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Suspect screening analysis in house dust from Belgium using high resolution mass spectrometry; prioritization list and newly identified chemicals

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11   **Abstract**

12   In recent years, several changes have been made to the composition of various products which are

13   used indoors. Plenty of new chemical additives have been incorporated to materials to comply with

14   current legislation and safety rules. Consequently, the emission profiles of contaminants detected

15   indoors may change over time, requiring continuous monitoring. In this study, dust samples were

16   collected from 25 homes located in the Flemish region of Belgium during different seasons (winter and

17   summer). Our aim was the development of a suspect screening workflow for the identification of new

18   chemicals which might have been applied to indoor goods, released into the indoor environment, and

19   accumulated in dust. An *in*-house suspect list was curated including selected groups of compounds,

20   namely "phthalates", "phosphates", "terephthalates", "citrates", "trimellitates", (di-, tri-, tetra-)

21   "carboxylic acids", "adipates", "azelates", "sebacates", (di-)"benzoates", and "succinates". 63

22   chemicals were prioritized based on their level of identification and detection frequency in samples.

23   Seasonal comparison was tested, indicating that higher temperatures of summer might facilitate the

24   release of few chemicals from the products into the indoor environment. Seven chemicals, to the best

25   of our knowledge not previously reported, were selected out of the 63 listed and identified for

26   structure confirmation using high-resolution mass spectrometry. Tributyl trimellitate (TBTM), bis

27   (3,5,5-trimethylhexyl) phosphate (Bis-3,5,5-TMHPh), iso-octyl 2-phenoxy ethyl terephthalate (IOPhET),

28   dimethyl azelate (DMA), dimethyl sebacate (DMS), dipropylene glycol dibenzoate (DiPGDB) and 3,5-di-

29   tert-butyl-4-hydroxybenzaldehyde (BHT-CHO) were detected at frequencies ranging from 8-52% in

30   winter and 4-56% in summer dust.

31

32   **Keywords:** suspect screening analysis, indoor dust, new chemicals, prioritization, LC-QTOF-MS

33

34 **1. Introduction**

35 During the last decades, indoor environment attracted scientific attention due to the need of constant

36 monitoring of its quality (Rostkowski et al., 2019). The modern living conditions include modified

37 materials for buildings and products and lower rates of renewed air in favor of the energy consumption

38 reduction. In combination with higher time spent indoors, the indoor environment has been

39 characterized as one of the major contributors to health problems due to the presence of numerous

40 chemicals (Laborie et al., 2016). In particular, indoor dust has been identified as a significant route of

41 human exposure to semi volatile organic compounds (SVOCs), including wide range of priority

42 pollutants such as flame retardants (FRs), polycyclic aromatic hydrocarbons (PAHs), plasticizers and

43 pesticides (Bui et al., 2016; Little et al., 2012; Harrad et al., 2010; Weschler & Nazaroff, 2008). The

44 main pathways of transfer for SVOCs from materials to indoor dust are (i) volatilization and subsequent

45 partitioning, (ii) transfer of particles or fibers from products to dust or (iii) direct contact between

46 surfaces and dust (Rauert et al., 2016). As a consequence, dust acts as a sink for SVOCs released from

47 indoor sources and through dust inhalation, ingestion and dermal contact, humans are exposed to a

48 wide range of chemicals.(Rauert et al., 2016; Kanazawa et al., 2010; Araki et al., 2014).

49 Recent evidence from biomonitoring studies in human blood and urine indeed indicates remarkable

50 human exposure to more than a hundred SVOCs (Calafat et al., 2017). Such exposure may lead to

51 increased health risks for sensitive subpopulations, such as infants and pregnant women (Calafat et

52 al., 2017;Zheng et al., 2015). In particular, children under 6 years of age tend to be more exposed to

53 indoor dust, due to their natural behavior of crawling and hand-to-mouth contact (Mercier et al.,

54 2011). Strong indications of harmful health effects have led to the restriction or ban of several SVOCs

55 (e.g. polybrominated diphenyl ethers-PBDEs, hexabromocyclododecanes-HBCDs, polychlorinated

56 biphenyls-PCBs, legacy plasticizers- bis(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP),

57 benzyl butyl phthalate (BBP), di-iso-butyl phthalate (DIBP) (Yadav et al., 2017;Reche et al., 2019;Calafat

58 et al., 2017). Such restrictions/bans for "legacy'' chemicals have resulted in their replacement by new

59 chemicals with SVOC properties which were frequently reported as "new", "alternative", "emerging",

60 "replacements", "chemicals of new generation" or "chemicals of emerging concern". For those ones

61 toxicological information is scarce and knowledge on potential exposure and adverse health effects in

62 humans from residential exposure remains still limited. (Subedi et al., 2017;Liu et al., 2012;Covaci et

63 al., 2011).

64   So far, several studies focusing on target analyses have been published reporting the levels of legacy

65 compounds in dust (Laborie et al., 2016;Little et al., 2012 ;Niu et al., 2019;Yadav et al., 2019;Dodson

66 et al., 2012;Christia et al., 2019;Eede et al., 2016;Larsson et al., 2017). Their main advantage of high

67 sensitivity is confronting the limited coverage of chemicals especially for a complex material like dust

68 which is hosting a wide range of them (Dong et al., 2019). Since replacements started being introduced

69 into global chemical market, the need to investigate the occurrence and fate of emerging contaminants

70 in indoor environment is urgent and could be achieved by alternative approaches (Ouyang et al., 2017;

71 Moschet et al., 2018; Rostkowski et al., 2019). Suspect screening analysis (SSA) is an analytical tool for

72 providing a comprehensive outlook in dust matrix. SSA represents a group of analytical workflows

73 developed for high-resolution mass spectrometry (HRMS). Molecular features of samples, which are

74 compound-specific data acquired by LC-QTOF-MS instrument , accompanied by accurate mass,

75 retention time and mass spectral information, are compared with information from lists of chemicals

76 or databases with the aim to identify potential matches (Oberacher et al., 2020; Phillips et al., 2018) .

77 Thousands of expected compounds belonging to various groups of interest (e.g. alternative

78 plasticizers, film forming agents, emollients, additives in food contact materials, etc.) can be

79 congregated in suspect lists. The application of databases combined with the reliable results that HRMS

80 can provide, reassures better evidence of their presence indoors. Since multiple candidates from the

81 suspect list can match positively with the same feature, Schymanski et al., 2014 developed a system

82 of identification levels or levels of confidence (LoC) that is widely adopted to communicate outcomes

83 derived from SSA approach.

84 Since the knowledge on new chemicals that may affect the quality of the indoor environment and

85 consequently human health is still at an early stage, SSA applications are required to investigate the

86 profile of alternative chemicals indoors. Ensuring that purpose, a sampling campaign was designed

87 and, in total 25 individual floor dust samples were collected from homes all over the Flemish region of

88 Belgium during winter and summer season of 2019 (total n=50 paired samples). The main aims were;

89 (i) to generate innovative information linked to the presence of alternative chemicals in residential

90 dust, (ii) to develop an in-house suspect list with alternative chemical groups and suitable workflow of

91 data analysis (iii) to build up prioritization lists of chemicals based on the obtained LoC, the relevant

92 indoor applications, and the calculated theoretical bio-accessibilities.

