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Exploring the hidden chemical landscape : non-target and suspect screening analysis for investigating solid waste-associated environments

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1 **EXPLORING THE HIDDEN CHEMICAL LANDSCAPE: NON-TARGET AND SUSPECT**
2 **SCREENING ANALYSIS FOR INVESTIGATING SOLID WASTE-ASSOCIATED**
3 **ENVIRONMENTS**

4
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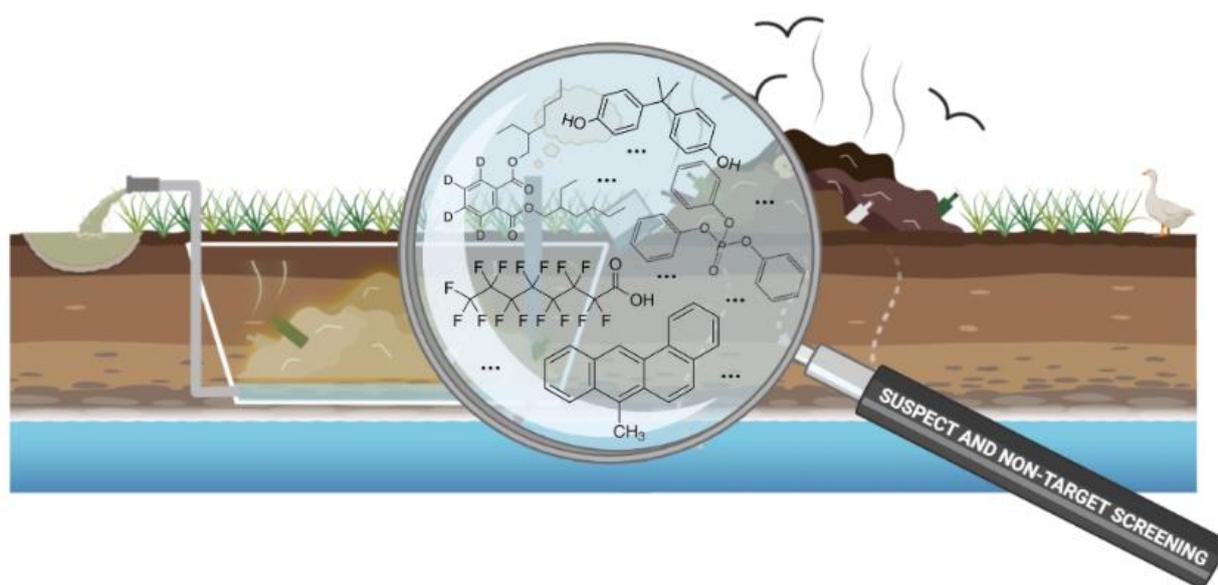
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19 **Abstract**

20 Solid waste is an inevitable consequence of urbanization. It can be safely managed in municipal
21 landfills and processing plants for volume reduction or material reuse, including organic solid waste.
22 However, solid waste can also be discarded in (un-)authorized dumping sites or inadvertently
23 released into the environment. Legacy and emerging contaminants have the potential to leach from
24 solid waste, making it a significant pathway to the environment. Non-target screening (NTS) and
25 suspect screening analysis (SSA) have become helpful tools in environmental science for the
26 simultaneous analysis of a wide range of chemical compounds. However, the application of these
27 analytical approaches to environmental samples related to Raw or Processed Solid Waste (RPSW)
28 has been largely neglected so far. This perspective review examines the potential and policy
29 relevance of NTS and SSA applied to waste-related samples (liquid, gaseous and solid). It addresses
30 the hurdles associated with the chemical safety of solid waste accumulation, processing, and reuse,
31 and the need for landfill traceability, as well as effectiveness of leachate treatments. We reviewed
32 the current applications of NTS and SSA to environmental samples of RPSW, as well as the potential
33 adaptation of NTS and SSA techniques from related fields, such as oilfield and metabolomics, to the
34 solid waste domain. Despite the ongoing technical challenges, this review highlights the significant
35 potential for the implementation of NTS and SSA approaches in solid waste management and related
36 scientific fields and provides support and guidance to the regulatory authorities.

37

38 **Graphical Abstract:**



39

40 **Keywords:** solid waste, non-target screening, suspect screening, high-resolution mass
41 spectrometry, landfill, dumping site

42

43 **1 Introduction**

44 The public and environmental health of a society depends on proper waste management. Solid
45 waste is defined as any material that was discarded by abandonment, is inherently waste-like, is
46 subjected to certain types of recycling, or is a discarded military munition. Thus, solid waste includes
47 various types of waste, such as garbage, refuse, sludge from a wastewater treatment plant or water
48 supply treatment plant, or air-pollution control residues and other discarded material. These
49 materials originate from many sources, including industrial processes, commercial activities, mining,
50 agricultural practices, and municipal activities (“Criteria for the Definition of Solid Waste and Solid and
51 Hazardous Waste Exclusions,” n.d.; “Harmful Substances and Hazardous Waste - United Nations Environment
52 Programme | UNEP - UN Environment Programme,” n.d.). It can encompass substances in liquid, semi-
53 solid or even partly gaseous physical form that are left behind as byproducts or remnants. Materials
54 classified as solid waste are subjected to regulations due to their potential negative impact on the
55 different environmental compartments, specifically on the biosphere and human health (“Criteria for
56 the Definition of Solid Waste and Solid and Hazardous Waste Exclusions,” n.d.). Consequently, the
57 management of solid waste is crucial to mitigate these potential adverse effects on the environment
58 and human health. Properly conducted municipal landfills and processing facilities play a vital role
59 in the safe management of solid waste and might include classification and grinding, recycling,
60 incineration and decomposition of organic solid waste. However, it is well known that solid waste can
61 also be discarded in (un-)authorized dumping sites or be unintentionally spread in the environment.
62 Either way, solid waste provides a potential pathway for legacy and emerging contaminants to enter
63 the environment and produces a stressful pressure on it (Beretsou et al., 2016; Blazy et al., 2014;
64 Mairinger et al., 2021; Pastore et al., 2018; Schollée et al., 2016). Chemicals of emerging concern
65 (CECs) are a diverse group of chemical compounds that are currently not subjected to regulation or
66 legislation (Ccanccapa-Cartagena et al., 2019; Gulde et al., 2021; Mairinger et al., 2021; Seiwert et
67 al., 2020). The CECs end up in landfills mainly due to disposed municipal solid wastes containing
68 everyday by-products, including plastic containers, and packaging materials, pharmaceuticals, food
69 wastes, textiles, wood and by-woods goods among others. Thus, a wide variety of emerging
70 contaminants such as per- and polyfluoroalkyl substances (PFAS) (Liu et al., 2022) , flame retardants
71 (Sibiya et al., 2019), pharmaceuticals (Preiss et al., 2012), cosmetics and other contaminants (Ruiz-
72 Delgado et al., 2020) with harmful effects have been detected in landfill leachates. Additionally, it is
73 worth mentioning that CECs discharged into the environment undergo biotic and abiotic
74 transformation resulting in transformation products (TPs) that might be more persistent and/or toxic
75 than their parent compounds and may be present at relatively higher concentrations (Ruiz-Delgado
76 et al., 2020). Thus, there is a global concern among scientists and policymakers, particularly
77 regarding CECs that might leach, or be released from Raw and Processed Solid Waste (RPSW) into

78 the surrounding environment affecting the biosphere as well as into the derived new products (Luo
79 et al., 2023).

80 Although ecosystem structures are flexible within homeostatic intervals, the impacted sites face
81 reversible and/or irreversible alteration leading to sub-regionals ecosystems with biogeochemical
82 structural dynamics (Bashkin, 2006). This change leads to several issues, including negative effects
83 on the health of humans and ecosystems. Therefore, it is necessary to develop effective landfill
84 characterization and treatment processes to protect the environment to know about the presence of
85 CECs and identify new ones to evaluate potential changes and risks to the ecosystem and human
86 health (Auger et al., 1998; Bashkin, 2006). In this sense, various technologies for landfill leachate,
87 including conventional physicochemical and biological processes, have been applied before its final
88 discharge into aquatic environment (Laor et al., 2011; Ruiz-Delgado et al., 2020). Additionally, it is
89 worth considering that solid waste can get into the circular economy loop, which is a desirable
90 process; however, it also requires characterization and control for safe management. Organic
91 residues can be reused form enriching and fertilizing the crop soil (Bugsel et al., 2022; Bugsel and
92 Zwiener, 2020) or sludge from landfills can be used as energy or heat for partially replacing the
93 heating resource (Unuofin, 2020). On the other hand, solid waste and debris can be incinerated for
94 reducing its volume and harmfulness, as well as, (partially)replace fuels (Li et al., 2022). Among the
95 predominant CECs found in environmental matrices associated with RPSW, volatile organic
96 compounds (VOCs) (Blazy et al., 2014; Hilaire et al., 2017; Laor et al., 2011) pharmaceuticals,
97 cosmetics, flame retardants and plasticizers, pesticides (Jernberg et al., 2013; Ruiz-Delgado et al.,
98 2020) per- and poly-fluoroalkyl substances (PFAS) (Bugsel et al., 2022; Koelmel et al., 2020) and
99 their degradation products have been reported. Additionally, due to the continuous innovation in the
100 chemical synthesis field, it keeps adding new chemicals to the already broad list of compounds that
101 could be of concern or of interest. Thus, the interest in tracking CEC without full knowledge of identity
102 to identify sources of contamination (Pastore et al., 2018) or understand degradation processes (Qiu
103 et al., 2020) keeps growing among scientist and policymakers. Most of these compounds are now
104 regulated, and targeted (or quantitative) analysis is required to evaluate compliance with the
105 established regulatory limits. The targeted analysis focuses on a selective and sensitive
106 determination of a predefined set of chemicals. However, the exhaustive sample preparation
107 protocols and the analytical instrumentation used can lead to a potential bias in the analysis (due to
108 pre-selection) and disregard other hazardous substances that can also occur at significant
109 concentration levels in the samples (Gago-Ferrero et al., 2016). To address these analytical issues,
110 there is a growing trend to analyse matrices associated with RPSW beyond pre-selected targeted
111 compounds by using non-target screening (NTS) and/or suspect screening analysis (SSA).

112 The term SSA refers to analytical methods in which observed but unknown features, typically defined
113 by accurate mass, retention time, and mass spectrum obtained from high-resolution mass

114 spectrometry (HRMS) are compared against a database of chemical suspects (Schymanski et al.,
115 2014). The goal of SSA is to identify potential matches or hits, of molecular formulas, chemical
116 structures, or fingerprints that are consistent with the observed features (Ccanccapa-Cartagena et
117 al., 2019; Ibáñez et al., 2014). However, when applying SSA, many potentially hazardous
118 substances are overseen; hence target screening of few preselected substances cannot provide a
119 comprehensive overview of the chemical pollution.

120 On the other hand, NTS is used for the identification of new compounds, without a priori, based on
121 features selection and components prioritization. The structure elucidation with a high confidence
122 level of unknown compounds is a laborious, tricky and time-consuming task if compounds are not
123 commercially available, relying on critical evaluation of the acquired HRMS and complementary data,
124 when available (Schymanski et al., 2014) NTS analyses are primarily qualitative and play a crucial
125 role when the primary or secondary chemical structures of the targeted compound are undefined or
126 unavailable in existing knowledge (Aalizadeh et al., 2021; Sibiya et al., 2019). The term “fingerprint”
127 refers to the composite presentation of multiple non-targeted signals derived from an analytical
128 method (Ballin and Laursen, 2019). The fingerprints can then be used to develop classification
129 models, such as characterizing different landfills or contaminant source patterns by analyzing
130 dissolved organic matter from the leachate (Pastore et al., 2018; Qiu et al., 2020) or to discover
131 novel entities like brominated and phosphorous flame retardants, or PFAS (Bugsel et al., 2022). The
132 synergy of NTS and SSA approaches provides a more complete understanding of the chemical
133 composition and the potential contaminants in the analysed samples by enhancing the ability to
134 elucidate the identity of the targeted compounds (Ccanccapa-Cartagena et al., 2019; Sibiya et al.,
135 2019).

