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Thorough investigation of non-volatile substances extractible from inner coatings of metallic cans and their occurrence in the canned vegetables

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Abstract

Since the decline of the use of bisphenol A, the chemistry of the varnishes and coatings which are applied to the inner surfaces of metallic food contact materials is poorly documented. We hypothesised that can coatings are now diverse and bring forth various non-intentionally added substances (NIAS) to be described. Investigating complex components such as NIAS requires demanding non-targeted approaches. We investigated the coatings of 12 vegetable cans from the French market. More than 125 substances were pinpointed, among them 84 oligoester combinations from 8 diols and 4 diacids. Thus, oligoesters were the dominant family. Additives such as epoxidised soybean oil, bisphenol A diglycidyl ether and benzoguanamine derivatives and phenol-formaldehyde oligomers were also identified. A software for exploring databases of theoretical combinations of polyester and phenol-formaldehyde resin components (NIAS-db 1.0) was made available. The stepwise organic synthesis of native and deuterated combinations of neopentyl glycol and isophthalic acid (4 and 8 units, linear and cyclic) enabled a higher confidence level and monitoring in vegetable extracts. Migration of oligoesters averaged 330 µg/kg in the drained vegetables (43 to 1600 µg/kg). This study sheds light on the need to fulfil a proper risk assessment on this NIAS family (exposure and hazard characterisation).

Keywords

Food contact material; non-intentionally added substance; stepwise synthesis; leachate; oligomer

Chemical compounds

ADK Stab NA 21E (PubChem CID: 16686081); Benzoguanamine (PubChem CID: 7064); DiNcH (PubChem CID: 11524680); Epoxidised soya bean oil (PubChem CID: 71306824); Irganox 3114 (PubChem CID: 93115); Triphenylphosphine oxide (PubChem CID: 13097)

1. Introduction

Food packaging fulfils several functions, among them containment, protection, storage or transport of food commodities, which contributes to food security and is essential to minimize food waste. At the European Union (EU) level, food contact materials (FCMs) are covered by the framework Regulation EC 1935/2004.

Regarding varnishes and coatings which are applied to the inner surfaces of metallic FCMs as polymeric protective barriers in order to prevent corrosion, no harmonised measures are in force, except for substances related to bisphenol A (BPA) and its diglycidyl ether derivative (BADGE) (EU 2018/213; EC 1895/2005). However, BPA has been under increasing regulatory pressure due to both consumers and the scientific community concerns (ECHA, 2016; Tarafdar et al., 2022), which led to restrictions at the EU level (EU 321/2011; EU 2018/213). Coating and can manufacturers have conceded enormous efforts to adapt through the evolution of technologies and conservation processes, particularly in France where BPA has been completely banned from FCM applications since 2014 (JORF, 2012), leading to a singular distortion of the EU single market. As we write these lines, the European food safety authority (EFSA) has launched a public consultation on its draft opinion on the re-evaluation of the risks to public health related to the presence of BPA in foodstuffs (EFSA, 2021). It is proposed to set the tolerable daily intake to 0.04 ng BPA/kg body weight, which is 100,000 times lower compared to the temporary tolerable daily intake previously set in 2015 (EFSA, 2015). A potential consequence is that BPA could be banned at the EU scale and the current situation in France would reflect what could happen at the EU level, and even beyond.

Regrettably, the specific adaptation of the market has not been reviewed yet, particularly in terms of exposure to alternative-related substances. In practice, industrial stakeholders usually rely on the Partial Agreement guideline ResAP(2004)1 (no legal status), specifying a positive list of authorized monomers and additives. Defined as intentionally added substances (IAS), their migration into foodstuffs is under control with well-suited *ad hoc* risk assessments and often specific migration limits (SMLs) below the overall migration limit of 60 mg/kg food. The exhaustive FCCdb database (Groh et

al., 2021) compiles 12,285 IAS that could possibly be used worldwide to produce FCMs, based on 67 lists from publically available sources, such as regulatory lists and industry inventories. However, beyond starting substances there is a need for evaluating non-intentionally added substances (NIAS). Indeed, defined as impurities from starting materials or products of incomplete polymerisation (e.g. oligomers) or thermal/hydrolytic degradation (EU 10/2011), NIAS should also be subjected to a risk assessment to comply with the framework Regulation (EC 1935/2004).

Among alternatives to epoxy-resins, polyester-based coatings have not yet drawn much attention, due to rather limited information regarding the extent of their use. They are applied as a thermoplastic to the welded seam or cross-linked with amino or phenolic resins to obtain varnishes applied to other metallic surfaces of the cans (Oldring and Nehring, 2007). About 35 polyol and polyacid monomers are listed in the ResAP(2004)1 (Tables S1), offering numerous polyester combinations after their polycondensation with the loss of water. When dealing with polyesters, cyclic oligoesters, which are not cross-linked and typically represent 0.5-2% of the resin in weight (Eckardt et al., 2019), have been reported as the main NIAS. Their composition may be predicted depending on the knowledge about the formulation (Omer et al., 2018). Oligoesters are NIAS inherent to a polycondensation reaction occurring during the synthesis of polyesters. They have been reported to be found for the first time in can coating in 2004 but earlier in thermoplastics such as polyethylene terephthalate (Schaefer et al., 2004).

Most NIAS have not yet been subjected to a robust risk assessment, due to analytical issues raised by their wide chemical diversity (Nerín et al., 2013; ILSI, 2016). So far, missing data relate to knowledge on the extent of BPA-free coatings' use on the market (France standing apart), to the comprehensive identification of NIAS, to the human exposure following migration into food, to their fate along the gastrointestinal tract, and to their biotransformation and related adverse effects. The lack of reference standards is a major bottleneck for undisputable quantification and mechanistic studies. Another analytical challenge in characterising the diversity of complex and yet undescribed components relates to the implementation of advanced non-targeted approaches (Kato and Conte-Junior, 2021). State-of-

101 the-art workflows involve non-selective sample preparation (Pourchet et al., 2021), fingerprinting by
102 using gas or liquid chromatographic techniques (GC, LC) coupled with full-scan high-resolution mass
103 spectrometry (HRMS) detection (Badea et al., 2020), and data mining supported by bioinformatics
104 tools (Léon et al., 2019; O'Shea and Misra, 2020) combined with labour-intensive data curation and
105 interpretation (Cariou et al., 2021).
106 In the present study, we hypothesised that can coatings are now diverse and bring forth various NIAS
107 to be described. We addressed some challenges related to the hazard identification of NIAS through
108 the stepwise synthesis of native combinations of neopentyl glycol (NPG) and isophthalic acid (iPA)
109 (linear 4-units, cyclic 4- and 8-units), as well as their site-specific deuterated congeners. Then, we
110 collected a dozen vegetable cans available on the French market without any *a priori* knowledge of the
111 formulation of their inner coatings. We investigated extractible substances from individual coatings
112 according to a non-targeted LC/HRMS analytical strategy. More than 125 substances were pinpointed.
113 We cumulated and examined useful information to level up confidence in their identification, allowing
114 to document the reality of the market. Then, we applied a non-selective sample preparation to food
115 items to monitor migration and, when appropriate, achieved semi-quantification.
116
117 **2. Material and methods**
118 *2.1. Synthesis of oligoester reference standards*
119 Reagents and solvents, monitoring and characterisation equipment (^{1}H and ^{13}C NMR, ESI-TOF-HRMS
120 and LC/ESI-Orbitrap-HRMS), general considerations on the selection of the synthesis strategy (stepwise
121 route, choice of the labelling isotope) as well as optimised syntheses are described in the
122 supplementary material.
123
124 *2.2. Chemicals for sample investigations*

The description of solvents, salts, reference and external standards is available in the supplementary material. A mixture of the 3 synthesised D-labelled oligoesters (dStd-Mix), namely D_4-lin(2NPG+2iPA), D_4-c(2NPG+2iPA) and D_8-c(4NPG+4iPA), was prepared in acetonitrile (ACN) at 4 ng/µL (each).

2.3. Samples

A set of twelve cans of various vegetables were purchased from a large-scale supermarket in October 2019 in France (Table 1). Cans of distinct National brands (n = 6) and of the retailer's brand (n = 6), including three-piece (n = 8, 3PC) and two-piece (n = 4, 2PC) cans were considered. Labelled total net weights ranged from 200 to 800 g. Emptied cans were gently washed with tap water and wiped, then representative pieces of each coating (n = 40) were cut and stored at ambient temperature until analysis. Indeed, 3PC welded cans comprise four coating surfaces ("a": top end; "b": body; "c": bottom end; "d": side seam stripe applied to the welded seam) while 2PC cans comprise two coating surfaces ("a": top end; "b": body/bottom end) (Fig. S1) (Oldring and Nehring, 2007), leading to a total of 40 coatings in the sample set. Juice was separated from drained weight using a 1 mm sieve. In addition, a third fraction was individualised for whole peeled tomatoes as being sauce, leading to a total of 25 food subsamples. Juice pH ranged from 4.1 to 6.6. Subsamples were homogenised, lyophilised, ground (except drained endives and whole peeled tomatoes which remained rubbery and were finely sliced, and juice of extra fine butter beans which was sticky) and stored at -20 °C until analysis. See Table S2 for more details.

2.4. Sample preparation

For each coating, a surface of 2 cm^2 was grated using a surgical blade (Table S3, Fig. S2) and extracted using 2 mL of acetonitrile at 40 °C during 24 h. A mixture of the 40 coating extracts (C-Mix, 2.5% *v/v* each) was prepared. For each coating and the C-Mix, an ACN extract aliquot (40 µL) was transferred into a vial containing dStd-Mix (3 × 40 ng, 10 µL ACN) and diluted in water (50 µL). Coating extracts

were analysed (8 µL) in a single LC/Orbitrap-HRMS sequence, along with procedural blanks (n = 3), ACN (n = 5), dStd-Mix (n = 5) and C-Mix (n = 5).

