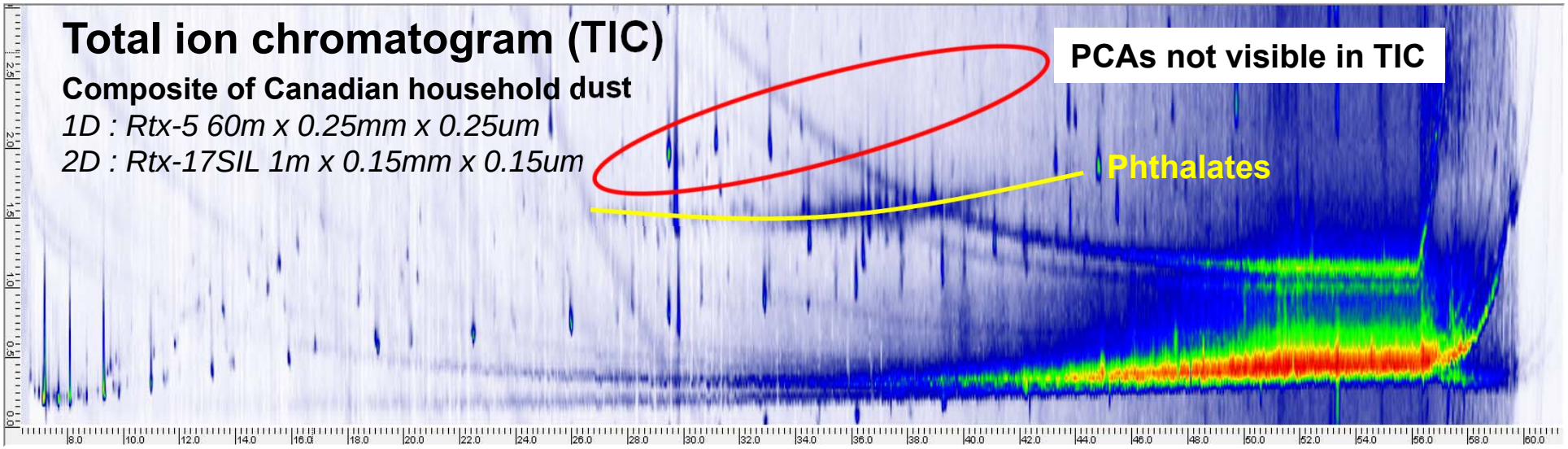
Mass defect filtered chromatogram : R.T. = 16 – 23 minutes

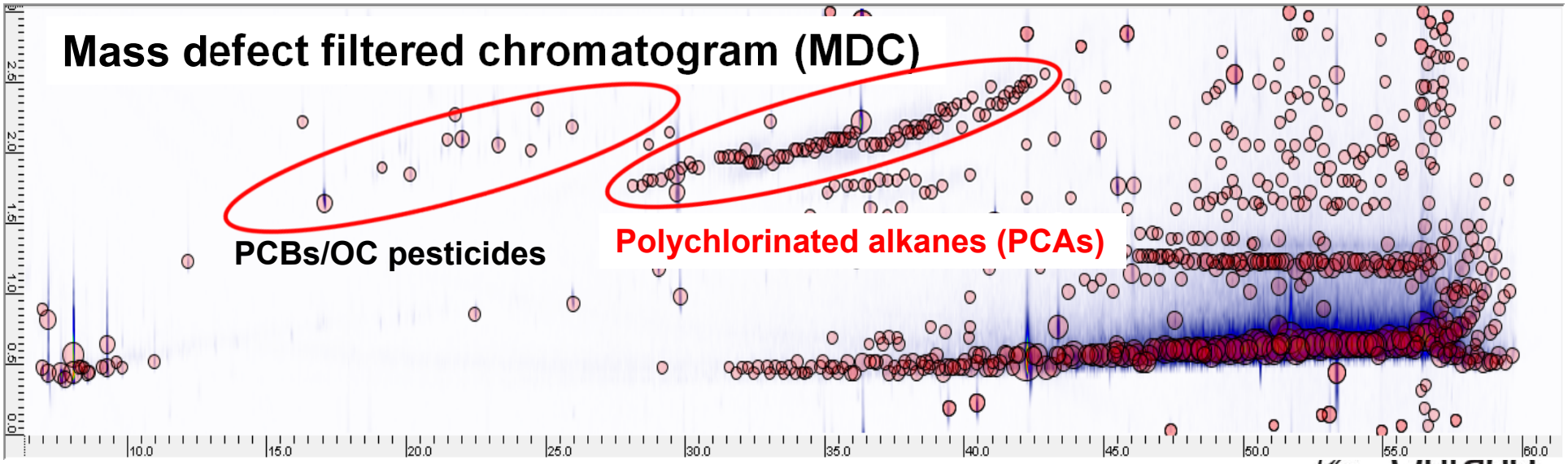
= Cl_4 and Cl_5-PCBs = OC pesticides and other halogenated compounds