136 For SSA studies, the combination of reliable highly efficient separation and analytical platforms, such
137 as gas chromatography (GC) (Cecchi, 2021; Ruiz-Delgado et al., 2020) or liquid chromatography
138 (LC) (Qiu et al., 2020), including their two-dimensional configurations (Hilaire et al., 2017), coupled
139 with low-resolution (LRMS) (Cecchi, 2021; Sait et al., 2021) is used. For NTS studies, high-resolution
140 mass spectrometry (HRMS) is required since it combines sensitive full-spectrum data with high mass
141 resolution (>25,000 FHWM), mass accuracy (mass error <5 ppm), and wide mass ranges (e.g., 50-
142 1000 Da) in the identification of unknown compounds at a highly confidence level (Koelmel et al.,
143 2020; Pastore et al., 2018; Ruiz-Delgado et al., 2020). However, other advanced instruments, such
144 as direct analysis in real-time-HRMS (Zhang et al., 2020), Fourier transform Infrared spectroscopy
145 (FTIR) (E. Smidt et al., 2011; Ena Smidt et al., 2011) or liquid chromatography coupled to nuclear
146 magnetic resonance (LC-NMR) (Preiss et al., 2012) can also be used to confirm the compound’s
147 identity. Software algorithms are used to process chromatographic and spectral information to match
148 the features in the databases to identify the compounds (Schymanski et al., 2014).

149 To deal with the complexity of the acquired datasets, several data mining software packages have
150 been developed. These include but are not limited to MS-DIAL, FluoroMatch, and HaloSeeker
151 (González-Gaya et al., 2021; Koelmel et al., 2020; Samanipour et al., 2018), which aim to extract
152 valuable information from the raw data. However, these packages are not universally applicable to
153 all datasets, matrices, or hyphenated systems. To ensure accurate identification, the intricacies of
154 the chromatographic peaks specific to the hyphenated systems or compounds are carefully
155 considered during the peak-picking process (lonas et al., 2015). In addition, chemometric tools,
156 including multivariate analysis such as principal component analysis (PCA) or modelling of class
157 analogy (SIMCA) (Bugsel et al., 2022; Zhang et al., 2020) are used to statistically assess the
158 relevance of the variables and determine their association across a limited number of samples.
159 These tools help extract meaningful insights from the vast amount of data generated by NTS and
160 SSA. By combining the exceptional broad search capability, selectivity and sensitivity of NTS and
161 SSA their applicability extends to the simultaneous analysis of suspect chemicals and the
162 identification of unknown chemicals in various types of samples (Ballin and Laursen, 2019).

163 NTS and SSA have become helpful tools in environmental science for the simultaneous analysis of
164 a wide range of chemical compounds (González-Gaya et al., 2021). However, the application of
165 these analytical approaches to environmental samples related to RPSW has been largely neglected
166 so far and can help technical and political bodies in controlling and monitoring landfills, incinerators,
167 recyclers, spills, treatments, etc. Thus, this perspective review aims to examine the technical
168 potential and policy relevance of NTS and SSA applied to solid waste-related abiotic samples (liquid,
169 gaseous and solid). It also included their applications for the characterization of solid wastes, as well
170 as experimental assays simulating environmental conditions for the degradation of chemicals. It
171 addresses the hurdles associated with the chemical safety of solid waste, processing, and reuse,
172 and the need for landfill traceability. Sample preparation, instrumental analytical analysis, data
173 acquisition and processing were considered, as well as the global regions where the studies were
174 carried out. Crucial knowledge gaps and needs in recent applications are pointed out and discussed.
175 It also explores the applications and adaptation of NTS and SSA to related fields, such as oilfield
176 and metabolomics to the solid waste domain. Despite the ongoing technical challenges, this review
177 highlights the significant potential for the implementation of NTS and SSA approaches in solid waste
178 management and related scientific fields and provides support and guidance to the regulatory
179 authorities.

180

181 **2 Reviewing strategy**

182 NTS and SSA have been applied for the analysis of diverse environmental matrices using different
183 instrumentation and software for a wide variety of purposes. To assess their current applications to
184 environmental samples related to RPSW, a literature search was carried out searching Web of

185 Science and SCOPUS considering the period 2010-2023. The search strategy (Table S1) combined
186 variations of topics in the article title, abstract and keywords, including i) non target and suspect
187 screening, ii) mass spectrometry, iii) solid waste, iv) degradation, v) landfill, vi) leaching, vii) airborne,
188 and viii) incineration. The keywords were inputted as follows: i) non target screening: “non\$target
189 screen*” or suspect* or fingerprint* or signature or “non\$target analysis”; ii) mass spectrometry: mass
190 spectrometr*; iii) solid waste: "solid waste" or "municipal waste" or "electronic waste" or “trash” or
191 "rubbish" or "construction waste" or "demolition waste" or “debris” or "urban waste" or "urban
192 residue"; iv) degradation: compost or biomass or mulch or loam or crush* or grind* or shred* or
193 blend* or mash*; v) landfill: landfill or dump* or municipal*; vi) leach: leach* or lixiviat* or sludge or
194 soil or sediment; vii) airborne: air* or dust or ash or "particulate matter" or soot or cinder or aerosol;
195 viii) incinerator: incinerat* or burn* or combust*.

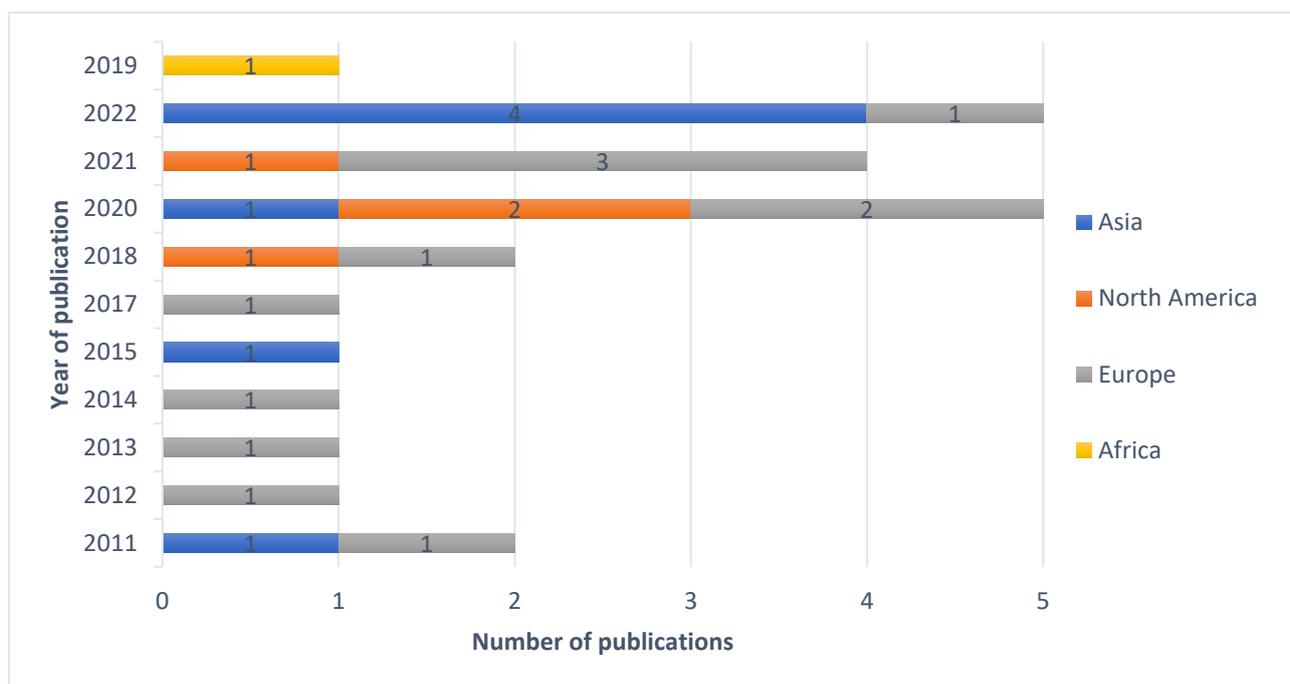
196 Inclusion criteria were formulated to comprise articles written in English about NTS and/or SSA
197 applied to solid waste or processed solid waste from landfills and environmental matrices (liquid,
198 gaseous, and solid). Additionally, studies focused on method development and relative applications
199 to environmental samples, as well as studies about degradation experiments of solid waste were
200 included in this review. Considering the extensive available literature on NTS and SSA related to
201 wastewater and environmental occurrence and exposure to xenobiotics, such articles were not
202 included in the current review strategy. Although there is a recent review about NTS in landfill
203 leachate and groundwater (Nika et al., 2023), the leachate matrix was included in this review since
204 more diverse analytical strategies and a broader period was considered in the present search.

205 The initial search was based on topics and abstracts before manually performing a full-text screening
206 according to the inclusion criteria. Furthermore, references to articles included were manually
207 scrutinized for further relevant studies.

208 Based on the set research criteria, 24 studies were considered to meet the set criteria, 15 of which
209 were published in the last five years by researchers from different geographical regions, been Europe
210 the one that reports 50% of the studies, followed by Asia (30%) and North America (17%) (Figure 1,
211 Table S2). This shows the increasing interest in these approaches to build up capabilities for
212 simultaneously investigating multiple classes of CEC related to anthropic activities with potential
213 impact on the environment and human health (González-Gaya et al., 2021). The main purposes of
214 the applications of NTS and/or SSA to RPSW-associated environmental samples in the revised
215 bibliography were associated with the identification of new CECs, landfill CEC chemical
216 characterization, source chemical traceability and RPSW treatment effectiveness.

217

218



219

220 Figure 1. Number of publications about NTS & SSA, SSA and NTS associated with RPSW per
 221 geographical region and year of publications.

222

223 3 Sample preparation methods

224 The sample preparation methodologies for SSA and target analysis require exhaustive isolation and
 225 clean-up stages to selectively and sensitively determine the analytes of interest. However, NTS
 226 mostly applies generic sample preparation protocols to allow the simultaneous analysis of a broad
 227 set of compounds with a certain affinity (Qiu et al., 2020). The main disadvantage of using generic
 228 sample preparation protocols relies in the low sensitivity of the resulting NTS or SSA methodology,
 229 which is generally solved by complementing SSA with different analytical instruments. NTS
 230 approaches can, in principle, detect and identify any compound present in the tested sample, the
 231 sample preparation method significantly influences the screening results. However, a single
 232 analytical method can neither extract nor analyse the totality of the chemicals present in the sample
 233 under investigation, no matter how generic it is. Thus, the compounds amenable to detection are
 234 conditioned by the followed analytical methodology, including sampling, sample preparation and
 235 data acquisition to screening parameters (Black et al., 2023). Thus, the chemical space accessible
 236 to the untargeted workflow should be investigated and optimized by using a set of known compounds
 237 to provide reliable findings (Han et al., 2022; Jernberg et al., 2013; Liu et al., 2022; Sibiya et al.,
 238 2019).

239 Given the uncertainty that must be managed in NTS and SSA, robust QA/QC needs to be applied
 240 so that the results have a high degree of credibility. Apart from the calibration of the analytical
 241 instrumentation, the recovery of the analytes and the effect of the matrix continue to be evaluated

242 through the analysis of field and procedural blanks, reference compounds, spiked samples, and
243 matrix samples compatible with the studied matrix. Furthermore, in the SSA or target analysis, the
244 use of internal standards is required. In the NTS it is advisable to validate the analytical methodology
245 through the detection and identification of known contaminants (enriched). In this sense, although
246 there are many efforts to develop this topic, a great heterogeneity is observed in the procedures,
247 which is expected to be harmonized in the future.

248 The studies on NTS and SSA in liquid samples associated with RPSW included mainly leachate
249 from landfills, and few also considered the associated groundwater. Most of them used a generic
250 sample conditioning protocol before the instrumental analysis (Table 1). They used filtration and/or
251 centrifugation and dilution before applying additional extracting stages for narrowing the plethora of
252 expected compounds to be analysed; however, the clean-up stage is avoided. The use of external
253 energy, such as ultrasonication, is unrecommended when analysing PFAS since it can degrade
254 (some of) these compounds (Koelmel et al., 2020). Instead, a soft alternative based on aeration
255 foaming was used to gently shake the liquid samples and displace the air–water interfacial
256 partitioning equilibria of PFAS and thus, extract and concentrate them before analysis. The solid
257 phase extraction (SPE) and liquid-liquid extraction (LLE) techniques were the most applied isolation
258 techniques for processing liquid samples related to RPSW. Although the extraction would condition
259 the type of analytes to be identified, it contributes to minimizing the matrix effect, in the case of
260 analysis by LC.

