ION MOBILITY-ENABLED LC-HRMS FOR THE ANALYSIS OF POLLUTANTS IN INDOOR DUST: IDENTIFICATION AND PREDICTIVE CAPABILITIES

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INTRODUCTION

Dust analysis provides a means to assess the degree of exposure to humans in an indoor environment to various xenobiotic contaminant classes. Recent publications have demonstrated implementation of non-targeted acquisitions using high resolution mass spectrometry (HRMS) to comprehensively profile these compounds in dust [1-8], and one challenge confronted is improving the confidence in proposed compound identifications, particularly when authentic standards are not available. Here, we investigate the use of a liquid chromatography-quadrupole time-of-flight (QTof) MS combined with ion mobility spectrometry (IMS) to provide further gas-phase characterization of xenobiotic contaminants observed in two e-waste processing facility and composite household dust samples. Specifically, IMS was used here to obtain collision-cross section (CCS) values for all ions, which represent the two-dimensional area of an ion's gas-phase conformation and is measured in units of $Å^2$ [9]. CCS values were used as an identification point for numerous compounds in this study. Further investigation in the use of predictive modelling to support identifications in HRMS data-independent acquisitions such as this was performed with two modern, easy-to-use CCS prediction model platforms.

METHODS

SAMPLE DESCRIPTION: Dust samples were collected from two different e-waste processing facilities in Canada, described in [3] and [10], and the composite household dust sample was collected from various Canadian homes and described in [11]. Samples were extracted through liquid extraction with dichloromethane and dried down under N_2. Extracts were reconstituted with 1:1 methanol: water for LC-MS analysis.

LC CONDITIONS:

LC System:	Waters ACQUITY I-Class (with isolator column)
Column:	ACQUITY UPLC BEH C18 2.1 x 50 mm, 1.7 µm
Column Temp:	65 ˚C
Sample Temp:	4 ˚C
Flow Rate:	0.450 mL/min.
Mobile Phase A:	2 mM ammonium acetate in 98: water:methanol
Mobile Phase B:	2 mM ammonium acetate in methanol
Total Run Time:	8.5 min.

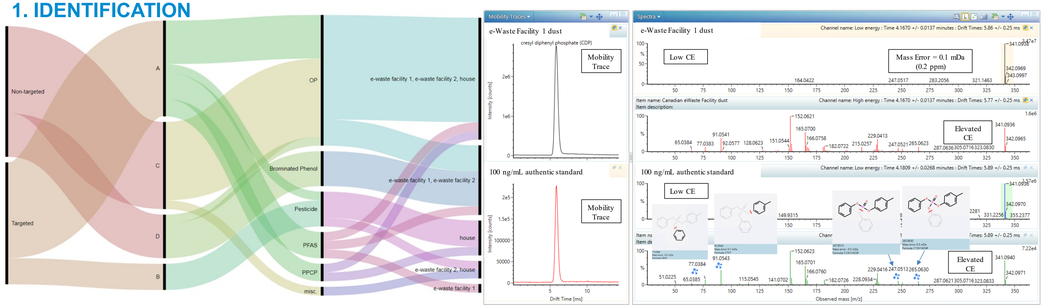
Gradient: 90% A starting, then 90% A at 0.5 min. to 0% A at 5.10 min., held for 1.50 min. then return to 90% A at 6.70 min. for remainder of run time.

IMS-MS CONDITIONS:

Instrument :	Vion IMS QTof
Ionization Mode:	$ESI^{+/-}$ (separate acquisitions)
Collision Energy (LE):	3 eV
Collision Energy (HE ramp):	20-55 eV
Scan Time:	0.25 sec
Acquisition Range:	50-1000 m/z
Drift Gas:	N_2
Capillary:	1.0 kV (positive) and 0.5 kV (negative)
Source Temperature:	120°C
Source Offset:	80
Desolvation Temperature:	550°C
Cone Gas Flow:	50 L/hr
Desolvation Gas Flow:	1000 L/hr
Lockmass:	Leucine Enkephalin (556.2766/554.2620m/z)
Mass and CCS Calibrant:	Major Mix