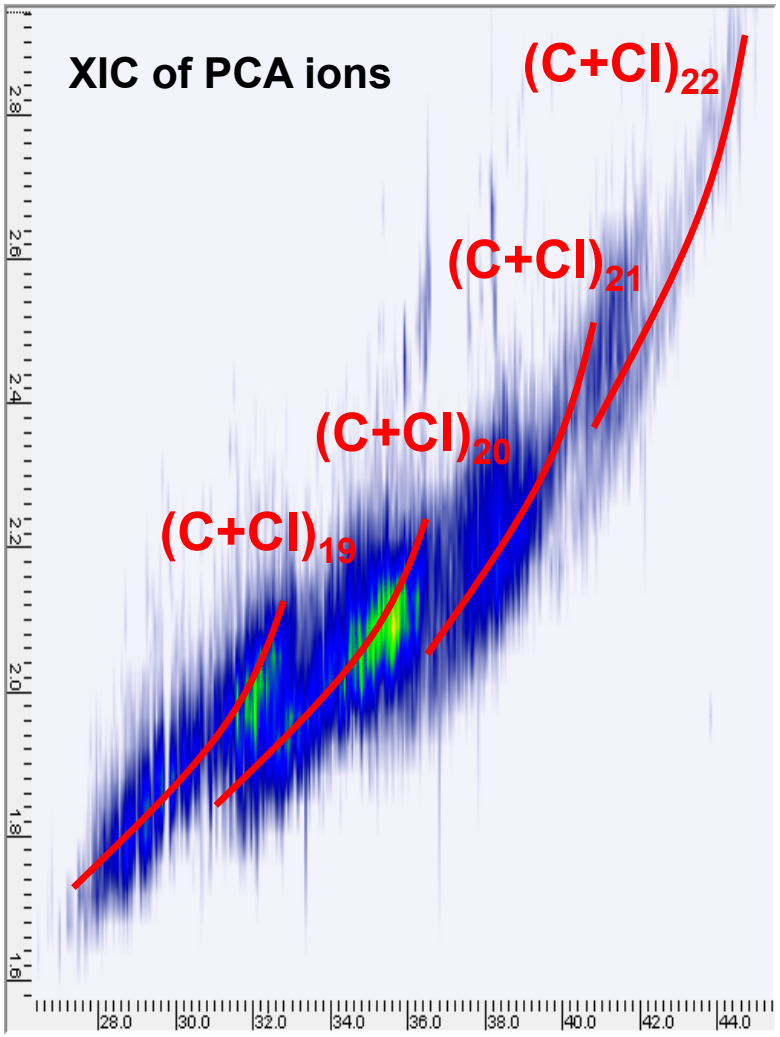
Ontario

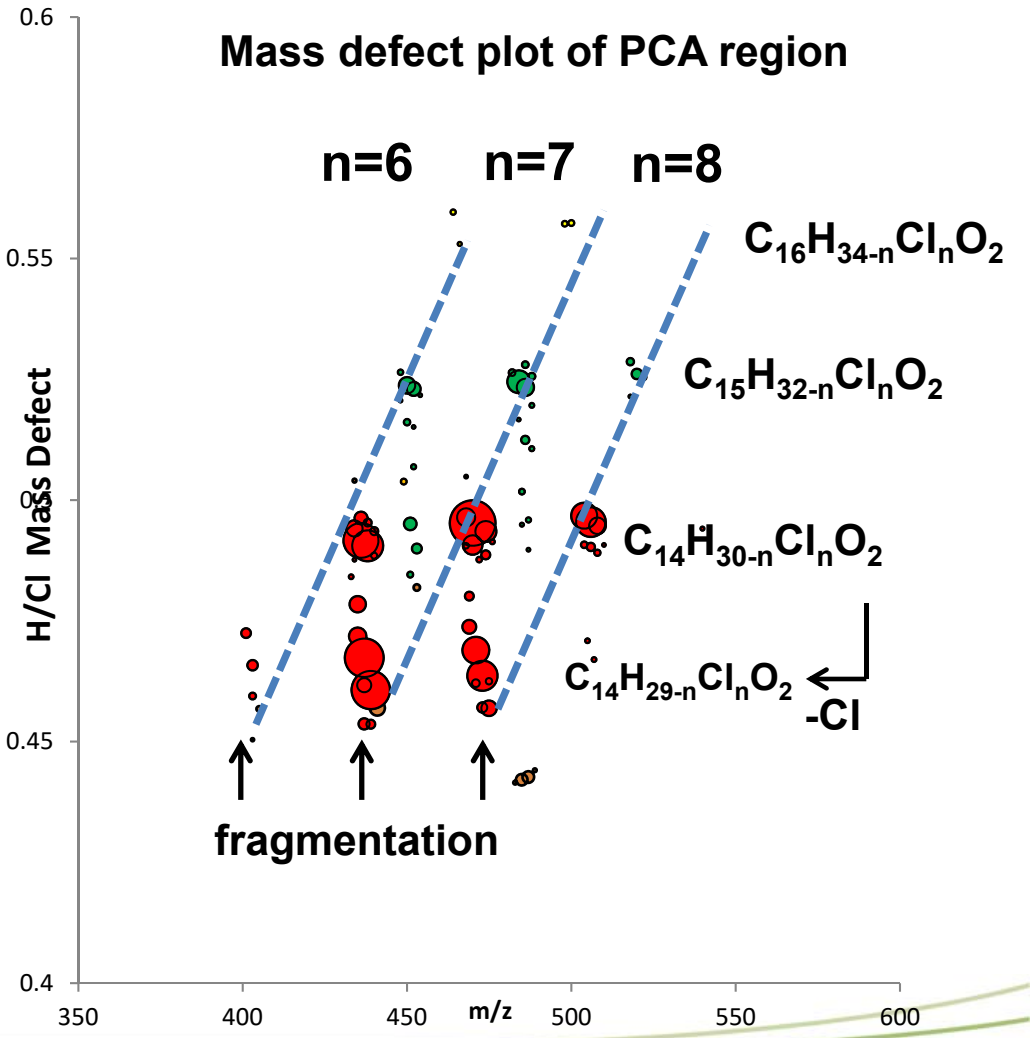
Mass defect filtered GC×GC chromatogram – -ve ion mode





Chlorinated alkanes identified in Canadian household dust





Ontario

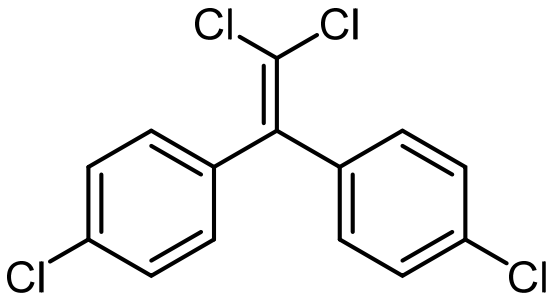
POPs /#SFEv#dqg#Sodfhqwdo#qvxiilflhqf|

- **Fetal growth is an important indicator of a child's health** because its impairment may be associated with poor neurodevelopment and with chronic diseases in adulthoood.

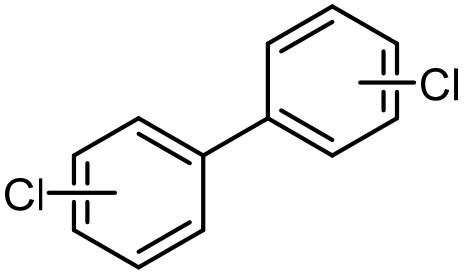
- **Fetal growth restriction** is often the result of **placental insufficiency**, whereby nutrient transport to the fetus is impeded by abnormal or poorly development placental vasculature.

- Maternal exposure to **P**ersistent **O**rganic **P**ollutants (POPs) has been implicated as a risk factor : these environmental toxicants have the potential to inhibit vascular development through interactions with the insulin-like growth factor (IGF) system.

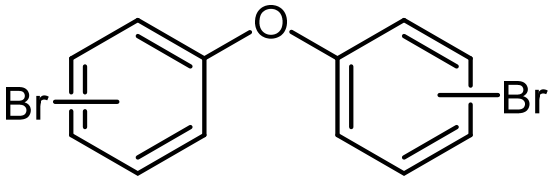
DDE – Degradation product of DDT



PCBs
(Polychlorinated Biphenyls)



PBDE
(Polybrominated Diphenylethers)