261 For GC analysis, the conditioning due to the extraction stage was even more restrictive since only
262 nonpolar compounds were considered. In addition, a combination of ultrasound and SPE were also
263 reported for sample preparation of liquid samples associated to RPSW. The SPE reported for NTS,
264 included ion exchange-solid phase stationary phase (MAX, WAX, MCX and WCX) and reverse
265 phase (Oasis HLB, Sep Pak C₁₈ and Bound Elute PPL) for either to retain the expected analytes or
266 to eliminate the salt content of the sample before analysis. Most of the NTS and/or SSA in liquid
267 samples associated with RPSW were analysed using liquid chromatography, thus polar solvents
268 (e.g.: methanol, ethyl acetate) were used in the sample preparation procedures independently of the
269 SPE cartridge, the purpose of the analysis or the type of reverse phase-chromatographic column
270 used. When the NTS or SSA was performed with gas chromatography, nonpolar solvents (e.g.:
271 dichloromethane, and n-hexane) were used for LLE before instrumental analysis. In liquid samples,
272 polar compounds were the predominant type of compounds analysed and determined, which also
273 was conditioned by the sample preparation and the analytical instrumentation used. Thus, direct
274 injection after leachate dilution was the preferable choice when intended to analyse a broad type of
275 analytes (Ruiz-Delgado et al., 2020). On the other hand, minimal sample preparation was required
276 when direct analysis in real-time-high resolution mass spectrometry (DART-HRMS) instrumentation
277 was used for SSA of microplastic groundwater related to a landfill. In this study, sample preparation

278 procedure was based on sample drying and sieving before analysis. The SSA allowed to identify
279 chemical fingerprints, antioxidant, plasticizer, UV stabilizer, and cross-link agent content in
280 microplastics (Zhang et al., 2020).

281 When carrying out SSA of gaseous samples related to RPSW for chemical characterization of VOCs
282 in soils treated with sludge samples or biogas, the extraction of the analytes was based on SPE
283 (Amberlite® XAD®-2) or SPME (divinylbenzene/ carboxen/polydimethylsiloxane, 50/30 µm). The
284 desorption of the analytes before analysis was carried out using Soxhlet extraction or pressurized
285 liquid extraction (PLE), in the case of SPE, or just thermal desorption into the injector when SPME
286 was used. The instrumentation used in these cases was GC-MS/MS, comprehensive two-
287 dimensional gas chromatography (GCxGC)-MS/MS (Blazy et al., 2014; Hilaire et al., 2017; Laor et
288 al., 2011). It is important to consider that, although SPE and SPME are efficient techniques for
289 extracting and concentrating a wide range of VOCs, some analytes that can potentially be present
290 as VOCs, such as thiosulfinates, are thermolabile and can be transformed along the sample
291 preparation process or analysis when the temperature is involved into the analytical process (Block,
292 2013, 1993). This can lead to misinterpreting the results since it could be reported VOC artefacts
293 generated along the analytical process, but not be originally present in the analysed sample. There
294 are alternative strategies that avoid raising the temperature for desorbing sulphur-containing and
295 analysing VOCs (S-VOCs) based on the use of solvents for eluting the analytes from the SPEM fibre
296 and LC for their analysis could be used (Locatelli et al., 2014). Additionally, it could be used
297 alternative techniques, such as ultrasonication or supercritical fluids extractions, for assisting the
298 desorption of the analytes from the solid phase after extraction and concentration; or a cold trapping
299 can be used for sampling VOC and/or a soft ionization source coupled to the mass analyser should
300 be used to avoid the analytes decomposition. For SSA of PAH derivatives (alkylated or with
301 heteroatoms), dioxins and their derivatives in fly ash and stack gas of municipal and medical solid
302 waste incinerator and cement plant, XAD-2 resins and microfiber thimble filters were used for
303 sampling the analytes. The Soxhlet extraction technique was used for desorption of the analytes
304 before GC-HRMS or atmospheric pressure photoionization Fourier-transform ion cyclotron
305 resonance mass spectrometry ((APPI)-FT- ICR MS) (Li et al., 2022). Alternative sampling
306 procedures, such as purge and trap, could be considered for NTS since it would allow condensation
307 and concentration of all analytes (or most of them) before analysis, independently of their affinity for
308 the extraction phase. This broad sampling capability would be desirable for the NTS approach to
309 characterize the gaseous samples. These types of devices are compatible, and commercially
310 available, for coupling to GC.

311 NTS was applied to solid samples related to RPSW for the chemical characterization of compounds
312 related to a loss on ignition, total organic and inorganic carbon and total nitrogen of dumped material,
313 to carry out a risk assessment in terms of reactivity and potential emissions. In this case, sample

314 preparation consisted only in grinding the samples before thermogravimetry/mass spectrometry and
315 preparation of KBr pellets for Fourier-transform Infrared Spectroscopy (FTIR), respectively (E. Smidt
316 et al., 2011; Ena Smidt et al., 2011). Additionally, another approach based on pressurized liquid
317 extraction (PLE) for SSA was used for the analysis of brominated or chlorinated organophosphorus
318 flame retardants and plasticizers in dust samples by GC-HRMS (Schreckenbach et al., 2021).

319 It is worth mentioning that although SSA as carried out for characterizing either VOCs or organic
320 pollutants in the gas column, soil, sediment and ash, none of the studies reported a clean-up step
321 after the SPE or PLE desorption and prior analysis gas chromatographic analysis; however, their
322 QA/QC results were satisfactory. Although this approach could be acceptable, the sampling and the
323 sample preparation methodologies of gaseous samples are controversial for the SSA in soil and
324 sediment samples, since possible concomitant compounds are reduced and did not produce a
325 significant matrix effect on the quantitative process (Xie and Ni, 2015).

326 Another notorious aspect in sample preparation for NTS and/or SSA for the analysis of solid samples
327 related to RPSW is the fact that no other type of extraction, such as microwave or ultrasonication or
328 supercritical fluids, was reported for the extraction of the analytes from the SPE adsorbent. They
329 could assist in the extraction of persistent organic pollutants for achieving exhaustive extraction in a
330 reduced time (Li et al., 2022; Sibiya et al., 2019; Zuloaga et al., 2012).

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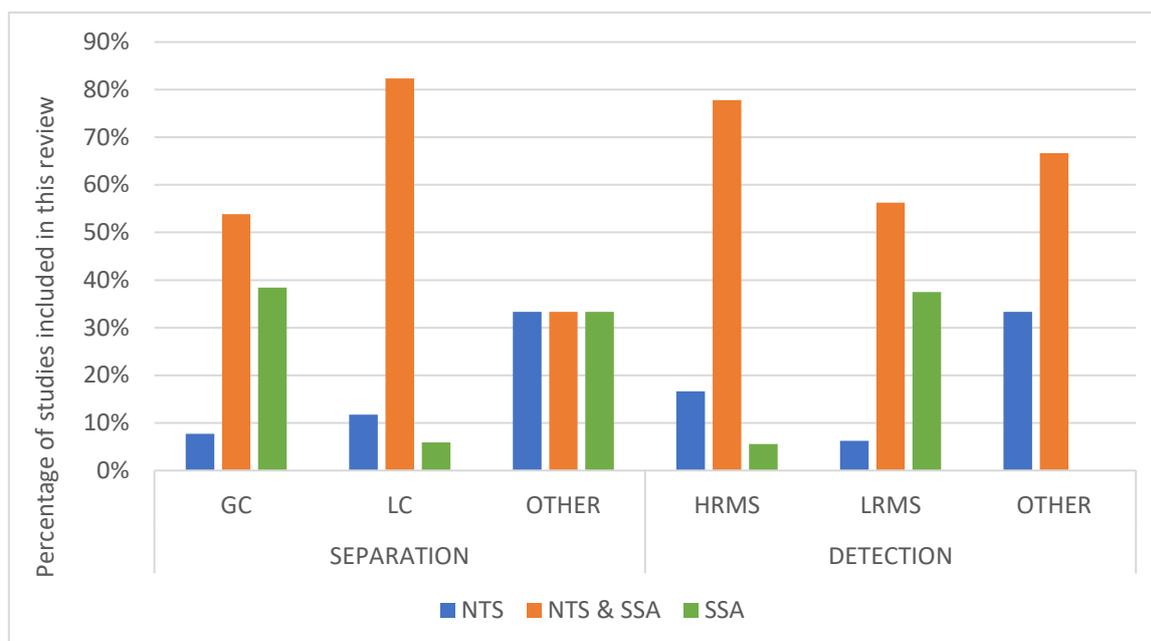
332 **4 Data acquisition**

333 Most of the NTS and/or SSA approaches used a separation technique coupled to a HRMS or LRMS
334 for the analysis of RPSW-associated samples. The LC followed by GC were the most used
335 techniques (Figure 2, Table S3); additionally, some studies used ion-rocket thermal desorption or
336 thermogravimetry prior mass spectrometry for analysing solid samples such as microplastics (Zhang
337 et al., 2020) or landfill material (Ena Smidt et al., 2011). The advantage of using these thermally
338 based techniques as a sample introduction to the mass spectrometer, rather than a separative
339 technique, was the possibility of analysing solid landfill material or leachate without extensive sample
340 preparation, although the possibility of carrying out quantitative analyses was limited. However, this
341 difficulty was not significant in this study since quantitative analysis is outside the objectives of the
342 NTS. The LC was the preferred technique applied for the NTS and/or SSA for the analysis of liquid
343 samples (leachate, groundwater, etc.) associated with RPSW. Various studies used more than one
344 LC or, LC and GC technique, each coupled to different mass spectrometers, LRMS or HRMS, for
345 elucidating complex mixtures of compounds. Some studies coupled LC to UV-Vis or fluorescence
346 (Zhong et al., 2022) or ¹H- or ¹³C-NMR (Preiss et al., 2012) to provide a higher confidence level for
347 compounds' identification in leachate samples from landfills. Spectroscopic analysis by FTIR also
348 was used, together with thermogravimetry-LRMS, in the same sense for the chemical
349 characterization of landfill material in terms of reactivity and potential emissions. Furthermore, an

350 analytical potential was identified in the application of hyphenated chromatographic techniques, such
351 as GCxGC-LRMS (Hilaire et al., 2017), for SSA of composition and quality of produced biogas and
352 biomethane. The analytical procedure based on GCxGC-LRMS was sensitive and resolutive: more
353 compounds can be detected than in GC-MS, and it provides easier identification of target
354 compounds using commercial library. Additionally, the sensitivity was 5 times higher than GC-MS.

355 For the analysis of liquid samples, reverse-phase liquid chromatography was the type of separation
356 mostly used considering its versatility for resolving a wide range of polar and a-polar compounds. In
357 this sense, considering the polar character and mobility of the analytes of interest, it is notorious
358 there are no reports yet about the use of HILIC chromatographic columns for NTS and/or SSA in
359 any type of sample associated with RPSW; however, there is a report about its use for NTS for
360 metabolomics (Damalas et al., 2018). The main application for GC was in SSA (50%) and NTS &
361 SSA (40%), while only 10% were in NTS studies for liquid or atmospheric samples associated to
362 RPSW. The reason for this choice could be associated to the limitation that imposes the fact that the
363 analytes must be volatile or volatilizable, thus must be molecular and with a relatively low molecular
364 weight (< 1500 DA). Additionally, the GC injection requires a nonpolar solvent to avoid back-flow in
365 the injector and gas line due to the expansion volume generated when the sample is volatilized in
366 the injector (Grob et al., 2004). The instrumental requirement conditions the extraction and clean up,
367 which imposes the use of nonpolar solvents for extracting molecular compounds, limiting thus, the
368 types of compounds than can be analysed by GC. These conditions reduce the use of GC in NTS
369 approaches, besides the type of detector used (Hilaire et al., 2017; Koelmel et al., 2020; Qiu et al.,
370 2020).

371 To avoid the use of nonpolar solvents during sample preparation, the cold trapping or supercritical
372 fluid extraction could be used for extraction and injection of the analytes into the GC, respectively
373 (Yang et al., 2016; Zuloaga et al., 2012). Although they are commercially available, they are not
374 commonly found in most of the laboratories. Both techniques would allow expanding the range of
375 compounds to be introduced and resolved chromatographically, which would be beneficial for NTS
376 approaches. It is worth noting the choice of MS detectors for NTS and/or SSA: HRMS was
377 predominantly used for NTS due to its precision in molecular elucidation, while LRMS was the choice
378 for SSA and multitarget analysis. This indicates that both types of MS detectors can be effectively
379 used to study solid waste-related environmental matrices but with different roles. In other words,
380 LRMS is more widely available, and it has the potential to address the analytical challenges for
381 multitarget analysis; however, HRMS is an unavoidable requirement to perform NTS of samples
382 associated with RPSW in an environmental context and can be applied for SSA.