93 **2. Materials and methods**

94 **2.1 Chemicals and reagents**

95 Organic solvents of LC-grade were used for the analyses. LC-grade ultrapure water (H_2O) was obtained

96 from a PURELAB Flexsystem (18.2 MΩ cm, Milli-Q, Millipore). Methanol (MeOH) was purchased from

97 Fischer Scientific (Loughborough Leics, United Kingdom) (≥99.9%). The solvents of toluene, acetone,

98 dichloromethane (DCM), ethyl acetate (EtAc) were purchased from Merck (Darmstadt, Germany) and

99 n-Hexane (n-Hex) was purchased from Acros Organics (Geel, Belgium). The SPE cartridges (Florisil®

4

100   ENVI 500 mg, 3 mL) were purchased from Supelco (Bellefonte, PA, USA). Centrifugal filters (modified

101   nylon membrane) 0.45 μm pore size were purchased from VWR™ (North America). Eight labeled

102   internal standards (ISs), native standards (Ns) (≥ 98) were used during the development of quality

103   assurance and quality control (QA/QC) actions. Newly identified standards were purchased from

104   AccuStandards (New Heaven, CT, USA), Sigma Aldrich, Chiron AS (Trondheim, Norway) or were custom

105   synthesized (Dr. Vladimir Belov, Max Planck Institute for Biophysical Chemistry, Göttingen, Germany)

106   and were used for structure confirmation (Table S1).

107   **2.2 Dust Collection**

108   Two sampling campaigns were organized with 25 homes located in the Flemish region of Belgium

109   during winter and summer 2019 (Figure S1). The two periods were selected for testing possible

110   seasonal variations in the chemical profile of indoor dust. The different cities/provinces were selected

111   to cover sufficiently the area of Flanders including urban and rural areas, the size of families ranged

112   from 3 to 5 people and the age of the houses and the indoor equipment varied along the cohort for

113   obtaining a better understanding of profiles. Relevant questionnaires were completed by the

114   participants during the sample collections. In total, 50 dust samples were collected during winter (W)

115   (*n=25*; January-March) and summer (S) (*n=25*; June-July). A regular vacuum cleaner equipped with

116   nylon socks (25 μm pore size, Allied Filter Fabrics Ltd, Berkeley Vale, Australia) was employed to collect

117   floor dust from living rooms under a previously applied protocol (Christia et al., 2019). Briefly, 4 m^2

118   bare floor was vacuumed for 4 min or 1 m^2 carpeted surfaces was vacuumed for 1 min. To prevent

119   cross-contamination, one nylon sock was used per each sample, and all involved parts of the cleaner

120   were thoroughly rinsed with ethanol before and after each sampling. Additionally, 3 field blanks

121   (FBLKs) (i.e. pre-cleaned Na_2SO_4; n-Hex washed using ultrasonication for 30 min followed by baking at

122   400°C overnight) were used per each sampling campaign. Briefly, 5 g of the pre-cleaned Na_2SO_4 were

123   sprinkled in aluminum foil and vacuum cleaned following the dust collection protocol. All socks were

124   firmly closed, placed into zip lock plastic bags and transferred to the laboratory. Each sample was

125   sieved using a 500 μm mesh sieve, each FBLK was divided in 2 aliquots (~20 mg) and all samples were

126   stored at room temperature until analysis.

127   **2.3 Extraction and clean up**

128   The sample preparation protocol was based on existing protocol of our laboratory after the necessary

129   modifications (Christia et al., 2019). It is a time and cost effective method (up to 24 samples can be

130   analyzed in parallel) and of relative low consumption of organic solvents. Briefly, dust aliquot of

131   approximately 20 mg was weighted in pre-cleaned glass tubes and spiked with 50 μL of labeled ISs for

132   positive and negative electrospray ionization mode (ESI+, ESI-) in concentrations ranging from 1-10

133   ng/µL (Table S1). The extraction cycle was performed by using 2.5 mL of a prepared mix of *n*-

134   Hex:Acetone (1:1 *v/v*) and 0.5 mL toluene, combined with 1 min vortexing and 5 min of ultrasonication.

135   The extracts were centrifuged at 3000 rpm for 3 min. The supernatants were transferred into pre-

136   cleaned glass tubes. The extraction cycle was repeated one more time and both supernatants were

137   pooled, evaporated near dryness under a gentle nitrogen stream, re-dissolved in 1 mL of *n*-Hex and

138   vortexed for 1 min. Florisil® ENVI cartridges (500 mg, 3 mL) were prewashed with 3 mL of MeOH, 3 mL

139   of EtAC and 3 mL of *n*-Hex. The extract was transferred into the cartridges, which were washed up with

140   8 mL of *n*-Hex: DCM (1:1 *v/v*) and compounds were eluted with 10 mL of EtAc:MeOH (1:1 *v/v*). The

141   elution fraction was evaporated to near dryness under a gentle nitrogen stream. After evaporation,

142   was re-dissolved in 100 µL of MeOH:Water (1:1 *v/v*) and filtered using filters of 0.45 µm in micro-

143   centrifuge at 8000 rpm for 5 min. Then each aliquot was transferred to injection vial for further liquid

144   chromatography combined with quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) analysis.

145   **2.4 LC-QTOF-MS analysis**

146   An Agilent 1290 Infinity UPLC coupled to an Agilent 6530 QTOF (Agilent, Santa Clara, CA, US) was

147   employed for the analysis of the dust extracts. For chromatographic separation, an Alltima HP C18-EPS

148   column (100 mm x 2.1 mm; 3 µm particle size, Grace, Belgium) was applied and the mobile phases of

149   Water with 0.1% *v/v* formic acid (A) and MeOH/Water (80:20 *v/v*) with 0.1% formic acid (B) were used

150   for ESI+. Water with 0.1% *v/v* acetic acid (A) and MeOH/Water (80:20 *v/v*) with 0.1% acetic (B) were

151   used for ESI-. Flow rate was set at 0.4 ml/min in both modes. The injection volume was set at 5 µL and

152   the column temperature at 30 °C. All samples were analyzed in both ESI+ and ESI-. Details of the applied

153   linear gradients are presented in Table S2. The QTOF-MS was operated in 2GHz, extended dynamic

154   range mode. Agilent Jet-Stream electrospray ionization (AJS-ESI) was applied for the ionization of the

155   compounds and the same parameters were applied for ESI+ and ESI-. Briefly, drying gas temperature

156   was set at 300 °C and the flow at 10 mL/min. The sheath gas was set at 350°C and 12 mL/min flow rate.

157   The nebulizer pressure was fixed at 45 psi, and the voltages of capillary, nozzle and fragmentor were

158   set at 3500 V, 500 V, and 120 V respectively. The mode of acquisition was selected in Auto MS/MS

159   operation in which the precursors ions were automatically selected by the software based on the

160   relative abundance. Target MS/MS option was applied only when the compound of interest was not

161   automatically selected for MS/MS spectra generation. By choosing this option, the instrument is able

162   to select specific precursors that will be forced to pass through the quadrupole and produce the

163   MS/MS spectra. The acquired mass range was 80-1100 m/z, the MS scan rate was 4 spectra/sec and

164   the MS/MS scan rate 7 spectra/scan. Two levels of collision-induced dissociations (CID) were used at

165   10 and 30 V. The active exclusion mode was enabled to prevent the repetitive acquisition of MS/MS

166   spectra for the same ion and was set at 0.1 min. The generated data files were stored in centroid mode

167   before exported for further data analysis.

168   **2.5 Quality assurance and quality control**

169   The quality assurance and quality control of the analysis included several steps. The analysis of a total

170   of 6 FBLKs and 6 procedural blanks (BLKs) along with the 50 dust samples (Ds) was applied to control

171   the background contamination. All glassware was pre-cleaned using *n*-Hex and baked at 400°C

172   overnight. To reassure the high quality of the instrumental performance, several steps were applied.