Liquid-liquid partitioning of the C-Mix in a ternary solvent mixture of nHex, EtOH and H_20 was optimised. The C-Mix (640 µL) was poured in a mixture of nHex/EtOH 1:1 (*v/v*, 64 mL). Aliquots of 4.04 mL were vortex-mixed and centrifuged after ACN addition of 150, 160, 170 or 180 µL H_2O (n = 3). The lower phase was reconstituted in 50 µL of ACN after fortification with dStd-Mix (10 µL) and analysed by LC/Orbitrap-HRMS (5 µL).

Each lyophilised food subsample (500 mg) was fortified with dStd-Mix (3 × 60 ng, 15 µL ACN, internal standards) and was subjected to microwave-assisted extraction (MAE, Monowave EXTRA, Anton Paar, Graz, Austria) using a mixture of acetone/dichloromethane 3:7 (*v/v*, 10 mL) at 80 °C during 10 min with a magnetic stirrer spinning at 200 rpm. Procedural blanks without (n = 3) or with C-Mix (40 µL, n = 3) were also subjected to MAE. After centrifugation (3500 rpm, 20 °C, 10 min), the liquid phase was transferred and stored in a glass flask. An extract mixture QC of the 12 drained subsamples (800 µL each) and 12 juices (400 µL each) was prepared. QC aliquots (2 mL) without (n = 3) or with C-Mix (8 µL, n = 3), as well as subsample and procedural blank aliquots (2 mL) were purified pending two successive liquid-liquid partitioning steps. Extracts were first concentrated to dryness under a gentle stream of nitrogen (40 °C), suspended in 2.6 mL DCM and partitioned with 2.6 mL of H_2O. After centrifugation (3000 rpm, 5 °C, 10 min), the lower phase was transferred to a new glass tube, concentrated to dryness under a gentle stream of nitrogen (40 °C) and suspended in 4 mL of a mixture of nHex/EtOH 1:1 (*v/v*). Then, after addition of H_20 (180 µL), phase separation and centrifugation (3000 rpm, 5 °C, 10 min), the lower phase was transferred to a new glass tube. Extracts were concentrated to dryness under a gentle stream of nitrogen (40 °C), suspended in 40 µL ACN containing 10 ng of $^2H_{15}$-triphenyl phosphate (dTPP) and 40 µL H_2O and transferred into vials. Pellets were removed after a gentle centrifugation. Vegetable extracts were analysed (7 µL) in a single LC/Orbitrap-HRMS sequence, along with procedural blanks (n = 3, n = 3 with C-Mix), QCs (n = 3, n = 3 with C-Mix), ACN (n = 7), dStd-Mix (n = 9) and C-Mix (n = 3).

176

177 *2.5. LC/ESI-Orbitrap-HRMS data acquisition*

178 Data acquisition on sample extract was performed on an Orbitrap Q Exactive instrument fitted with a
179 heated electrospray source operated in the positive mode (Thermo Fisher Scientific, San José, CA,
180 USA). One-dimensional full scan data was acquired according to Omer et al. (2018), pending slight
181 modifications. Targeted-MS^2 experiments were performed as well for structural elucidation.
182 Parameters are detailed in the supplementary material.

183

184 *2.6. Post-acquisition data treatment of the coatings data set*

185 The one-dimensional full-scan HRMS sequence raw data set related to coatings was processed using
186 an in-house user-friendly interface under the open source programming *R* environment, as previously
187 described by Omer et al. (2018) pending major improvements precisely described in the
188 supplementary material. Briefly, componentisation (which pairs signals likely originating from a same
189 compound in a so-called peak correlation group – PC-group) included sample alignment. The output
190 table, composed of features characterised by a PC-group increment, a sample to which it belongs, a
191 retention time (t_R), a centroided *m/z* and an intensity (area), was exported in an Excel® sheet for
192 manual data curation and mining.
193 In that respect, PC-groups were possibly split or merged, depending on the expert interpretation. A
194 few PC groups, not intense enough to be peak picked, were also manually created to complete
195 consistent series. Mobile phase and procedural blank PC-groups were annotated as *discard* while
196 PC-groups of interest were annotated as *substance*, mostly by decreasing order of cumulative intensity
197 or number of features, until remaining PC-groups were of very low significance.

198

199 *2.7. Identification and structural elucidation*

200 In order to gain structural information, one or two ion adducts were selected and fragmented for each
201 PC-group annotated as *substance* (MS^2 experiments), generally including the base peak ion which, in

the case of $[M + Na]^+$, $[M + K]^+$ or $[M + NH_4 + ACN]^+$, did not always provide valuable information due to charge retention on the adduct moiety. In-source adducts and fragmentation patterns are described for each PC-group in the supplementary material. Finally, identification was proposed using the scale proposed by Schymanski et al. (2014) after putting together all available information. The lowest level 5 starts with the accurate mass measurement (precise signal mass-to-charge ratio). An annotated unequivocal molecular formula increases confidence to level 4. Level 3 can be claimed if several candidate structures are plausible. Level 2 is reached when a unique probable structure (or in our case combined units) is suggested from diagnostic evidence (2b), involving for example MS^2, or library spectrum match (2a). The confirmed structure (ultimate level 1) is reached only after comparison alongside a reference standard. In the present study, the following criteria were used:

- relative retention time and chromatographic shape;
- pattern of in-source adducts;
- MS^2 fragmentation pattern, paying attention to co-eluting interferences;
- reference standard when available;
- hierarchical clustering (see supplementary material for data table preparation);
- in-house software database "NIAS-db 1.0" of theoretical combinations of polyester and phenol-formaldehyde resin components (freely available, see supplementary material);
- consistency of series according to deformulated monomers;
- for oligoesters at level 2a, a match with an in-house LC/ESI(+)-Orbitrap-HRMS data set acquired according to Omer et al. (2018) from 11 metallic plates coated with distinct polyester-polyurethane-based formulations according to manufacturer recommendations and of partially known formulations involving DEG, EG, BD, NPG, HD, CHDM, TCDDM as diol monomer units and iPA, tPA and AA as diacid monomer units;
- scientific literature.

2.8. Semi-quantification of substances in food

The list of observed *m/z* used for hierarchical clustering in coatings, with adjusted t_R ranges, was used to generate a suspect screening data set from the vegetable analytical sequence, using the *trapz* function (±5 ppm, *pracma R* package). Areas were then normalised and curated in the same way. Semi-quantification was considered with a response factor of 1 relative to those of the assigned internal standard, pending recoveries and high enough signal intensities. Results were expressed according to the wet weight, considering the moisture content determined at the lyophilisation step (Tables S2).

3. Results and discussion

3.1. Standards synthesis

In general, the lack of NIAS reference standards is a major bottleneck for their undisputable identification, quantification and for mechanistic studies. Regarding oligoesters, only two combinations of EG with tPA are commercially available: lin(2EG+tPA) and c(3EG+3tPA) (Paseiro-Cerrato et al., 2016a). Some authors isolated c(2BD+2tPA), c(3BD+3tPA) and c(3EG+3tPA), with 1,4-butanediol as BD monomer, from pelleted polyethylene and polybutylene terephthalate materials (Eckardt et al., 2019). Others attempted syntheses of lin(CHDM+NA) and lin(CHDM+iPA) (Paseiro-Cerrato et al. 2016a), c(DEG+AA) and c(2DEG+AA+PA) (Úbeda et al., 2017) and lin(2NPG+iPA), lin(2MPD+iPA), lin(2HD+iPA), lin(2HD+2tPA), c(2HD+2tPA), c(2HD+2iPA), c(2NPG+2tPA), c(2NPG+2iPA), c(2MPD+2tPA), c(2MPD+2iPA), c(MPD+HD+2iPA), c(NPG+HD+2iPA), c(3HD+3iPA), c(2NPG+iPA+tPA), c(2HD+iPA+tPA) (Pietropaolo et al., 2018), with varying recovery rates and approximate purity degrees. With such native compounds, the choice of internal standards for quantification remains delicate. To meet the need, Pietropaolo et al. (2018) have synthesised a cyclic oligoester, c(2HD+2DPA), from 2,6-pyridinedicarboxylicacid (DPA), a diacid that is not used for coatings. Labelled compounds would pave the way to a more accurate quantification through the isotope dilution method but, so far, none have been produced.

To address the unavailability of reference standards, our first efforts were focused on the organic synthesis of an oligoester series derived from NPG and iPA units. As this first objective was the

production of reference standards for quantitative studies (native and D-labelled), a stepwise synthesis enabling control of cyclisation by a daunting macrolactonisation as final step (Parenty et al., 2006) was considered in order to produce pure analytical batches with recovery yields minimising the waste of expensive labelled precursors. Considering the molecular structure of c(2NPG+2iPA), a multistep synthesis that could be conveniently reproduced in labelled-series following the use of well-identified isotope-labelling reagents was designed. To this end, the integration of deuterium by the readily accessible D_4-NPG intermediate was preferred (see supplementary material for justification). The resulting 11-step synthesis is shown Fig. 1. Desilylations and the final macrocyclization represented the most tedious steps to be optimised (see supplementary material). Eventually, desilylations were promoted with HF.Pyridine (yields >80%) and macrolactonisation by DMAP leading to c(2NPG+2iPA) **10-H_4** in 69% isolated yield accompanied with the native cyclic c(4NPG+4iPA) **11-H_8** as side product (15% yield).

