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Three-way PARAFAC decomposition of chromatographic data for the unequivocal identification and quantification of compounds in a regulatory framework

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Abbreviations[2]

ABSTRACT

The growing demand for controls of foodstuffs, personal care products, medicines and the environment is unquestionable, as well as a better understanding of the toxicity of chemical products. This causes a growing need to propose methods of analysis for the unequivocal identification and quantification of analytes in complex samples.

Several official organizations that regulate these aspects in pesticides, migrants or additives, have increased the requirements regarding the figures of merit, among others, for the unequivocal identification of the target analytes. The general recommendation is the use of the information provided by chromatographic techniques on the test sample, for example, the use of HPLC-DAD or GC-MS data. Therefore, for each sample, a data matrix formed by the response vector (absorbances or abundances) recorded at each retention time is available. A data array is obtained when the matrices corresponding to the calibration standards and the test samples are concatenated.

There are several chemometric techniques with the second-order advantage that can handle data arrays, so target analytes can be identified and quantified using them even in the presence of interferents. In this work, PARAFAC has been considered as a good option. If the data array is trilinear, its analysis using PARAFAC/PARAFAC2 enables the unequivocal identification and quantification of the target analyte so that the result is valid according to the criteria imposed by the authorities.

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[2] Benzophenone (BP), benzophenone-3 (BP3), bisphenol A (BPA), bisphenol F (BPF), capability of detection (CCβ), cooled injection system (CIS), core consistency diagnostic (CORCONDIA), decision limit (CCα), 2,6-dichlorobenzamide (BAM), 2,6-dichlorobenzonitrile (DIC), 3,5-dichlorobenzonitrile (ISDIC), diisobutyl phthalate (DiBP), diisobutyl phthalate-3,4,5,6-d_4 (DiBP-d_4), identification point (IP), melamine kitchenware (melaware), programmed temperature vaporizer (PTV), quick easy cheap effective rugged and safe (QuEChERS), relative ion abundance (I_R), relative retention time (RRT), specific migration level (SML), world anti-doping agency (WADA).

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In this work, the chemometric methodology is explained through four different case studies related to the determination of analytes in complex matrices (bisphenol A migrated from polycarbonate, dichlobenil in onion, oxybenzone in sunscreen cosmetic creams and melamine migrated from melaware). This multi-way methodology solves the problems of the coelution of interferents that have a similar absorbance spectrum in HPLC-DAD (or share m/z ratios in GC-MS) with the target analyte or with the internal standard causing false-negative results with conventional identification methods. In addition, the PARAFAC decomposition of trilinear arrays enables the joint optimization of several analytical parameters (extraction, clean up, etc.) that control different sample pretreatments prior to the chromatographic determination of complex samples.

Keywords: PARAFAC; PARAFAC2; GC-MS; HPLC-DAD; Unequivocal identification;

1. Introduction

The aim of this work is to show the usefulness of *n*-way techniques when there are legal requirements to comply with in the performance characteristics of analytical methods, as it is the case of methods for determining residues of veterinary substances, pesticides or some monomers and additives that migrate into food. For these cases, the performance characteristics of the methods are defined in different regulations: Guidance document on analytical quality control and method validation procedures for pesticide residues and analysis in food and feed SANTE/11813/2017 [1] (which updates the contents of SANCO/12495/2011 [2] for pesticides), Decision 2002/657/EC [3] for veterinary drugs residues and EUR 27529 for migration test [4], among others.

There are several chemometric techniques with the second-order advantage that can handle data arrays, so target analytes can be identified and quantified using them even in the presence of interferents that are not included in the calibration standards [5]. In this work, PARAFAC has been considered as a good option. Applications of PARAFAC and PARAFAC2 to chromatographic analysis (in particular, GC-MS and HPLC-DAD) in this regulated context can be found in Refs. [6,7,8] for pesticides and in the determination of monomers and additives that migrate into food in [9,10]. In all these cases, the performance of the analyses is regulated.

The usefulness of three-way techniques is also shown with other chromatographic techniques, for example, in the determination of veterinary residues with HPLC-DAD in Ref. [11] or fungicides with LC-MS/MS in Ref. [12]. In addition, Ref. [13] shows the use of these techniques for non-target analyses.

This work explains four case studies with relevant aspects that require to comply with the current legislation, due to the nature of the substances analysed (pesticides and migrants in food, cosmetic additives, etc.). In these cases, the usefulness of *n*-way techniques (PARAFAC or PARAFAC2) becomes apparent. The results obtained by using the conventional methods are also included to compare them with those obtained with PARAFAC or PARAFAC2.

Although the analytical procedures are focused on two chromatographic techniques (GC-MS and HPLC-DAD), the shown mode of operation is much broader, and can be used with data obtained using a multivariate detector. The most important novelty is the use of the ‘uniqueness property’ to unequivocally identify and quantify the analytes at the same time through the factors of the decompositions.

Uniqueness property is known as the ‘second-order advantage’ [14] in chemical analysis. A trilinear data array is built with the K slabs corresponding to $K - \text{h}$ samples of known concentration of a target analyte (calibration standards) together with the h slabs of the test samples. The uniqueness property means that if one of the factors corresponds to the analyte, then the concentration of this analyte can be computed in the test sample even in the presence of interferents that were not in the calibration samples. This property guarantees that there is only one sample profile linked to the analyte of interest, independently of the remaining factors.

2. Software and experimental

2.1. Software

MSD ChemStation version E.02.01.1177 (Agilent Technologies, Inc.) with Data Analysis software was used for acquiring and processing data in the case of GC-MS.

OpenLab CDS ChemStation software for an Agilent 1260 Infinity HPLC chromatograph (Santa Clara, CA, USA) was used when the measurements were recorded by means of an HPLC-DAD.

PARAFAC and PARAFAC2 decompositions were carried out with the PLS_Toolbox [15] for MATLAB [16]. Regression models, accuracy lines and kinetic models were fitted and validated using STATGRAPHICS Centurion XVII [17]. Decision limit (CCα) and capability of detection (CCβ) were calculated using the DETARCHI programme [18].

2.2. Instrumental and experimental details

2.2.1. Cases I-II-III (GC-MS)

An Agilent 7890A gas chromatograph coupled to an Agilent 5975C mass spectrometer detector (Agilent Technologies, Santa Clara, CA, USA) were used to conduct the analyses in the three cases of Section 4.1 to 4.3. The gas chromatograph was equipped with an Agilent HP-5MS Ultra Inert column (30 m×0.25 mm i.d., 0.25 μm film thickness). Helium was used as the carrier gas and held at a constant flow rate of 1.1 mL min^{-1}, except for case III at 1.3 mL min^{-1}.

In case I (Section 4.1), the injection system consisted of a septumless head and a programmed temperature vaporizer (PTV) inlet (cooled injection system (CIS 6) from GERSTEL GmbH & Co. KG) equipped with an empty multi-baffled deactivated glass liner.

The PTV inlet operated in the solvent-vent mode. The details of the experimental procedure of the migration test in this case can be consulted in Ref. [9].

In case II (Section 4.2), the analytes were extracted using the Quick Easy Cheap Effective Rugged and Safe (QuEChERS) method, derivatized and injected in the chromatographic system using a PTV following the experimental procedure optimized by means of a D-optimal design [8].

In case III (Section 4.3), the injection system consisted of a septumless head CIS 6 and a PTV inlet equipped with a straight-with-notch quartz glass liner from GERSTEL GmbH & Co. KG (Mülheim an der Ruhr, Germany). The injections were performed using a 10 μL syringe and the MultiPurpose Sampler MPS2XL from GERSTEL. Other details of the experimental procedure can be seen in [19].

2.2.2. Case IV (HPLC-DAD)

To quantify melamine, an Agilent 1260 Infinity HPLC chromatograph (Santa Clara, CA, USA) was used. This HPLC consisted of a quaternary pump (G1311C), a sampler (G1329B), a thermostatic column compartment (G1316A) and a diode array detector (G7117C). The column chosen for the separation was a Kinetex EVO-C18 column (150 mm × 4.6 mm, 5 μm). Acetonitrile and deionized water were used as mobile phase. The conditions for the melamine chromatographic analysis were an injection volume of 20 μL, temperature of the column compartment fixed at 20 °C and an isocratic mobile phase (acetonitrile:water, 15:85, v/v) at a flow rate of 0.6 mL min^{-1}. The emission spectra were recorded between 200 and 500 nm, each 2 nm.

Other details about the analytes, the experimental procedure to obtain the extracts from the melamine kitchenware, the migration tests and the procedure for building the migration kinetic model can be seen in [20], though three-way techniques were not used in this last reference.

3. Theory

3.1. PARAFAC/PARAFAC2 models

A PARAFAC model of rank F for the array $\underline{\mathbf{X}} = (x_{ijk})$ is written [21,22] as

$$x_{ijk} = \sum_{f=1}^{F} a_{if} b_{jf} c_{kf} + e_{ijk}, \quad i = 1, 2, \ldots, I; \; j = 1, 2, \ldots, J; \; k = 1, 2, \ldots, K \tag{1}$$

where e_{ijk} are residuals of the fitted model. PARAFAC is a trilinear model, as can be seen in Eq. (1), since it is linear in each of the three profiles.