173   The QTOF instrument was automatically recalibrated during analyses by continuously infused into the

174   source the Agilent calibration solution via a calibration delivery system two characteristic ions,

175   121.05058 and 922.0098 for ESI+, 112.9856 and 966.0007 for ESI-, were monitored. Samples were

176   spiked with ISs suitable for both ESI+ and ESI- (Table S1) before the extraction step to estimate the

177   ppm tolerance in terms of the mass accuracy (±5 ppm), the retention time shifting (retention time

178   delta) (±0.2 min) and the isotopic pattern match score (≥85%). These parameters were further used

179   for setting the criteria in the suspect screening analysis- algorithm "Find by Formula" against a

180   database/ library and test the inter batch repeatability of the produced results. A quality control

181   solution (QC) including all ISs was injected multiple times along the sequence and the results were

182   evaluated for the instrument performance on the same analytes. Solvent blanks were applied every

183   6th injection for checking any impurities or additives in MeOH and Water. Both MeOH and water

184   produced reproducible signals of low intensity.

185   **2.6 Data analysis workflow**

186   An *in-house* suspect list was formed called "HECHIER" using Agilent MassHunter Quantitative Library

187   Editor software (version 10.0). Relevant keywords were used for retrieving compounds belonging to

188   the groups of interest such as "*phthalates*", "*phosphates*", "*terephthalates*", "*citrates*", "*trimellitates*",

189   (di-, tri-, tetra-) "*carboxylic acids*", "*adipates*", "azelates" "*sebacates*", (di-) "*benzoates*", "*succinates*",

190   from open access databases (e.g. NORMAN, HBM4EU, PubChem, US EPA dashboard) and international

191   chemical agencies (e.g. ECHA, US EPA, EFSA, ANSES). A list of 2108 compounds was formed including

192   the information of compound names, compound formulas, monoisotopic masses, chemical

193   classifications, CAS numbers, InChIKeys, and canonical smiles (Calafat et al., 2017).

194   A new workflow for data analysis was developed based on a suspect screening approach for both W

195   and S samples analysis (Figure 1). Four sets of data files, two for ESI+, two for ESI-, were generated and

196   used for feature extraction using Agilent MassHunter Qualitative software (version B.07.00). Feature

197   extraction was performed by applying the algorithm "Find by Formula" combined with "HECHIER"

198   suspect list. Alignment and peak selection was done according to criteria of mass tolerance for parent

199 ions at ±10 ppm for ESI+ and ±7 ppm for ESI-, mass tolerance for product ions at ±25ppm for both

200 ionization modes, selected matching score above 75%, and the isotope abundance score set at 80 %

201 between the measured and the predicted one, based on the ISs results as described previously (*2.5*

202 *Quality control and quality assurance*). Mass Profiler Professional Software (version 15.0) was used for

203 statistical analysis. All features below a fold change of 5 against the FBLKs were excluded (ANOVA test

204 for significance of fold change, p<0.05) reducing the number of the features for manual identification.

205 Four final lists of compounds were produced and used for one-by-one tentative identification starting

206 from match of formula and monoisotopic mass (LoC 5) and match scores between the measured

207 isotopic patterns and the theoretical ones predicted by Agilent Isotope Distribution Calculator (version

208 7.0.7024.0) (LoC 4). Further identification was achieved based on the available MS/MS spectra. Product

209 ions that were formed at collision induced dissociation (CID) 10 and 30 V were identified by applying

210 Agilent formula Calculator tool (version 7.0.7024.0) and/or checking compound structures (LoC 3). On-

211 line spectra libraries (Mass Bank of North America, MoNA and m/z cloud) were used to cross check the

212 MS/MS spectra (where available) (LoC 2). The LoCs were provided for each step following Schymanski

213 et al., 2014 methodology.

214 **2.7 Seasonal Variation**

215 To assess the seasonal difference in dust composition for winter and summer, compounds reported as

216 native standards in Table S1, were identified (LoC 1) following the developed workflow. The selected

217 compounds were belonging to the groups of organophosphate flame retardants (PFRs), phthalates

218 (PHs) and alternative plasticizers (APs) which are frequently detected in indoor dust worldwide and

219 thus were expected to be present in Flemish dust (Larsson et al., 2017;EPA Comptox; Shoeib et al.,

220 2012; Dodson et al., 2017;Bu et al., 2019;Abb et al., 2009). Additionally, the availability of analytical

221 standards provided the highest LoC. To enrich the seasonal estimation, we include compounds

222 belonging to five chemical groups: "azelates", "benzoates", "citrates","sebacates" and, "trimellitates",

223 which were identified at LoC 3. Since our SSA developed workflow is qualitative, the detection

224 frequencies and the abundancies of the identified compounds were employed to test disparities

225 between winter and summer (t-test:two sample assuming unequal variances). Regarding the

226 abundance, a response factor was calculated and used based on the following equation:

227 $Abundance\ Response\ Factor\ (x) = \dfrac{\text{Abundance of compound}(x)}{\text{Mean Abundance of DBzP}-d4(x)}$ *(1)*

228 where the abundance of the compound was the instrumental abundance (counts) derived in sample

229 (x) and mean abundance of DBzP-d4 was the mean instrumental abundance of an IS derived from the

230 fortified samples. The selection of DBzP-d4 was due to its higher abundance and to generate

231 abundance response factors based on the same parameter for all the compounds.

232 **2.8 LogK$_{ow}$ and theoretical bio-accessibility**

233 Theoretical bio-accessibility, that refers to the fraction of total amount of a substance that is

234 potentially available for absorption, was estimated in this study based on the LogKow values of the

235 tentative identified compounds. The logK$_{ow}$ values were predicted by EPIWEB software (version 4.1)

236 and theoretical bio-accessibility was calculated based on methodology reported by Dong et al., 2019

237 as described in the following equation:

238 $B_a = a + \dfrac{(b-a)*(8-logKow)}{8-5}$ *(2)*

239 where B$_a$ is the theoretical bio-accessibility when logK$_{ow}$ value is between 5 and 8, a and b are the

240 constants assumed as 0.2 and 0.8 respectively. In case of LogK$_{ow}$<5, B$_a$ assumed to be 0.8 and in case

241 of LogKow > 8, Ba assumed to be 0.2 [25],[17].

242 **3. Results and discussion**

243 **3.1 Quality control and quality assurance results**

244 Mass accuracy was performed by recalibrating the mass axis for every injection by monitoring the 4

245 ions; 121.0508, 922.0098 (ESI+) and 112.9856, 966.0007 (ESI-) Reference mass solution was introduced

246 into the system through the calibrant delivery system during the whole acquisition. ISs were identified

247 with LoC 1 in all fortified samples in terms of mass accuracy, Rt consistency, isotopic match > 90% and

248 identification of fragments (CID 10 & 30V). The results of QC vials for the same ISs were equivalent for

249 mass accuracy, match of isotopic pattern and fragment identification. Total ion chromatograms (TICs)

250 for both cases were reproducible along the instrumental run. The selected compounds were identified

251 at LoC 1 with DF% ranging from 8 to 100% for PFRs, 16 to 92% for PHs and 28 to 88% for APs (Table

252 S1). Background contamination was controlled by the analysis of FBLKs combined with BLKs. Molecular

253 features detected in dust samples were cross checked in FBLKs and BLKs. The majority of them were

254 not detected (n.d.) in blank-type samples. For those who were detected, abundance response factors

255 were calculated and compared with the dust ratios (as *Equation 1*) indicating lower presence compared

256 to dust. The quality of the suggested workflow was assured following exclusion of the false positives

257 and false negatives during Mass Profiler Professional data analysis, and by applying the algorithm "Find

258 by Formula" using specific formulas which were tested for all samples.