The optimised synthetic strategy was applied to the native series giving rise to size-controlled linear lin(2NPG+2iPA) **9-H_4** and its cyclic congener c(2NPG+2iPA) **10-H_4** with a 35% overall yield. The sequence was thus gratifyingly achieved from the site-specific deuterated D_4-NPG unit **3'-D_4**, affording the size-controlled linear D_4-lin(2NPG+2iPA) **9-D_4** and cyclic D_4-c(2NPG+2iPA) **10-D_4** species, as well as the cyclic D_8-c(4NPG+4iPA) **11-D_4** as side product.

Characterisation data (NMR, ESI-TOF-HRMS, LC/ESI-Orbitrap-HRMS) are provided in the supplementary material. Chemical purities of the final products **9**, **10** and **11** yielded >95% (NMR estimations) while no impurities could be identified by LC-ESI(+/-)-HRMS except for **11-D_8** containing less than 1% of **10-D_4**. Considering the isotopic purity of lithium aluminium deuteride (>98%), the observed isotopic impurities were in line with the expected value for D_4- and D_8-containing compounds (92% and 85%, respectively).

3.2. Data mining in coatings

3.2.1. Approach

Twelve vegetable cans were collected in a supermarket in France, in order to produce a picture of leachable substances relevant to the market reality. The study was confined to vegetables in order to contain difficulties arising from the presence of fat during sample preparation (see Table S2 for fat contents). Indeed, fat impairs chromatographic and ionisation systems, and was perceived as the most difficult macronutrient to eliminate during the purification steps, most NIAS being suspected to be lipophilic. A variety of vegetables, brands, as well as can shapes and capacities were considered. No information on the formulation of inner coatings was available. Cans being shaped and filled with food, it appeared impractical to perform migration testing using food simulants according to standardised guidelines (EU 10/2011). Consequently, our strategy was to identify extractible substances from individual coatings and then to investigate their presence directly in foodstuffs. Indeed, although some sorption was expected, coatings remained simpler matrices to investigate than foodstuffs. A base assumption was that the depletion was not complete in case of migration from the coating to the food. The sample set comprised 40 inner coatings that we separated from food and rinsed. Most top-end coatings were translucent while the other coatings were mainly white (Table S3). The white colour is likely due to the TiO_2 pigment, an additive listed in the ResAP(2004)1, possibly used in combination with an extender (Bradley et al., 2009). Side seam stripe coverages ranged from 7.2 to 11.8 g/m^2, except for S02d which was badly grated (0.62 g/m^2) (Table S3). Other coating coverages ranged from 0.51 to 2.15 g/m^2. These results were expected because side seam stripes are typically thicker. Estimated coverages do not necessarily reflect the coverage specifications for the can manufacturing considering that coatings have been dried, that a migration/sorption phenomenon took place during the processing and storage, and that the sampling method (surgical blade scraping, static electricity) remains delicate. However, the objective remained qualitative at this step.

ACN extracts of grated coatings were fortified with the synthesised D-labelled compounds and subjected to a non-targeted analysis based on LC/ESI(+)-Orbitrap-HRMS that has previously been shown to be adequate for the detection of oligoesters (Omer et al., 2018). One-dimensional full scan

data ranged from 155 to 1064 *m/z*, thus excluding most monomers (out of the scope of the present study) and allowing for the detection of typical adducts of compounds up to 1000 Da.

Chemicals with a molecular weight above 1000 Da are generally not considered, as they are very unlikely to be absorbed through the gastrointestinal tract, unless previously degraded (EFSA, 2020). In reality the 1000 Da criterion is not a clear upper-cut limit for absorption in the gastrointestinal tract (Groh et al., 2017). Indeed, Hamdani et al. (2002) showed hydrolysis of 1,2-propanediol and adipic acid polymer in intestinal-simulating solutions but not under saliva and gastric conditions.

3.2.2. Data quality

Retention times of labelled standards were stable along the sequence with a maximum standard deviation of ±0.5 s. Trueness deviation of mass was 0.10 ± 0.07, -0.21 ± 0.07 and -1.23 ± 0.10 ppm for D_4-lin(2NPG+2iPA), D_4-c(2NPG+2iPA) and D_8-c(4NPG+4iPA). A set of 20 ions from the mobile phase (*m/z* range 186-1007; ~5000 features) was used to estimate the intermediate mass precision as being 0.77 ppm. These performances allowed us to narrow down the candidate formulas arising from the formula decomposition searches.

3.2.3. Data curation

The post-acquisition processing of the sequence data set (including ACN, standards, procedural blanks, QCs and coatings) resulted in 5,267 PC-groups. They were manually refined to 5,336 PC-groups due to obvious co-elutions misleading the script efficiency (*e.g.* labelled standards with corresponding native compounds) or to the addition of poorly intense compounds completing consistent series (no features). Indeed, the script signal threshold was set at a relatively high value in order to limit the output number of features (n = 17,256). Isomers were also merged when relevant, resulting in 5,038 remaining PC-groups. This way, oligomers which are composed of the same units ordered differently, or which are diastereoisomers, were gathered in a unique PC-group.

As regards the 40 coating extracts only, 13,105 features were obtained. Extensive review of the signals allowed the annotation of more than half those features as arising from the mobile phase solvents (34%), from mobile phase impurities or procedural blank peaks (9%) or from deuterium-labelled standards (13%). A set of 1,572 features accounting for 15.3×10^9 AU of cumulative signal area were considered as minor signals from diverse and unchecked 978 PC-groups.

3.2.4. Selected PC-groups of interest

The remaining features (n = 4,188), belonging to 139 PC-groups, reflected 94% of the relevant information (252×10^9 AU, cumulative area with unchecked signals) and constituted the set of distinct substances (single compounds or more often isomer mixtures) selected for the next steps of the study. Each PC-group was meticulously reviewed and most of the features were annotated either as an adduct or as a ^{13}C contribution (up to M+3). Adducts were predominantly $[M + H]^+$, $[M + NH_4]^+$, $[M + Na]^+$, $[M + K]^+$ or $[M + NH_4 + ACN]^+$. Dimers (even trimers) and doubly charged adducts were also observed, as well as sodium acetate adduct series (up to 9 repeating units of *m/z* 82.002). The monoisotopic molecular mass could be determined for all PC-groups. It ranged from 187 to 2013 Da, seven substances being above the threshold of 1000 Da and only one below 250 Da. The molecular formula mass could be determined for all PC-groups as well (identification confidence level ≤4).

Some chromatographic humps being imperfectly integrated with the *xcms* package, signals from ions above 20% of the base peak were properly reintegrated in a targeted way, and summed for each PC-group. The resulting data set (290×10^9 AU of cumulative area) was used for the hierarchical clustering (Figs. S8). Side seam stripes exhibited the most intense cumulative areas (Fig. S9), in line with the relatively higher thickness and the absence of cross-linking in such coating type, favouring migration. Half of top-end coatings had also relatively intense cumulative areas, although much thinner.

Then, depending on the pieces of evidence, identification confidence levels remained at 4 (n = 13), reached 3 (n = 12), 2b (n = 47), 2a (n = 43) or even 1 (n = 24). Summary tables and detailed sheets are

356 available in the Excel® file supplementary material. Fig. S11 shows that mass deviations remain well
357 within ±5 ppm, a criteria required for identification by HRMS in official guidelines, these latter
358 remaining globally inadequate for unknown screening (EU 2021/808). Compounds were categorised in
359 7 groups for which the relative contribution to the cumulative area is shown Table 2 and which are
360 further described hereafter.
361
362 *3.3. Substance families identified in coatings*
363 *3.3.1. Oligoesters*
364 Most PC-groups (n = 84) were annotated as oligoester, in consistent series, either as cyclic (n = 65),
365 linear (n = 18) or undetermined (n = 1) combinations. They accounted for 78% of the cumulative area
366 (227×10^9 AU). Confidence levels reached 2a or 2b in most cases, c(2NPG+2iPA) and c(4NPG+4iPA)
367 being unequivocally identified thanks to the synthesised standards. Lin(2NPG+2iPA) was not observed.
368 Each can was composed of at least one polyester-based coating. Actually, only 2 coatings did not
369 present any detectable trace of oligoester (S04b White beans body/bottom end; S10c palm hearts
370 bottom end) and 2 coatings exhibited relatively low levels (S01b Button mushrooms and S12b
371 chickpeas body/bottom end). Three of these samples corresponded to the body/bottom-end coatings
372 of 3 out of the 4 two-PC cans. In the 36 remaining coatings, oligoesters contributed between 38% to
373 almost 100% of the signal intensities (average 85%). These unexpected results demonstrate how
374 prevailing the polyester-based coatings have become on the French market, at least for vegetables.
375 In terms of units, cyclic combinations were dominated by 4-unit (n = 33, 120×10^9 AU), followed by
376 6-unit (n = 20, 71×10^9 AU) and 8-unit (n = 12, 22×10^9 AU) oligoesters. Linear forms were also
377 observed, mostly in top-end and seam coatings. They were mostly diol-terminated (EG, BD or NPG),
378 thus exhibiting an odd number of units, more precisely 5-unit (n = 7, 5.0×10^9 AU), 7-unit (n = 5,
379 5.2×10^9 AU) and 9-unit (n = 4, 2.2×10^9 AU) combinations. Two doubly charged PC-groups revealed
380 the presence of a 16-unit (thus including a terminal acid) and 17-unit combinations. In-between
381 combinations were not observed since out of *m/z* ranged (monocharged) or too small to be doubly

charged. No conclusion could be drawn on any preferential formation among linear forms of diol-terminated combinations since the positive ESI mode was not indicated to detect oligomers with free carboxylic functions, which can be deprotonated quite easily.