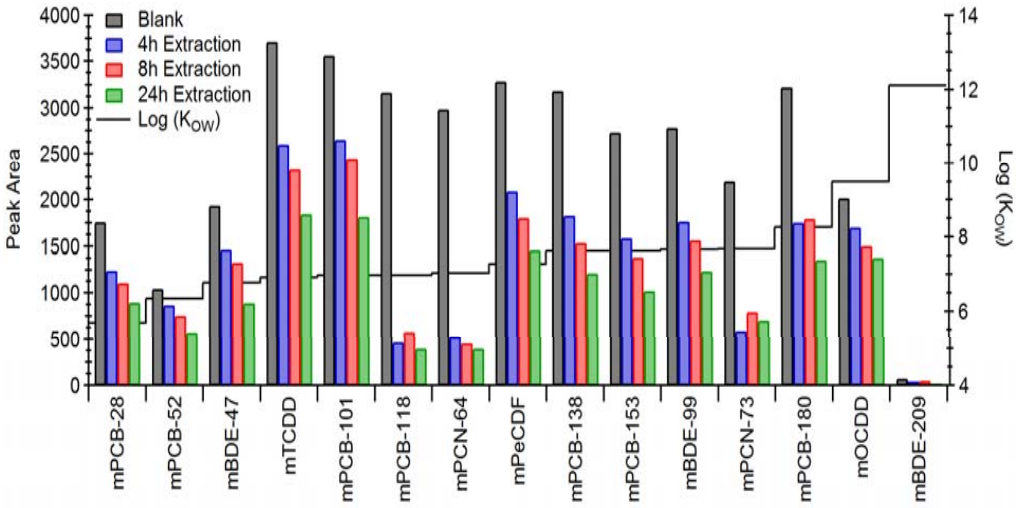


Ontario

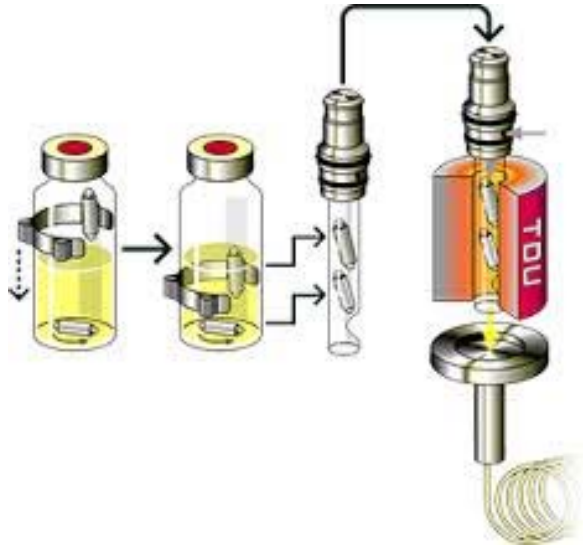
Extraction: Stir-bar sorptive extraction of serum

- Stir bar sorptive extraction: A magnetic stir bar, coated in PDMS is used to extract the (mostly lipophilic) compounds of interest from a 10mL 30% MeOH/H_2O solution containing 100µL of serum.

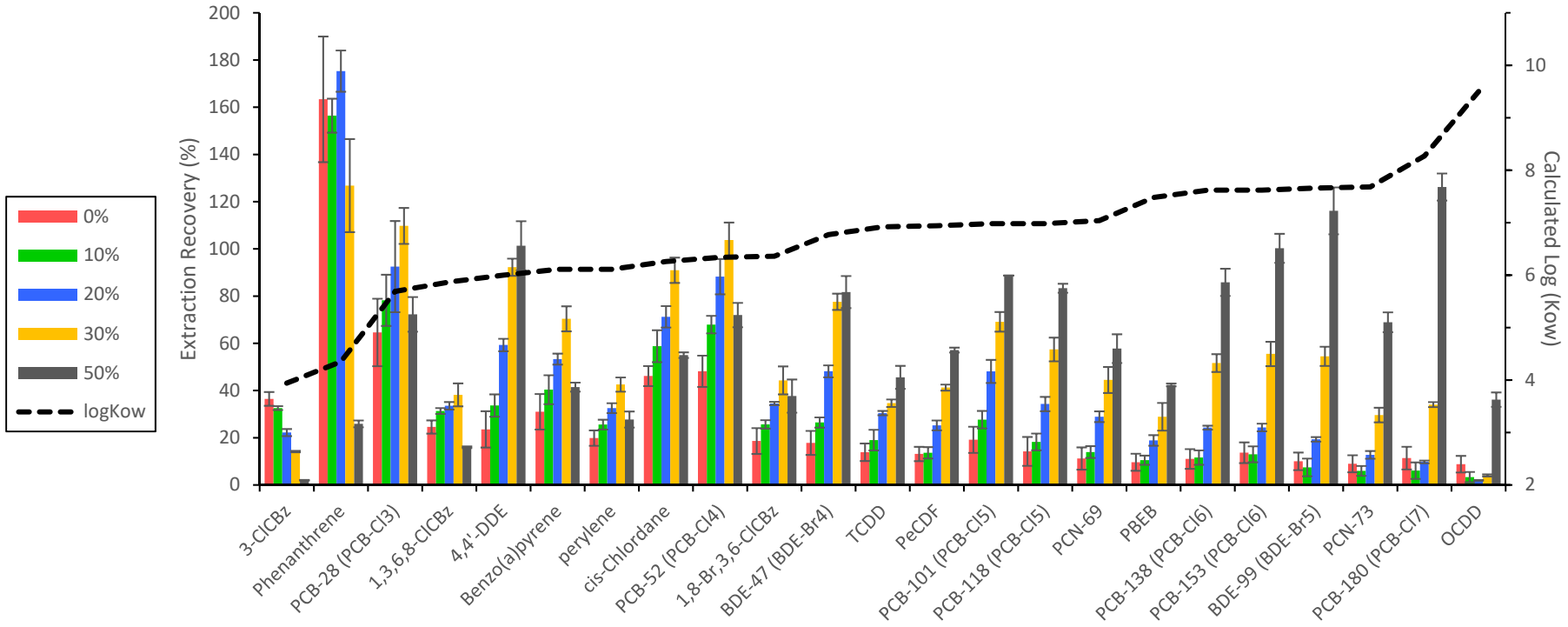
- Method requires ~4 hours for extraction of 20 samples and 15 minutes / sample for instrumental analysis



Stir bar sorptive extraction (SBSE)



Our method for analysis : Optimization



Adding an organic modifier (methanol) ↓ **polarity** of extraction **medium** and ↑ **solubility** of **hydrophobic compounds**

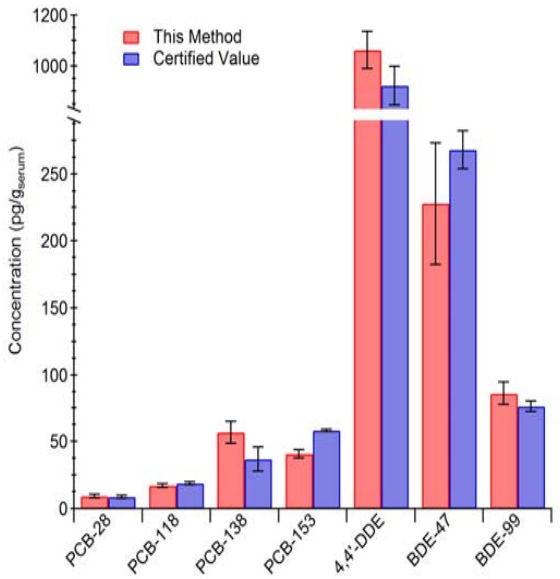
Recoveries at **50%** methanol ↑ as **log K_{ow}** ↑, **but** for **less hydrophobic compounds** (lower log K_{ow}), ↑ methanol percent ↓ recovery

Ontario

The method yields accurate results with 0.2 mL of serum

	Current MDL (S/N)	NHANES MDL	NHANES 50th Percentile	NHANES 95th Percentile
TCDD	**0.22**	**0.00074**	<LOD	0.00502
OCDD	**0.25**	**0.0226**	<LOD	0.913
PeCDF	**0.07**	**0.00088**	<LOD	0.0123
PCB-28	**15***	**0.7**	4.96	11.3
PCB-52	3	0.3	2.74	7.60
PCB-101	2	0.3	1.70	5.83
PCB-118	2	0.3	5.19	31.3
PCB-138	3	0.3	15.1	75.3
PCB-153	3	0.3	20.8	97.1
PCB-180	4	0.3	18.0	81.5
4.4'-DDE	5	1.4	203	1860
BDE-47	**6.01***	**0.6**	19.2	163
BDE-99	**17.74***	**0.6**	<LOD	42.2

Accurate quantitation of targets



NIST 1957
Serum reference material

*Background limited

Ontario

Enhancing the sensitivity of GC-APCI using the multi-mode modulator

Collaboration with Dr. John Seeley – Oakland University

ELSEVIER

Journal of Chromatography A

Volume 1536, 9 February 2018, Pages 6-15

The multi-mode modulator: A versatile fluidic device for two-dimensional gas chromatography

John V. Seeley [a], Nicolaas E. Schimmel [a], Stacy K. Seeley [b]