RESULTS AND DISCUSSION

1. IDENTIFICATION



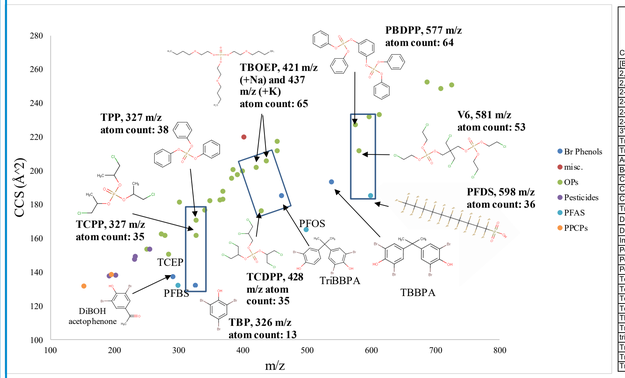
Searching for likely xenobiotic compounds used a mix of targeted and non-targeted processing approaches. These were comprised of four tactics:

A. Comparison to retention time (+/- 0.1 min.), collision cross section (CCS, +/- 2.0%), exact mass (mass error < +/- 5 ppm)) and expected product ions of compounds analyzed using authentic standards on the same chromatographic method as the sample analysis.
B. Comparison to CCS (+/- 2.0%), exact mass (mass error < +/- 5 ppm) and expected product ions of >400 pesticides analyzed as authentic standards in ESI+.
C. Isolation of exact mass/retention time pairs using PCA, followed by chemical compound database searching (KEGG, ChemSpiderman, PubChem, DSSTox, EPA Toxcast). Proposed identifications were within a +/-5ppm mass error tolerance and at least 1 proposed product ion structure.
D. Isolation of exact mass/retention time pairs which had Cl/Br isotopic distribution patterns from full mass table. Chemical database searching and identification criteria as in "C" including isotopic fidelity matching.

These methods resulted in 29 proposed identifications across the dust samples. Classes included organophosphorus compounds (OPs), brominated phenols, pesticides, perfluoroalkyl substances (PFAS) and PPCPs, representing previously reported classes in indoor dust. Where available, solvent standards were purchased to confirm Group C and D identification proposals. Shown in the figure above is the matching high definition (ion mobility) MS^E ($HDMS^E$) spectrum and mobility trace of OP cresyl diphenyl phosphate as observed in the e-waste facility dust 1 (top) and 100ng/mL authentic standard (bottom).

2. CCS CHARACTERIZATION

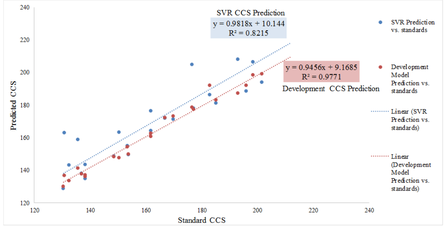
Comparison of CCS values vs. m/z for the identifications showed a generally positive linear relationship, consistent with previous IMS studies of small molecules [12-14]. Uniquely observed in this data set was multiply halogenated (Cl, Br, F) compounds having significantly smaller CCS values than compounds without halogens with similar m/z (illustrated in the figure below). Although m/z is similar due to the heavier halogens present, the atom count difference indicates the structurally more compact nature of these compounds, thus explaining their more rapid passage through the ion mobility drift cell, and hence lower CCS value, then the non-halogenated counterparts. Shown in the table below, repeatability of CCS values across injections (CCS_{obs}) had a mean of 0.24% RSD, and comparisons to solvent standard CCS values where within the 2% relative error criteria ascribed for screening studies [13,15] and therefore were suitable for further assessment with predictive CCS modelling.