Oligoester combinations involved 8 diols (EG, DEG, PD, BD, NPG, HD, CHDM and TCDDM) and 4 diacids (AA, PA, HHA and SeA) all belonging to the ResAP(2004)1 (Tables S1). Their names and structures are detailed in Fig. 2. In the cases of BD, PD, PA and HHA, several isomers, which can hardly be distinguished by MS, are possible.

A rough estimation of the formulation units was performed by disaggregating PC-group areas according to their corresponding combination. A great diversity was observed from one formulation to another. On average, for the diols, BD accounted for 49%, followed by NPG (28%) and HD (11%). A closer look showed that BD was the dominant diol in seam coatings (87% in average) while it remained minor (<2%) in other coating types. On the opposite, NPG and HD dominated these other coating types and remained minor in seam coatings.

NPG was the most frequently observed diol (n = 39 combinations) and was combined with all other diols and diacids, except PD and TCDDM. TCDDM is a high molecular weight diol that is conveniently used to increase the average molecular weight of uncontrolled oligomers, in order to minimise both their migration and the fraction below 1000 Da considered as toxicologically relevant. Its monoisotopic mass is 196 Da while those of BD and NPG are 90 and 104 Da, respectively. TCDDM was present in at least 3 out of the 4 coatings of the 3-PC cans of samples S02 (endives), S05 (mixed vegetables), S07 (salsifies) and S10 (palm hearts), suggesting that combined efforts have been made for minimising migration from these cans. However, there was no obvious difference in the cumulative areas of oligoesters from these cans. Although TCCDM could be observed as the dominant diol in a few formulations, its use remained low on average (4%). Seventeen out of the 40 coatings (7 cans) contained oligoester combinations of TCDDM with PA and BD. EG and DEG accounted for 5% of the diols and were frequent but always minor components. PD (3%) appeared in only one coating (S02a endives top end), in combination with SeA only. CHDM, for which the identification level was only 3,

remained a minor diol (0.1%). Yet, it has been reported in 6, 20 and 7 combinations of undescribed coatings by Bradley et al. (2009), Paseiro-Cerrato et al. (2016b) and Lestido-Cardama et al. (2022), respectively. Paseiro-Cerrato et al. (2019) also quantified lin(MPD+CHDM+PA) in 6 canned foodstuffs. Interestingly, when EG, DEG, PD, NPG or HD were present in the same coating, no oligoester combination of these diols with TCDDM was observed. A first hypothesis is that combinations of TCDDM with diols other than BD are hardly formed during the elongation step. It is more likely that those coatings were prepared from different resins applied as one single or several layers, TCDDM being polymerised with BD as the only diol in a proportion of about 90:10 to 95:5, respectively.

For the diacids, PA accounted for 86%. Whatever the polyester formulation (38 out of the 40 coatings), PA was always involved, generally as the dominant diacid. It was also the only diacid in about half the combinations, most of which were previously reported in metal can (Schaefer et al., 2004; Bradley et al., 2009; Paseiro-Cerrato et al., 2016b; Pietropaolo et al., 2018; Omer et al., 2018; Lestido-Cardama et al., 2019, 2022; Terrasse et al., 2022) or press-twist closure (Eckardt et al., 2020a) coatings. PA is the most common polyacid in polyester resins for FCMs, usually as iPA, tPA or a mixture of both.

Another frequently mentioned diacid for polyester formulations is AA but, to the best of our knowledge, no AA-based oligoester has been reported so far in can coatings. In the present study, 15 cyclic and 6 linear PC-groups involved AA, in combination with PA, EG, BD and/or NPG. AA accounted for only 6% on average but was the major diacid in 2 body/bottom-end coatings (S01b button mushroom; S12b chickpeas). As regards SeA (8%) and HHA (0.5%), they are the only possibilities explaining 26 cyclic combinations (level 2b), considering the fragmentation patterns and the ResAP(2004)1. SeA (8%), which we previously hypothesised to be present in oligoesters (Omer et al., 2018), seems to be a common raw material in polyester manufacturing (Zhang et al., 2020). More precisely, 14 cyclic and 7 linear combinations involved SeA, with EG, DEG, PG, BD, NPG and PA. Depending on the coating, SeA was either the major diacid (83%; S02a endives top end) in combination with PD only, minor (9-17%) or possibly an impurity (<2%). For HHA (0.5%), cyclic (n = 5) and linear (n = 3) combinations involved NPG as the only polyol and PA. Surprisingly, HHA-containing cyclic

combinations were observed in top-end coatings only (except 2 combinations in coating 05d) while linear combinations were observed in side seam stripes only. HHA was observed in only 5 coatings, either as minor diacid in top-end coatings (15-20%, in association with PA and NPG mostly) or likely as an impurity (<1%). To the best of our knowledge, no AA- or HHA-based oligoester has been reported so far in can coatings. Nadic acid (NA) did not contribute to any of the combinations. Yet, although NA is not listed in the ResAP(2004)1, NA-based polyester coatings are likely marketed. Linear (n = 8) and cyclic (n = 4) NA-containing oligoesters have been tentatively identified in empty cans provided by an industrial partner (Paseiro-Cerrato et al., 2016b). Driffield et al. (2018) also tentatively identified up to 35 undescribed oligoesters migrating from 2 undescribed coatings based upon nadic anhydride to a range of canned foodstuffs.

While up to 9 diols and diacids were present in a coating, the diversity of units remained lower than 4 in each combination. This could be due to several individual or combined reasons, such as separate resins of more simple formulations and lower probabilities of producing large oligoesters, including from minor units. The signals of combinations based on BD and PA (4- to 8-units) stood as the most intense, by far. Along with the related linear 5- and 7-unit combinations, they were present exclusively in the 8 side seam stripes (76×10^9 AU). The second most intense combination series arose from NPG and PA and was more widely distributed (32 out of the 40 samples; 25×10^9 AU). Most ion chromatograms of c(2NPG+2PA) showed 3 peaks annotated as the 3 possible combinations of iPA and tPA (t_R = 11.45, 11.76 and 11.91 min). Interestingly, an intense fourth peak (t_R = 12.30 min) appeared in several top-end coatings. The latter was identified as c(BD+HD+2PA), an isomer of distinct diol composition, thanks to the MS^2 fragmentation pattern.

Concerning the adduct types, $[M + Na]^+$ was the most frequent base peak, occasionally $[M + NH_4]^+$ that remained major. Other important adducts (>20% compared to the base peak) were mostly $[M + NH_4 + ACN]^+$, sometimes $[M + H]^+$, $[M+Na+ACN]^+$ or $[M+Na+AcNa]^+$. $[M + K]^+$ ion adduct was observed only once above 20% of relative intensity. A few $[2M+Na]^+$ dimers were observed, even if most of the theoretical values were out of the *m/z* range. It should be noted that heterodimers of

native c(2NPG+2iPA) with the co-eluting D-labelled compound were formed. Within PC-groups, relative intensities could vary significantly from one isomer to another.

No in-source fragmentation was observed, except for c(2BD+2PA) for which minor losses of BD or BD+PA fragments occurred.

MS^2 fragmentation patterns complied with the general rule of preferential cleavages at ester bonds with/without H_2O losses, giving rise to oligomeric ion series quite easily annotated. Specific *m/z* values appeared as diagnostic signals for the heaviest units and many unit combinations. The obtained data Table S8 of annotated fragments will be of valuable interest for future generic suspect screening of targeted polyol and polyacid unit contributions or their combinations.

3.3.2. Additives

Five substances were considered as additives supposedly added intentionally (or related oxidation products), after being confirmed with reference standards (n =4, level 1) or based on diagnostic evidence (n = 1, level 2b). The related 13 PC-groups accounted for 17% of the cumulative area (50×10^9 AU).

The chemical formulas of the dominant substance (9 PC-groups, 49×10^9 AU) matched those of epoxidised triglycerides (3 to 7 epoxides). The ResAP(2004)1 mentions epoxidised soya bean (EBSO, SML = 60 mg/kg) and linseed (ELSO, temporary list) oils as additives. While all PC-groups matched purchased reference standards, their chromatographic shapes (complex isomer mixtures) and relative abundances clearly balanced in favour of EBSO. ESBO is a plasticiser commonly found in PVC-based FCMs and exposure assessments seem to disregard exposure from metal can coatings (EFSA, 2004; Bandele et al., 2018). It was mostly present in 8 out of the 12 top-end coatings.

Three other confirmed compounds were 1,2-cyclohexanedicarboxylic acid diisononyl ester (DiNcH), tris(3,5-di-tert-butyl-4-hydroxybenzyl) isocyanurate (Irganox 3114) and triphenylphosphine oxide (TPPO). They were identified in 2, 5 and 1 coatings, respectively, at relatively low intensities. Although it is not mentioned in the ResAP(2004)1, DiNcH is approved for plastic FCMs, without SML. It was

detected mostly in body/bottom-end coating of the button mushrooms can (S01b), which exhibited relatively low levels of oligoesters, with AA as the major diacid. Introduced in 2002, DiNcH is the most widely known substitute for bis(2-ethylhexyl) and diisononyl phthalates in medical devices, toys and food packaging materials (Bui et al., 2016). Irganox 3114 is an antioxidant approved for plastic FCMs, varnishes and coatings (SML = 5 mg/kg). It was identified in 3 out of the 4 coatings of the endives can. TPPO has been tentatively identified in 2 out of 12 emptied food cans by Lestido-Cardama et al. (2019). It is listed neither in the ResAP(2004)1 guideline nor in the EU 10/2011 regulation. However, it is described as an oxidation product of triphenylphosphine (not observed), which is listed as temporary additive in the ResAP(2004)1 guideline and is used as a catalyst in epoxy-phenol polymerisation reactions and as a coupling agent (Zhang et al., 2020). Also, TPPO is listed as a photo-initiator that has not been fully evaluated in a provisional list of printing inks and varnishes for the non-contact side of food packaging can of the EuPIA (2018). TPPO is one of the most abundant organophosphate esters considered as flame retardants accumulating in environmental matrices and biota (Garcia-Garin et al., 2020).