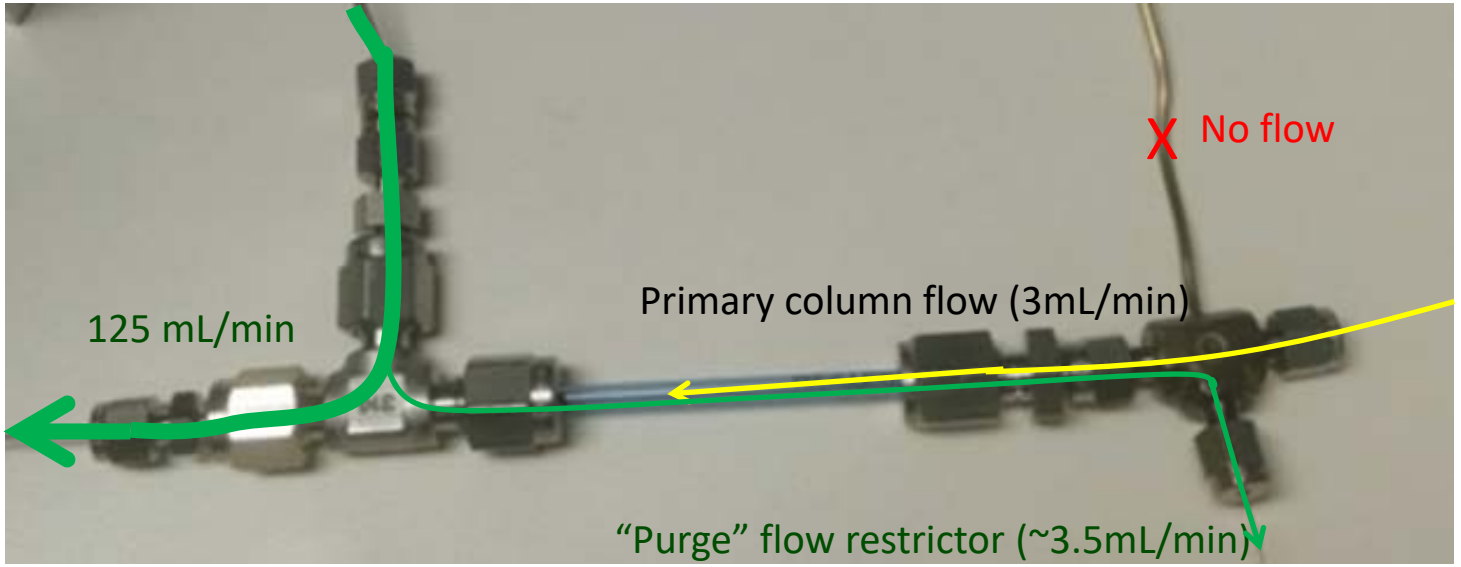
⊞ Show more

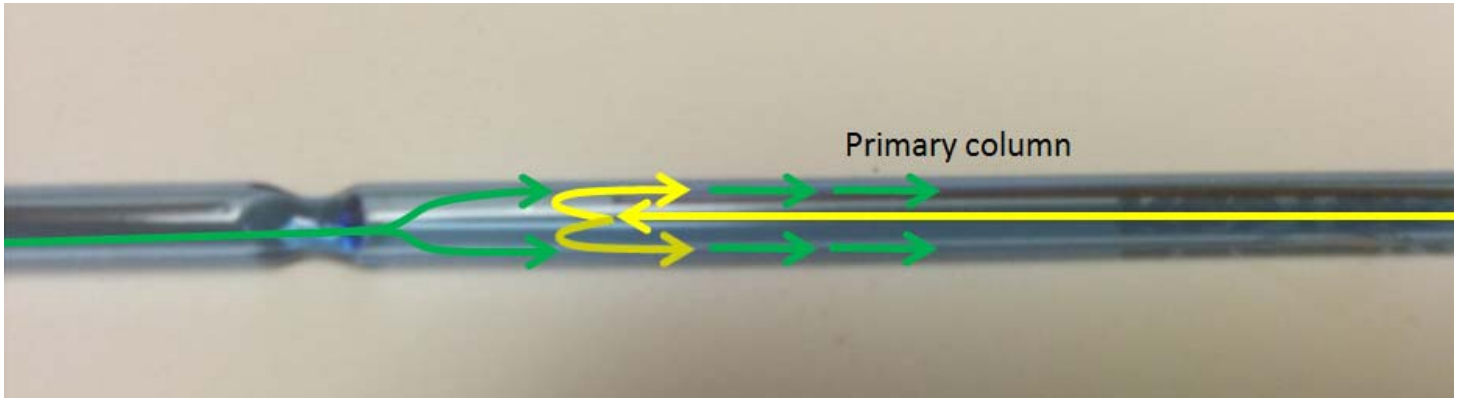
https://doi.org/10.1016/j.chroma.2017.06.030

Highlights

- A new flow modulator for multi-dimensional gas chromatography (MDGC) is introduced.
- The modulator can be used for heart-cutting MDGC, low duty cycle GCxGC, and full transfer GC x GC.
- The theory of operation is described.
- The modulator is demonstrated in three modes by separating gasoline samples