383

384

385 Figure 2. Relative use of instruments for sample introduction (LC, GC, other) and detection
 386 (HRMS, LRMS, other) in the applied analysis (NTS, NTS & SSA or SSA).

387 Regarding the spectrometers' resolution and the ionization sources used for either SSA or NTS,
 388 traditionally, electron ionization (EI) sources are coupled to GC-LRMS and soft ionization sources
 389 (electrospray ionization (ESI), chemical ionization (CI) and atmospheric pressure chemical ionization
 390 (APCI)) to LC-MS and atmospheric pressure photoionization (APPI) to FT-ICR-MS (Table 1).
 391 Although APCI was reported in two studies (Dal Bello et al., 2022; Ruiz-Delgado et al., 2020) and
 392 APP in one study (Li et al., 2022) considered in this review; however, it can potentially expand the
 393 analysis (Rostkowski et al., 2019). A soft ionization source, such as chemical ionization, has later
 394 been applied to GC-HRMS analysis (Fang et al., 2020; Niu et al., 2020). Using soft ionization
 395 sources, less in-source fragmentation and more pseudo-molecular ions are observed in the mass
 396 spectra compared to traditional EI, thus facilitating the identification of chemicals that are not present
 397 in commercial EI libraries (Niu et al., 2020; Tranchida et al., 2018). One of the most extensive
 398 collections of GC-EI-MS spectra, with more than 200,000 substances, is that from the National
 399 Institute of Standards and Technology (NIST). It is the most applied library for SSA and/or NTS with
 400 GC-LRMS, for the identification of volatile or semi-volatile unknown compounds, while it is not used
 401 for LC coupled to low-resolution spectrometers. HRMS, including quadrupole time-of-flight (QToF)
 402 or Orbitrap mass spectrometers, is the most coupled spectrometric technique, as it allows the
 403 acquisition of highly resolved full-scan mass spectrometric data. ESI in positive or negative ionization
 404 mode coupled to LC-HRMS/MS is the most common choice for SSA and NTS (Table 1). For LC-
 405 based analyses, the ionization source predominately used for analyzing polar compounds was
 406 electrospray ionization (ESI), which decreases in-source fragmentation led to simpler mass spectra

407 and significant intensity of the acquisition of pseudo-molecular ions required for the identification of
408 unknowns (Bugsel et al., 2022; Pastore et al., 2018; Ruiz-Delgado et al., 2020). Different data-
409 acquisition approaches can be implemented within SSA and NTS studies depending on the
410 analytical question. This consideration applies to LC-ESI-MS/MS (fragmentation by CID) and not to
411 GC-EI-MS (fragmentation in source) types of instruments. The acquisition of full-scan spectra in
412 mass ranges depending on the compound groups of interest and/or the applied instrumentation, and
413 ionization techniques is a widely used approach. Thereby, a scan of the full mass spectrum is
414 recorded within a predefined m/z range (Cecchi, 2021; Jernberg et al., 2013; Ruiz-Delgado et al.,
415 2020; Sait et al., 2021). Even though this approach does not include the generation of fragmentation
416 spectra, it allows higher scan rates resulting in an increased number of data points per peak, which
417 can be advantageous for further data-processing steps. Often, the acquisition of fragmentation
418 (MS/MS) spectra are included as they can yield higher confidence in compound annotation
419 (Schymanski et al., 2014) . If the selection of the precursor ions for which MS/MS spectra are
420 generated is performed in an automated software-based manner (based on the signal intensity
421 and/or a predefined list containing m/z ratios preferred for fragmentation), this is referred to as a
422 data-dependent (DDA) (Koelmel et al., 2020; Qiu et al., 2020) or information-dependent (IDA)
423 acquisition. However, this only allows obtaining MS/MS spectra of a limited number of (most
424 abundant) parent ions. To overcome this limitation, data-independent (DIA) or all-ions (AI) acquisition
425 modes are applied whereby the fragmentation spectra of all ions included in the full mass scans are
426 generated (Koelmel et al., 2020; Schreckenbach et al., 2021). This approach requires additional
427 post-acquisition data treatment steps to link the obtained fragment ions with the corresponding
428 precursors.

429

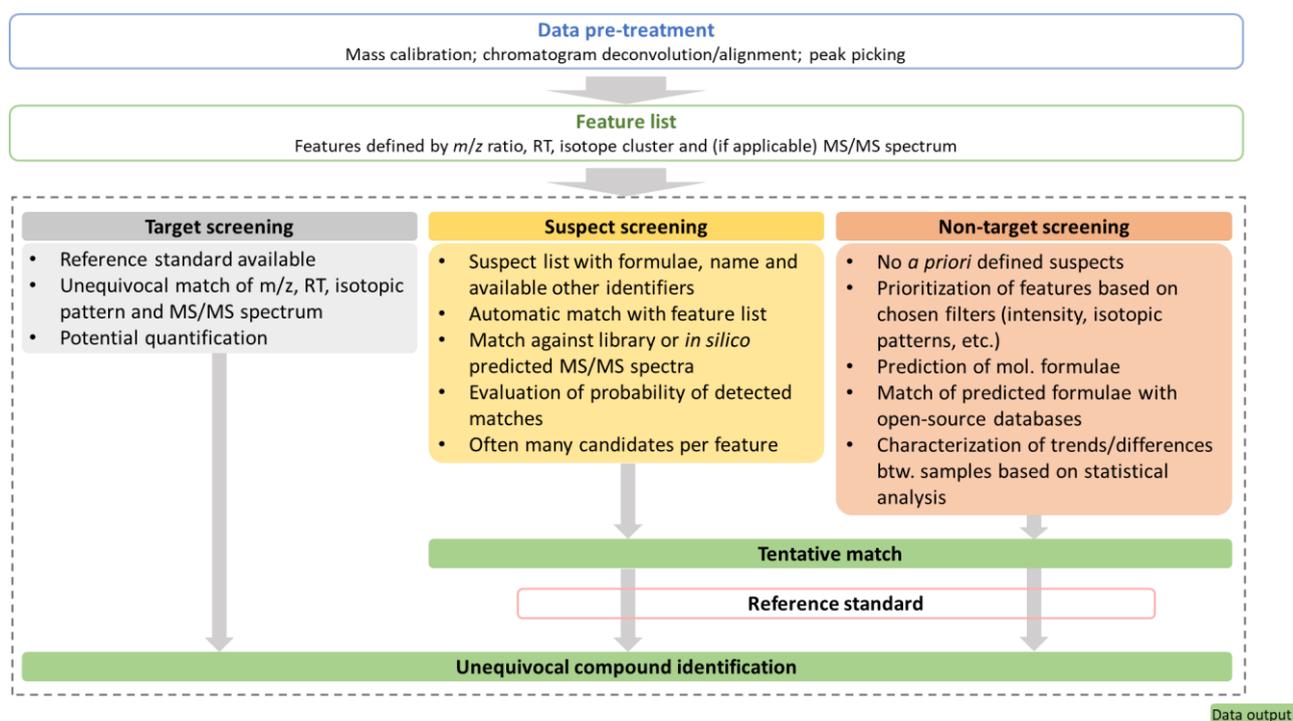
430 **5 Data processing and analysis**

431 Numerous compounds can be identified through the application of NTS and/or SSA approaches,
432 leading to the exhaustive chemical characterization of samples related to RPSW. It is well known
433 that data treatment and feature annotation are the bottleneck of NTA and/or SSA, especially for
434 complex and diverse samples such as those considered in this review. The structure elucidation with
435 a high confidence level of unknown compounds is a laborious, tricky and time-consuming task if
436 compounds are not in the lab or commercially available, relying on critical evaluation of the acquired
437 HRMS and complementary data, when available. In this sense, data pre-treatment, SSA workflows
438 and NTS workflows are necessary for an unequivocal identification (Schymanski et al., 2014).

439 **5.1. Data pre-treatment**

440 Before compound annotation and/or identification or other data processing steps, SSA and NTS
441 often share similar generic data pre-treatment steps, which are independent of the scope of the
442 study. These most common steps include post-acquisition mass calibration, chromatogram

443 deconvolution and alignment followed by a peak-picking step. Ultimately, peak picking aims at the
 444 extraction of peaks defined by a certain m/z ratio and retention time (most referred to as '(molecular
 445 feature') which subsequently can be used for further data analysis, possibly including the annotation
 446 of (predicted) formulae or compounds. Thereby, data pre-treatment steps can be chosen to retain
 447 as many molecular features as possible or introduce filtering steps based on the analytical question.
 448 For example, extracted features can be further filtered based on abundance cut-offs, mass defects
 449 indicating the presence of, e.g., halogen atoms or mass ranges and retention time windows of
 450 interest. Both data pre-treatment steps and consecutive specific data analysis approaches have
 451 been described in detail in previous studies and are graphically summarized in Figure 3.



452

453 Figure 3. Generic data processing workflow for target, suspect and non-target screening.

454

455 5.2. Suspect screening workflow

456 The pre-treated dataset can subsequently be analyzed by applying SSA. These are mostly based
 457 on matching the obtained dataset against a pre-defined list containing compounds suspected to be
 458 present in the sample. Matches are based on the exact masses and isotopic patterns and can be
 459 expanded by the implementation of additional identification points, such as (predicted) retention
 460 times and fragmentation spectra. Therefore, the composition of the suspect list depends on the
 461 scope of the study and can include known compounds, metabolites, and transformation products as
 462 well as predicted formulae. For GC-derived data, the extensive NIST library is often applied for
 463 compound identification within SSA (Sait et al., 2021). The NIST library is the largest database
 464 commercially available and includes more than 200,000 compounds. The size of the NIST library

465 and the consistency of EI spectra across instrument types are advantages for GC/EI instruments.
466 There are open-source repositories of suspect lists available for LC/ESI instrumentation, such as the
467 NORMAN suspect list exchange repository. While the focus on a limited, predefined group of
468 compounds within SSA eases the data processing and allows a more in-depth analysis of certain
469 classes, such a focus leaves non-included compounds undetected potentially biasing data
470 interpretation. Ultimately, SSA can allow the identification of compounds with a confidence level (CL)
471 of up to 2 according to the scheme of levels of identification confidence introduced by Schymanski
472 et al. (Schymanski et al., 2014) given that reference fragmentation spectra are available.

473 The detailed screening criteria for the CL are summarized as follows: i) Level 1 is determined by
474 authentic standards; ii) Level 2 is determined by matching with the literature database or Metfrag
475 calculations; iii) Level 3, MS/MS matches to peaks fail to be acquired within the scan range for
476 MS/MS spectrum but is supported by evidence of authentic standards or homologues and is
477 calculated by CFM-ID; iv) Level 4 represents only MS monoisotopic signature matched to the
478 database; V) Level 5 is determined by the exact mass of interest defined by homologues. The
479 majority of the reviewed studies, communicated the identification confidence via the well-established
480 five-level Schymanski scale, whereas other studies informed level 4 (Pastore et al., 2018; Sibiya et al.,
481 2019; Zhang et al., 2020), 1-3 (Schreckenbach et al., 2021), and 3 (Dal Bello et al., 2022; Koelmel et
482 al., 2020) confidence scheme, while Jernberg et al. reported level 6 (Jernberg et al., 2013).

483

484 5.3. Non-target screening workflow

485 In contrast to SSA, NTS processes the mass spectrometric data without any *a priori* assumption of
486 the compounds to be identified (Figure 3). After data pre-processing steps, features can be further
487 prioritized based on the focus of the specific study. For example, datasets can be processed aiming
488 at identifying groups of features differentiating in occurrence or intensity between groups of samples.
489 More specific filters can be based on, e.g., the occurrence of halogens (applying open-source
490 software, such as HaloSeeker or FluoroMatch) or characteristic neutral losses observed in the
491 fragmentation spectra. Subsequently, for the resulting list of prioritized features molecular formulae
492 can be predicted. Thereby, the inclusion and allowed numbers of elements again depend on the
493 scope of the study. Predicted formulae can be matched against extensive open-source databases,
494 such as ChemSpider or PubChem. This approach is often limited by an extensive number of possible
495 candidates per predicted formulae hampering an unequivocal compound annotation and increasing
496 the risk of false positive annotations.

497 For GC-derived data, the extensive NIST library is often applied for compound identification within
498 NTS approaches (Sait et al., 2021). This approach does not necessarily have to contain a formula
499 prediction step. Again, compounds can be identified with a confidence level of up to 2 (Schymanski

500 et al., 2014), given that reference fragmentation spectra are available. As an alternative to formula
501 prediction and database matching, statistical analyses, such as PCA, can be carried out to identify
502 differences between samples, e.g., comparing contaminated and non-contaminated samples or
503 different waste treatment samples, or characterize general chemical fingerprints of samples.