Lastly, a PC-group with a monoisotopic mass of 1014.5473 Da did not return a chemical formula at first. Exploring the FCCdb database, we used the PubChem and the Chemical Translation Service to import chemical formulas for about 64% of the substances (see Fig. S12 for more details). Then, we obtained a match with the monoisotopic mass of 2,2-methylene-bis(4,6-di-tert-butylphenyl) phosphate aluminium hydroxide salt (CAS 151841-65-5) of chemical formula $C_{58}H_{85}AlO_9P_2$. Aluminium was not initially considered in formula decomposition but MS^2 data corroborated the chemical formula as well as the structure. Unfortunately, comparison with a purchased standard did not succeed. This standard showed a peak at an earlier t_R, matching only the $C_{29}H_{43}O_4P$ moiety. This Al-containing substance is commercialised as ADK Stab NA 21E, a patented particulate nucleating agent. Although not mentioned in the ResAP(2004)1, it is approved for plastic FCMs (SML = 5 mg/kg) and present in several other source lists of the FCCdb. It was identified in the bottom-end coating of the cut palm hearts can (10c, devoid of oligoesters) in association with TPPO.

512

513 *3.3.3. Sorption*

514 All coatings contained traces of at least one fatty acid among palmitic, oleic, linoleic and α-linolenic
515 acids. Although the ionisation process produces a negative deprotonated species, adducts with two
516 sodium ions ($[M - H + Na_2]^+$) were observed in the used positive mode, along with relatively intense
517 series of sodium acetate adducts. Unambiguous identification was confirmed in the negative mode.
518 These fatty acids are listed in the ResAP(2004)1 either as monomers or additives without specific
519 restriction. Considering that they are common components of the human diet, their presence in the
520 coating appears to be rather due to sorption from the food contents. Indeed, a given fatty acid is often
521 present at similar intensities in all coatings from the same can. The uncertainty is higher for the can of
522 cut palm hearts for which intensities were more than 100 times higher in the seam coating compared
523 to the others for the 4 fatty acids. However, such combined intentional use would raise questions.
524 Another compound likely arising from sorption was a $C_{45}H_{78}O_{10}$. It was mainly observed in the coatings
525 in contact with sweetcorn and whole peeled tomatoes. No structural hypothesis could be made but
526 the numerous MS^2 fragments were similar to ESBO fragments.
527 As shown in these examples, sorption remains a major drawback when working on filled cans. In
528 addition to the pollution of the sample with interfering compounds, it can raise a doubt on the way
529 compounds are travelling (migration or sorption). Using ethanol to remove a layer of adsorbed fatty
530 food components from the coating surface will help minimise these artefacts.

531

532 *3.3.4. BADGE derivatives*

533 The palm hearts bottom-end coating (S10c), devoid of oligoesters, was characterised by a specific
534 series of 10 PC-groups (2.1×10^9 AU), accounting for 94% of the signal of interest in this coating.
535 Surprisingly, this series matched with butoxyethyl derivatives of BADGE (levels 3–2b) (Berger and
536 Oehme, 2000; Schaefer and Simat, 2004; Paseiro-Cerrato et al., 2017), among them 2 epoxides and
537 1 chlorinated homologue. Many isomeric combinations were observed. Butoxyethanol is a surfactant

538 and solvent typically used with BADGE and possibly containing by-products that hold more oxyethylene
539 moieties (Beszterda et al., 2021), slightly more polar, and that we also observed. Although the
540 methodology was likely adequate (Berger and Oehme, 2000; Gallart-Ayala et al., 2011),
541 *tert*-butylphenol derivatives of BADGE with H_2O and/or HCl derivatives of a single BADGE moiety were
542 not observed. Suspect screening allowed to also hypothesise the presence of low levels of
543 di-BADGE·BuOEtOH and cyclo-di-BADGE. Overall, the compliance of this coating to current National
544 restrictions appears questionable. Lastly, it is unclear why these compounds have often been observed
545 in other coatings at much lower levels (they are possibly NIAS). One explanation could be a set-off
546 phenomenon during the manufacturing process and storage of unshaped metal plates involving
547 phenoxy-based coatings on the external side (Lestido-Cardama et al., 2019).
548
549 *3.3.5. Phenolic oligomers*
550 The white beans body/bottom end (S04b), devoid of oligoesters, was characterised by a specific series
551 of 5 PC-groups (0.8×10^9 AU), accounting for 98% of the signal of interest in this coating. Traces of
552 some of these compounds were also observed in the endive top-end coating (S02a). They turned out
553 to be characteristic oligomers of phenolic-formaldehyde resins prepared from phenols (phenol,
554 cresols, *tert*-butylphenol), formaldehyde and butanol (Table S5). An alkaline catalyst (and usually a
555 molar excess of formaldehyde) is used to make resole resins that can be used as cross-linkers (Eckardt
556 et al., 2020b) while an acidic catalyst and a molar excess of phenol to formaldehyde are conditions
557 used to make novolac resins.
558 Based on chemistry of phenol-formaldehyde resins summarised by Biedermann and Grob (2006a), we
559 prepared a database of theoretical combinations (NIAS-db 1.0). Each PC-group returned 12 to 31
560 possible combinations (Table S9). MS^2 data was not decisive to further refine from level 3 but,
561 hypothesising no methylol linkage nor free reactive sites (*o*/*p* positions and free methylol group), we
562 suggested opC as main backbone unit with methylene and possible methoxy linkages, with butoxylated
563 methylol substituents as well. It should be noted that cyclised components such as 4 *o*/*p*-cresols bound

564 by 4 methylene linkages were among the hypotheses. Terrasse et al. (2022) recently proposed phenolic
565 structures for 37 NIAS arising from polyester-phenolic coatings (20% resole-based) using
566 GC/EI(+)-Orbitrap. However, none of the chemical formulas matched with the compounds of the
567 present study.
568
569 *3.3.6. Benzoguanamine (BG) derivatives*
570 Considering known N-containing IAS, neither isophorone diisocyanate (IPDI) nor caprolactam or
571 methylethylketone oxime (MEKO) were identified. IPDI is a listed cross-linker widely used in polyester-
572 based varnishes but not detectable with the present method (Omer et al., 2019). Caprolactam and
573 MEKO are volatile blocking agents. If present, caprolactam would have eluted before the acquisition
574 window in the present study (Omer et al., 2018).
575 Actually, apart from the additive Irganox 3114 and an unknown $C_{33}H_{33}NO_4$, the other N-containing
576 PC-groups (n = 13, 0.84×10^9 AU) were all related to BG. Eluting early in the acquisition window
577 (t_R = 2.03 min, truncated peak), when identified (level 1) in one coating, BG was generally present in
578 the other coatings of the same can (21 coatings, 7 cans). BG ($C_9H_9N_5$) is a cross-linking agent mentioned
579 in the ResAP(2004)1, which is commonly reacted with formaldehyde to form hydroxymethyl groups
580 and is further condensed with alcohol (Okuno et al., 2003). BG has been identified in coatings of
581 marketed beverage and foodstuff cans, some being polyester-based (Lestido-Cardama et al., 2019,
582 2022). It has been reported to migrate from PVC and acrylic-phenolic coatings into food simulants as
583 well (Vaclavikova et al., 2016; Paseiro-Cerrato et al., 2017).
584 In BG-containing coatings, a series of BG oligomers (up to 5 units) with methylene linkages were also
585 identified (level 2b, accumulation with BG at 0.35×10^9 AU).
586 The tetrahydroxymethyl derivative of BG was one of the hypotheses for a PC-group of chemical
587 formula $C_{19}H_{29}N_5O_4$. Unavailable as a pure standard, it could be found in a mixture of
588 (hydroxymethyl)benzoguanamine, methylated/ethylated, with no known CAS. Absent from the FCCdb,
589 this substance is described as a cross-linking agent by the standard provider. The compound not only

590 matched the standard but the 4 other methylated/ethylated combinations were also unambiguously
591 identified in other tightly related PC-groups. This substance was present in 4 top-end coatings
592 (0.28×10^9 AU).
593 Considering the fragmentation patterns of the above-mentioned BG-derivatives, another PC-group
594 was hypothesised in various coatings as bis(butoxymethyl)benzoguanamine, the ether functions being
595 located on the phenyl cycle (level 2b).
596 Lastly, 2 related PC-groups ($C_{21}H_{23}N_5O_2$, $C_{26}H_{33}N_5O_2$), mostly present in the body/bottom end of 2
597 coatings with low levels of oligoesters (S01b Button mushrooms and S12b chickpeas), exhibited double
598 bond equivalents (DBE) of 13 (against 8 or multiples of 8 for other BG derivatives). They shared BG MS^2
599 fragments with the other BG-derivatives but we failed to propose structures.
600 Except BG itself, BG-derivatives are NIAS that could arise from uncontrolled reactions with BG from
601 one of the few substances listed in the FCCdb which are BG- and formaldehyde-based polymers (CAS
602 63130-56-3, 159002-24-1, 68002-26-6, 25035-72-7, 26160-89-4 and 196823-49-1), none being listed
603 in the ResAP(2004)1. Vaclavikova et al. (2016) have previously suspected the presence of BG-based
604 NIAS in PVC-based coatings but, considering retention times and masses, none of these were common
605 with those suggested in the present study.
606
607 *3.3.7. Remaining unknown*
608 A series of 5 PC-groups ($C_{33\text{-}43}H_{48\text{-}76}O_{6\text{-}10}$; DBE = 4-6) present mostly in seam coatings exhibited distinct
609 fragmentation patterns that we did not relate to any structure. A PC-group ($C_{28}H_{32}O_9$; DBE = 13) of
610 several isomers, observed in the side seam stripes likely contained BD and PA units. Considering the
611 absence of match with the theoretical database of oligoesters, we suspected an oligoester derivative.
612 Two PC-groups of chemical formulas $C_{29}H_{42}O_6$ (DBE = 9) and $C_{33}H_{52}O_6$ (DBE = 8), observed in 3 top-end
613 coatings (S02a, S05a, S07a), could not be annotated with any structure, although exhibiting MS^2
614 fragments specific of phenol-formaldehyde compounds with phenolic butoxy losses. A $C_{24}H_{44}O_5$
615 unknown (DBE = 3) was observed in top-end coatings. No match came out from the databases and no

structural hypothesis was made on the basis if the MS^2 fragmentation. Lastly, a $C_{33}H_{33}NO_4$ (DBE = 18) unknown was correlated to some top-end coatings but no match came out from the interrogated databases. N-free fragments matched phenol-formaldehyde fragments.