In general, a three-way data array $\underline{\mathbf{X}}$ ($I \times J \times K$) is made up of real numbers, x_{ijk}, $i = 1,\ldots, I$; $j = 1,\ldots, J$; $k = 1,\ldots, K$. In the case of GC-MS data, each value x_{ijk} would be the abundance recorded at the k-th elution time, from the j-th m/z ratio and the i-th sample. In practice,

each profile (way or mode) of the array is identified by its meaning, for example, chromatographic, spectral or sample profiles for GC-MS data. The order of the profiles is not predetermined, and the researcher decides it. However, the vectors $\mathbf{b}_f$ and $\mathbf{c}_f$ in Eq. (1) of the second and third mode are usually normalized, while the first one, $\mathbf{a}_f$, is not. This is the reason why the sample profile is usually placed in the first mode because a calibration model is built as a function of the concentration.

Chromatographic data are trilinear if the experimental data array is compatible with the structure in Eq. (1). The core consistency diagnostic (CORCONDIA) [23] measures the trilinearity degree of the experimental three-way array when $F \geq 2$. If the three-way array is trilinear, then the maximum CORCONDIA value of 100 is achieved. The PARAFAC least squares solution is unique when the three-way array is trilinear and the appropriate number of factors has been chosen to fit the PARAFAC model [24]. The uniqueness property makes it possible to identify compounds unequivocally by their chromatographic and spectral profiles as laid down in some official regulations and guidelines, even in the presence of a coeluent that shares ions with the analyte of interest.

PARAFAC2 is used to correct deviations from trilinearity when small shifts in the retention time of the analytes from sample to sample appear in the chromatogram [25,26]. In this case, PARAFAC2 applies the same profiles ($\mathbf{b}_f$, f = 1,…,F) along the spectral mode and enables the chromatographic mode to vary from one matrix to another. Then, Eq. (1) should be modified as in Eq. (2) to describe a PARAFAC2 model:

$$\underline{\mathbf{X}} = \left(x_{ijk}\right) = \left(\sum_{f=1}^{F} a_{if}^{k} b_{jf} c_{kf} + e_{ijk}\right), \quad i = 1, 2, \ldots, I; \quad j = 1, 2, \ldots, J; \quad k = 1, 2, \ldots, K \qquad (2)$$

where the superscript k is added to account for the dependence of the chromatographic profile on the k-th sample. Thus, for PARAFAC2 models, the sample profile is the third mode whereas the chromatographic profile is the first one.

The chromatograms cannot be aligned as in other kind of studies [27,28] since the shifts in the retention time of the analytes must be compulsory evaluated to guarantee that the retention times are within the tolerance intervals laid down in regulations. If the chromatogram does not fulfil with that requirement, then the unequivocal identification of the analyte is not possible.

3.2. Several compulsory regulations related with the unequivocally identification

World Anti-Doping Agency (WADA) in Ref. [29] gave the minimum criteria for chromatographic-mass spectrometric confirmation of the identity of analytes for doping control purposes. It is stated that: *"The ability of a method to identify an analyte is a function of the entire procedure (sample preparation, chromatographic separation, mass analysis and data assessment). Any description of the method for purposes of documentation should include all parts of the method. The appropriate analytical characteristics shall be documented for the entire identification method and should be sufficiently proven as being fit-for-purpose through proper method validation".* This guides

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the chromatography analyst to obtain some minimum criteria for the confirmation of the identity of analytes for doping control purposes when GC-MS is used before reporting a positive/negative result of the analysis.

However, this is not the only document guiding the analyst on how the target analytes (toxic residues of veterinary medicinal products, pesticides or migrants) have to be unequivocally identified. In general, these guidelines consider two independent ways for the unequivocal identification.

In 2002, Commission Decision 2002/657/EC [3] concerning the performance of analytical methods and interpretation of results for veterinary residues in food and feed was published. This is one of the first documents that specifies the tolerances for the retention time and for the diagnostic ions, m/z, that must be met in order to consider the analysis to be valid from the point of view of the analyte identification.

In addition, document SANTE/11813/2017 [1] (implemented in 2018), which supersedes SANTE/11945/2015 and previous documents named SANCO [2], shows the method validation and quality control procedures for pesticide residues analysis in food and feed.

The guidelines mentioned above suggest the use of chromatographic techniques (GC or LC) coupled to multivariate detectors (usually: MS^1, MS^n) for the unequivocal identification. The number of diagnostic ions (m/z) considered for the identification depends on which MS technique is used and on the type of analyte (forbidden or with a permitted limit). In the case of MS^1, 1 identification point (IP) per m/z diagnostic ion is needed, whereas 1 IP per precursor ion and 1.5 IP per product ion is necessary if the detection is MS^n. In addition, the relative retention time (RRT) of the analyte in the sample compared to the one in a reference sample should not differ more than ±0.5 % in GC (or ±2.5 % in LC). When using single-stage MS^1, four or three diagnostic ions shall be acquired depending on whether the analyte is forbidden or with a permitted limit, respectively.

If GC-MS (fragmentography, in SIM mode) is used, it is advised that the selected ions be the molecular ion and characteristic adducts, characteristic fragmented ions and all their isotopic ions. These ions should not exclusively come from the same part of the molecule. In addition, the maximum permitted tolerances for the relative ion abundances of the diagnostics ions (m/z) must be controlled. The permitted tolerances are based on the relative abundance of diagnostic ions written as percentage of the base peak [1,3]. There are tables to control this tolerance based on the percentage of this ratio, which can be slightly different from one regulation to another.

Figure 1 contains the table of tolerances of Ref. [2] and a diagram of how to proceed in the hypothetical case of a pesticide with 3 diagnostic ions selected, namely m/z=201 (base peak or the one with the greatest abundance), m/z=68 and m/z=158. The steps to follow will be: i) record the spectrum of a reference sample at the chosen m/z ions; ii) build the tolerance intervals according to the table for the relative ion abundances of each m/z ion with regard to the base peak using the reference samples; iii) acquire the abundances at the same m/z ions for the test sample and calculate the relative intensities (I_R, in %); iv)

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check if the I_R of each m/z ratio is within the tolerance interval built with the reference sample.

<Here Figure 1>

As can be seen in Figure 1, m/z=201 is the base peak, so the intensity of the rest of the ions (m/z=68 and m/z=158) is divided by the intensity of the base peak. The values of I_R obtained were 30.13 % and 22.08 %, respectively. The table shows that the permitted tolerance for those I_R is ±15. The tolerance intervals are also depicted in Figure 1 and only the m/z 68 is within the tolerance interval in the case of the test sample. The conclusion is that the test sample does not contain the pesticide since the I_R of m/z 158 is not within the corresponding tolerance interval. When the test sample is a complex matrix or an extract, then one or more interferents may coelute with the target analyte and even share some m/z ratio with the chosen diagnostic ions. This will lead to a false-negative result. However, the false-negative result would have been avoided applying a chemometric technique with the second-order advantage such as PARAFAC or PARAFAC2 to the same experimental data.

This important consequence of the unequivocal identification and the second-order advantage is also useful in chemical analysis. The current chromatographic methods consist of many stages: sample preparation (extraction, clean up, derivatization), injection (PTV, etc.) and chromatography (injection temperature, heating ramps, flow, composition of the mobile phase in HPLC, etc.) When a new chromatographic method is optimized, the joint consideration of all these experimental parameters is practically impossible. Besides, their effect cannot be observed alone since there can be interactions between one another. Consequently, calibration models are needed in each combination of factors (different runs in an experimental design for example) to quantify the effect of these factors because the amount of the analyte in each combination of them should also be quantified. Therefore, if K different combinations of the factors are going to be analysed, K calibrations should be performed. Assuming that each calibration consists of ‘c’ chromatographic injections, then K×c injections have to be done, so the experimental effort is multiplied by the number of standards. However, if a three-way array is built with the same experimental data (K slabs), only ‘c’ additional slabs are necessary (K+c in total) to identify and quantify the target analyte and the effect of the experimental factors on the result of the analysis. This problem is solved using a chemometric technique such as PARAFAC or PARAFAC2 [8].

3.3. Unequivocal identification and quantification through PARAFAC/PARAFAC2

In Ref. [24], the similarity between the PARAFAC model and the physical model underlying the data acquisition by GC-MS (or HPLC-DAD) is shown. In both cases, the experimental data are arranged in a three-way array, $\underline{\mathbf{X}}$, of dimension $I \times J \times K$. In this work, a data array considering the elution times around the retention time of each target analyte is used. In GC-MS, for each of the K samples analysed, the abundance of J characteristic ions is recorded at I elution times around the retention time of each analyte, so a mass

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spectrum is obtained at every elution time. If the data acquisition is made by HPLC-DAD, only the meaning of the J index changes, being the absorbance recorded at each wavelength. The rest of the indices have the same meaning as in the previous case.