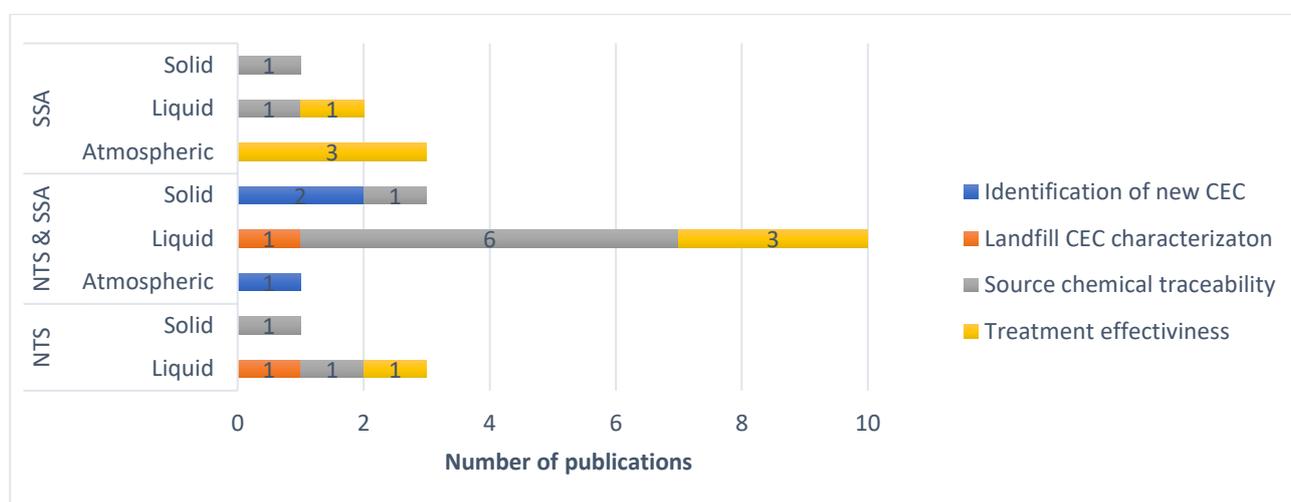
504 In most of the reviewed studies, the applied workflow and the MS/MS data are provided either in the
505 manuscript or in the supplementary material. However, many studies do not clearly include the
506 MS/MS interpretation to justify the elucidated compounds. Considering the relevance of informing
507 new compounds found in the analysed samples, it is important that the MS/MS of the reported
508 compounds (elucidate and non-elucidate) are shared in NTS-published studies or in spectral libraries
509 for tradability and or build up collaboratively the knowledge in this new scientific field.

510

511 6. Application of NTS and SSA to environmental samples associated with RPSW

512 Among the 24 considered studies, 14 followed a complementary NTS and SSA approach to address
513 the analysis of samples related to RPSW, while either SSA or NTS was used in 6 and 4 publications,
514 respectively (Figure 4, Table S2). This NTS and SSA distribution in the number of papers suggests
515 that a higher synergy can be obtained when applying both techniques for the simultaneous analysis
516 of multiple classes of CECs.

517



518

519 Figure 4. Number of publications based on general application purposes considering the type of
520 analysis (NTS & SSA, SSA or NTS) and type of sample matrix (atmospheric, liquid or solid).

521

522 The main purposes of applying NTS and/or SSA to environmental samples associated with RPSW
523 include the traceability of the chemical source, degradation treatment effectiveness, screening
524 and/or identification of unknown/new compounds, or landfill chemical characterization (Figure 4,

525 Table 1). Additionally, it is interesting to note that, for environmental analysis (González-Gaya et al.,
526 2021)LC-HRMS was the instrumentation predominantly used for the analysis of samples associated
527 with RPSW (Figure 2); however, other instrumentation techniques were also successfully used,
528 individually or combined, including GC-HRMS (Jernberg et al., 2013; Li et al., 2022; Schreckenbach
529 et al., 2021)LC-MS/MS (Sait et al., 2021), GC-MS (Blazy et al., 2014; Cecchi, 2021; Laor et al., 2011;
530 Ruiz-Delgado et al., 2020; Sait et al., 2021), GCxGC-MS/MS (Hilaire et al., 2017), direct analysis-
531 mass spectrometers (Li et al., 2022; Ena Smidt et al., 2011; Zhang et al., 2020), or other
532 spectrometry, such as FTIR (Ena Smidt et al., 2011). This analytical instrumentation diversity for
533 NTS and/or SSA of samples associated with RPSW was not observed in previous reviews focusing
534 only on environmental analysis (González-Gaya et al., 2021).

535 Application of NTS and SSA to samples associated with RPSW mainly refers to landfill surroundings
536 as well as to the RPWS materials or degradation processes. Here, they were classified into liquid,
537 atmospheric, and solid samples for description and analysis and sub-classified according to the type
538 of sample considered (Figure 5). Among the revised literature, SSA and/or NTS were mainly applied
539 for the analysis of liquid (63%), followed by solid (20%) and atmospheric samples (17%) associated
540 with RPSW (Figure 4). Liquid samples were mostly landfilling leachate (Jernberg et al., 2013;
541 Koelmel et al., 2020; Ruiz-Delgado et al., 2020), however, there were studies based on the aquatic
542 environment associated with landfill (Cecchi, 2021; Liu et al., 2022; Zhang et al., 2020),laboratory
543 assays simulating solid waste degradation in seawater and freshwater media (Sait et al., 2021),and
544 treatment process (Pastore et al., 2018). The surveillance of landfills by analysing their leachate can
545 give relevant and global information about the site.

546 In this sense, there are two studies based on NTS and SSA that performed a complete
547 characterization of landfills based on the composition of leachates at different time intervals and
548 seasons revealing thus, the impact of the high temperatures (degradation of contaminants in
549 wastes), rainfall (more production of leachates), and other climatic conditions (Han et al., 2022; Liu
550 et al., 2022). In the same way, the surveillance of multiple leachate landfills revealed differences in
551 the composition, years of operation, open or closed landfills, types of wastes received, and treatment
552 processes (Dal Bello et al., 2022; Liu et al., 2022; Martin et al., 2021; Sibiya et al., 2019; Zhong et
553 al., 2022). When monitoring the effectiveness of different treatment processes of landfill leachate,
554 several relevant aspects were considered including raw and treated leachates, and different
555 treatment processes (biological treatment, reverse osmosis, etc.) (Dal Bello et al., 2022; Pastore et
556 al., 2018).The evaluation of the treatment is of utmost importance to assure effective treatment and
557 prevent pollution spills. Moreover, the treatment processes may generate numerous TPs with higher
558 toxicity potential (Dal Bello et al., 2022),which also must be monitored. The studies that involved
559 groundwater samples associated with RPSW from municipal landfills provided valuable information

560 on the potential pollution of such resources due to leachate leaks in the surrounding aqueous (Han
561 et al., 2022; Liu et al., 2022; Preiss et al., 2012).

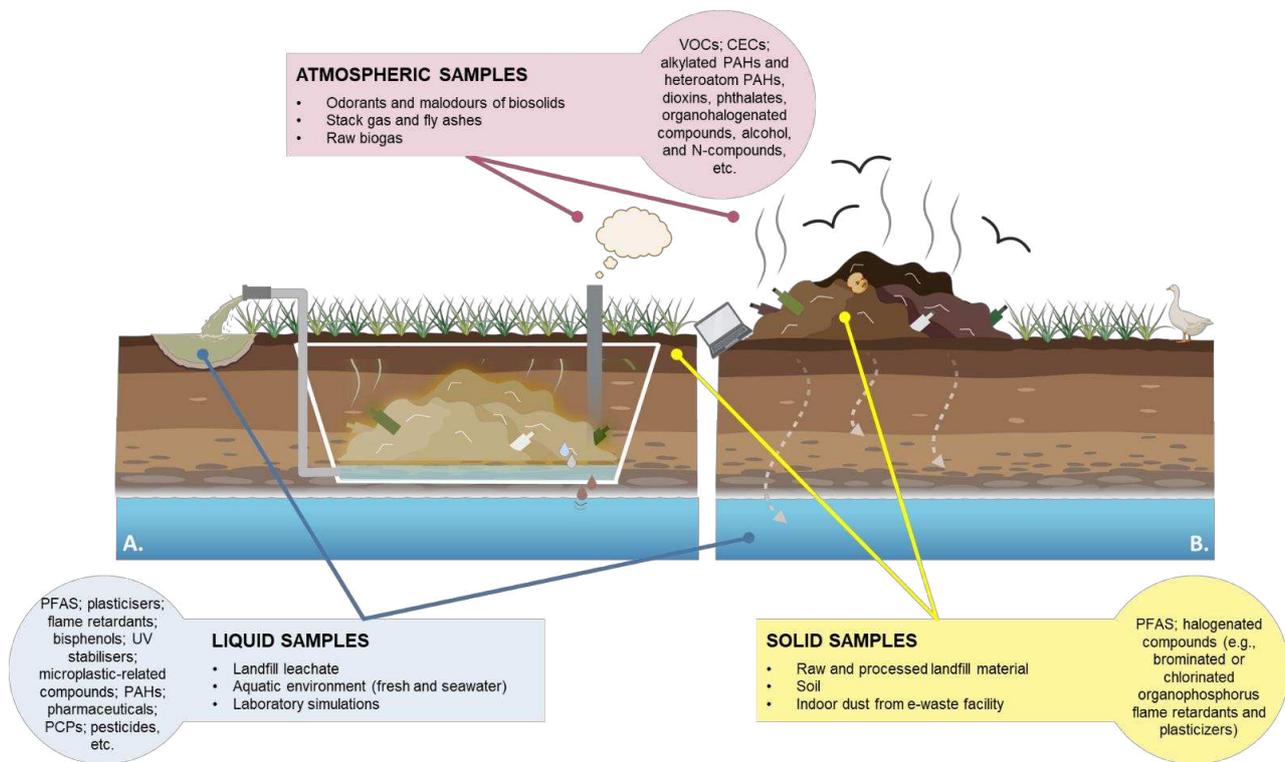
562 The other investigated matrices associated to liquid samples from the landfill sites include sediments
563 and particulate matter from leachates. There is only one study investigating sediments and
564 performing target screening (Sibiya et al., 2019), whereas in another two studies the particulate
565 matter of leachates was analysed separately from the liquid phase of the sample (Han et al., 2022;
566 Liu et al., 2022). The investigation of both particulate matter and sediment can provide important
567 information on the fate of contaminants and thus support the management of contaminated sludge,
568 especially if it will be used as fuel replacement of the industry, or for enriching crop fields or
569 combustion for final disposal (Fernández-Puratich et al., 2015; Hernández et al., 2023).

570 Reviewed literature on atmospheric samples included mainly SSA of VOCs analysis related to
571 odorants and malodours of biosolids after land-application (Laor et al., 2011), slaughterhouse sludge
572 (Blazy et al., 2014), and raw biogas (Hilaire et al., 2017). Those studies of VOCs related to the
573 organic material decomposition in bioreactors or on enriched crops fields or biogas are closely
574 related to metabolomics, although it is not mentioned in those studies. Unfortunately, this is a
575 scarcely explored scientific and biotechnological field, which development could contribute to find
576 the appropriated microorganism community and its optimum physical-chemical conditions for
577 degrading the characteristic organic matter as well as manage (select) the emanated VOC
578 (Hernández et al., 2019, 2018). In this sense, NTS approach would be crucial for chemical
579 characterize the metabolites of the studied microorganism's communities.

580 On the other hand, the NTS and SSA approaches were applied for the characterization of stack gas
581 and fly ashes from a solid waste incinerator (Li et al., 2022). Their combination allowed for finding
582 new contaminants and persistent organic pollutants like and studying their potential toxicity. As can
583 be seen in Table 1, the number of publications on this topic is insignificant; however, the application
584 of NTS and/or SSA could be useful for industries with incineration processes, such as cement, where
585 incineration of diverse types of solid residues are incinerated as final disposal of other processes,
586 additionally to their own.

587 Solid samples for NTS and SSA included raw and processed landfill material (Ena Smidt et al.,
588 2011), soils from arable land (Bugsel et al., 2022; Bugsel and Zwiener, 2020) and indoor dust from
589 an e-waste facility (Schreckenbach et al., 2021). The NTS and SSA approaches played an important
590 role in characterizing the solid-waste material and predicting the ignition hazard, as well as in
591 characterizing the dust of the RPSW facility for evaluating the working environment safety.
592 Additionally, soil enriched with paper paste was analyzed along an extension of a field to determine
593 the source of contamination. Although the number of publications of NTS and/or SSA approaches
594 for the analysis of samples associated with RPSW is scarce, it is possible to observe their versatility

595 for the analysis of samples in different aggregation states, which is promising for the continue grow
596 of this research field.