Compound	n (inj.)	CCS_{obs}	% RSD CCS_{obs}	% error from $CCS_{standard}$
[Bis(2-hydroxyethyl)amino]methyl stearate	20	219.62	0.22	--
2,4,6-Tribromophenol	20	131.91	0.32	0.95
2,6-Dibromo-4-[2-(3-bromo-4-hydroxyphenyl)propan-2-yl]phenol	20	184.92	0.22	--
2-Ethylhexyl diphenyl phosphate (EDP, DPEHP)	20	200.57	0.21	-0.50
2-Ethylhexyl diphenyl phosphate (EDP, DPEHP)_ISF	24	153.28	0.17	-0.34
2-Isopropylphenyl diphenyl phosphate	24	182.81	0.18	-0.07
2-tert-Butylphenyl diphenyl phosphate	24	195.11	0.32	-0.41
3',5'-Dibromo-4'-hydroxyacetophenone	20	137.12	0.16	1.09
Tris(2-propyl phenyl) phosphate_CCS 211.6	20	211.60	0.24	--
Tris(2-propyl phenyl) phosphate_CCS 217.3	20	217.33	0.40	--
Acetominophen	4	131.45	0.31	0.80
Benzyl hydrogen [2-(4-biphenylyl)-2-hydroxyethyl]phosphonate	24	187.41	0.32	--
Caffeine	20	138.19	0.22	-0.01
Carbendazim	18	137.40	0.16	0.28
Cresyl diphenyl phosphate (CDP)	24	176.53	0.22	-0.31
Triphenyl phosphate	24	170.77	0.21	--
Diuron ([M-H]-)	4	147.18	0.08	--
Diuron ([M+H]+)	4	148.99	0.31	0.36
Imidacloprid	4	153.60	0.28	0.10
Perfluorobutanesulfonic acid	20	131.90	0.28	-0.42
Perfluorodecanesulfonic acid	16	185.05	0.35	-0.07
Perfluorooctanesulfonic acid	24	164.72	0.29	-1.27
Tetrabromobisphenol A (TBBPA)	20	193.21	0.19	0.13
Tetrakis(2,6-dimethylphenyl) 1,3-phenylene bis(phosphate)	20	252.19	0.38	--
Tetrakis(2-chloroethyl)dichloroisopentyl diphosphate (V6)	24	211.69	0.20	-0.20
Tetraphenyl 1,3-phenylene bis(phosphate)	20	226.44	0.37	--
Thiabendazole	4	137.98	0.36	-0.17
Triphenylphosphine oxide	24	161.62	0.20	-0.06
tris(1,3-dichloro-2-propyl)phosphate (TCDPP, TDCP)	24	176.16	0.18	-0.17
Tris(1-chloro-2-propanyl) phosphate (TCPP)	24	161.71	0.18	-0.11
Tris(2-butoxyethyl) phosphate	24	199.71	0.29	0.69
Tris(2-chloroethyl) phosphate	24	150.16	0.23	-0.17

3. CCS PREDICTION ASSESSMENT

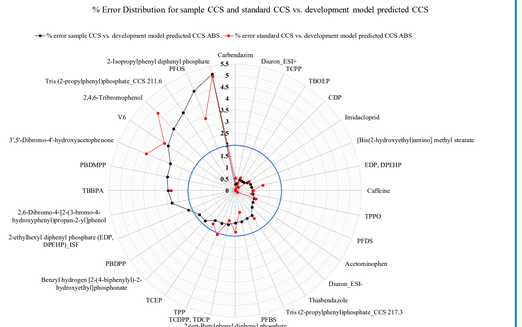
Assessment of two different machine-learning derived CCS prediction programs was performed on the compound identifications where authentic standard confirmation was performed. The resulting linear regression model is displayed below, with the Development CCS prediction model having the closest fidelity (R^2=0.977) to observed CCS values from authentic standards of the compounds identified in the dust. This model was then used to generate CCS values for all proposed identifications in dust samples where the relative percentage error was within 5.15% for predicted vs. experimental CCS, as shown in the adjacent figure. Overall, 68% of the 29 compound identifications within the 2.0% relative error criteria typically employed for confirmation with authentic standards. It is postulated that increasing the number of compounds similar in class those outside the 2% error tolerance would improve the fidelity for this study, and current results show promise of CCS predictive modelling for compound identification support.



Single Vector Regression (SVR) based CCS prediction program [16]

Development CCS prediction program [17]

Differences between models include:
-Number of compounds in model creation training set (400 in SVR vs. 3031 in Development model)
-Number and type of molecular descriptors.



CONCLUSIONS

- **29 xenobiotic compounds were isolated and identified in industrial and domestic indoor dust samples and where possible confirmed with standards**
- **CCS values were used as an additional confirmatory point for identifications**
- **Assessment of diverse xenobiotic compound class ion mobility behavior shows evidence for multi-halogenated compounds trending to significantly lower CCS values than non-halogenated compounds of a similar m/z**
- **Use of a recently developed CCS prediction model shows improved fidelity to experimental values of identified compounds in this study over previously developed model**
- **CCS prediction presents a promising avenue for support of non-targeted study identification proposals, with 60% of compounds identified in dust samples having relative CCS errors <2% from predicted values**

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