259 Twelve features were detected only in FBLKs indicating the dust sampling equipment as a possible

260 source, two compounds were detected only in BLKs indicating low contamination from the laboratory

261 environment and 13 in both types of blank samples. However, the comparison of the abundance

262 response factors between dust samples and both types of blanks, was higher from 4 up to 67 times for

263   the majority of the compounds, indicating stable and reproducible results in in terms of instrumental

264   performance. The fold change (FC) that was applied was ≥5 (Table S5).

265   **3.2 Flemish indoor dust profile**

266   Two lists of the identified compounds in Flemish dust are reported in Tables S3 and S4. In total, 44 and

267   12 compounds were identified for ESI+ and ESI-, respectively. Information of identifiers (Name,

268   Formula, ICHI Key, Canonical Smiles), sampling season, detection frequency in dust samples (DF%),

269   LoC, chemical category, relevant exposure sources, estimated $logK_{ow}$, and theoretical B_a are provided

270   in both tables. The compounds were prioritized based on their LoC ≥3 due to MS/MS spectra

271   availability and product ion confirmation. Additionally, DF% in dust samples were reported but no

272   threshold was set for this parameter. The possible exposure sources and theoretical Ba were taken

273   into consideration for the final selection of standards purchased for the final confirmation. In the ESI+

274   list, 9% of the compounds were identified at LoC 2 after the successful match of their MS/MS spectra

275   with the equivalent ones of the online libraries of MoNA and mzCloud. The rest of the compounds

276   reached only LoC 3 due to lack of available online spectra. In the ESI- list, all identified compounds

277   reached LoC 3 and were classified by chemical groups for comprehension of the new substitutes. The

278   group of (di-) carboxylic acids was the dominant family for both ionization modes, followed by

279   phthalates for ESI+ and phosphates for the ESI-. In ESI+, a larger diversity of chemical groups was

280   noticed than ESI-, including citrates, terephthalates, acrylates, hexanoid, cinnamic and salicylic acids,

281   benzoates, and sebacates. This might indicate ESI+ as a suitable ionization mode for these chemicals.

282   On the other hand, the group of butoxides were identified only in ESI- (Figure 2). The indoor sources

283   possibly responsible for the presence of these chemicals were included in priority lists, aiming to a

284   better understanding of the home environment. Main applications were additives in food packaging

285   materials and children toys, food flavors or food residues, additives in personal care products (PCPs),

286   emulsifiers, plasticizers, lubricants, adhesives and sealants, UV filters, flame retardants, emollients,

287   paints, heat stabilizers, fragrances, automotive, and pet care products. It is evident that all reported

288   applications can be directly related with goods and materials that are used indoors. The wide range of

289   applications and the multiple functionality of many listed compounds complicate the relation of

290   compound-specific indoor source.

291   The next introduced parameter was the theoretical bio-accessibility (B_a) and was taken into

292   consideration for the final selection of compounds used in standard confirmation (LoC 1). Based on

293    $logK_{ow}$ (see Section 2.7), a theoretical Ba ≥0.8 was calculated for a considerable number of the listed

294   suggesting a potential risk increase of human intake (Dong et al., 2019). In the ESI+ list, 53% of the

295   compounds could be considered as major contributors to human exposure, as their estimated Ba was

296 > 0.8. Lower percentages of 17% and 23% were calculated for compounds with Ba ranging between
297 0.8 to 0.2 and < 0.2, respectively. The latter indicate that these compounds are less likely to contribute
298 to human exposure (Figure 3). In the ESI- list, 67% of the compounds could be considered as higher
299 contributors with Ba > 0.8, 16% as medium contributors with Ba between 0.8 and 0.2, and 17% as
300 lower contributors to human exposure with Ba < 0.2. However, our approach is theoretical and not
301 experimental based. The bio-accessible fraction of a chemical is a complex factor which requires a
302 particular study setup focused on *in vitro* digestion models by using synthetic bio-fluids (Collins et al.,
303 2015).

304 **3.3 Newly identified compounds in Flemish dust**

305 Seven compounds belonging to different chemical groups and applications related to indoor
306 environment, were selected based on their LoC (≥3) and DF% were reported for Ds. Analytical
307 standards were used in order to confirm a LoC 1 (Table 1). The theoretical Ba of the compounds and
308 the availability of the analytical standards was considered for the selection. Individual solutions of the
309 analytical standards of tributyl trimellitate (TBTM), bis (3,5,5-trimethylhexyl) phosphate (Bis-3,5,5-
310 TMHPh), isooctyl 2-phenoxy ethyl terephthalate (IOPhET), dimethyl azelate (DMA), dimethyl sebacate
311 (DMS), dipropylene glycol dibenzoate (DiPGDB) and 3,4-di-tert-butyl-4-hydroxy benzaldeyde (BHT-
312 CHO) at concentration level 5 ng/μL (in MeOH) were analyzed by LC-QTOF-MS to generate MS/MS
313 spectra. Figure S2 (a) to (g) presents the MS/MS spectra in CID 10 and 30 V together with the structures
314 of the precursor and the product ions. The confirmed structure was achieved by matching the MS/MS
315 spectra of the chemical in the analytical standard and the dust sample. Retention times were
316 confirmed, the mass accuracy was <5 ppm, match of isotopic patterns were > 90%, and characteristic
317 products ions for both levels of CID were confirmed (Table 1).

318 TBTM is a trimellitate that is usually found in market with the commercial name Morflex[TM] 540 or
319 DIPLAST TM 4 (PubChem, ECHA). It is used as a plasticizer and additive in adhesives, printing inks, nail
320 coatings or nail coating removers (CompTox Chemical Dashboard; EPA; Pubchem). The DF was
321 calculated at 8% and 24% for W and S samples respectively. Bis-3,5,5-TMHPh is a diester phosphate
322 with DF 32% in W samples and 8% in S samples. It is applied as a chemical blowing agent for
323 polyurethane foams (Pubchem). The term "blowing agent" is referred to chemicals which have the
324 ability to produce a cellular structure through a foaming process, during hardening or phase transitions
325 processes of materials such as polymers, plastics, and metals.

326 IOPhET is the next chemical from the group of terephthalates that was structurally confirmed. It is an
327 additive in adhesives and was detected in 52% and 4% between seasons.

DMA, classified in the group of azelates, was found in dust samples with DF 28% and 56% in W and S and it is used as an additive in food packaging materials. It can also be present in pesticide mixtures as an active ingredient (CompTox Chemical Dashboard, EPA; Pubchem).

DMS is a sebacate applied as additive in paints, adhesives, fillers, and pesticides. Its DF in dust was 12% and 20% for W and S seasons, respectively.

DiPGDB is a classified benzoate that it is commercially known as Finsolv® PG-22, VELSIFLEX® 328, or Velsiflex 342 (PubChem, ECHA). It showed rather ubiquitous presence in dust with DFs of 40% and 48% for both seasons. Main applications are considered adhesives, building construction materials, paints and personal care products. Additionally, it can be used for the manufacture of furnishing equipment (CompTox Chemical Dashboard, EPA; Pubchem).

Finally, BHT-CHO, detected in ESI-, belongs to the chemical group of aldehydes. The dust DF was 8% and 28% for the two seasons. It is an additive in toys and drug products, or it is related with the manufacture of the drugs (CompTox Chemical Dashboard).

In literature, there is scarce toxicological information regarding these compounds with the majority of them to be derived by toxicological prediction models. Only for TBTM, *in vivo* studies in rats and rabbits are reported by ECHA, but no adverse effects were observed to these animals. All available information is reported in Table S6. Nevertheless, there is a lack of *in vivo* studies testing the carcinogenicity and endocrine disrupting behavior of the newly identified chemicals.