However, the diagnostic of the trilinearity of the experimental data is not a consequence of the similarity mentioned above, so it should be verified in each individual case. It is possible that an experimental data array is not trilinear even if the data have been obtained using a technique that theoretically should be trilinear. On the other hand, it is also possible that experimental deviations, which could lead to non-trilinear data, in fact do not invalidate the second-order advantage in specific data.

It must be taken into account that for F PARAFAC factors of a data array of dimension $I \times J \times K$, only the $(I+J+K) \times F$ values need to be estimated, so the statistical effect of this 'smoothing' is very important. In the case of chemical analysis, the evaluation of the trilinearity of the data together with the advantage that the chromatographic and spectral profiles of the target analyte are experimentally known from the reference samples are useful for this task. Therefore, it can be verified that the estimated PARAFAC or PARAFAC2 profiles correspond to them. This diagnosis is sometimes summed up as an analysis of the coherence of the fitted model.

The steps followed for the unequivocal identification and quantification using a PARAFAC or PARAFAC2 decomposition are described in this section. The order of the indices of the arrays can be swapped in each case of Section 4 due to different technical reasons (mentioned in the section 3.1). The steps followed in the four cases have been:

i) For each sample, record the matrix of abundances of J m/z ratios acquired at I elution times for each chromatographic peak in the case of GC-MS (or record the matrix of absorbances at J wavelengths and I elution times for each peak in the case of HPLC-DAD).

ii) Estimate the corresponding tolerance intervals for the relative retention time and for the relative ion (m/z) abundances with the loadings of the chromatographic and spectral profiles obtained with the PARAFAC (or PARAFAC2) decomposition of an array, $\underline{\mathbf{X}}_i$, that contained some K_i reference samples. In the case of HPLC-DAD, the unequivocal identification in the spectral profile is made by means of the correlation coefficient between the spectral profile of a reference sample and the one obtained with the PARAFAC (or PARAFAC2) decomposition.

iii) Build the three-way array, $\underline{\mathbf{X}}_1$, made up by the K_1 samples of the calibration set (calibration standards).

iv) Perform the PARAFAC (or PARAFAC2) decomposition of that array to obtain the chromatographic and spectral profiles of the different compounds present in those samples in each window.

v) For each PARAFAC (or PARAFAC2) decomposition, use the Q residuals and Hotelling's T^2 statistics to check if there is any outlier.

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vi) Identify the factor of the model which corresponds unequivocally to the analyte of interest using the tolerance intervals. In the case of HPLC-DAD, the identification of the spectral profile is carried out using the correlation coefficient.

vii) In the case of GC-MS data, the sample loadings of each analyte must be standardized by dividing each of them by the corresponding sample loading of its internal standard.

viii) A calibration model “sample loading versus true concentration” using the calibration standards is fitted and validated. In the case of GC-MS data, the standardized sample loadings are used.

ix) Build another three-way array, $\underline{\mathbf{X}}_2$, made up by the K_2 samples of the new sample set. These samples can come from different origins (extracts of a complex matrix, design of experiments or migration kinetics).

x) Determine the concentration of the analyte in these new samples through the sample loadings (or the standardized ones in the case of GC-MS data) with the calibration model of previous step viii). All the target analytes must be previously unequivocally identified.

4. Results and discussion

4.1. Case I: Interferents with overlapping peaks to the internal standard and the target analyte (BPA)

The internal standard used in the determination of bisphenol A (BPA) by GC-MS was its deuterated compound, BPA-d_{16}, so both compounds closely elute. When analysing samples from the migration test of BPA from polycarbonate tableware, several interferents coeluted. Figure 2 shows the total ion chromatogram obtained in full scan mode (500 μg L^{-1} of each analyte in the extract obtained from the simulant (ethanol:water)). The experimental details of the multiresidue analysis of BPA, bisphenol F (BPF), and their corresponding diglycidyl ethers (BADGE and BFDGE, respectively) can be seen in reference [9]. In this section, the attention is focused on BPA and its internal standard since both compounds closely elute. The diagnostic ions chosen are listed in Table 1 where it is seen that there is no problem in the PARAFAC decomposition with the calibration standards prepared in solvent since these ions are not the same in both compounds. To carry out this PARAFAC decomposition, an array $\underline{\mathbf{X}}_1$ of dimension (15×9×8) was used. In this case, 15 refers to the number of scans, 9 corresponds to the number of diagnostic ions and 8 are the standard samples. The PARAFAC decomposition of $\underline{\mathbf{X}}_1$ has two factors that explained 89.7 % of variance with CORCONDIA index equal to 100 %. Figure 3 shows the three profiles of the PARAFAC decomposition: the chromatographic (Fig. 3A), spectral (Fig. 3B) and sample (Fig. 3C) profiles.

< Table 1>

< Figure 2>

< Figure 3>

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This proves that the identification of both analytes and the calibration of BPA by means of the loadings of the PARAFAC decomposition are viable. The difficulties came up when analysing samples from the migration test of BPA from polycarbonate tableware, whose experimental data are depicted in Figure 4. Figure 4A shows the experimental chromatogram, whereas the mass spectrum registered at the maximum of the peak considered as BPA-d_{16} appears in Figure 4B. As can be seen in this last figure, the abundance of the base peak (m/z = 224) was not the highest one in this analysis, contrary to the behavior in the standards in Figure 3B. Therefore, a PARAFAC decomposition was carried out with a new data array, $\underline{\mathbf{X}}_2$, of dimension (11×9×34) where 11 are the number of scans, 9 are the diagnostic ions and 34 corresponds to the number of samples that included the ones obtained in the migration test. The chromatographic profile obtained in the PARAFAC decomposition with four factors (CORCONDIA index equal to 87 % and explained variance of 83 %) is shown in Figure 4C, whereas the spectral profile of BPA-d_{16} can be observed in Figure 4D. The other two factors of this PARAFAC decomposition were related to two interferents that eluted before BPA in the samples of the migration test. In this decomposition, the m/z 224 is the one with the highest abundance for BPA-d_{16} and we can check the relative abundances of the detected ions of BPA that were within the permitted maximum tolerances so it was unequivocally identified.

< Figure 4>

4.2. Case II: When coeluting compounds share ions with the internal standard and shifts in the retention time of the analytes appear from sample to sample

This case illustrates the solution of the problems that came up in the determination of the pesticide 2,6-dichlorobenzonitrile (DIC), which is commonly known as dichlobenil, and its main metabolite 2,6-dichlorobenzamide (BAM) by PTV-GC-MS in the context of regulated analysis. The experimental details can be seen in Ref. [8]. PARAFAC (PARAFAC2) allows solving the problem when coeluting compounds share ions with the internal standard used in the analysis and shifts in the retention time of the analytes appear from sample to sample.

As previously mentioned, the first step is to measure reference samples to calculate the tolerance intervals for the chosen diagnostic ions. The determination of DIC in onion by PTV-GC-MS was carried out using 3,5-dichlorobenzonitrile (ISDIC) as internal standard. For the present case II, we will only use the data array to identify ISDIC, since the aim is to show the usefulness of PARAFAC in the calculation of the tolerance intervals. To carry out the PARAFAC decomposition, a first data array $\underline{\mathbf{X}}_1$ (3×16×5) was used, where 3 refers to the number of samples of ISDIC in solvent (30, 50 and 70 µg L^{-1}), 16 are the number of scans and 5 corresponds to the number or diagnostic ions (m/z: 100, 136, 171, 173 and 175).

The first problem appears when the m/z ratios used for the unequivocal identification of ISDIC are shared with an interferent that coelutes with this internal standard. The

tolerance intervals for each analyte are obtained dividing the spectral loading of the chosen m/z ratio by the loading of the base peak. Then, the tolerance interval is calculated with that ratio according to the requirements of the regulation in force [2]. Table 2 contains the tolerance intervals of the target analyte that will be used to identify its presence in the test samples.

< Table 2>

If ISDIC is not well-identified, then DIC could not be quantified correctly since the sample loading of DIC has to be standardized by the sample loading of the internal standard, ISDIC, before being used as a “signal” in the calibration line.

The PARAFAC decomposition of the array $\underline{\mathbf{X}}_1$ for ISDIC had two factors that explained 96.75 % of variance with a CORCONDIA index equal to 99.97 %. Figure 5A shows the chromatographic profile where an interferent (in blue) at higher elution times coelutes with ISDIC (in green). The loadings of the spectral profile of these factors are shown in Figure 5B and shows that the interferent (in blue) shared the m/z ratio 136 with ISDIC. If this is not detected before carrying out the standardization of the loadings of DIC, two errors would be made, namely: i) a wrong calculation of the tolerances for the identification and ii) an error in the quantification when considering m/z ratio 136 as base peak since it has greater abundance than m/z ratio 171, which is the true base peak.