3.4. Migration of coating substances into food subsamples

3.4.1. Sample preparation and limitations

Once the identification of small molecules in coatings was achieved, the next step consisted in determining if some of them presented the ability to migrate in foodstuffs and, if so, to complete the study with some quantitative aspects. To this end, it was necessary to develop a sample preparation that would enable the purification of a maximum of target substances from subsamples prior to analysis. A mixture of acetone/dichloromethane was used as a generic approach aiming at extracting the wide diversity of identified substances from dried subsamples. Then, a liquid-liquid partitioning was optimised, based on a ternary solvent mixture involving miscible and equivolumetric nHex and EtOH with an addition of H_2O to create a phase separation. An additional liquid-liquid partitioning between DCM and H_20 aimed at removing more matrix components and pigments. The same LC/ESI(+)-Orbitrap-HRMS separation and detection were preferred over other approaches (e.g., UV), considering the required specificity and sensitivity. Details on the sample preparation developments and the related performances are provided in the supplementary material.

Prior to interpreting the results on the vegetable subsamples, limitations of the approach must be emphasised. Many factors contribute to uncertainty such as the matrix effects, the differential recoveries between a compound of interest and its assigned internal standard (one of the 3 D-labelled standards or the average of the two cyclic standards, depending on the structure and the retention time), their relative response factors in ESI or the adduct patterns that vary from sequence to another. Response factors of 12 oligoesters synthesised by Pietropaolo et al. (2018) differed by up to a factor of 14.7. Also, the choice of the considered adduct is of the utmost importance and the contributions of $[M + Na]^+$ ions were found to be relatively higher in the vegetable analytical sequence compared to

642 those in the coating analytical sequence. Following non-targeted approaches, the limited number of
643 proxy compounds provides semi-quantifications rather than accurate concentrations (Malm et al.,
644 2021). The 3 synthesised D-labelled compounds remain good proxies for oligoesters and optimal
645 choices mimetic native compounds but are less appropriate for other substance categories. For these
646 reasons and bearing in mind that we achieved semi-quantification only, relative response factors of 1
647 with assigned internal standards were considered and no more complex corrections were performed.
648 This way, any identified compound could be semi-quantified. However, the non-observation of a
649 compounds of interest cannot entirely be ascribed to its presence. It could have been lost during
650 sample preparation.
651
652 *3.4.2. Oligoesters*
653 At least 4 and up to 40 oligoester combinations were identified in each subsample, with an average of
654 15 and 17 in juices and drained vegetables, respectively. All 12 above-mentioned monomers were
655 involved in the 68 migrating combinations (out of 84 in the coatings).
656 As shown in Fig. 3 with the distribution of semi-quantification ranges, drained vegetables were much
657 more contaminated (even based on dried weight), showing that the drained contents acted like a sink
658 after migration through the fluid fraction. In juices, levels were generally lower than 1 µg/kg; only the
659 tomato juice showed combinations above 10 µg/kg. For the latter, it seems that the tick sauce limited
660 the migration into the drained tomatoes, as suggested by the concentration gradient of 220, 560 and
661 100 µg/kg of oligoesters (cumulative) for the juice, the sauce and the drained tomatoes, respectively,
662 dried matter contents being similar in the three cases (7.2-9.1%).
663 In drained fractions, at least one combination exceeded 10 µg/kg for each subsample, and two
664 subsamples (butter beans and sweetcorn) had 3-4 combinations above 100 µg/kg, up to 362 µg/kg for
665 c(DEG+NPG+2PA) in butter beans. The only combination being identified in all drained samples,
666 c(2NPG+2PA), is also the one with the highest mean concentration, at 54 µg/kg (range: 6-254 µg/kg).
667 The sum concentration of oligoesters in drained vegetables averaged 330 µg/kg, ranging from 43 to

1600 µg/kg in white and butter beans, respectively. Fig. 4 shows a radar plot of the concentrations of the 18 oligoester combinations exceeding 5 µg/kg on average in the drained vegetables (see Table S10 for data). PD, TCDDM and HHA are not involved in those combinations. HHA emerges as being a minor contribution to the migrating fraction. However, although observed in fortified procedural blanks, all 5 TCDDM-containing combinations observed in coatings were lost in fortified QC extracts, showing that the sample preparation was inadequate for these compounds and that no conclusion as regards their migration could be drawn. In terms of chain length, the migrating fraction had an average weighted mean (semi-quantification) of 4.3 units in the drained vegetables while the identified combinations in the 38 coatings had an average weighted mean (signal intensity) of 5.0. This result illustrates the fact that smaller molecules migrate more easily.

These results support the fact that oligoesters are a major NIAS family of diverse combinations to which the French population is systematically exposed when consuming canned vegetables. So far, two other studies reported levels of oligoesters in homogenised entire contents of canned foodstuffs. Using polyester polyurethane diol, Driffield et al. (2018) semi-quantified oligoesters migrating from two known but partly described coatings based on nadic anhydride and phthalic acid, in canned aqueous and acidic processed foods stored up to the end of their shelf-life. Cumulative migration of up to 35 undescribed combinations averaged 224 µg/kg (up to 943 µg/kg) in 19 out of the 24 samples. Paseiro-Cerrato et al. (2019) sampled 53 canned foodstuffs sampled in local grocery stores in Washington D.C. and Maryland without initial knowledge on the formulation of their inner coatings. Using lin(2EG+tPA), they semi-quantified lin(2MPD+PA) and lin(MPD+CHDM+PA) in 6 samples at sum values ranging from 391 to 767 µg/kg. Others sample coatings were polyester-based and other oligomers were suspected. Thus, our results corroborate these two studies on the fact that oligoesters migrate at several hundreds of µg/kg food.

3.4.3. BADGE derivatives

693 Six BADGE derivatives were semi-quantified above 1 µg/kg in 6 drained subsamples (Table S11,
694 Figs. S17). Their sum reached 75 µg/kg in palm hearts (S10), for which the bottom-end coating was
695 dominated by BADGE derivatives, but was even higher in drained sliced button mushrooms (S01,
696 130 µg/kg). Although observed at trace levels in corresponding coatings, their prevalence raises
697 questions about their origin and their migration. H_2O·BADGE·BuOEtOH, HCl·BADGE·BuOEtOH and
698 BADGE·2BuOEtOH were previously observed to migrate into food simulants from an epoxy–based
699 coating (Paseiro-Cerrato et al., 2017). Moreover, reaction products of di- to penta-BADGE with butanol
700 were previously identified in canned tuna and its oil (Berger et al., 2001).
701
702 *3.4.4. Benzoguanamine (BG) derivatives*
703 BG, considered as an IAS, was not monitored in food subsamples (out of *m/z* range). However, BG
704 di- and trimers with methylene linkages were semi-quantified in drained sliced button mushrooms
705 (S01) and chickpeas (S12) at relatively low levels (<5 µg/kg). Recoveries for this series seemed to
706 decrease following the chain length increase so that no conclusion could be drawn for the longer chain
707 derivatives.
708 Drained sweetcorn showed low levels of (hydroxymethyl)benzoguanamine, methylated/ethylated,
709 roughly estimated at 3 µg/kg or slightly lower considering the response factor from the reference
710 substance.
711
712 *3.4.5. Phenolic oligomers*
713 Due to the dilution effect in C-Mix, the recoveries of the method could not be evaluated. Only traces
714 of c(4opC)4me ($C_{32}H_{32}O_4$) were identified in the juice of white beans (S04, <1 µg/kg)
715
716 *3.4.6. Sorption*
717 The 4 fatty acids and the ESBO-like compound were identified in all subsamples, so that their food
718 origin was confirmed.

719

720 *3.4.7. Additives and remaining unknowns*

721 The sample treatment was not suitable for recovering additives and remaining unknowns so that no
722 conclusion could be drawn on the migration of these substances. However, the IAS are not of concern
723 since supposedly known and controlled.

724

725 **4. Concluding remarks and perspectives**

726 Using a non-targeted LC/ESI(+)-HRMS approach, dozens of small molecules in inner coatings of
727 vegetable metallic cans have been identified. Oligoesters, a diverse family of unwanted compounds
728 arising from the synthesis of polyesters, prevailed in the data set. Although based on a limited sample
729 size, it can be deduced from this survey that those polyester-based coatings have become a major
730 alternative to BADGE-based coatings in France. Minor identified NIAS included (i) BADGE derivatives
731 that were not expected, (ii) phenolic oligomers and (iii) benzoguanamine derivatives described for the
732 first time.