3.4 Seasonal variation in Flemish dust

Analytical standards were used to investigate seasonal differences of indoor dust profile between winter and summer where the temperatures and the type/frequency of ventilation varied. Since results are qualitative, calculated abundance response factors (*equation 1*) were compared (Figure 4, Table 2). The 5th, median and 95th percentiles were calculated for 15 compounds for W and S. The order of dominant compounds in winter according to their calculated mean abundance response factors was DEHP/DEHT (isomers) (2.28) > DIBP/DNBP (0.92) > DIDP = DINP = DINCH (0.86) > TBOEP (0.72) > ATBC (0.63) > BBP (0.30) > THTM (0.23) > TCIPP (0.21) > TIBP/TNBP (0.13) > DMP (0.11) > TEHP (0.09) > DEP (0.08) > TPHP (0.03) > TDCIPP (0.01). The order for summer was DIBP/DNBP (1.67) > DEHP/DEHT (1.06) > DINCH (0.86) > ATBC (0.79) > TBOEP (0.73) > DMP (0.63) > BBP (0.60) > THTM (0.45) > TCIPP (0.43) > DINP (0.42) > TIBP/TNBP (0.40) > DEP (0.38) > TEHP (0.15) > TPHP (0.11) > TDCIPP (0.13), respectively. Mean abundance ratios of TPHP, TCIPP, DMP and DEP were significantly higher in samples which were collected during S (p<0.05). That might indicate that elevated temperatures of the season combined with relatively higher vapor pressures of the compounds may enhance their migration from materials

360 to the indoor environment (Table 1). Only DINP showed higher abundance ratio during W compared

361 to S (p<0.05). For the rest of the compounds, no significant difference was observed between the two

362 seasons (p>0.05).

363 Ten compounds belonging to chemical families of azelates (*n=1*), benzoates (*n=1*), citrates (*n=3*),

364 sebacates (*n=3*), terephthalates (*n=1*) and trimellitates (*n=1*) and which were identified at LoC 3, were

365 used for season comparison (Figure 5, Table 2). The order of dominant compounds for the W season

366 was 2,3-bis(acetyloxy)propyl 2-methyl tetradecanoate (0.97) > 2-hydroxyethyl 3-hydroxypropyl

367 benzene-1,4-dicarboxylate (0.80) > trihexyl trimellitate (0.41) > 11-oxoundecyl benzoate= dimethyl

368 azelate (0.23) > 3-[(2-ethylhexyl)oxy]-2-hydroxypropyl 2,2-dimethyl octanoate (0.21) > diethyl 2-(1-

369 hydroxybutyl)propanedioate (0.19) > diethyl decanedioate (0.17) > dimethyl decanedioate (0.15) >

370 diethyl undecanedioate (0.08). The order for the S season was dimethyl azelate (0.47) > dimethyl

371 decanedioate (0.40) > diethyl 2-(1-hydroxybutyl) propanedioate = diethyl undecanedioate (0.30) >

372 diethyl decanedioate = 3-[(2-ethylhexyl)oxy]-2-hydroxypropyl 2,2-dimethyl octanoate (0.20) > 2-

373 hydroxyethyl 3-hydroxypropyl benzene-1,4-dicarboxylate (0.17) > 11-oxoundecyl benzoate (0.14) > tri-

374 hexyl-trimellitate (0.11). Statistical season variations were proved only for 2 of the 10 reported

375 compounds. 11-oxoundecyl benzoate found to be higher in W samples whereas diethyl decanedioate

376 found to be higher in S season, according to their abundance response factors (p<0.05). This could be

377 attributed to the difference in the vapor pressures as explained previously for the analytical standards.

378 For the rest of the compounds, there was no seasonal statistical difference (p>0.05).

379 Dimethyl azelate was presented in 28% of W and in 56% of the S samples. 11-oxoundecyl benzoate

380 ($C_{18}H_{26}O_3$) belongs to chemical group of benzoates and was detected in 64% of winter samples and

381 36% of the summer ones. For the group of citrates, three compounds were identified; 2,3-bis

382 (acetyloxy) propyl 2-methyl tetradecanoate ($C_{22}H_{40}O_6$) in 40% only in W samples, 3-[(2-ethylhexyl)oxy]-

383 2-hydroxypropyl 2,2-dimethyl octanoate ($C_{21}H_{42}O_4$) in 72% and 80% in winter and S samples

384 respectively and diethyl 2-(1-hydroxybutyl) propanedioate ($C_{11}H_{20}O_5$) in 24% and 32% in W and S

385 samples. No further information regarding their applications was available up to our knowledge. Three

386 compounds were identified for the group of sebacates; diethyl sebacate ($C_{14}H_{26}O_4$) in 16% W and 20%

387 S, dimethyl sebacate ($C_{12}H_{22}O_4$) in 12% of W and 20% of S samples and diethyl undecanedioate

388 ($C_{15}H_{28}O_4$) in 16% of W and 20% of S samples. Relevant information for the application was available

389 only for diethyl sebacate which is reported as a side ingredient of drug products and dimethyl sebacate,

390 which is classified as additive in paints, pesticides, fillers and adhesives (CompTox Chemical Dashboard,

391 EPA, PubChem). 2-Hydroxyethyl 3-hydroxypropyl benzene-1,4-dicarboxylate ($C_{13}H_{16}O_6$) and trihexyl

392 trimellitate ($C_{27}H_{42}O_6$) from the chemical groups of terephthalates and trimellitates respectively were

393 found in dust in 4% W and 32% S and 8% W & S samples. No further information was found regarding

394 their uses.

3.5. Limitations

396 An important limitation is the lack of information in on-line libraries preventing the achievement of

397 LoCs 3 and 2, along with the low availability of commercial analytical standards which prompts to costly

398 and time consuming solution of the custom synthesis. The lack of fragmentation (MS/MS spectra

399 generation) is an ambiguous characteristic of suspect screening analyses, which can be solved by

400 applying target MS/MS analytical mode, but in the same time cannot guarantee the accurate results

401 and requires time for sample batch re-analysis.

402

4. Conclusions

404 A suspect screening analysis workflow was developed and applied successfully in indoor dust with

405 regards to efficiency, repeatability, acceptable control of background contamination and appropriate

406 elimination of false positives/negatives. The available generated lists of compound prioritization

407 indicate the new profile of indoor dust in the Flemish area of Belgium and are useful for identification

408 of emerging contaminants. The application of the lists can be relevant to other matrices of interest (eg.

409 environmental matrices). An important outcome of our study is the reporting of seven new compounds

410 which up to our knowledge, have not been previously reported in dust. These compounds, TBTM, Bis-

411 3,5,5-TMHPh, IOPhET, DMA, DMS, DiPGDB, and BHT-CHO, have relevant applications in domestic

412 products or materials, thus would be of high importance their further investigation in indoor

413 environments. The season appeared to influence the indoor chemical profile of some compounds.

414 Compounds with higher vapor pressure values showed higher abundance ratios during summer,

415 supporting the hypothesis that higher temperatures favored their increased migration from products

416 to the indoor environment and dust.