< Figure 5>

To obtain the extract of DIC from the onion, a D-optimal design (that involves ten experimental variables) to optimize the extraction procedure was carried out [8], where the response to be optimized was the sample loading of a PARAFAC2 model. Matrix-matched standards were prepared by adding the appropriate volume of the intermediate standards to blank onion samples, which were subsequently treated according to the experimental procedure described in this reference. The determination of the analytes in this matrix implies, in general, the presence of coeluents that have a similar retention time and share some m/z ions with the target analyte. The presence of non-target analytes can cause false negatives during the pesticide identification. When matrix-matched standards were prepared, the problem got more complicated since two interferents appeared that shared some m/z ratios with ISDIC and the retention time of the analyte shifted. This is the reason why PARAFAC2 was used instead of a PARAFAC model since there were changes in the retention time between samples and the relative ion abundances were not within the tolerance interval established in Ref. [2]. This new data array, $\underline{\mathbf{X}}_2$ (22×16×5), contains the matrices recorded for the reference samples of the array $\underline{\mathbf{X}}_1$ together with the spiked samples used in the D-optimal design. In this new array, 22 are the samples, 16 corresponds to the number of scans and 5 are the m/z ratios above mentioned. From those 22 samples, 19 belong to the experimental plan and each of them has been carried out under different experimental conditions. It must be taken into account that if the loadings obtained with the PARAFAC2 decomposition had not been used, a calibration function would have been necessary for each of the 19 conditions in which the design was

carried out. Therefore, the use of a PARAFAC2 decomposition significantly reduced the time and cost of the analysis.

A PARAFAC2 model was built with the array $\underline{\mathbf{X}}_2$ and 3 factors were needed (explained variance of 99.79 %, CORCONDIA index of 99.92 %). Figure 6A shows the chromatographic profile, whereas the spectral profiles of this decomposition are displayed in Figure 6B. In this case, new interferents appeared in the window of ISDIC when the onion matrix was analysed. One of the interferents in Figure 6A (the one in blue) is the same as the one in Figure 5A, whereas the other one (in red) elutes before ISDIC. The tolerance interval for the relative retention time of ISDIC is shown in yellow in Figure 6A.

< Figure 6>

The relative abundances calculated from the spectral loadings of ISDIC (in green in Fig. 6B) which are within the tolerance intervals in Table 2 lead to the unequivocal identification of ISDIC according to the regulations. If the contribution of the m/z ratios of the interferents had not been detected by means of the three-factor PARAFAC2 model, the relative abundances of some of the diagnostic ions would have not been correct and, therefore, they would not be within the tolerance intervals estimated with the reference samples.

With comparative purposes, Table 3 contains the tolerance intervals that would have been obtained if the data were analysed with the conventional procedure. As can be seen, 5 out of 22 cases do not comply with the criteria for the unequivocal identification of the IS, which will cause wrong quantification.

< Table 3>

The m/z ratios of each interferent are shown in the same colour in the spectral profile contained in Figure 6B. As can be seen in this figure, the interferents shared up to 4 m/z ratios with ISDIC. Consequently, the determination of DIC would be wrong as ISDIC is the internal standard.

4.3. Case III: Oxybenzone in sunscreen cosmetic creams

Regulation (EC) No 1223/2009 [30] on cosmetic products *establishes rules to be complied with by any cosmetic product made available on the market, in order to ensure the functioning of the internal market and a high level of protection of human health.* The content of oxybenzone, or benzophenone-3, was modified in Commission Regulation (EU) 2017/238 [31] and must not exceed 6 % (w/w). In addition, if the product is not for protection purposes, the label of the cosmetic product must include the wording “contains benzophenone-3″ when the concentration is greater than 0.5 % (w/w).

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This section analyses the problem that arises when UV filters and additives, which can be contained in sunscreen creams, are determined together. Some of these compounds are: 2-hydroxy-4-methoxybenzophenone (BP3), benzophenone (BP) and diisobutyl phthalate (DiBP). The analysis was carried out using a gas chromatograph coupled to a mass spectrometer detector with a single quadrupole mass analyser and the injection system consisted of a programmed temperature vaporizer (PTV) inlet with a septumless head. The internal standard used was diisobutyl phthalate-3,4,5,6-d_4 (DiBP-d_4). Sunscreen creams were purchased at local stores in Spain and ethanol was used to extract BP3 and other compounds from the creams. The details of the sample preparation method, instrumental and GC-MS conditions are specified in Ref. [19]. In that work, the attention was focused on BP3, but the problem came up when an interferent coeluted with DiBP and DiBP-d_4 and also shared m/z ratios with DiBP. Table 4 shows the diagnostic ions used for the three target analytes (BP3, DiBP and DiBP-d_4).

< Table 4>

The data array that contained the calibration set for BP3 was $\underline{\mathbf{X}}_1$ of dimension (56×5×20), where 56 corresponds to the number of scans, 5 are the m/z ratios and 20 are the samples. As can be seen in Figure 7, there were some asymmetries and shifts in the retention time of that analyte in the samples. These shifts might be due to the increase in the flow velocity with increasing solute concentration, so that regions of high concentration tend to move more rapidly through the column than do regions of low concentration [32]. Consequently, a PARAFAC2 decomposition was needed which is able to handle this possible lack of trilinearity.

Only one factor was necessary in that PARAFAC2 model (explained variance of 99.79 %). Figure 7A shows the chromatographic profile, whereas the spectral profile is displayed in Figure 7B. The PARAFAC2 decomposition overcome the shifts in the retention time of BP3 in the samples and the analyte was unequivocally identified although the shift in the retention time is limited in regulated analyses. In the case of BP3, the median of the retention times obtained in the corresponding PARAFAC2 decomposition was considered.

< Figure 7>

On the other hand, only one window of scans was considered for DiBP and DiBP-d_4 due to the closeness in their retention times. A data array, $\underline{\mathbf{X}}_2$ (24×41×10) with 24 samples, 41 scans and 10 diagnostic ions was used. The PARAFAC decomposition of this array needed three factors (explained variance of 99.08 %, CORCONDIA index of 100 %). Figure 8 shows the chromatographic and spectral profiles of this decomposition.

< Figure 8>

In the chromatographic profile (Figure 8A), the first factor corresponds to DiBP (in purple), the second factor is the internal standard (DiBP-d_4, in light pink) and the third one is the interferent (in orange). As can be seen in the spectral profile (Figure 8B, where the

compounds are identified with the same colours as in Figure 8A), some of the m/z ratios of the interferent are shared with the diagnostic ions of DiBP. Therefore, the unequivocal identification and quantification of each analyte according to the requirements established by EU regulations were possible using a PARAFAC or PARAFAC2 decomposition despite some of the m/z ratios of a coeluting interferent were shared with DiBP (or DiBP-d_4).
The tolerance intervals for the relative retention times and for the relative ion abundances of the three analytes are listed in Table 4. Table 4A contains the ones for the relative retention times, whereas the tolerance intervals for the relative ion abundances estimated from the loadings of spectral profiles are contained in Table 4B. The identification of each analyte in the analysis of the sunscreen cosmetic creams is listed in the sixth column of Table 4. As can be seen in this table, all the relative retention times and the relative ion abundances are within the tolerance intervals estimated using the reference samples.
The results of the tolerance intervals computed by conventional means are included in Table 5. As can be seen, 13 out of 24 cases do not comply with the criteria for the unequivocal identification. Moreover, three of them correspond to the identification of the IS, which will cause wrong quantification.

< Table 5 >

4.4. Case IV: Migration test and migration kinetics for melamine with HPLC-DAD

In this case, the migration of melamine (2,4,6-triamine-1,3,5-triazine) from melamine kitchenware (melaware) into food simulant B (3 % acetic acid (w/v) in aqueous solution) was analysed according to the regulation in force [33,34]. European legislation [35] sets the specific migration level (SML) for melamine from plastic materials at 2.5 mg kg^{-1}. For this study, three bowls (A, B, C) were exposed to three consecutive migration tests (exposures 1, 2, 3) and analysed in triplicate. The quantification and identification were carried out using PARAFAC2 decomposition with the signals obtained from HPLC-DAD. The experimental procedure to prepare the extract from melaware for the migration test and to perform the migration kinetics has been described in Ref. [20].