733 In terms of methodology, sample preparation should be adapted to compounds that were lost and to
734 other food types. Negative ESI will be helpful to extend the picture with diacid-terminated linear
735 oligoesters, and other techniques to compounds that are not amenable to ESI (Nerín et al., 2013, 2022;
736 Omer et al., 2019). Further automation is required for data mining, from the peak picking of non-
737 Gaussian peaks to the database queries.

738 As regards the consumer, the exposure assessment is applicable to leachates only. Several factors drive
739 the migration of residues, including multilayer design. Migration testing on food simulants being
740 impractical, we investigated the edible contents directly. After sample preparation development, many
741 oligoesters were found to migrate at cumulative concentrations up to 1.6 mg/kg. Regardless of
742 potential mutagenicity and carcinogenicity that remain to be considered, most of these oligoesters
743 belong to the higher toxicity class III of the Cramer classification (Gómez Ramos et al, 2019), leading to
744 a threshold of toxicological concern (TTC) of 1.5 µg/kg body weight per day (EFSA, 2012). Comparing

745 the cumulative concentrations in canned vegetables with this TTC value sheds light on the need to fulfil
746 a proper risk assessment on this NIAS family (exposure and hazard characterisation, including
747 genotoxicity and endocrine disruption), as recently stressed out by Lestido-Cardama et al. (2022).
748 Complete exposure assessment is required from a broadened range of food matrices such as seafood
749 and meat products, ready-made dishes, beverages and infant milk formulas. Taking advantage of the
750 described stepwise synthesis of oligoesters, efforts should be made to extend the range of available
751 reference standards for identification and quantification purposes. Those reference standards are also
752 a prerequisite for undertaking toxicological studies more informative than *in silico* models. Attention
753 should be paid to BADGE and BG derivatives as well, even though quantified to a lower extent. At last,
754 can coatings should be considered in the exposure assessment to ESBO.
755
756 **CRediT authorship contribution statement**
757 Ronan Cariou: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources,
758 Data Curation, Writing - Original Draft, Visualization, Funding acquisition. Matthieu Rivière: Formal
759 analysis, Investigation, Writing - Review & Editing. Sébastien Hutinet: Software, Visualization. Asmaa
760 Tebbaa: Investigation. Didier Dubreuil: Methodology, Writing - Review & Editing. Monique Mathé-
761 Allainmat: Methodology. Jacques Lebreton: Methodology, Resources, Supervision. Bruno Le Bizec:
762 Resources, Funding acquisition, Supervision. Arnaud Tessier: Methodology, Formal analysis,
763 Resources, Writing - Original Draft, Visualization. Gaud Dervilly: Writing - Review & Editing,
764 Supervision, Project administration.
765
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Declaration of Competing Interest

The authors assert that they have no conflict of interest (financial or non-financial) in the subject matter discussed in this manuscript.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:XXXXXXXXXXXXXX.

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Figure captions

Fig. 1. Stepwise synthesis of linear and cyclic oligomers derived from iPA and NPG in native and deuterated series. Compounds **9**, **10** and **11** correspond to the final products lin(2NPG+2iPA), c(2NPG+2iPA) and c(4NPG+4iPA), respectively. (i) Et_3N, MeOH, H_2O; (ii) BnBr, DMF; (iii) LAH or LAD, THF; (iv) TBDMSCl, Et_3N, DMAP, DCM; (v) EDC.HCl, DMAP, DCM; (vi) H_2, $Pd(OH)_2$, iPrOH; (vii) HF.Pyr, THF; (viii) EDC.HCl, DMAP, DCM; (ix) HF.Pyr, THF; (x) H_2, $Pd(OH)_2$, iPrOH; (xi) 2,4,6-Trichlorobenzoyl chloride, Et_3N, DMAP, 10 mM in THF.

Fig. 2. Structures of the monomers (8 diols, 4 diacids) involved in the 84 oligoester combinations identified in the coatings, and their possible isomers according to the ResAP(2004)1.

Fig. 3. Number of oligoester combinations identified in juice (left), drained vegetables (middle) and sauce (right; tomato only) of food can contents according to the semi-quantification range, and sum concentrations (blue numbers).

Fig. 4. Semi-quantification levels (µg/kg, log scale) of the 18 oligoester combinations exceeding the average of 5 µg/kg in drained vegetables.

1011 **Table 1.** Description of sampled cans.

Can ID	Food labelling	Brand type	Total net weight (g)	Can type	Best before date
S01	Sliced button mushrooms	National	400	2PC	01 Apr 2022
S02	Endives	Retailer	800	3PC	31 May 2022
S03	Extra fine butter beans	Retailer	400	3PC	31 Aug 2022
S04	White beans	Retailer	400	2PC	01 Jan 2023
S05	Five mixed vegetables	Retailer	800	3PC	31 Oct 2022
S06	Sweetcorn	Retailer	300	3PC	31 Aug 2022
S07	Salsifies	Retailer	400	3PC	31 Aug 2021
S08	Green peas	National	200	2PC	30 Jun 2023
S09	Chopped spinach	National	395	3PC	31 May 2021
S10	Cut palm hearts	National	200	3PC	Jan 2022
S11	Whole peeled tomatoes	National	400	3PC	31 Mar 2021
S12	Chickpeas	National	400	2PC	31 May 2023

1012

1013 **Table 2.** Relative contribution of each PC-group category to the data set of interest in coatings.

PC-group category	No of PC-groups	Contribution to area dataset
Oligoesters	84	78%
Additives	13	17%
Sorption	5	2.2%
BADGE derivatives	10	0.9%
Phenolic oligomers	5	0.3%
Benzoguanamine derivatives	13	0.3%
Remaining unknowns	9	0.8%

1014

Figure 1

Click here to access/download;Figure;Figure 1 R0b.pptx

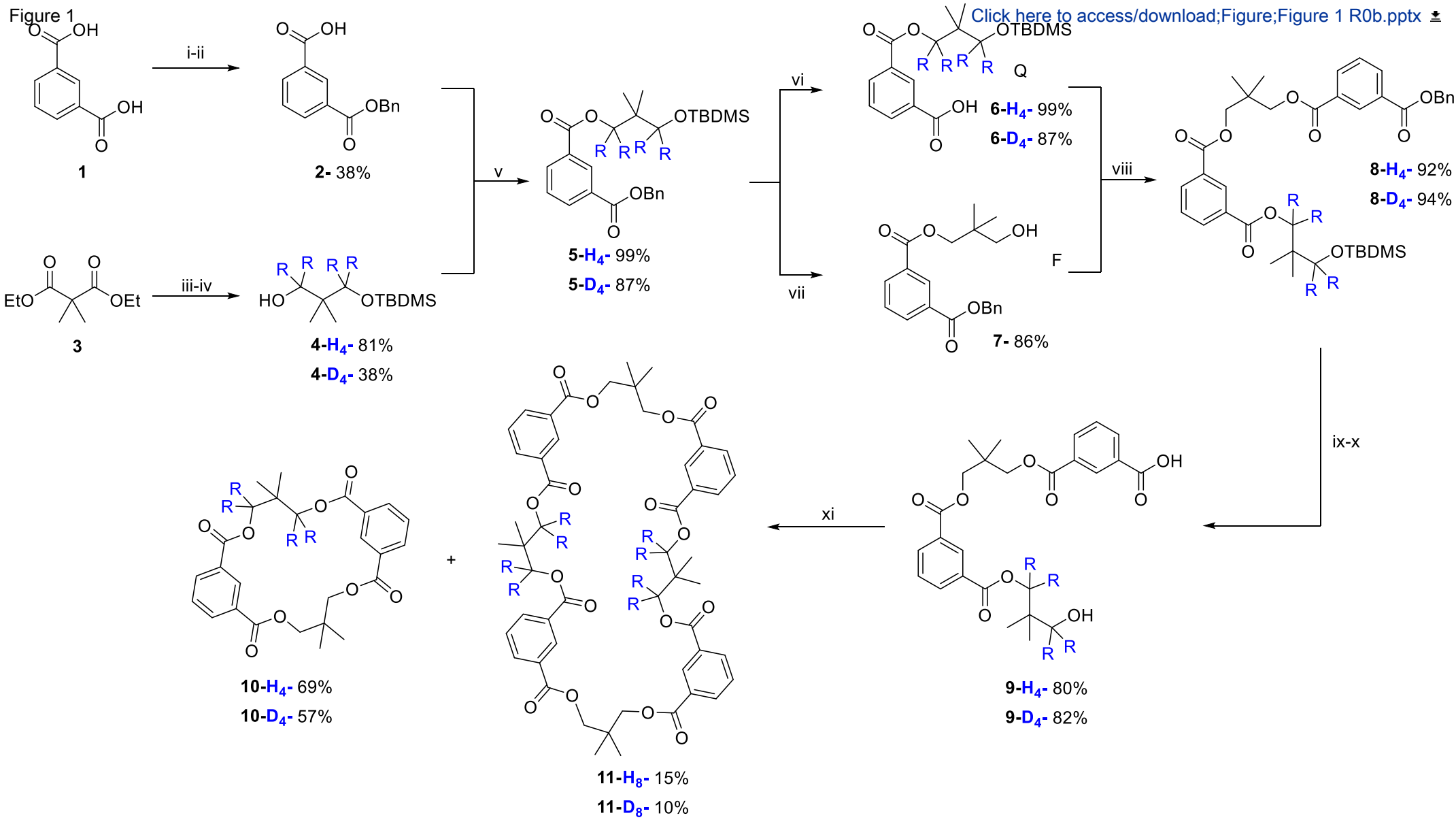
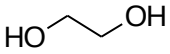