Conflicts of interest

418 The authors declare that they have no conflict of interest.

423

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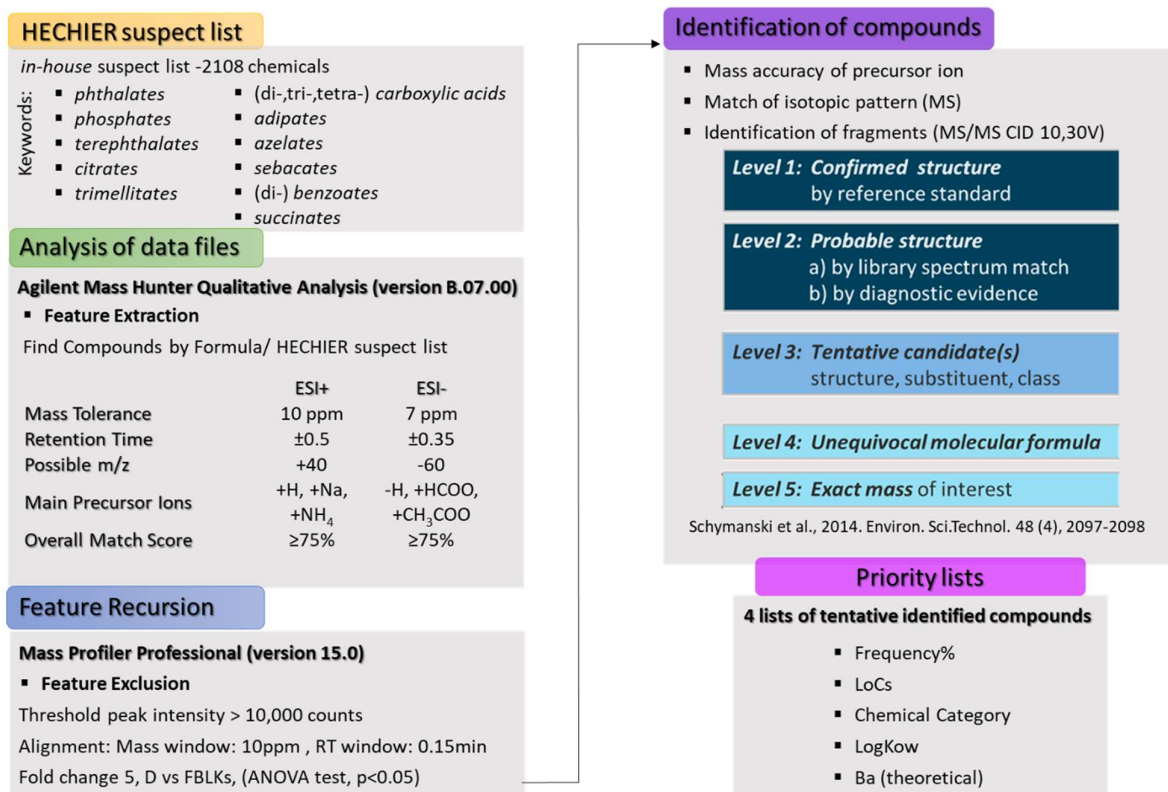540   Composition variations and implications for human exposure. Environ. Int. 78, 1–7.

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542

HECHIER suspect list

in-house suspect list -2108 chemicals

Keywords:
- *phthalates*
- *phosphates*
- *terephthalates*
- *citrates*
- *trimellitates*
- (di-,tri-,tetra-) *carboxylic acids*
- *adipates*
- *azelates*
- *sebacates*
- (di-) *benzoates*
- *succinates*

Analysis of data files

Agilent Mass Hunter Qualitative Analysis (version B.07.00)
- **Feature Extraction**

Find Compounds by Formula/ HECHIER suspect list

	ESI+	ESI-
Mass Tolerance	10 ppm	7 ppm
Retention Time	±0.5	±0.35
Possible m/z	+40	-60
Main Precursor Ions	+H, +Na, +NH$_4$	-H, +HCOO, +CH$_3$COO
Overall Match Score	≥75%	≥75%

Feature Recursion

Mass Profiler Professional (version 15.0)
- **Feature Exclusion**

Threshold peak intensity > 10,000 counts

Alignment: Mass window: 10ppm , RT window: 0.15min

Fold change 5, D vs FBLKs, (ANOVA test, p<0.05)

Identification of compounds
- Mass accuracy of precursor ion
- Match of isotopic pattern (MS)
- Identification of fragments (MS/MS CID 10,30V)

Level 1: Confirmed structure by reference standard

Level 2: Probable structure
a) by library spectrum match
b) by diagnostic evidence

Level 3: Tentative candidate(s) structure, substituent, class

Level 4: Unequivocal molecular formula

Level 5: Exact mass of interest

Schymanski et al., 2014. Environ. Sci.Technol. 48 (4), 2097-2098

Priority lists

4 lists of tentative identified compounds
- Frequency%
- LoCs
- Chemical Category
- LogKow
- Ba (theoretical)

543

544 **Figure 1.** Workflow of the data analysis. Possible m/z; parameter of the expansion of values for chromatogram
545 extraction. The values were set based on the predicted adducts. ESI; electrospray ionization, RT; retention time,
546 D; dust samples, FBLKs; field blanks, CID; collision-induced dissociation, LoC; level of confidence, LogKow;
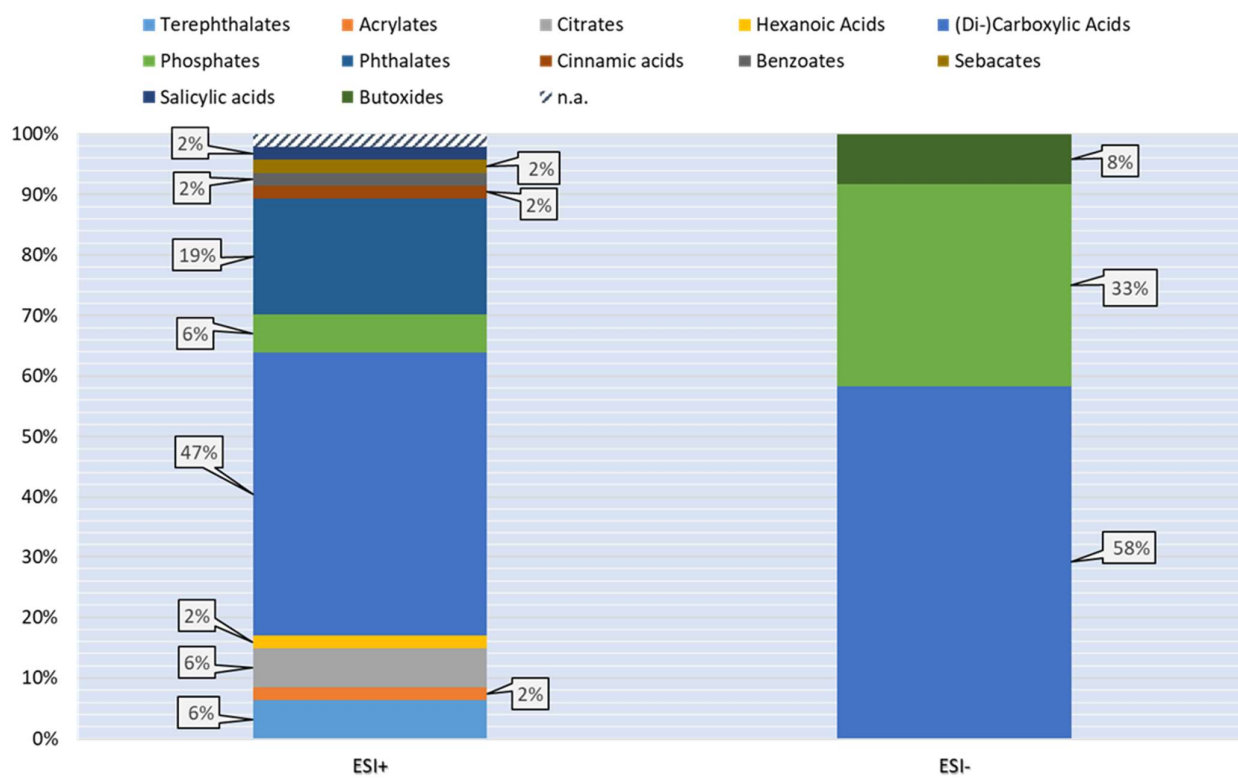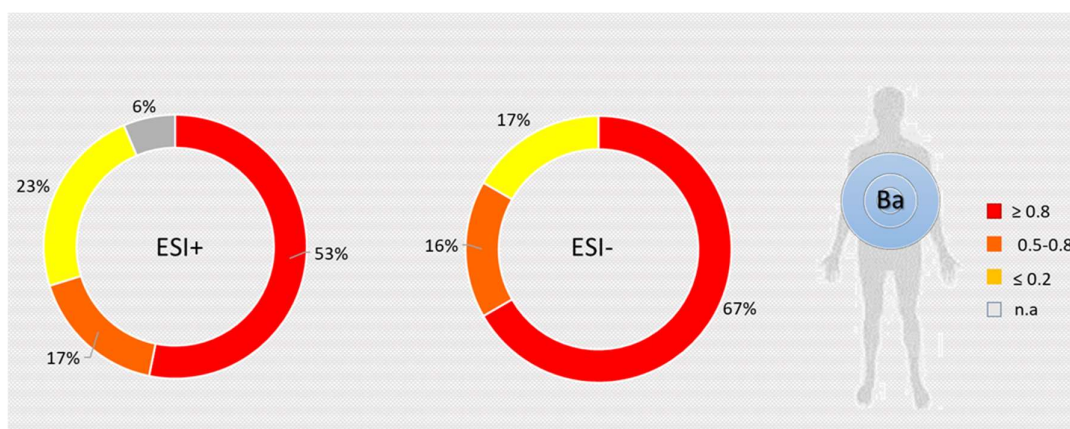547 logarithmic octanol-water partition coefficient, Ba; bioaccessibility.