For the migration testing from bowls, a data array $\underline{\mathbf{X}}_1$ (76×151×41) was needed to build a PARAFAC2 model. In that array, 76 are the scans (recorded between 1.7 and 2.2 min), 151 corresponds to the number of wavelengths (between 200 and 500 nm) and 41 are the samples. From these samples, 14 were calibration standards and 27 were samples obtained in the migration tests (three exposures of three bowls where the extract of each exposure was measured three times). The use of the PARAFAC2 decomposition was necessary due to a shift in the retention time of melamine. The CORCONDIA index of the two-factor model obtained was equal to 100 % and explained a 97.46 % of the variance. Figure 9 shows the chromatographic, spectral and sample profiles of the two factors. As can be seen in Figure 9A, an interferent (in orange) coeluted with melamine (in blue) and both compounds had the same retention time. The absorption spectra of melamine and the interferent are displayed in Figure 9B with the same colours as in the chromatographic profile. The correlation coefficient between the spectrum of the calibration standards and

the melamine spectrum obtained from the PARAFAC2 model was 0.999 (greater than 0.993, which is the one obtained from the spectrum recorded at the maximum of the peak). This calculation was done only with the first 25 wavelengths since the absorbance of melamine was nearly zero in the rest of the wavelengths. The samples 1 to 14 in Figure 9C correspond to the calibration standards where the fourth and ninth samples were measured in duplicate. It is clear that the loadings of the interferent (in orange in that figure) in these calibration standards were zero. The rest of the samples correspond to the migration tests. The amount of melamine migrated in the first exposure is greater than in the other two exposures independently of the bowl analysed. The European regulation establishes that the values obtained have to be expressed after the third migration [34]. After the validation of the calibration model (sample loading versus true concentration), the amount of melamine migrated from the bowl in the third exposure was calculated, being 0.34 mg L^{-1} (n=9), which was below the SML [35].

< Figure 9>

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Taking into account that melamine kitchenware is made for a repeated use, a new PARAFAC model was fitted and validated, to study the tendency of the accumulated concentration of melamine migrated from a bowl after several consecutive migration cycles. The data was arranged in a new array $\underline{\mathbf{X}}_2$, of dimension 76×151×30. In this case, the 30 samples correspond to 14 calibration standards together with 16 consecutive migration cycles (each one of 30 min) with the same bowl. The matrices used in the building of the array were calculated as the sum of the HPLC-matrix data of each cycle and the HPLC-matrices of the previous cycles. By way of example, the matrix of the cycle number 10 contained in the array consists of the HPLC-matrix of the cycle number 10 together with the HPLC-matrix of the 9 previous cycles.

This procedure is justified by Eq. (3). The chromatographic and spectral profiles of the F factors are the same from one cycle to another since the model is trilinear and the migration tests were performed with the same bowl. Therefore, if the c first matrices are summed up, then the following equation is obtained:

$$\sum_{k=1}^{c}\left(\sum_{f=1}^{F} a_{if} b_{jf} c_{kf} + e_{ijk}\right) = \sum_{f=1}^{F} a_{if} b_{jf} \left(\sum_{k=1}^{c} c_{kf}\right) + e'_{ijk} \ , \tag{3}$$

$i = 1, 2, \ldots, I;\ \ j = 1, 2, \ldots, J;\ \ c = 1, 2, \ldots, K$

So, the sample profile is composed of the cumulative sum up to c of the sample profiles of the c migration cycles.

The PARAFAC model had a CORCONDIA index equal to 97 % and explained 84.27 % of the variance. Figure 10A shows the chromatographic profile of the three factors obtained in the PARAFAC decomposition. High overlapping signals were obtained for the profiles corresponding to the interferent and melamine, which were the factors in orange and blue in that figure, respectively.

The spectral profiles corresponding to the three PARAFAC factors are collected in Figure 10B. The correlation coefficient between the spectrum of a standard of melamine and the one obtained in the PARAFAC decomposition was equal to 0.9999 (greater than 0.9733, which is the one obtained from the spectrum recorded at the maximum of the peak), when using the first 25 wavelengths, so the factor in blue in that figure was related to the presence of melamine in the samples analysed. In addition, the spectrum obtained for one of the interferents (in yellow in Figure 10B) had a correlation coefficient of 0.9879 (n=25) with the spectrum of a mixture of food simulant and mobile phase. The other interferent (in orange) was unidentified.

The loadings of the calibration standards and the samples from the bowl are shown in Figure 10C. Both interferents (in orange and yellow) appeared in some calibration standards and in all the samples from the bowl. The loadings of the three factors in the samples from the bowl followed an increasing pattern. The tensor was built with the accumulated matrices, so the linearity observed on the right side of Figure 10C indicates that the amount of melamine migrated from the bowl in each cycle was approximately the same, except for the first cycle.

< Figure 10>

A calibration model was built for melamine using the sample loadings of the 14 calibration standards. The accuracy line (predicted concentration versus true concentration) indicated that the procedure was unbiased at a significance level of 5 %. The values of the decision limit (CCα) and capability of detection (CCβ) were 0.29 and 0.58 mg L^{-1}, respectively, with the probabilities α and β fixed at 0.05.

Then, the equation of the migration kinetic curve (accumulated quantity of melamine) from the bowl was $y = 0.301 + 0.044\ x$, where x is the number of cycles of 30 min (up to 16). The percentage of explained variance of this kinetic model was R^2 =99.5 %. After sixteen cycles, the accumulated amount found was 1.03 mg L^{-1} of melamine, which was below the SML [35].

Therefore, this study led to the conclusion that the use of PARAFAC/PARAFAC2 was needed in migration testing and migration kinetics to avoid the overestimation of the amount of melamine since one interferent coeluted and the other one is overlapped with this analyte. In addition, in both migration analyses, the relative errors of the calibration standards (0.25 to 10.00 mg L^{-1}) calculated in the usual way with the chromatographic peak areas were greater than the values obtained with the PARAFAC loadings, especially at the lowest levels of concentration (see Table 6).

< Table 6>

5. Conclusions

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The use of PARAFAC/PARAFAC2 models enables the unequivocal identification of the target compounds according to the regulation in force in each case analysed.

The internal standard used in the determination of bisphenol A (BPA) by GC-MS was its deuterated compound, BPA-d_{16}, so both compounds closely elute. When analysing samples from the migration test of BPA from polycarbonate tableware, several interferents coeluted preventing the identification of BPA. The relative abundances of the detected ions of this analyte were within the permitted maximum tolerances using a PARAFAC decomposition, so BPA was unequivocally identified.

Another problem in practice is when coeluting compounds share ions with the internal standard and shifts in the retention time of the analytes appear from sample to sample, which must be within the allowable tolerance limits of the standard. This double problem appeared in the determination of the pesticide DIC in onions which has been solved using a PARAFAC2 decomposition. In addition, the use of the PARAFAC2 decomposition reduced the time and cost of the analysis when an experimental optimization is performed by means of a D-optimal design.

In the determination of oxybenzone in sunscreen cosmetic creams, the PARAFAC2 decomposition overcome the shifts in the retention time of BP3. In addition, the closeness in the retention times of DiBP and the internal standard DiBP-d_4, forces to consider only one window of scans for both compounds. PARAFAC decomposition enables the unequivocal identification of DiBP in spite of a coeluting interferent with some shared m/z ratios.

The use of PARAFAC/PARAFAC2 in migration testing and migration kinetics avoids the overestimation of the amount of the migrated melamine despite the fact that an interferent coeluted with this analyte.

PARAFAC/PARAFAC2 decomposition can also be employed as a quality control tool due to their capability to detect and handle the effect of any interferent present in complex matrix samples.

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Declaration of competing interest:

There are no conflicts of interest to declare.

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Figure captions

Fig. 1. Scheme of the unequivocal identification of a test sample.

Fig. 2. Total ion chromatogram for BPA, BPA-d_{16}, BPF, BFDGE and BADGE (500 µg L^{-1} of each analyte). Oven temperature program: 40 ºC (2 min), 10 ºC min^{-1} to 175 ºC (2 min) 6 ºC min^{-1} to 280 ºC (3 min).

Fig. 3. Loadings of the PARAFAC model built for BPA with the array $\underline{\mathbf{X}}_1$ (15×9×8). The first factor is BPA (in blue) and the second factor is BPA-d_{16} (in green). A) Chromatographic profile, B) spectral profile and C) sample profile.

Fig. 4. Experimental signals: (A) total ion chromatogram and (B) mass spectrum recorded at the maximum of the peak considered as BPA-d_{16}. Loadings of the four factors of the PARAFAC model built for BPA with the array $\underline{\mathbf{X}}_2$ (11×9×34): (C) Chromatographic profiles of BPA (in blue), BPA-d_{16} (in green), and the two interferents (in cyan and red); (D) Spectral profile for BPA-d_{16}.

Fig. 5. Loadings of the PARAFAC model built for ISDIC for data array $\underline{\mathbf{X}}_1$ (3×16×5). The first factor in green corresponds to ISDIC, and the second one is the interferent (in blue). A) Chromatographic profile, B) spectral profile.

Fig. 6. Loadings of the PARAFAC2 model built for ISDIC for data array $\underline{\mathbf{X}}_2$ (22×16×5). The factor in green corresponds to ISDIC, the ones in blue and red are the two interferents. A) Chromatographic profile, B) spectral profile.

Fig. 7. Loadings of PARAFAC2 model for BP3. A) Chromatographic profile and B) spectral profile.

Fig. 8. Loadings of the PARAFAC model for DiBP and DiBP-d_4. A) Chromatographic profile of DiBP in purple (first factor), the internal standard (DiBP-d_4, in light pink) and the interferent (in orange). B) Spectral profile with the same colour codes as in Figure 8A.