Multi-mode modulator : Sample collection state





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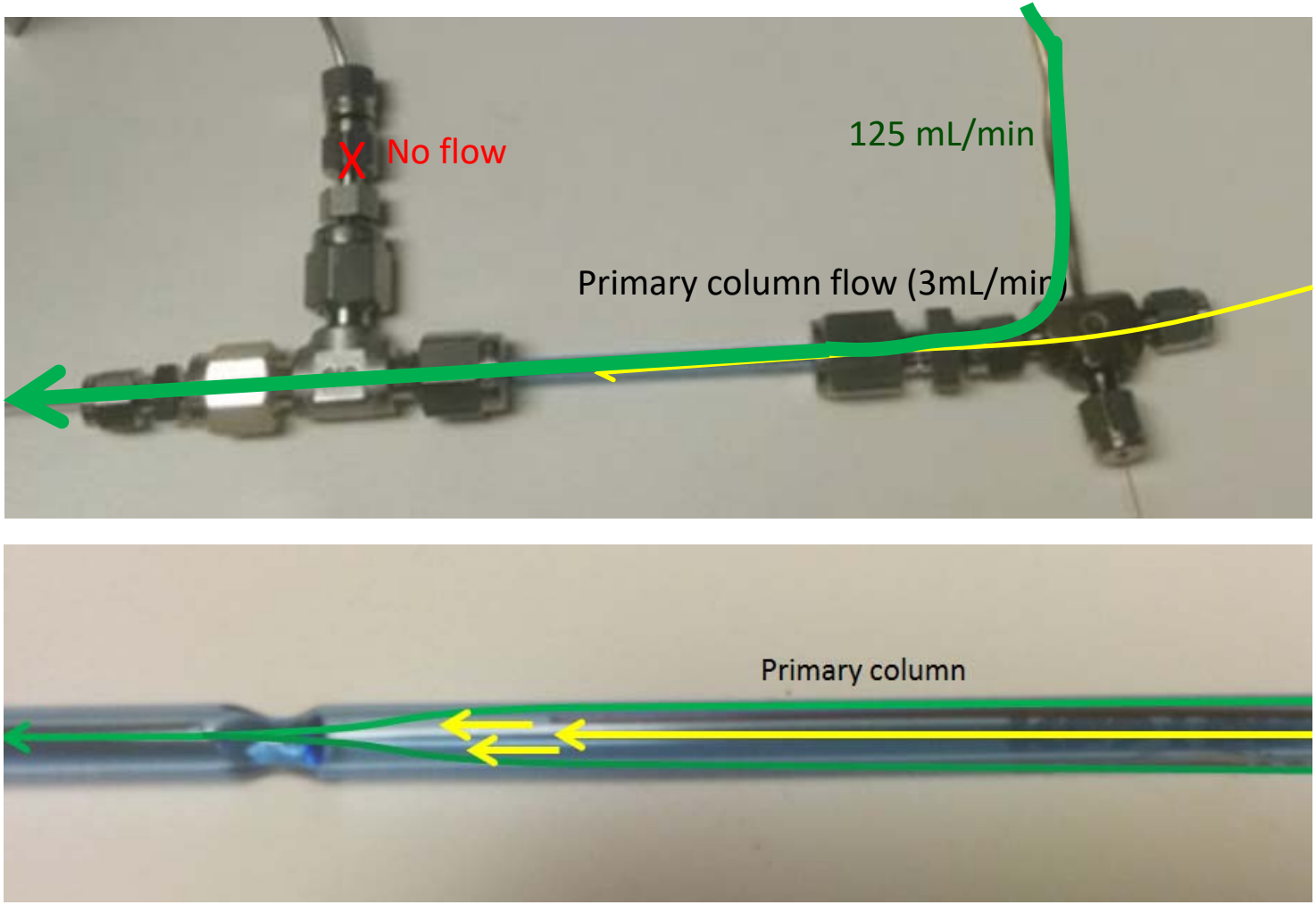
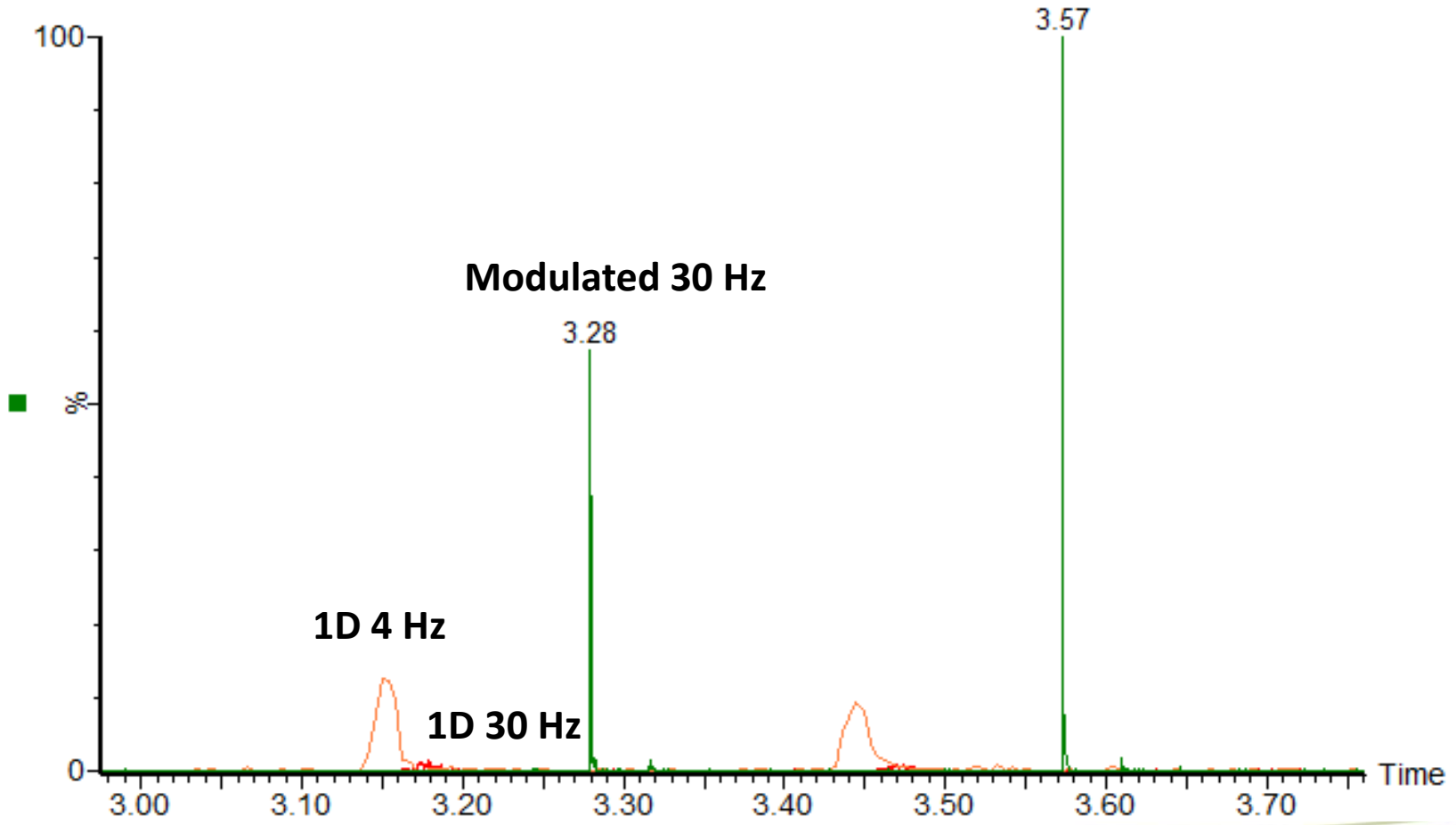
Multi-mode modulator : Pulsed injection



Flow modulation provides to 10-fold S/N enhancement!