548

549
550   **Figure 2.** Main chemical groups in priority lists for ESI+ and ESI-.

551

552

553

554 **Figure 3.** Theoretical bio-accessibility (Ba) and compound classification in priority lists.

| Name	Abbrev.	Trade name	Formula	±	RT	Exact mass	m/z	Adduct	(ppm)	%	CID 10V	CID 30V				Applications
...tyl ...llitate (...-23-4)	TBTM	DIPLAST TM 4, Morflex TM 540	$C_{21}H_{30}O_6$	+	18.7	378.2041	379.2116	[M-H]+	-0.13	99.95	305.135, 249.074, 193.012, 57.070	249.0742, 193.0124, 57.0704	8/24	5.92	0.61	Plasticizer, additive in adhesives or printing inks, nail coatings, nail coatings removers
...5,5-...thylhexyl) ...phate (...-98-2)	Bis-3,5,5-TMHPh	n.a.	$C_{18}H_{39}PO_4$	+	14.8	350.2585	351.2623	[M-H]+	0.52	94.08	98.9839, 71.0856, 57.0699	98.9833, 71.0850, 57.0698	32/8	6.8	0.44	Chemical blowing agent in polyurethane foams
...tyl 2-...oxy ethyl ...nthalate (...2-75-5)	IOPhET	n.a.	$C_{24}H_{30}O_5$	+	18.6	398.2094	399.21161	[M-H]+	1.19	95.23	305.1750, 261.1468, 149.0205	305.1778, 261.1507, 149.0255, 121.0288, 65.0414	52/4	6.76	0.44	Additive in adhesives
...thyl ...te (...-10-1)	DMA	n.a.	$C_{11}H_{20}O_4$	+	12.2	216.1361	217.1436	[M-H]+	-0.2	99.73	125.0950, 97.1005, 83.0860, 55.0545	55.0546, 125.0927	28/56	2.86	0.8	Additive in materials of food packaging, active ingredient in pesticide products
...thyl ...te (...79-6)	DMS	n.a.	$C_{12}H_{22}O_4$	+	13.8	230.1518	231.1596	[M-H]+	-2.29	99.95	199.1334, 171.1365, 139.1114, 69.0705, 55.0502	69.0703, 55.0547	12/20	3.35	0.8	Additive in paints, fillers, adhesives, pesticides and ingredient used in automotive industry
...pylene ...zoate (...8-31-4)	DiPGDB	VELSIFLEX® 328, Velsiflex 342, Finsolv® PG-22	$C_{20}H_{22}O_5$	+	14.9	342.1467	343.1544	[M-H]+	-1.26	99.88	163.0755, 105.0338, 77.0395	163.0753, 105.0340, 77.0393	40/48	3.9	0.8	Additive in adhesives, building construction materials, paints, manufacture of furniture, personal care products
...i-tert-...4-hydroxy ...ldehyde (...-98-0)	BHT-CHO	n.a.	$C_{15}H_{22}O_2$	-	14.3	234.162	233.1547	[M-H]-	-1.25	99.8	217.1226, 59.0147	217.1221, 59.0147, 133.0656	8/28	4.2	0.8	Additive chemical in toys, drug product or related with the manufacturing of drugs
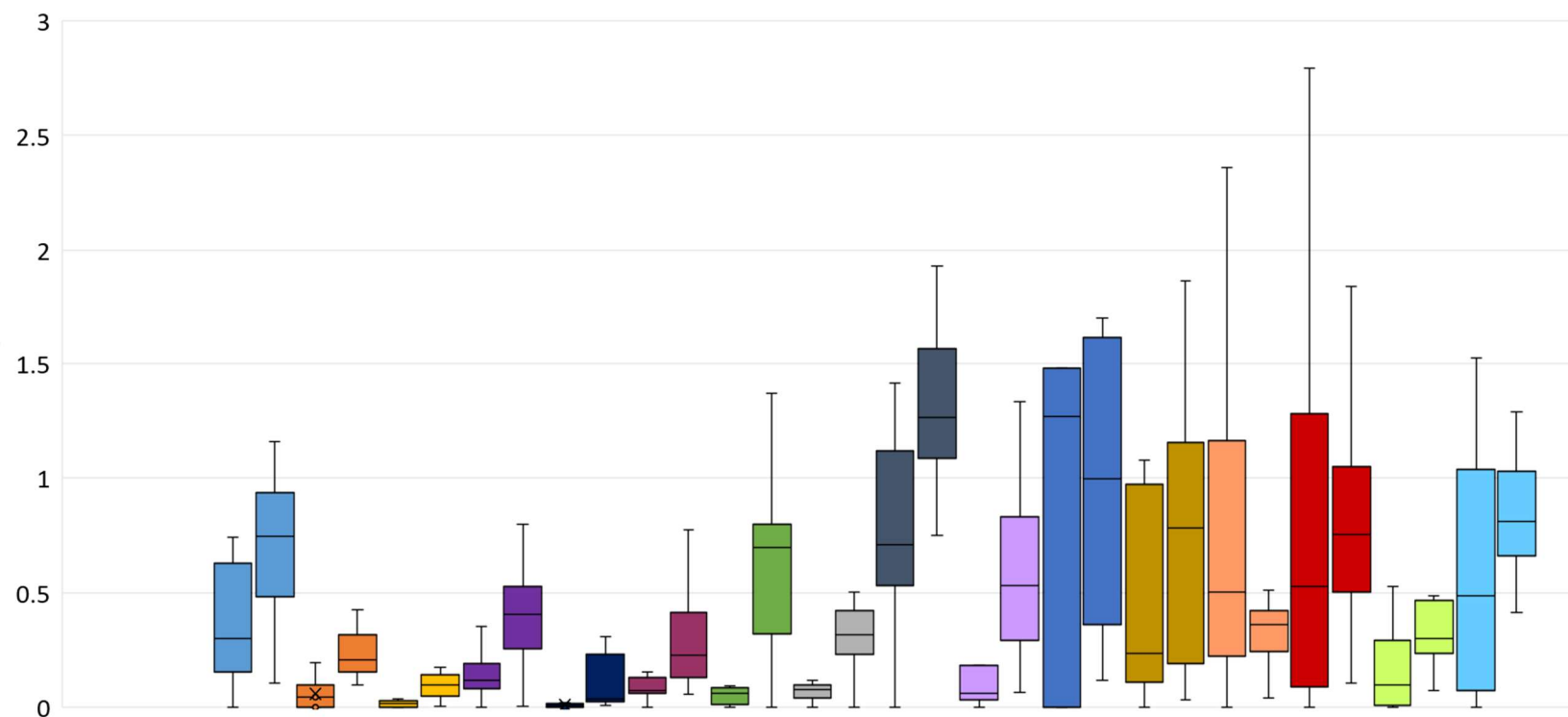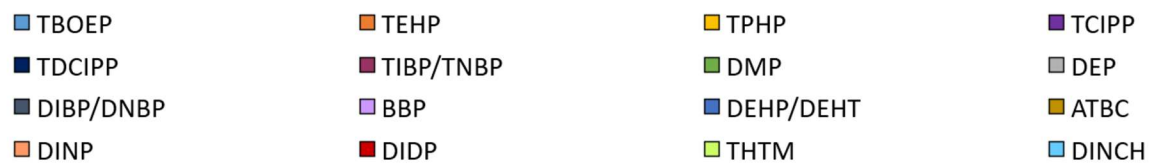
Figure 4. Abundance ratios of 15 native compounds identified in dust at LoC 1 (color-coupled error bars winter/summer).
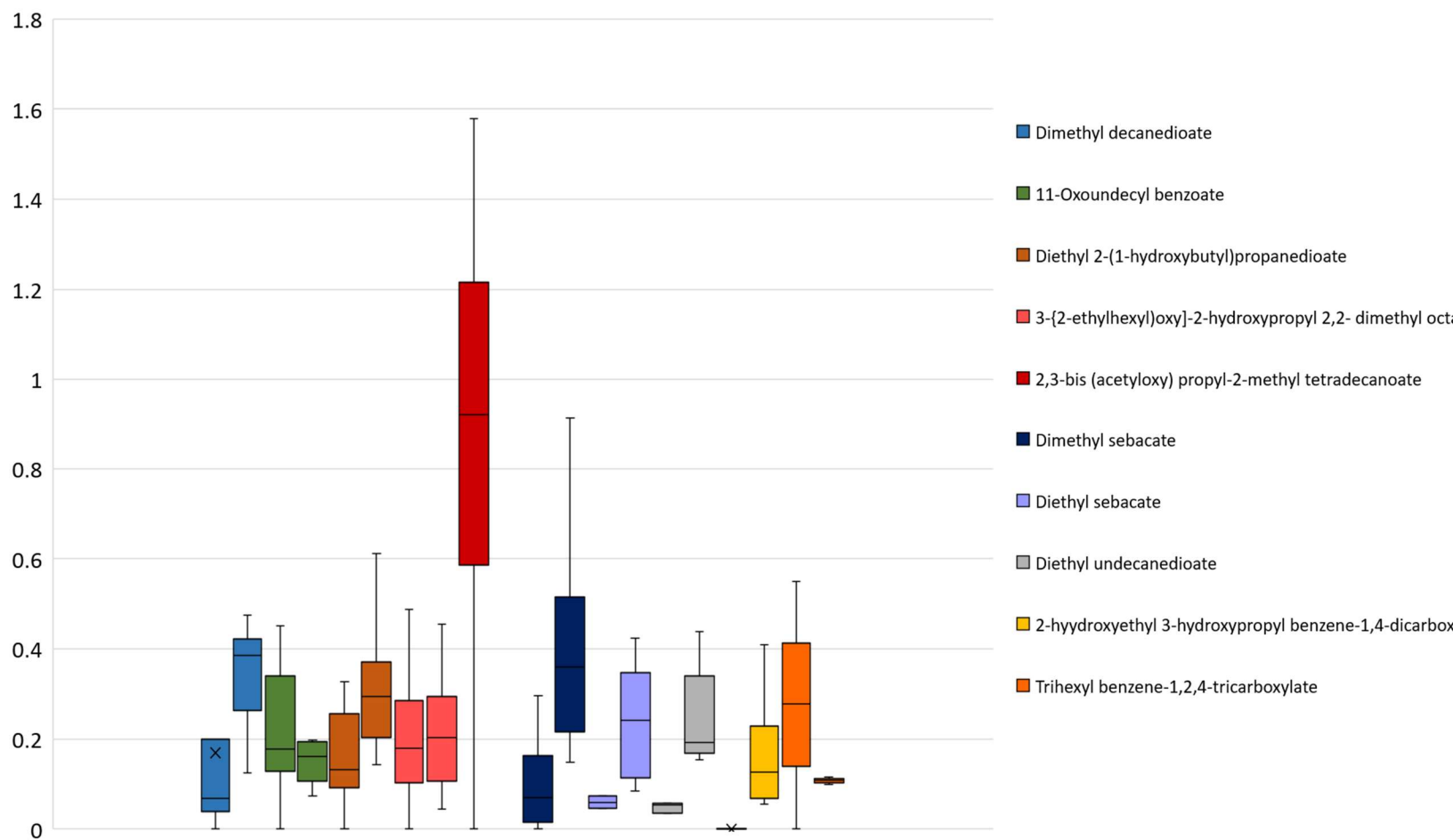
Figure 5. Abundance ratios of 10 alternative compounds identified in dust at LoC 3 (color-coupled error bars winter/summer).