Fig. 9. Loadings of the PARAFAC2 model obtained for the migration testing from three bowls: A) chromatographic profile, B) spectral profile and C) sample profile.

Fig.10. Loadings of the PARAFAC model obtained for the migration kinetics. Loadings of: A) chromatographic profile, B) spectral profile and C) sample profile.

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Table 1. Structures of the diagnostic m/z ions chosen for the identification of BPA and its deuterated BPA-d_{16}.

BPA	BPA-d_{16}
m/z=91	CD_2 m/z=125
m/z=10	m/z=224
m/z=119	m/z=242
m/z=213	Molecular ion m/z=244
m/z=228	

[a] Base peak.

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Table 2. Minimum and maximum tolerance intervals of ISDIC (3,5 dichlorobenzonitrile).

m/z	100	136	171[a]	173	175
Spectral loading	0.1962	0.1664	0.8132	0.5155	0.0829
Ratio (%)	24.13	20.46		63.39	10.19
minimum	20.51	17.39		57.05	8.15
maximum	27.75	23.53		69.73	12.23

[a] Base peak.

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Table 3. Tolerance intervals for the relative ion abundances estimated for ISDIC by conventional means from the abundances of the chromatograms and relative ion abundances for the experimental design samples. In bold, the relative ion abundances of the m/z ratios which are not within their corresponding tolerance intervals.

		m/z ratio				
		100	136	171[b]	173	175
Tolerance interval (%)[a]		(19.79-26.77)	(14.92-22.38)	-	(56.75-69.37)	(8.34-12.51)
Relative ion abundance (%)	Sample 1	**29.90**	19.45	-	59.39	9.18
	Sample 2	**29.45**	19.30	-	59.84	8.48
	Sample 3	**27.51**	19.77	-	60.84	**8.25**
	Sample 4	**27.76**	19.61	-	63.56	9.09
	Sample 5	**28.18**	19.21	-	60.68	**7.36**
	Sample 6	**28.89**	19.35	-	60.47	**8.16**
	Sample 7	**29.38**	18.92	-	58.67	8.45
	Sample 8	**29.51**	20.02	-	61.21	9.15
	Sample 9	**27.58**	19.72	-	62.02	**8.06**
	Sample 10	**28.97**	20.26	-	63.69	8.94
	Sample 11	26.54	19.30	-	62.81	9.45
	Sample 12	26.40	19.45	-	64.41	9.90
	Sample 13	25.49	20.15	-	60.76	8.60
	Sample 14	26.62	18.88	-	62.67	8.57
	Sample 15	**26.92**	20.45	-	63.33	9.42
	Sample 16	26.39	18.87	-	60.29	9.32
	Sample 17	25.42	**23.35**	-	**76.45**	10.88
	Sample 18	25.70	18.93	-	62.62	10.34
	Sample 19	22.22	19.17	-	62.06	9.43
	Sample 20	23.28	18.65	-	63.06	10.43
	Sample 21	25.12	19.46	-	63.71	9.33
	Sample 22	26.58	19.53	-	61.78	9.46

[a] Computed according to the table contained in Fig. 1.
[b] Base peak.

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Table 4. Tolerance intervals for (A) the relative retention time, and (B) the relative ion abundances estimated from the loadings of the chromatographic and spectral profiles, respectively. Identification of every analyte in the analysis of sunscreen creams. In the case of BP3, the median of the retention times obtained in the corresponding PARAFAC2 decomposition was considered.

A) Retention time

Analyte	t_R (min)	Relative t_R	Tolerance interval	Identification in the analysis of the creams
				Relative t_R
DiBP-d_4	10.211	1.000	(0.995-1.005)	1.000
DiBP	10.220	1.001	(0.996-1.006)	1.001
BP3	11.120	1.089	(1.083-1.094)	1.089

B) Diagnostic ions

Analyte	m/z ratio	Spectral loading	Relative abundance (%)	Tolerance interval (%)	Identification in the analysis of the creams
					Relative abundance (%)
DiBP-d_4	80	$5.65 \cdot 10^{-2}$	5.68	(2.84-8.52)	5.70
	153[a]	$9.94 \cdot 10^{-1}$	100	-	100
	171	$2.48 \cdot 10^{-2}$	2.50	(1.25-3.75)	2.57
	209	$1.17 \cdot 10^{-2}$	1.18	(0.59-1.77)	1.23
	227	$4.95 \cdot 10^{-2}$	4.98	(2.49-7.47)	5.14
DiBP	104	$7.82 \cdot 10^{-2}$	7.86	(3.93-11.79)	7.66
	149[a]	$9.95 \cdot 10^{-1}$	100	-	100
	167	$2.75 \cdot 10^{-2}$	2.76	(1.38-4.14)	2.75
	205	$1.37 \cdot 10^{-2}$	1.38	(0.69-2.07)	1.39
	223	$5.24 \cdot 10^{-2}$	5.27	(2.64-7.91)	5.27
BP3	77	$1.56 \cdot 10^{-1}$	22.86	(19.43-26.29)	22.33
	105	$8.16 \cdot 10^{-2}$	11.99	(9.59-14.39)	11.74
	151	$5.73 \cdot 10^{-1}$	84.19	(75.77-92.61)	83.43
	227[a]	$6.81 \cdot 10^{-1}$	100	-	100
	228	$4.21 \cdot 10^{-1}$	61.86	(55.67-68.05)	61.80

[a] Base peak.

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Table 5. Tolerance intervals for the relative ion abundances estimated from the abundances of the chromatographic profiles by conventional means. Identification of every analyte in the analysis of sunscreen creams. In bold, the relative ion abundances of the m/z ratios which are not within its corresponding tolerance intervals.

Analyte	m/z ratio	Tolerance interval (%)[a]	Identification in the analysis of the creams: Relative ion abundance (%)									
			Cream 1	Cream 2	Cream 3		Cream 4		Cream 5		Cream 6	Cream 7
DiBP-d_4	80	(2.85-8.55)	5.45[b]	5.54[b]	5.39[b]	**8.78**[c]	6.00[d]	4.88[c]	5.63[e]	**9.58**[c]	6.01[f]	5.46[g]
	153[h]	-	-	-	-	-	-	-	-	-	-	-
	171	(1.30-3.89)	2.92[b]	3.35[b]	2.63[b]	**10.88**[c]	3.48[d]	**73.01**[c]	2.94[e]	**6.54**[c]	2.76[f]	3.13[g]
	209	(0.81-2.44)	1.77[b]	1.52[b]	**3.92**[b]	**4128**[c*]	**25.20**[d]	**1846**[c*]	1.66[e]	1.22[c]	1.74[f]	**13.85**[g]
	227	(2.73-8.19)	5.41[b]	5.80[b]	5.71[b]	**21.25**[c]	6.36[d]	**25.43**[c]	6.32[e]	**11.02**[c]	5.64[f]	5.47[g]
DiBP	104	(3.83-11.49)	8.40[b]	7.89[b]	8.82[b]		4.60[d]		7.66[e]		6.88[f]	6.00[g]
	149[h]	-	-	-	-		-		-		-	-
	167	(1.36-4.08)	**4.17**[b]	**5.28**[b]	3.85[b]		3.45[d]		3.98[e]		**4.89**[f]	3.95[g]
	205	(0.65-1.94)	1.76[b]	**2.69**[b]	**16.77**[b]		**59.31**[d]		1.65[e]		**2.43**[f]	**43.88**[g]
	223	(2.74-8.23)	**91.12**[b]	**129.41**[b*]	**64.54**[b]		**205.06**[d*]		**34.42**[e]		**93.18**[f]	**154.16**[g*]
BP3	77	(19.82-26.81)	21.83[b]	21.86[b]	**13.66**[c]		**59.24**[c]		26.27[c]		**7663**[f]	21.52[g]
	105	(9.64-14.46)	11.56[b]	11.23[b]	**31.79**[c]		**245.02**[c*]		**3527**[c*]		**22175**[f*]	11.32[g]
	151	(75.07-91.75)	81.04[b]	80.62[b]	**60.28**[c]		**156.87**[c]		**243.92**[c]		**93.75**[f]	82.56[g]
	227[h]	-	-	-	-		-		-		-	-
	228	(56.39-68.92)	61.60[b]	62.68[b]	**55.63**[c]		**36.02**[c]		**230.98**[c]		**75.00**[f]	61.33[g]

[a] Computed according to the table contained in Fig. 1.
[b] The concentration value was calculated using the extract diluted 10000 times (n = 2).
[c] The concentration value was calculated using the extract diluted 10 times (n = 1).
[d] The concentration value was calculated using the extract diluted 1300 times (n = 2).
[e] The concentration value was calculated using the extract diluted 1000 times (n = 2).
[f] The concentration value was calculated using the extract diluted 8000 times (n = 2).
[g] The concentration value was calculated using the extract diluted 3000 times (n = 2).
[h] Base peak.
[*] Peaks with anomalous abundance.