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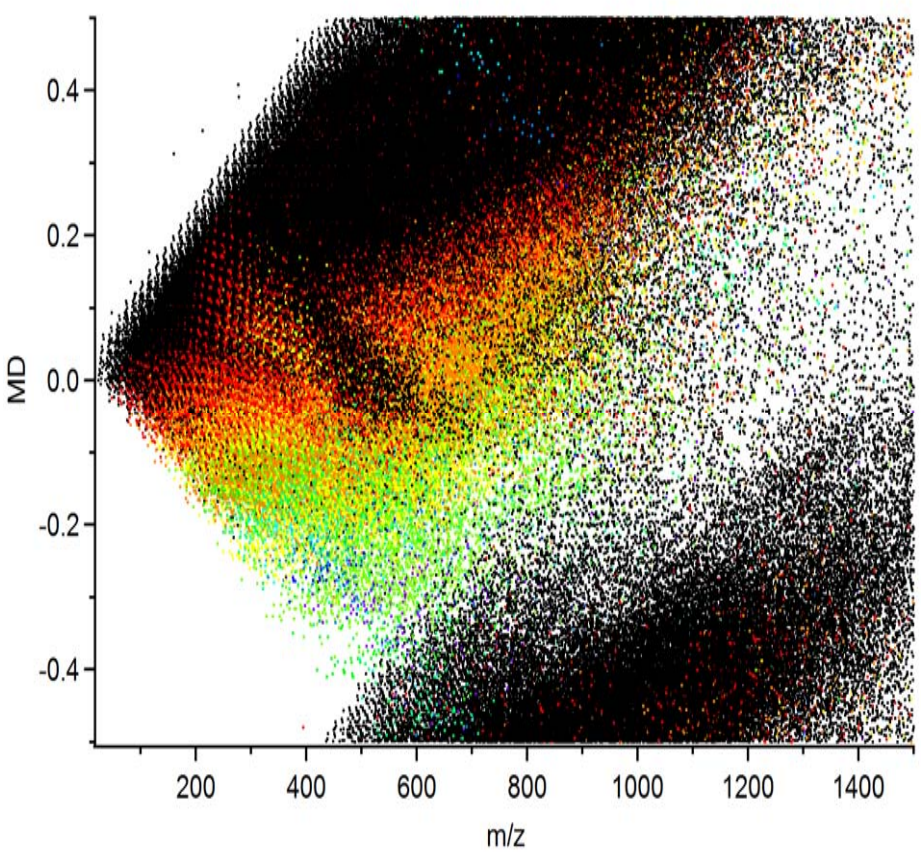
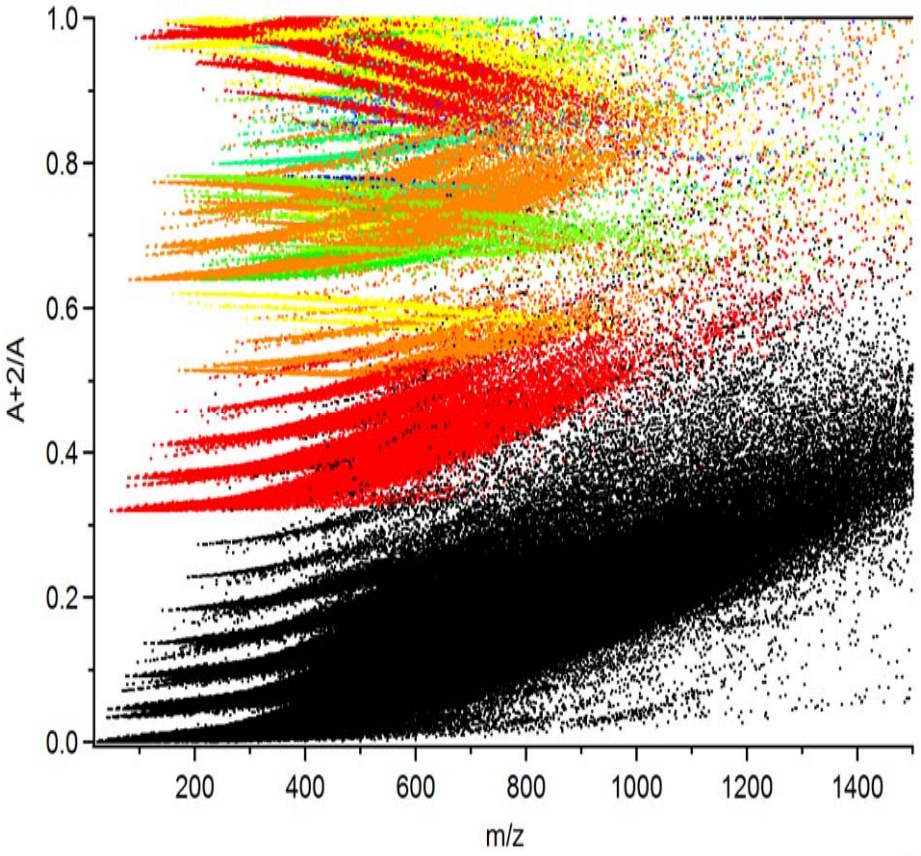
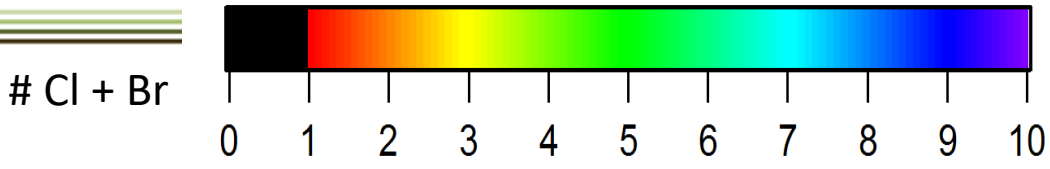
Identifying POPs by their position in compositional space

The PubChem database through the eyes of a mass spectrometer
(*m/z*, mass defect, isotope ratios)







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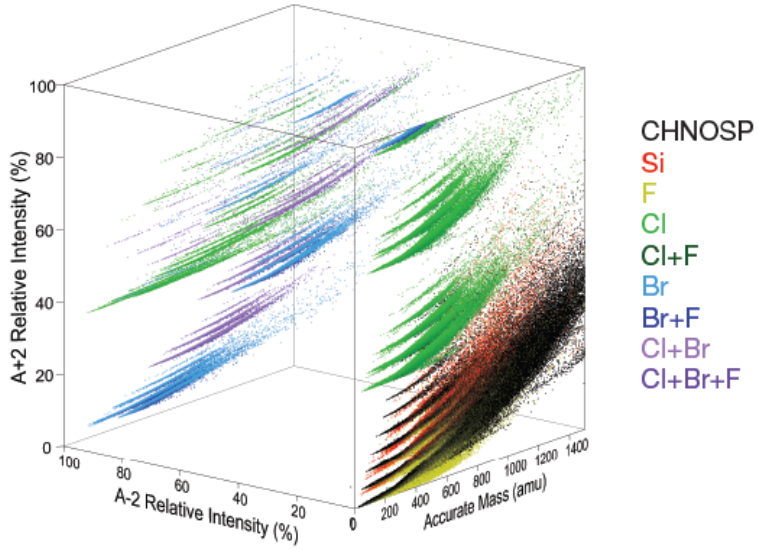
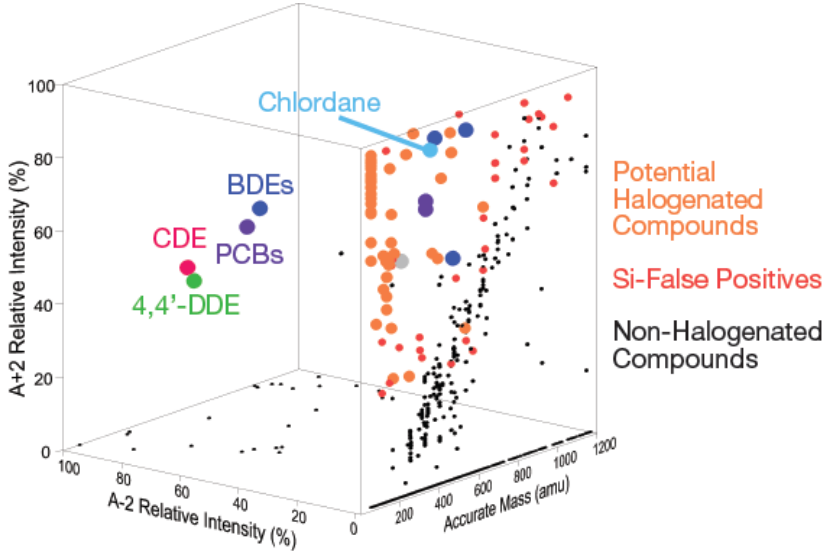
Identifying POPs by their position in compositional space

PubChem Database



Compositional space of entire PubChem database (>700 000 unique molecular formulae) based on A+2 and A-2 isotope ratio

Experimental Data – NIST SRM 1958 (serum)



Visualization of non-target analysis of NIST SRM 1958 (fortified serum), highlighting known POPs and unknown halogenated components