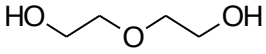
Figure 2

Click here to access/download;Figure;Figure 2 R0b.pptx

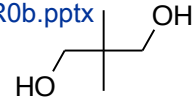
Diols



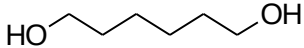
Ethyleneglycol (EG)



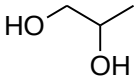
Diethyleneglycol (DEG)



Neopentylglycol (NPG)



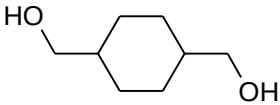
1,6-Hexanediol (HD)



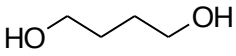
1,2-Propanedilol (Propylene glycol)

1,3-Butanediol

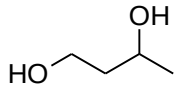
Propanediol (PD)



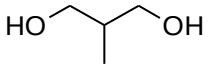
1,4-Bis(hydroxymethyl) cyclohexane (CHDM)



1,4-Butanediol

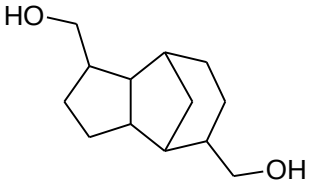


1,3-Butanediol



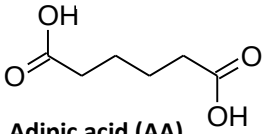
2-Methyl-1,3-propanediol

Butanediol (BD)

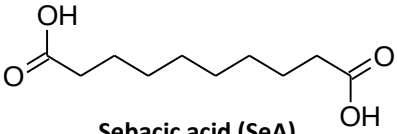


Tricyclodecanedimethanol (TCDDM)

Diacids

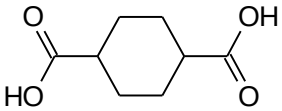


Adipic acid (AA)

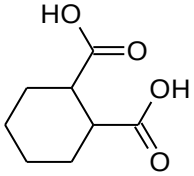


Sebacic acid (SeA)

Hexahydrophthalic acid (HHA)

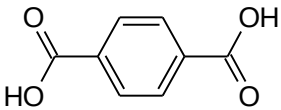


Hexahydroterephthalic acid



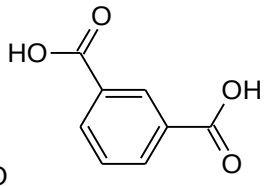
Hexahydroorthophthalic acid

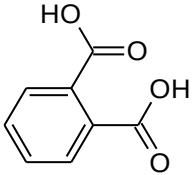
Phthalic acid (PA)



Terephthalic acid (tPA)

Isophthalic acid (iPA)





Orthophthalic acid (oPA)

Figure 3

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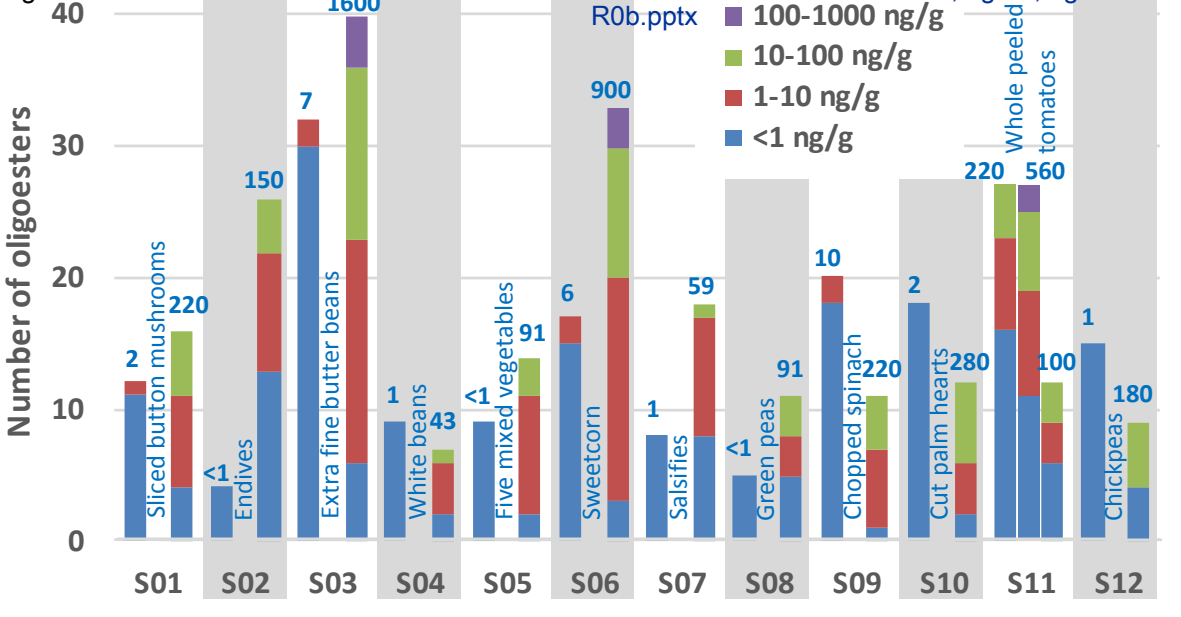
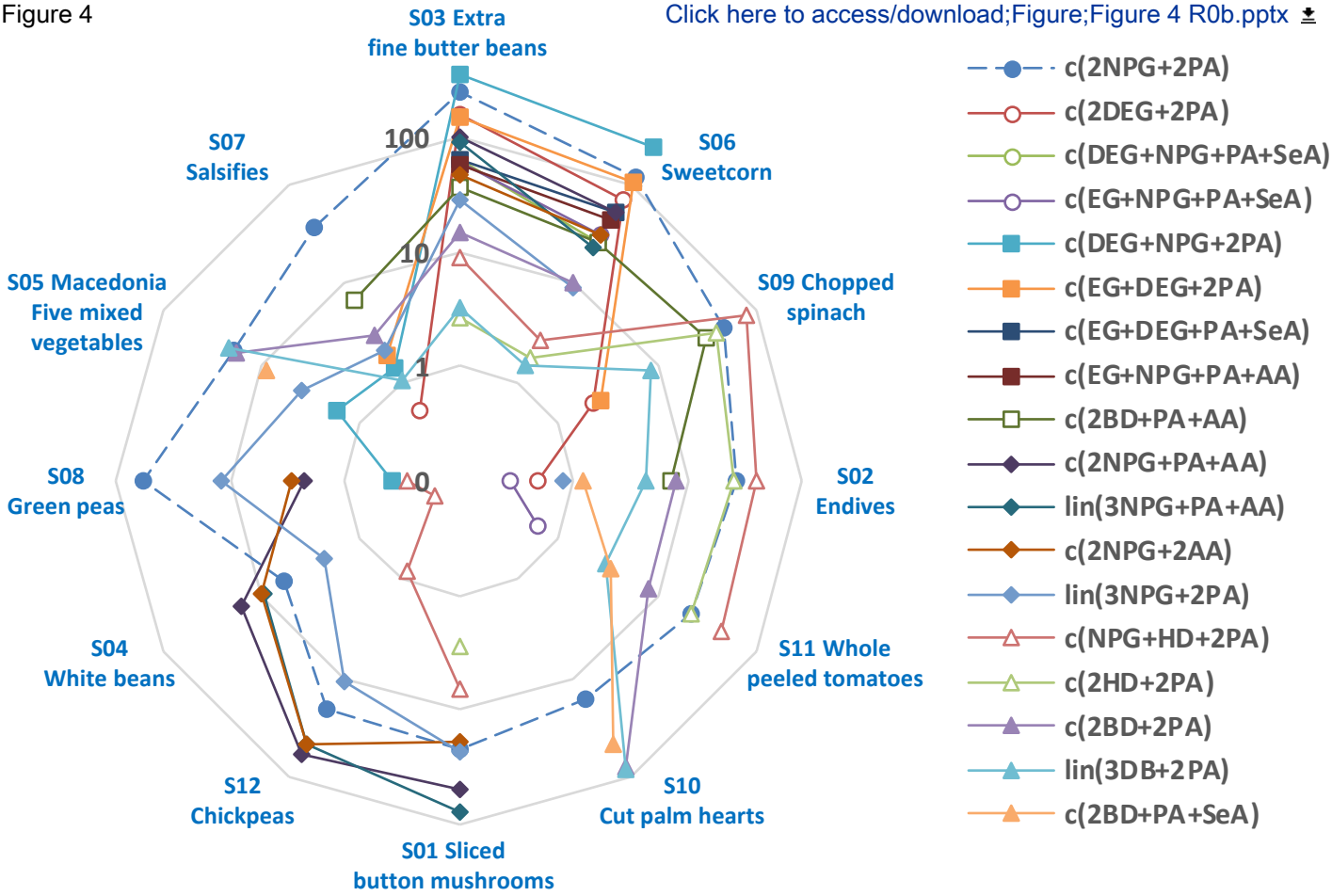


Figure 4

Click here to access/download;Figure;Figure 4 R0b.pptx



CRediT authorship contribution statement

Ronan Cariou: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization, Funding acquisition. Matthieu Rivière: Formal analysis, Investigation, Writing - Review & Editing. Sébastien Hutinet: Software, Visualization. Asmaa Tebbaa: Investigation. Didier Dubreuil: Methodology, Writing - Review & Editing. Monique Mathé-Allainmat: Methodology. Jacques Lebreton: Methodology, Resources, Supervision. Bruno Le Bizec: Resources, Funding acquisition, Supervision. Arnaud Tessier: Methodology, Formal analysis, Resources, Writing - Original Draft, Visualization. Gaud Dervilly: Writing - Review & Editing, Supervision, Project administration.