597

598 Figure 5. Schematic representation of the application of NTS and SSA to solid waste-related
599 environmental samples. A. authorized landfill and B. unauthorized dumping site.

600

601 6.1. Application of NTS and SSA to liquid samples

602 Among the considered publications about liquid samples, 6 papers used NTS and SSA for studying
603 CECs and/or their degradation products in the leachate of landfills, in groundwater and freshwater
604 of lakes and lagoons, and aqueous media of experiments on solid waste degradation simulating
605 seawater or freshwater. Specifically, NTS and SSA were applied to qualitatively determine the
606 presence of PFAS in leachate samples from landfills, which would have not been found using
607 traditional target analysis techniques (Koelmel et al., 2020; Liu et al., 2022). Koelmel et. al introduced
608 an open-source data analysis software, FluoroMatch, for the SSA of PFAS (Koelmel et al., 2020). It
609 is based on *in-silico* PFAS fragmentation libraries and rule-based annotation for compound
610 identification. The NTS and SSA of PFAS were carried out using LC-HRMS, while target analysis
611 used LC-MS/MS. By using this software workflow, it was possible to lead a particular analytical
612 strategy combining SSA and NTS: a wide range of PFAS were screened, and the evidence for each
613 PFAS was based on libraries with experimental fragmentation data sets, leading to a more reliable
614 tool for both screening and qualitative analysis. Although the usefulness of NTS was unquestionable,
615 some limitations, which may cause the analytes to remain undetected, were reported. These

616 included the low sensitivity of certain analytes, co-eluting components, complex sample background
617 noise or decisions made by the analyst. Unequivocal identification was not possible in some cases,
618 specifically for isomers. Consequently, the identification using NTS remained tentative until it was
619 confirmed with a reference standard.

620 In the study conducted by Guang-Guo et. al, NTS and SSA of per- and poly-fluoroalkyl substances
621 were conducted in three landfills and groundwater from Guangzhou, South China (Liu et al.,
622 2022).The analysis was performed using UPLC(ESI)-MS/MS and the identification was based on
623 database matching and multivariate statistical analysis based on PCA. A total of 651 PFAS
624 compounds were identified, indicating a wide range of PFAS contamination in the landfills under
625 investigation. Specifically, out of the 57 target PFAS compounds, 33 were detected in the leachate
626 samples, while 28 were found in the groundwater samples. This suggests that PFAS contamination
627 is not only limited to the waste leachate but also extends to the surrounding groundwater, posing
628 potential risks to nearby ecosystems and water sources. Moreover, the presence of both legacy and
629 emerging PFAS compounds in both leachate and groundwater samples further emphasizes the
630 complexity and persistence of PFAS pollution in these landfills. It highlights the urgent need for
631 effective waste management practices and remediation strategies to mitigate the risks associated
632 with PFAS pollution in landfill environments. In addition, it was suggested that the type of
633 impermeable layer of landfill sites could affect the content of PFAS in groundwater.

634 The same research group conducted an NTS and SSA study to identify CECs in the same samples
635 from Guangzhou, South China (Han et al., 2022). A total of 242 chemicals were identified using NTS
636 and 37 chemicals were detected and quantified using target analysis. The CECs in the raw leachates
637 were efficiently removed with removal efficiencies greater than 88.7%. However, it was confirmed
638 that the CECs found in groundwater originated from landfill leachate. Interestingly, no significant
639 differences were observed in the occurrence and distribution of CECs between different samplings
640 and sites.

641 In the NTS and SSA study conducted by Preiss et. al (Preiss et al., 2012)groundwater samples
642 collected downgradient from a former municipal solid waste landfill near Berlin, Germany, were
643 analysed by GC-MS, HPLC-MS, and LC-NMR to comprehensively characterize the content of CECs.
644 These compounds were isolated by HPLC fractionation, and their structures were elucidated by
645 offline NMR and MS measurements. A variety of CECs, products of the dye industry, degradation
646 products of polyethylene glycol, and some heterocyclic compounds were identified. Furthermore, a
647 semi-quantitative estimation of the identified compounds was given. The results demonstrate that
648 the NTS carried out with HPLC-NMR and HPLC-MS techniques and further off-line NMR and MS
649 investigations is a powerful analytical approach to identify unknown polar EC in complex samples
650 related to RPSW landfills. With modern NMR techniques, identifications down to the lower parts-per-
651 billion range are possible. However, much more sensitive MS is often necessary as a supporting

652 technology for structure elucidation. On the other hand, the diversity of possible compound classes
653 limits the chances of identifying unknown CECs on-line by the exclusive analysis of HPLC-NMR and
654 LC-MS data, which is much easier for samples consisting of components with comparable partial
655 structures. In some cases, the unknown CEC was isolated by HPLC fractionation and enriched for
656 structural elucidation using the 2D NMR method.

657 The applications of NTS combined with SSA for studying environmental microplastic
658 photodegradation and additive lixiviation to seawater or freshwater led to tentatively identified
659 multiresidue plasticizers and degradation products by GC-MS/MS and bisphenols (BPs) and
660 benzophenones (BzPs) by LC-MS/MS (Sait et al., 2021). Although some UV stabilizers and
661 degradation products were tentatively identified by NTS, a considerable number of identified
662 chemicals could not be classified based on known uses. It was evident from the NTS results that
663 further investigation of leachates using HRMS is needed to elucidate the identity of chemicals
664 present in plastic and plastic leachates, but progress on the automated data analysis front is also
665 needed to handle the complexity of these datasets for high-throughput characterization.

666 A study about VOCs in Venice lagoon water samples revealed the impact of plastic debris and mass
667 tourism, among other sources of contamination, by comparing samples from 2019 and during the
668 first COVID-19 lockdown (Cecchi, 2021). The study was addressed by using SSA based on GC-
669 MS/MS analysis. The list of identified compounds from Venice Lagoon water samples includes 40
670 analytes related to (i) the presence of polymer debris in seawater (e.g., plasticizers and their
671 degradation products, monomers, intermediates in the synthesis of synthetic rubbers and their
672 degradation products, flame retardants, stabilizers, and other additives), (ii) water traffic (e.g.,
673 markers of incomplete combustion in the exhaust gas, volatile fuel components, contaminants linked
674 to boats and ships construction and repairing lubricants, and corrosion inhibitors), (iii) tourists'
675 presence and habits (e.g., smoke-related compounds, cosmetics, pharmaceuticals, personal care
676 components, human-related compounds, and metabolites), and (iv) plants and microorganisms
677 (e.g., natural flavours, metabolites). Most identified VOCs were linkable to plastic debris and many
678 other possible origins. Compounds' identification was based on commercial standards, when
679 available, or NIST library matching or retention indexes relative to relative to n-alkanes. Although the
680 GC-MS/MS was successfully applied for the SSA, there was still some doubt about the reasons for
681 the observed decrease in the studied CECs when comparing concentrations found before and after
682 the first COVID-19 lockdown. They were potentially related to the seasonal and location variations
683 in the studied aqueous environment. Although the work proposed to extend the sampling for studying
684 the variations, it does not propose applying complementary analytical strategies, which would be
685 useful for identifying unknown compounds that might not have been identified by GC-MS/MS.

686 Additionally, NTS and SSA were also applied for rapid fingerprinting by chemical characterization of
687 environmental microplastics and screening of additives content in freshwater lakes using a non-

688 chromatographic approach (Zhang et al., 2020). Specifically, pyrolysis and thermal desorption Direct
689 Analysis in Real Time (DART)-high-resolution mass spectrometry was proposed for such purpose.
690 The approach led to characterizing differences among plastic types, microplastic source materials,
691 and environmental water samples. Multivariate statistics and elemental composition analysis
692 approaches were used to analyze the data and visualize the fingerprint by Kendrick mass defect and
693 van Krevelen diagrams. This study shows that highly complex mixtures of chemicals are generated
694 during pyrolysis that cannot be distinguished by LRMS alone. This promising analytical approach is
695 sensitive, (potentially) high-throughput, and can aid in the elucidation of possible sources of
696 microplastics. On the other hand, there are not many reports of chemical signature identities of
697 plastics using DART-HRMS yet, and some of the more convincing attempts at quantitation
698 (Montaudo et al., 1993) have not been reproduced. Reliable quantitative measurements of
699 microplastics and nanoplastics will require the firm identification of target compounds, potential
700 interferences and the synthesis of authentic (isotopically labelled) standards.

701 Among the NTS applications for studying environmental liquid samples associated with RPSW, 3
702 studies used only this approach (Jernberg et al., 2013; Pastore et al., 2018; Qiu et al., 2020).
703 Jernberg et. al developed an NTS approach for qualitatively determining CECs and/or their
704 degradation products in the leachate of landfills (Jernberg et al., 2013). The NTS approach was
705 tested and validated by applying it to a landfill leachate sample spiked with 11 organic pollutants that
706 were treated as unknowns. GC-HRMS analysis and deconvolution computer application for data
707 processing were combined for the identification of pharmaceuticals, plasticizers, flame retardants,
708 pesticides, and musk compounds. The process was based on the forward fit value of the library hit
709 the number of deconvoluted ions and the accurate mass scoring of the measured ions. The main
710 obstacle to the use of the NTS method was the software, which led to laborious work for manually
711 confirming the compounds' chemical identity.

712 The NTS approach proposed by Qiu et. al focused on the analysis of dissolved organic matter
713 content of landfill leachate by LC-HRMS for characterization based on chemical features that were
714 observed in all samples (20% of the detected mass peaks), although specific groups of compounds
715 were not fully identified (Qiu et al., 2020). These features were considered fingerprints of the
716 dissolved organic compounds content, and it was used to distinguish the dissolved organic matter
717 content among diverse sources (e.g., waste landfill sites and storage pits) of possible environmental
718 monitoring scenarios, and to recognize the evolution from young to old leachate based on molecular
719 insights. These are valuable contributions, being a key tool to support quality control of landfill
720 leachate before ending up in the environment and for studying the evolution of the degradation
721 process of solid waste in landfills. NTS was also used for investigating the performance of three
722 different chemical oxidation processes in terms of their capability to degrade organic chemical
723 components of real mature landfill-leachate in combination with biological treatment run in a

724 Sequencing Batch Biofilter Granular Reactor (Pastore et al., 2018). The NTS was based on LC-HRMS
725 analysis of the residual organics contained in the final effluent and the resulting chemical features,
726 without full identification, were further classified and processed using Venn Diagram and tri-
727 dimensional plot and PCA. Apart from determining leachate treatment differences, a series of
728 recalcitrant compounds was determined in all treatments and partly identified as hetero-poly-
729 aromatic species (humic acids-like species). It is worth noticing, however, that the use of new
730 versions of the open-source software tool for NTS (e.g., enviMass 3.2) would allow to implementation
731 of SSA, as well as it would be able to easily link the MS/MS spectra of selected compounds, with
732 open-source MS databases (e.g., MassBank, ChemSpider, etc.). In this way, the capability to get
733 some relevant compounds to be identified would be much higher. In this sense, Ruiz-Delgado et. al
734 applied SSA to study advanced and intensive degradation treatments for the decontamination and
735 possible reuse of landfill leachates based on solar photo-Fenton and an aerobic biological reactor
736 (Ruiz-Delgado et al., 2020). The processes were evaluated in terms of their capability for degrading
737 12 organic micropollutants representing recalcitrant pharmaceuticals, plasticizers, flame retardants,
738 pesticides and musk compounds. The analytical approach included: (i) a target analysis (115
739 analytes) by LC-MS/MS; and two SSA approaches using (ii) LC-HRMS (a database with >1300
740 compounds) and (iii) GC-MS/MS (a database with >900 compounds). The SSA by LC-HRMS and
741 GC-MS/MS allowed the identification of 16 compounds not previously determined by LC-MS/MS.
742 Thus, the combination of LRMS and HRMS instrumentation allowed for precisely identifying the
743 expected analytes deriving from the degradation processes, and it was confirmed that the overall
744 elimination of the quantified OMCs was 94%.