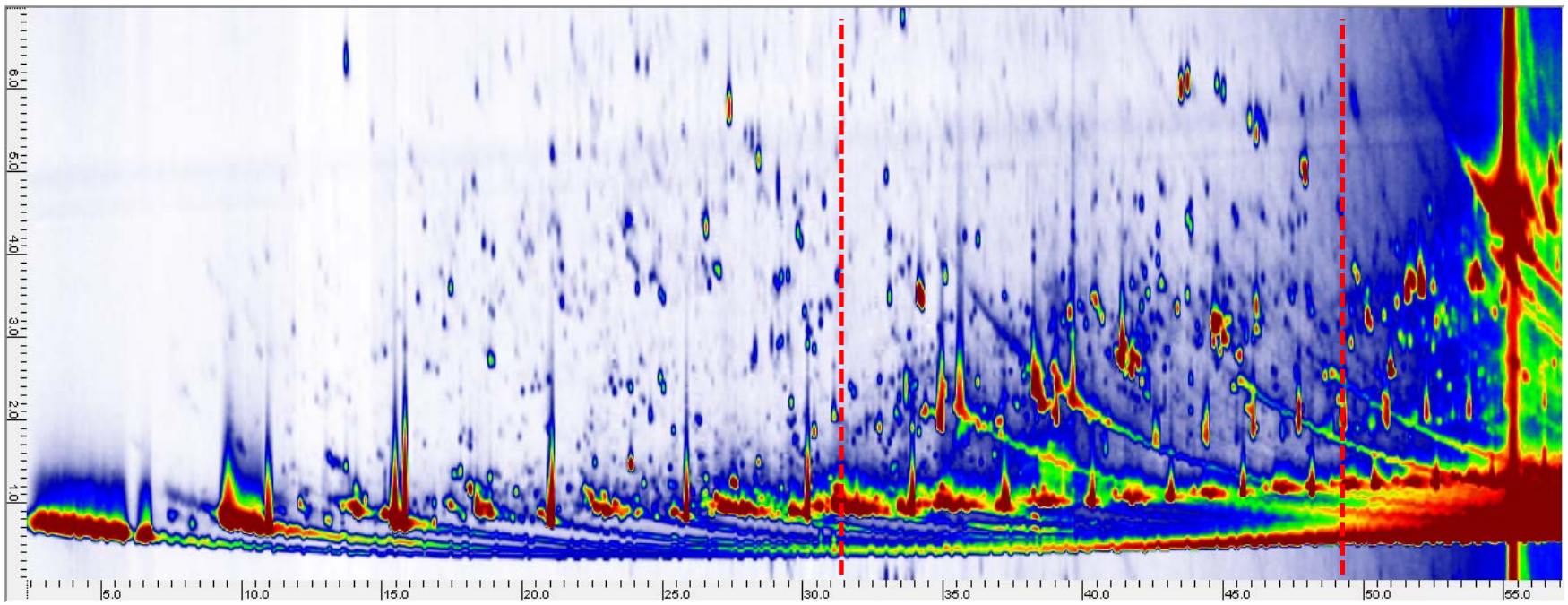
Workflow:

1) Isotope clusters are identified from diagnostic *m/z* differences (e.g. 1.0034 for ^{13}C peaks; 1.997 for Si, S, Cl and Br isotopic peaks).

2) Peaks corresponding to halogenated compounds are filtered on the basis of isotope ratios.

The GCxGC contour plot provides a picture of environmental exposure

Data obtained from a pooled sample of high risk subjects



- The sample contains thousands of chemical compounds.
- The identities are known for only a small fraction of these chemicals

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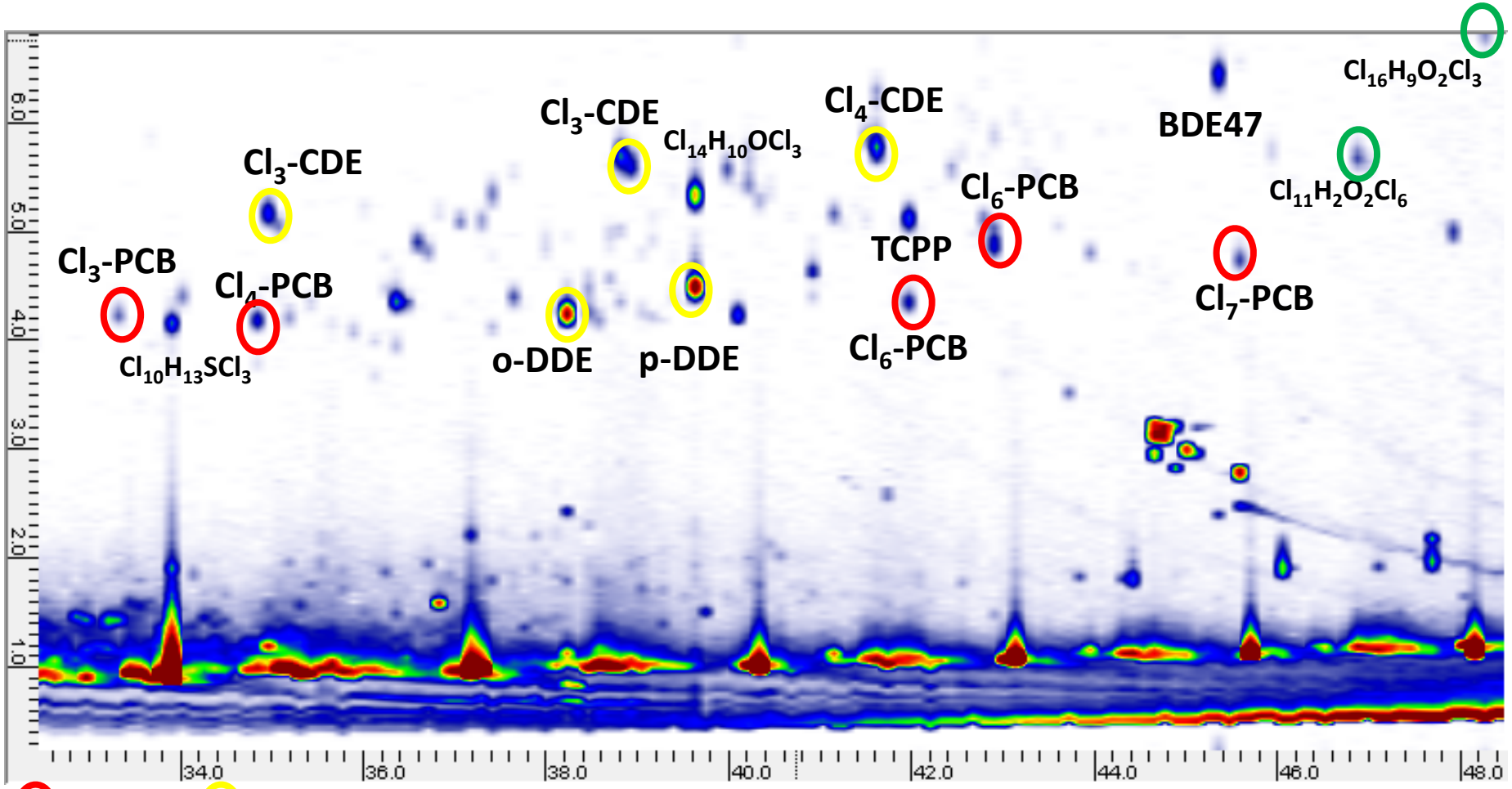
Expanded view of the region occupied by (un)known POPs