e 2. Comparison of representative compounds between winter and summer season.

| | | Winter | | | | Summer | | | | |
| | | | | | | | | | t-test (p-value)) | Vapor Pressure (mmHg) |
mpound	DF %	Mean Abundance Response Factor	5th perc.	95th perc.	DF%	Mean Abundance Response Factor	5th perc.	95th perc.		
Rs										
DEP	84	0.72	0.11	2.7	80	0.73	0.16	1.7	0.960	5.51E-06
IP	16	0.09	0.04	0.18	8	0.15	0.10	0.20	0.426	8.25 E-08
P	8	0.03	0.03	0.03	32	0.11	0.04	0.17	0.002	2.39E-05
PP	96	0.21	0.03	0.64	100	0.43	0.13	0.92	0.003	4.44E-03
IPP	12	0.01	0.01	0.02	20	0.08	0.01	0.25	0.295	2.60E-05
BP/TIBP	60	0.13	0.05	0.37	32	0.40	0.13	0.94	0.055	1.13E-03
& APs										
P	16	0.11	0.05	0.20	92	0.63	0.21	0.95	6.07E-07	3.08 E-03
P	60	0.08	0.03	0.12	88	0.38	0.17	1.0	6.51E-06	2.10E-03
P/DNBP	64	0.92	0.32	1.7	72	1.7	0.83	2.8	0.06	2.23E-05
	44	0.30	0.02	1.1	88	0.60	0.15	1.1	0.06	8.25E-06
HP/DEHT	12	2.28	1.3	3.8	28	1.1	0.19	1.7	0.33	1.42E-07
C	48	0.63	0.08	1.7	44	0.79	0.07	1.8	0.59	7.97E-07
P	76	0.86	0.17	2.1	56	0.42	0.09	0.96	0.04	5.40E-07
P	100	0.86	0.06	2.6	88	0.80	0.36	1.3	0.77	5.28E-07
TM	28	0.23	0.01	0.47	40	0.45	0.21	0.97	0.07	2.57E-08
CH	80	0.86	0.05	2.8	72	0.83	0.46	1.2	0.92	1.85E-07