745

746 **6.2. Application of NTS and SSA to atmospheric samples**

747 To date, studies in which NTS and/or SSA are used to monitor CECs in atmospheric samples
748 associated with RPSW are still scarce. Unlike NTS and/or SSA applications for liquid samples, most
749 of the instrumentation used for the analysis of atmospheric samples associated with RPSW was
750 based on gas chromatography, including bidimensional and coupling of low and high-resolution MS.
751 The applications to atmospheric samples associated with RPSW are mostly based on SSA (3 out of
752 4) (Blazy et al., 2014; Hilaire et al., 2017; Laor et al., 2011) followed by the combination of NTS and
753 SSA (Li et al., 2022). SSA applications focused on the VOCs' chemical characterization of odorants
754 and malodors related to biosolids before and during alkaline stabilization and after incorporation into
755 the soil, or from composting pig slaughterhouse sludge (Blazy et al., 2014; Laor et al., 2011). In both
756 cases, the purpose was to study the effect of different degradation conditions (e.g., aerobic or
757 anaerobic) on the VOC emission. SSA was also applied for the analysis of raw and treated biogas
758 and biomethane to study the sample origin and efficiency of a purification process based on charcoal
759 (Hilaire et al., 2017). SSA allowed to quantitatively determine VOCs by GC-MS/MS of GCxGC-

760 MS/MS, or semi-quantitatively determined when GC-MS was used for the study. In these studies,
761 neither multivariate statistical analysis nor HRMS was applied. Precise characterization of the VOCs
762 might contribute to a better understanding of the biological process and to characterize the
763 microorganisms, which could be useful for further designing specific processes for a more efficient
764 degradation process.

765 In this sense and considering the surge that metabolomics has had due to the contributions of
766 advanced instrumentation, multivariate statistical analysis and software processing, this would be a
767 field where the application of NTS combined with SSA would enhance its development and link to
768 other fields. The studied VOCs included families of metabolic products naturally occurring in aerobic
769 and/or anaerobic degradation of the organic residues of the solid waste (e.g., S-, N-, O- organic
770 compounds, terpenes, alcohols, hydrocarbons, benzene, toluene, ethyl benzene, and xylene-BTEX,
771 halogenated organic compounds, etc.).

772 Despite the low number of current applications combining NTS and SSA in atmospheric samples
773 associated with RPSW, the only contribution in this matter was carried out for studying known and
774 unknown CECs in air stack and fly ash of municipal and medical solid waste incinerator and cement
775 plant (Li et al., 2022). The NTS and SSA approach was applied using FT ICR MS and GC-HRMS for
776 the identification of organic pollutants, including alkylated and heteroatom PAHs, dioxins, phthalates,
777 halogenated organic compounds, alcohol, and N-compounds. Compounds were identified using the
778 Kovats retention index, analytical standards, and library matching. This modern analytical approach
779 yields valuable information to detect unregulated POP-like chemicals that may be more persistent
780 and mobile than the regulated ones. Besides the NTS and SSA, in this work, the ToxCast library and
781 machine-learning were applied to the toxicity evaluation of the new POP-like chemicals, which is a
782 key step for prioritizing compounds for regulatory purposes. This work provides information for better
783 recognizing and regulating the emissions of POPs formed by the incineration of solid waste.

784

785 **6.3. Application of NTS and SSA to solid environmental samples**

786 NTS and/or SSA approaches for analysing solid environmental samples associated with RPSW are
787 scarce and include different analytical strategies using advanced instrumentation. In this sense, LC-
788 HRMS (Bugsel et al., 2022; Bugsel and Zwiener, 2020), GC-HRMS (Schreckenbach et al., 2021), as
789 well as a non-chromatographic approach combining FTIR spectroscopy and thermogravimetry/MS
790 (Ena Smidt et al., 2011), were proposed for the analysis of soil, sludge, dust, raw and processed
791 landfill materials, respectively. NTS approaches based on LC-HRMS screening by Kendrick mass
792 analysis, systematic retention time shifts and assignment of homologous series in combination with
793 sensitive SSA were applied to fully or tentatively identify a complex mixture of PFAS and degradation
794 products soil samples from sites enriched with paper sludge (Bugsel et al., 2022; Bugsel and

795 Zwiener, 2020). By using this analytical approach, it was also possible to differentiate patterns of
796 transformation products between paper sludge and soil samples, which could be attributed to
797 sorption and leaching processes dependent on carbon chain lengths. Although the contamination
798 source of the studied soils and ground water was identified, the low availability of technical standards
799 and suitable database entries, especially for transformation products, limited the identification of
800 several unknowns.

801 NTS combined with the SSA approach using GC-HRMS was applied to identify halogenated
802 compounds (e.g., brominated or chlorinated organophosphorus flame retardants and plasticizers) in
803 indoor dust samples from an e-waste facility (Schreckenbach et al., 2021). By using scanning
804 quadrupole data-independent acquisition (SQDIA), false-positive rates were found to be class-
805 dependent: 20% for Br, 37% for Cl, 75% for OPFRs, and approaching 100% for all other classes.
806 SQDIA produced an order of magnitude fewer false-positive identifications than DIA, owing in part
807 to the presence of fewer interference peaks. This enables greater confidence in putative
808 identifications, which is crucial in SSA and NTS. Indeed, the results of this study indicated that SSA
809 and NTS, coupled with GC-APCI and SQDIA, can broaden the number of chemicals measured,
810 enabling the detection of novel compounds. The complementation of FTIR spectroscopy and thermal
811 analysis mass spectrometry in NTS has proven to be adequate tools for the RPSW characterization
812 of landfill materials in terms of reactivity and potential emissions. The FTIR and thermal-MS spectral
813 patterns were defined as fingerprints of the material. The classification model was based on soft
814 independent modelling of class analogy (SIMCA) (Ena Smidt et al., 2011). Degradation experiments
815 based on aerobic and anaerobic conditions were compared to samples of a reactor landfill and to
816 the landfill fraction to demonstrate the efficiency of the biological pretreatment before final disposal.
817 In addition, a degradation prediction model was calculated utilizing a partial least squares regression
818 (PLS-R) using spectral and thermal information. The NTS approach provides a reliable basis for the
819 classification, assessment and decision on appropriate remediation measures in terms of organic
820 matter stabilization. However, as a disadvantage, it requires representative sampling according to
821 statistical procedures and therefore, many samples, for risk assessment of unknown abandoned
822 landfills regarding their reactivity and the future emission potential.

823 Xie et. al conducted a study based on a fingerprint chromatographic method for evaluating the
824 source-sink relationships among environmental compartments for polybrominated diphenyl ethers
825 (PBDEs), which were taken as the representative contaminants (Xie et al., 2013). They established
826 a library of various sources of products containing contaminants (e.g., plastics) analysed by GC(Cl)-
827 MS. A data matrix containing all peaks and their relative proportions after matching the peaks, based
828 on retention times and peak areas. The matrix profile was compared to environmentally complex
829 samples (e.g., sediment, soil). A similarity between soil and sediment indicated that they have a
830 source-sink relationship. This comparison was used as the first step in source tracking. The

831 comparison methodology based on fingerprint chromatograms did not require a quantitative or
832 qualitative analysis of all chemicals in the real-world mixtures. The cosine similarities between plastic
833 and soil or sediment ranged from 0.53 to 0.68, suggesting that plastic in electronic waste is an
834 important source of PBDEs in the environment, but it is not the only source. One caveat of this study
835 is that only a simple computational method was applied for source tracking of environmental
836 pollutants. In the future, a more effective and robust method (e.g., “pollution trees” (Zheng et al., 2012))
837 for identifying similarities among pollutant mixtures in the environment is required for source
838 identification. Additionally, since the fingerprints are strongly dependent on the analytical conditions,
839 it is crucial to maintain consistency during the entire analytical procedure.

840

841 Table 1. Applications of NTS and SSA to environmental matrices associated with solid waste.

842

Parent compounds or Groups of substances	Sample types	Purpose of the analysis	Location	Sample preparation	Applied Analysis	Instrumental technique(s)	Data analysis/prioritization	Ref.
Liquid samples								
Pharmaceuticals, plasticizers, flame retardants, musks, pesticides	Landfill leachate	Development of a six-stage NTS method for emerging contaminants in a complex matrix.	Lahti, Southern Finland	Filter, dilution and LLE	NTS	GC-EI-TOF-MS	Library matching, standard injections	(Jernberg et al., 2013)
Acidic, basic and neutral compounds as well as some recalcitrant (humic acids-like species)	Landfill leachate	Comparison of aerobic biological treatment combined with H ₂ O ₂ , H ₂ O ₂ +UV exposure and O ₃	Apulia, Southern Italy	Dilution and SPE: MAX, WAX, MCX and WCX	NTS	UPLC-Q Exactive Orbitrap MS/MS UPLC(DSIS & CDS)-QTOF-MS/MS	Tridimensional PCA and Venn Diagram	(Pastore et al., 2018)
Per- and Polyfluoroalkyl substances	Municipal landfill leachate	Introduction of open-source software for characterization of per- and polyfluoroalkyl substances. Application to landfill leachate	Central Florida, U.S.A.	Aeration foaming	NTS	UPLC(ESI)-Q Exactive Orbitrap MS/MS	Fluoromatch consists of in-silico fragmentation database PFAS subclasses and SMILES structures for representative compounds	(Koelmel et al., 2020)
					SSA	UPLC(ESI)-MS/MS		
Pharmaceuticals, plasticizers, flame retardants, pesticides, musks	Urban landfill leachates	Evaluation and comparison of leachate treatments based on oxidation processes (solar photo-Fenton) and an aerobic biological reactor	Vila Real, North of Portugal	Filter and dilution	SSA	LC(ESI)- QTRAP - MS/MS	Library matching	(Ruiz-Delgado et al., 2020)
				LLE		LC(ESI & APCI)-QTOF-MS/MS		
Dissolved organic matter	Old municipal landfill leachate	Fingerprinting of dissolved organic matter from aged	Various Cities, in	SPE	NTS	GC (EI)-MS	Non-metric multidimensional scaling intensity of	(Qiu et al., 2020)
						UPLC(ESI)- Q Exactive Orbitrap MS/MS		

		waste. Searching for landfills leaking.	Eastern China				precursor ions and ordinary parameter (NMDS), Venn diagrams, Spearman Correlations	
Antioxidants, plasticizers, UV stabilizers, cross-link agents and microplastic markers	Lake water	Develop a novel approach for rapid fingerprinting of environmental microplastics and synthetic fibres	Lake Ontario and Lake Erie	Sieving and rinsing	NTS & SSA	Ion-rocket thermal desorption/pyrolysis inlet-DART-Q-Exactive Orbitrap MS	Fingerprinting, Multivariate statistical analysis. Library matching	(Zhang et al., 2020)
Polar compounds: dye industry, degradation products of polyethylene glycol, and heterocyclic compounds	Groundwater collected downgradient from municipal solid waste landfill	Investigate capabilities of HPLC-MS and HPLC-NMR for determining polar compounds in leachate sample	Belin, Germany	LLE, SPE	NTS	HPLC(ESI)-MS, HPLC-(¹ H/ ¹³ C) NMR, ¹ H-NMR LC-UV fractionation: 2D (¹ H/ ¹³ C)NMR, MS ⁿ	SSA: Library matching, ¹ H-NMR NTS: ¹ H-NMR; 1D, 2D NMR; flow injection MS/MS	(Preiss et al., 2012)
				LLE	SSA	GC(EI)-MS, ¹ H-NMR		
Per- and poly-fluoroalkyl substances	Raw and treated leachate from municipal landfills and groundwater	1-To identify and quantify legacy and emerging PFAS in three municipal landfills 2- To investigate the correlation between leachate and groundwater in landfills	Guangzhou, Southern China	SPE: WAX	NTS & SSA	UPLC(ESI)-QTOF-MS/MS	Database-based suspect screening, homologue and diagnostic PFAS fragment-based non-target screening. Multivariate statistical analysis	(Liu et al., 2022)
					SSA	UPLC(ESI)-MS/MS		
Pharmaceuticals personal care, food additives, industrial chemicals (flame retardants, plasticizers, antioxidants and catalysts), pesticides,	Raw and treated leachate from municipal landfills and groundwater	Investigate the occurrence of EC in leachate landfills and their surrounding groundwater	Guangzhou, Southern China	SPE	NTS & SSA	UPLC(ESI)-QTOF-MS/MS	An in-house database and three online databases including MoNA, MassBank EU and GNPS	(Han et al., 2022)

transformation products and other organic compounds					SSA	UPLC(ESI)-MS/MS	Library matching, Standard injections	
Multiresidue plasticizers, bisphenols and benzophenones	Simulated solid-waste in environmental degradation	Investigate UV degradation of MPFS in marine and freshwater environments.	Norway	SLE	NTS	GC(EI)-MS	Kruskal-Wallis test, Dunn's multiple comparison	(Sait et al., 2021)
				SLE and LLE	SSA	UPLC(ESI)-MS/MS	Library matching, Standard injections	
Chemical markers of polymers, water traffic, tourists' habits and natural from humans, sea plants and sea microorganisms	Venice lagoon	Screening pollution possible contamination sources Before and after the first COVID-19 lockdown	Grand Canal in Venice, Italy	HS-SPME	SSA	GC(EI)-MS	Library matching, Standard injections	(Cecchi, 2021)
Dissolved organic matter and pharmaceuticals, food and cosmetics preservatives	Leachate from active bioreactor municipal solid waste landfill and a closed landfill.	To better understand dissolved organic matter composition and improve located pollution tracing	Florida, USA	SPE	NTS	(ESI)FT-ICR-MS	Full scan	(Martin et al., 2021)
				SPE	SSA & TA	LC(ESI)-QTOF-MS/MS	Library matching, Standard injections	
Musks	Leachate from landfill	Identify, characterize and semi-quantify R-limonene and p-cymene transformation products (TPs) derived from heterogeneous photocatalysis mediated by TiO ₂	North of Italy	Purge and Trap	SSA	GC-(EI)ITMS	Library matching, Standard injections	(Dal Bello et al., 2022)
				SPE	NTS	LC(APCI)-Ion Trap Orbitrap MS/MS	Software Xcalibur 4.0	