= PCBs = Pesticides and Chlorinated Diphenyl Ethers (CDEs) = Unknown POPs

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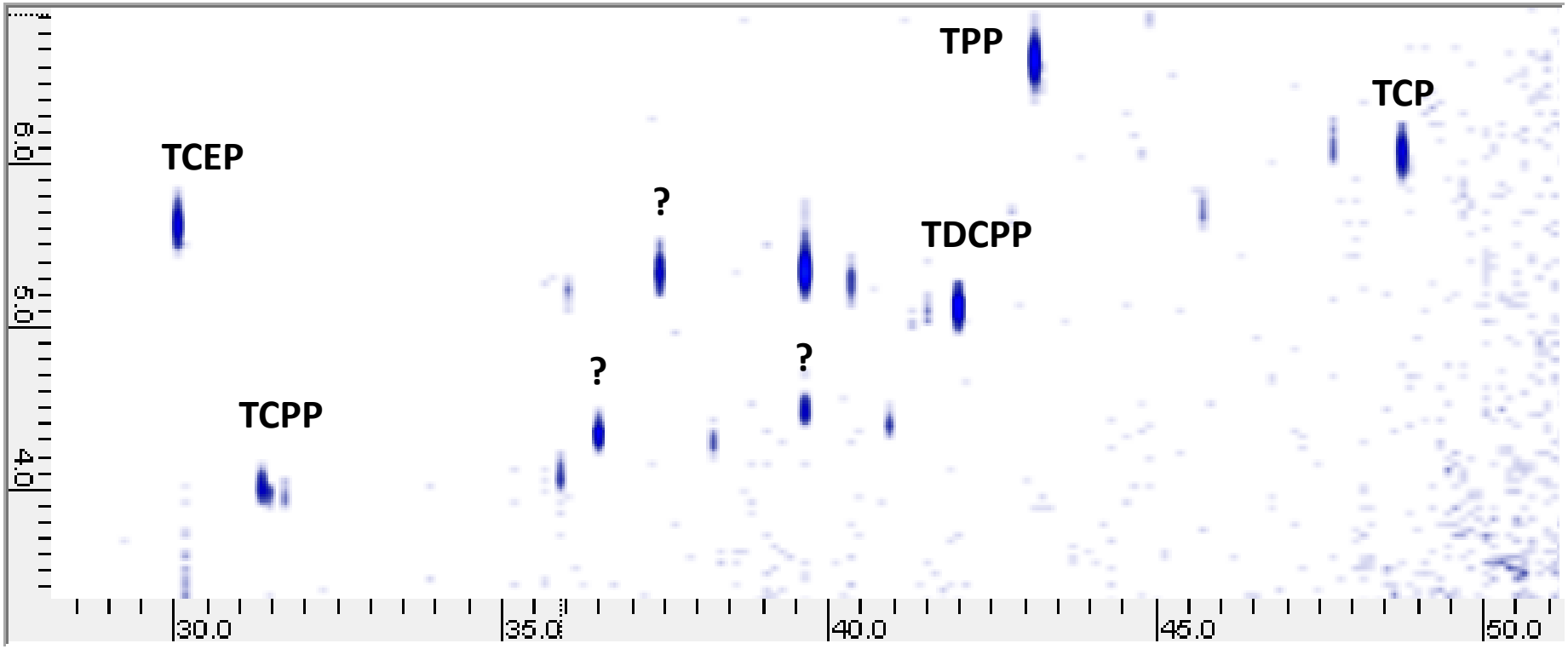
Building a digital archive of exposure

Several well known organophosphate ester flame retardants are detected



- This digital archive can be searched for suspected contaminants
- Do raw data points (mass and RT of ? compounds) correlate to birth weight?

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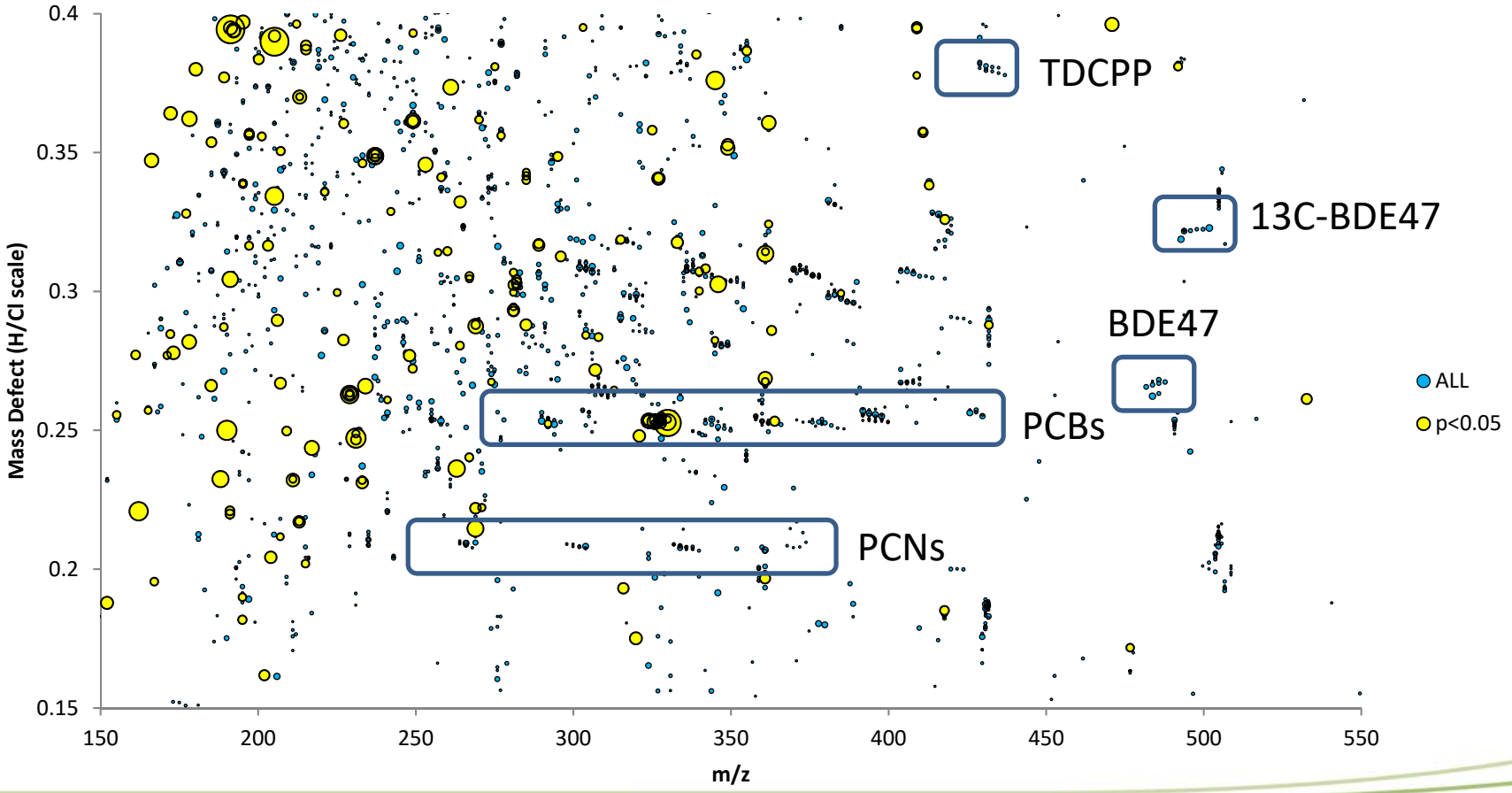
Correlating (un)known compounds to birth weight

Mass defect spectrum 7938 compound ions across control (n=34) and high risk groups (n=34)



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Conclusion : GC(xGC)-API-MS is a powerful tool for studies of the exposome

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