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Table 6. Relative error (%) for melamine in the calibration standards obtained with the standardized loadings of the PARAFAC/PARAFAC2 decomposition and with the peak area.

Concentration (mg L^{-1})		0.25	0.50	0.75	1.50	3.00	4.00	5.00	6.00	7.50	9.00	10.00
Migration test	PARAFAC2 decomposition	17.2	10.8	7.9	-1.6	-1.6	-0.3	-2.1	4.3	-0.3	0.3	0.8
	Peak area	32.2	16.7	5.0	-6.4	-1.7	-1.5	-3.9	1.9	-0.9	0.3	1.6
Migration kinetics	PARAFAC decomposition	28.0	14.1	10.0	-3.0	-4.4	-2.5	-4.0	3.6	-0.3	-1.2	1.8
	Peak area	65.9	32.1	2.1	-14.4	2.0	1.5	-6.1	0.7	-0.3	-1.4	2.8

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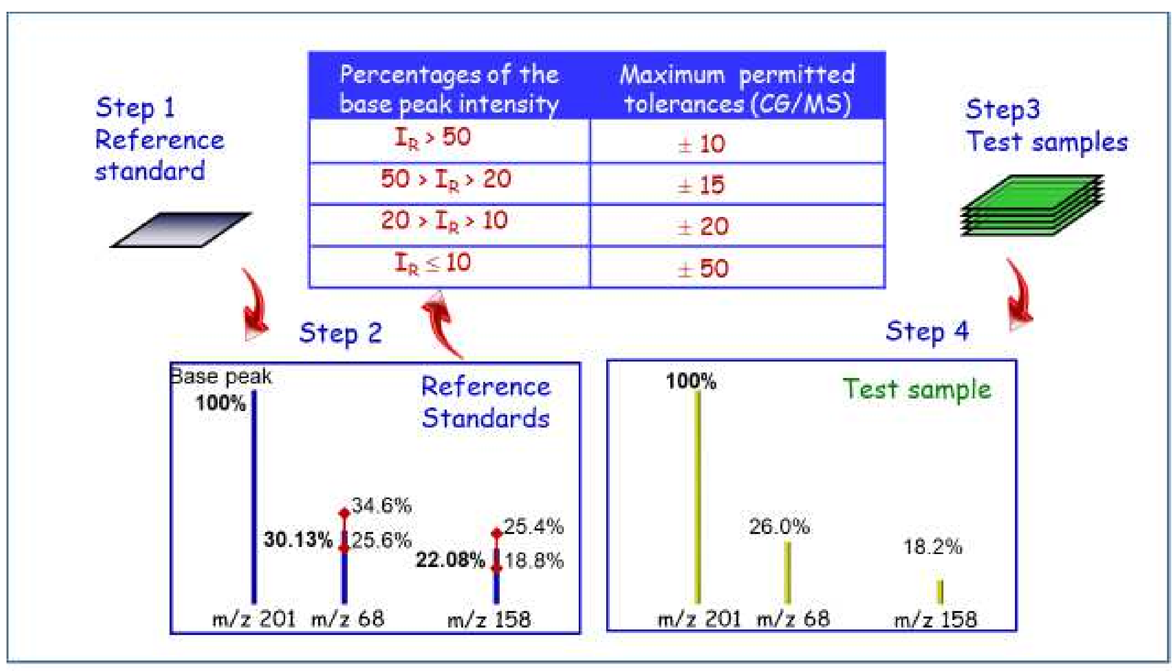

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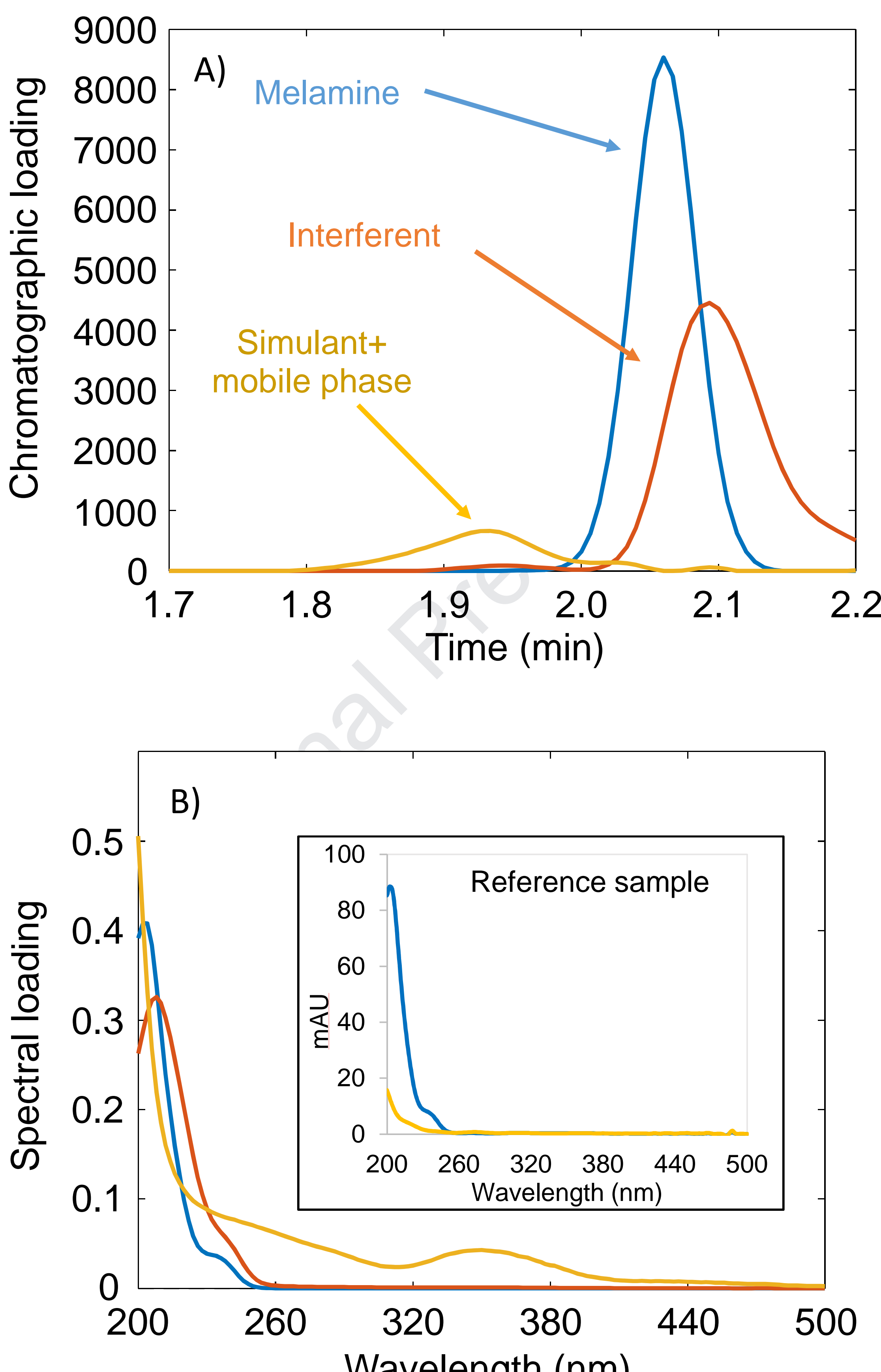
Figure 1


A)
Melamine
Interferent
Simulant+
mobile phase
Chromatographic loading
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1.7
1.8
1.9
2.0
2.1
2.2
Time (min)
B)
Reference sample
100
80
60
40
20
0
mAU
200
260
320
380
440
500
Wavelength (nm)
Spectral loading
0.5
0.4
0.3
0.2
0.1
0
200
260
320
380
440
500
Wavelength (nm)