Persistent organic pollutants, organophosphorus flame-retardants and plasticizer	Leachate and sediment from a landfill	Report of POPs in South Africa and identification of the most commonly found organophosphorus flame retardants.	Gauteng, South Africa	Dilution + LLE + Sonication	NTS	UPLC(ESI)-QTOF-MS/MS	Mass-Hunter Qualitative analysis software. Possible formulas with a structure that resembles the obtained MS spectra were checked using ChemSpider and PubChem MATLAB algorithms and restricted elements' combination. UV and fluorescence absorption confirm the molecular weight and aromaticity of the detected chemicals.	(Olukunle et al., 2015)
				S-L extraction + SPE	SSA	GC-MS/MS		
Dissolved organic matter transformation products.	Leachate from landfill	Investigate the molecular transformations of dissolved organic matter induced by HO [•] and Cl ₂ ⁻	Shenzhen, China	SPE	NTS	LC(ESI)-Orbitrap MS/MS		(Zhong et al., 2022)
Atmospheric samples								
VOCs	Biosolids	Characterize the chemical fingerprint of the odour annoyance associated with the incorporation of anaerobically digested sewage sludge.	Haifa, Netanya, and Herzliya, Israel	HS-SPME	SSA	GC(EI)-MS	Library matching, Standard injections	(Laor et al., 2011)
VOCs	Sludge	Evaluation of aeration treatment	France	HS-SPE	SSA	GC(EI)-MS	Shapiro–Wilk test, Pearson correlations	(Blazy et al., 2014)
VOCs	Biogas and biomethane	Characterization of the biogas based on their chemical	France	HS-SPE, PLE	SSA	GCxGC(EI)-MS	Standard injections	(Hilaire et al., 2017)

		profile for quality control						
Persistent organic pollutants	Fly ash and stack gas	Identification and toxicity evaluation of non-recognized emitted chemicals	China	HS-SPE, SLE	NTS & SSA	(APP)FT-ICR-MS	DDA	(Li et al., 2022)
						GC(EI)-QTOF-MS	Kovats retention index, library matching, Standard injections	
Solid samples								
Compounds related to loss on ignition, the total organic and inorganic carbon and total nitrogen.	Landfilled materials	Characterization, classification and parameter prediction of different landfill materials to evaluate risk assessment in terms of reactivity and potential emissions	Austria	Grinding	NTS	FTIR spectroscopy, Thermogravimetry/mass spectrometry	Multivariate statistical analysis. Molecular models	(Ena Smidt et al., 2011)
Poly- and perfluoroalkyl substances	Soils from sludge fields	Identification of precursor PFAS and their transformation products to trace contamination with paper paste	Hügelsheim and Mannheim, Germany	SLE	NTS & SSA	LC(ESI)-QTOF-MS	Library matching against OECD PFAS database, standard injections. Confirmed compounds using ProFinder 10.0 from Agilent Technologies	(Bugsel and Zwiener, 2020)
Poly- and perfluoroalkyl substances	Soils from sludge fields	Identification of precursor PFAS and their transformation products to trace contamination with paper paste	Hügelsheim and Mannheim, Germany	SLE	NTS & SSA	LC(ESI)-QTOF-MS	Kendrick mass analysis and assignment of homologous series in combination with suspect screening.	(Bugsel and Zwiener, 2020)

Brominated or chlorinated organophosphorus flame retardants and plasticizers	Indoor dust from e-waste facility	Identification of anthropogenic chemicals of potential concern related to electronic waste	An electronics recycling facility in Toronto, Canada	PLE	NTS & SSA	GC(EI)-QTOF-MS	Peak deconvolution, library matching, standard injections	(Schreckenbach et al., 2021)
PBDEs	Soil, sediment and plastics	To develop a fingerprint method for identifying source-sink relationships between environmental compartments.	Shenzhen, Southern China	SLE	SSA	GC(CI)-MS	Library matching. Data matrix containing all peaks and their relative proportions after matching the peaks based on retention times and peak areas.	(Xie and Ni, 2015)

843 Note: NS: not specified; HESI: heated ionization source; DSIS: duo-spray ion source; CDS: calibrant delivery system; DDA: data-dependent
844 acquisition; DIA: data-dependent acquisition.

845 **7. Current knowledge gaps and future perspectives**

846 This review summarized recent NTS and SSA studies on samples associated with RPSW. Based
847 on the collected information, these matrices are still poorly studied for CECs, even though they
848 represent a significant input of chemicals into the environment that could affect ecosystems leading
849 to (ir)reversible changes in their structural dynamics. NTS and SSA are powerful analytical tools for
850 source tracing, residue monitoring, identification of new markers of pollution and evaluation of
851 remediation strategies or monitoring the effectiveness of the treatment processes. The application
852 of orthogonal techniques (e.g., analysis by both LC-MS and GC-MS or reverse-phase and HILIC
853 chromatography) is needed to broaden the monitored chemical space and achieve a better
854 understanding of the occurrence of chemicals in the environment or RPSW matrices.

855 However, there are currently some knowledge gaps on technical aspects that hamper the scopes of
856 the SSA or NTS approaches and their application to RPSW-related samples. Specifically, sample
857 preparation for detection at trace concentration levels is often a limitation, considering that
858 environmental samples related to RPSW are complex matrices, independently of the sample state
859 of aggregation (liquid, gaseous, or solid). Thus, the co-extraction of potential compounds of interest
860 and interferences from the matrix can overload the analytical capability of the instrumentation,
861 deteriorating its sensitivity and selectivity. For selecting a suitable analytical approach among non-
862 targeted, suspect or targeted analysis, it is important to carefully define the environmental question
863 to be addressed to focus compounds to be screened. While for NTS, the sample preparation method
864 needs to be non-selective and universal to ensure an unbiased broad compound coverage, sample
865 preparation can be optimized specifically for certain (classes of) compounds in a targeted approach.
866 Thus, the synergy of NTS and SSA approaches provides a more complete understanding of the
867 chemical composition and potential contaminants in the analysed samples by enhancing the ability
868 to elucidate the identity of the targeted compounds.

869 Therefore, suitable sample preparation for SSA and/or NTS in environmental samples related to
870 RPSW, such as solvent extraction, ultrasonication or supercritical fluid extraction, solid-phase
871 extraction and cold trapping, together with detection techniques, including quality assurance/quality
872 control workflows, should be optimized for efficiently identify chemical entities. An agreement on the
873 minimum requirements for quality assurance/quality control and harmonization of sample
874 preparation and NTS workflows remains a future challenge for the NTS community. Efforts towards
875 this direction can be accomplished via the organization of collaborative trials. Aspects related to the
876 sampling methodologies of particulate matter, dust and flash ash associated with solid waste could
877 also be addressed. In this sense, silicone rubber strips are a suitable alternative for trapping
878 particulate matter for further solvent extraction. They allow preconcentration of the particles and
879 minimization of matrix effects in the analysis of a wide range of compounds (Amato et al., 2018).
880 Multivariate statistical approaches are applied for differentiating among groups of related chemical
881 structures, even if no complete compound identification is achieved. These approaches should be

882 designed interdisciplinary with chemometrics to avoid bias or overfitting the data matrix; and thus,
883 properly reveal the reality of the data classification achieved.

884 Besides analytical workflow considerations, challenges concerning the solid waste composition
885 and/or environmental perspective should be envisaged, like the sample homogeneity, punctual or
886 composite samples, as well as the aggregation stage of the sample to be considered according to
887 the question of the study. Since the intra and inter-variability of landfills or dumping sites is unknown,
888 a suitable sample size must be established during the design of the experiment for counting on
889 representative samples of the site of study.

890 The application of NTS and SSA to leachate samples from landfills covers a wide range of purposes,
891 which proves its utility and needs for the analysis of environmental samples associated with RPSW.
892 However, the profiling of petroleum-derived chemicals has not been explored yet in the leachate,
893 e.g., oil spills. SSA for naphthenic acids content has been extensively explored in the oilfield for
894 tracing oil origin, pond tail content and water production quality using different instrumentation based
895 on GC-MS, SFC-MS or LC-MS techniques (Ortiz et al., 2014; Petersen and Grade, 2011; Wang et
896 al., 2016). Determining the chemical profile in the leachate would help to better understand the
897 landfill's identity based on its content, ageing and origin.

898 Advanced and intensive treatments are needed for the decontamination and possible recycling of
899 landfill leachates. In this sense, conventional wastewater treatments were applied; however, they
900 are not usually effective in the degradation of specific landfill leachates due to their high content in
901 toxic and recalcitrant compounds, thus more efforts are needed in this sense. NTS and SSA have
902 been applied for monitoring the degradation process of landfill leachate, although to an incipient
903 extent. Thus, due to the relevance of this matter, it is expected that the number of NTS and SSA
904 applications will further increase due to the accessibility of more advanced instrumentation and
905 multivariate strategies for boarding the analytical challenges.

906 Although there are SSA applications for the chemical characterization of odors and malodors that
907 emanate from soils enriched with sludge or in biogas production, there is a lack of application of NTS
908 approaches in this topic. On the other hand, considering that the determined analytes are
909 (bio)transformation products resulting from an aerobic or anaerobic process, it is evident that this
910 issue fits also into the metabolomics field for a better understanding of the microbiological processes
911 occurring during the degradation of solid waste. Precise characterization of the VOC emissions from
912 enriched soils with sludge or in biogas production may contribute to a better understanding of the
913 biological degradation process and to characterize the involved microorganisms, which in turn could
914 be useful for the design and development of sample degradation procedures and waste
915 management.

916 There are other gaps related to the analysis of VOCs in enriched soils with sludge or sludge related
917 to the analytical instrumentation or data-processing tools. Published works of the SSA approach
918 included the use of GC-LRMS for the analysis of VOCs; however, currently, there is still a lack of

919 HRMS-based applications and/or multivariate statistical analysis in this research field. Additionally,
920 it was noticed that several S-containing metabolic VOCs were reported by GC-MS. However,
921 thiosulfates are thermolabile compounds, which means that their chemical form may change during
922 analysis, leading to erroneous results (Block, 2013, 1993). For studying thermolabile compounds,
923 alternative analytical methodology avoiding high temperatures should be used to avoid formation of
924 artifacts and confirm the chemical identity (Block, 2013). Thus, expanding the NTS and SSA
925 applications in solid-waste-related environmental studies could help the scientific community and
926 governmental environmental agencies to better understand and accurately evaluate the potential
927 threat that RPSW represents to the environment and organisms.

928

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938

939 **Authors' Contributions**

940 Jorgelina Cecilia Altamirano: Conceptualization, Methodology, Writing – original draft,
941 Visualization, Funding acquisition

942 Shanshan Yin: Conceptualization, Methodology, Investigation, Writing – Review & editing,
943 Visualization

944 Lidia Belova: Conceptualization, Methodology, Investigation, Writing – original draft, Visualization

945 Giulia Poma: Conceptualization, Methodology, Investigation, Writing – Review & editing,
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947 Adrian Covaci: Conceptualization, Methodology, Writing – Review & editing, Supervision, Funding
948 acquisition

949

950 **Availability of Data and Materials**

951 Additional data for this study are presented in the Supplementary Material.

952

953 **Conflicts of interest**

954 The authors declare no conflicts of interest.

955

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