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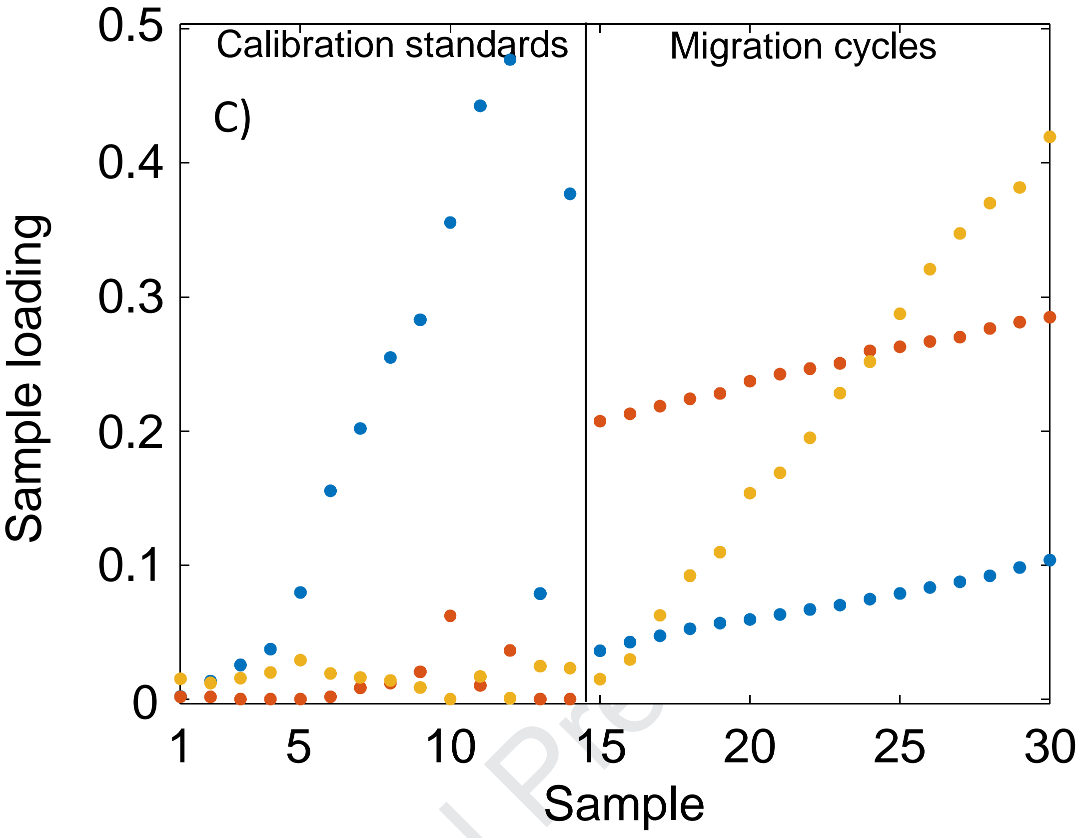

Figure 10

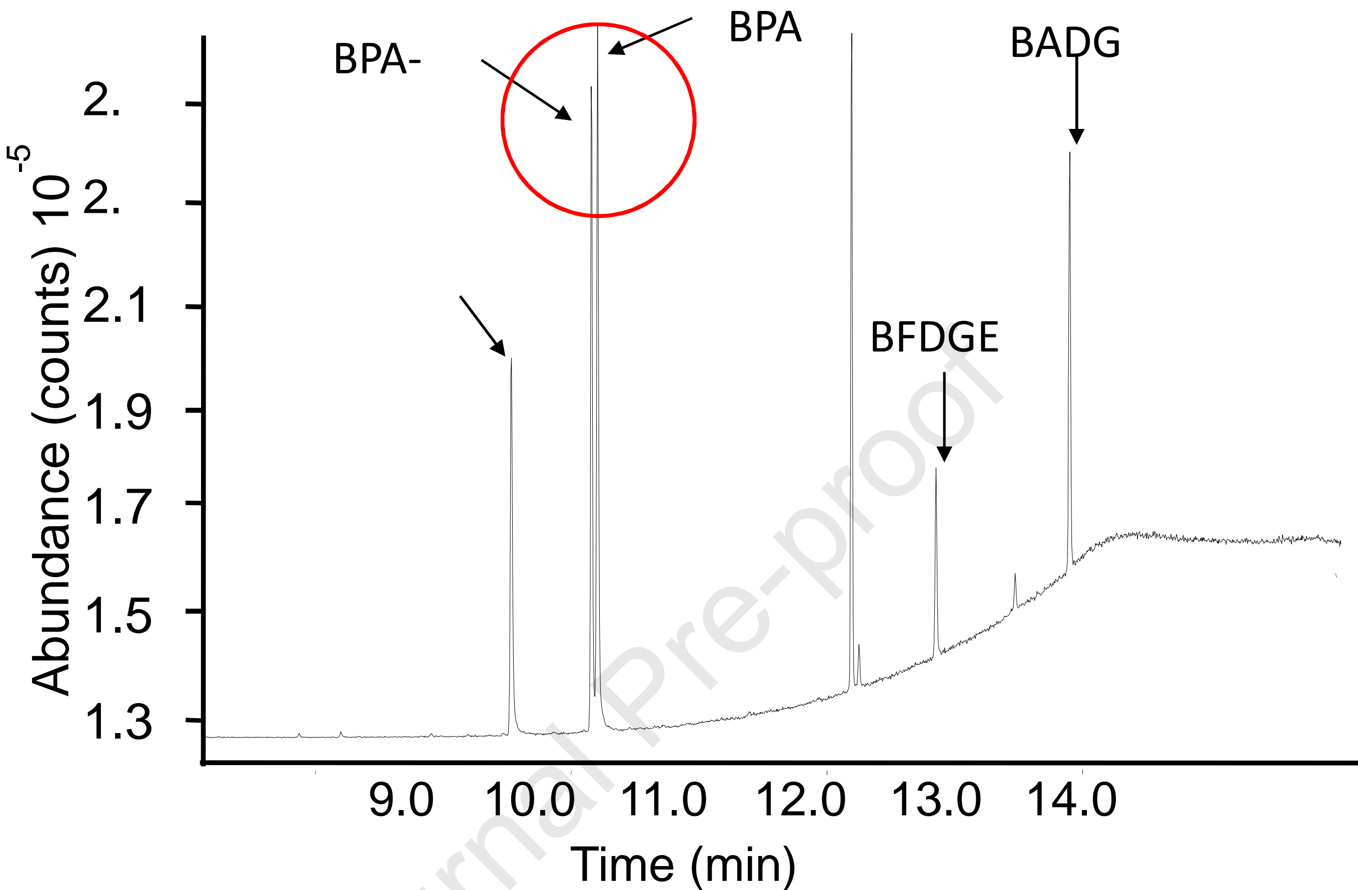

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FIGURE 2

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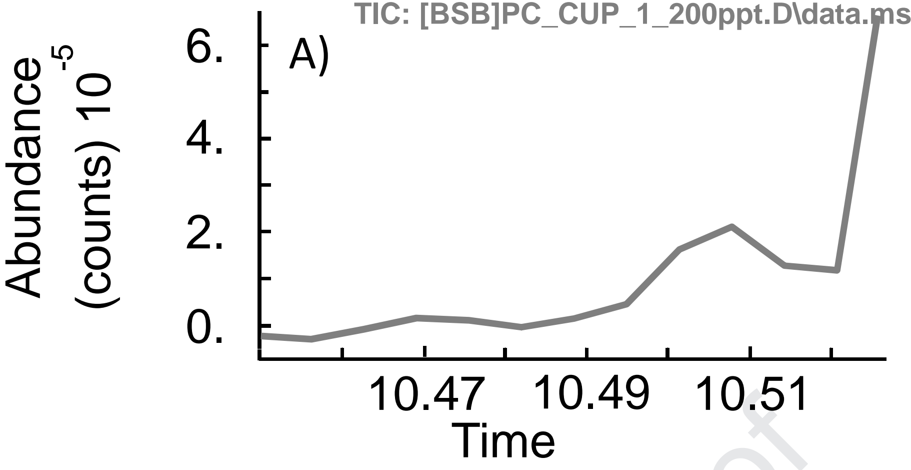
A)
x10^5
Chromatographic loading
5
3
1
BPA
BPA-d16
10.3 10.3 10.3 10.4 10.4
Time (min)

B)
Spectral loading
0.9
0.7
0.5
0.3
0.1
91 107 119 125 213 224 228 242 244
100 120 140 160 180 200 220 240
m/z

C)
Sample loading
0.
0.
0.
BPA-d16 (100 µg L-
0 10 20 30 40 50 60 70 80
BPA concentration (µg L-

Figure 3



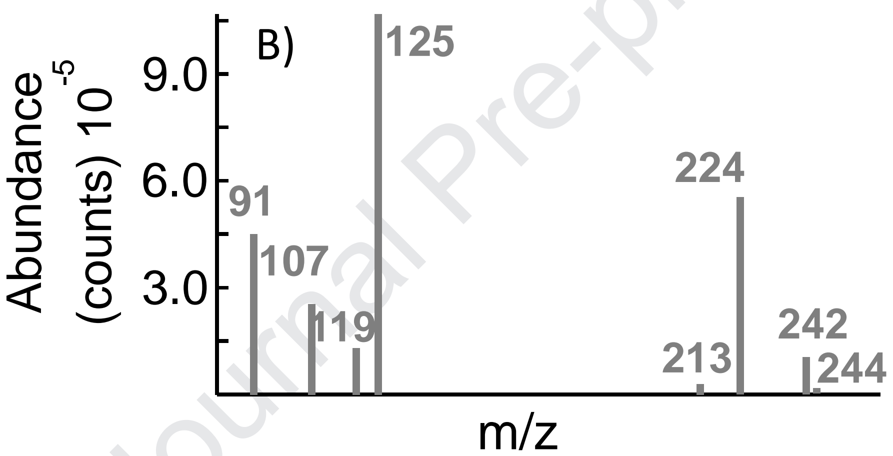


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Figure 4 (A-B)

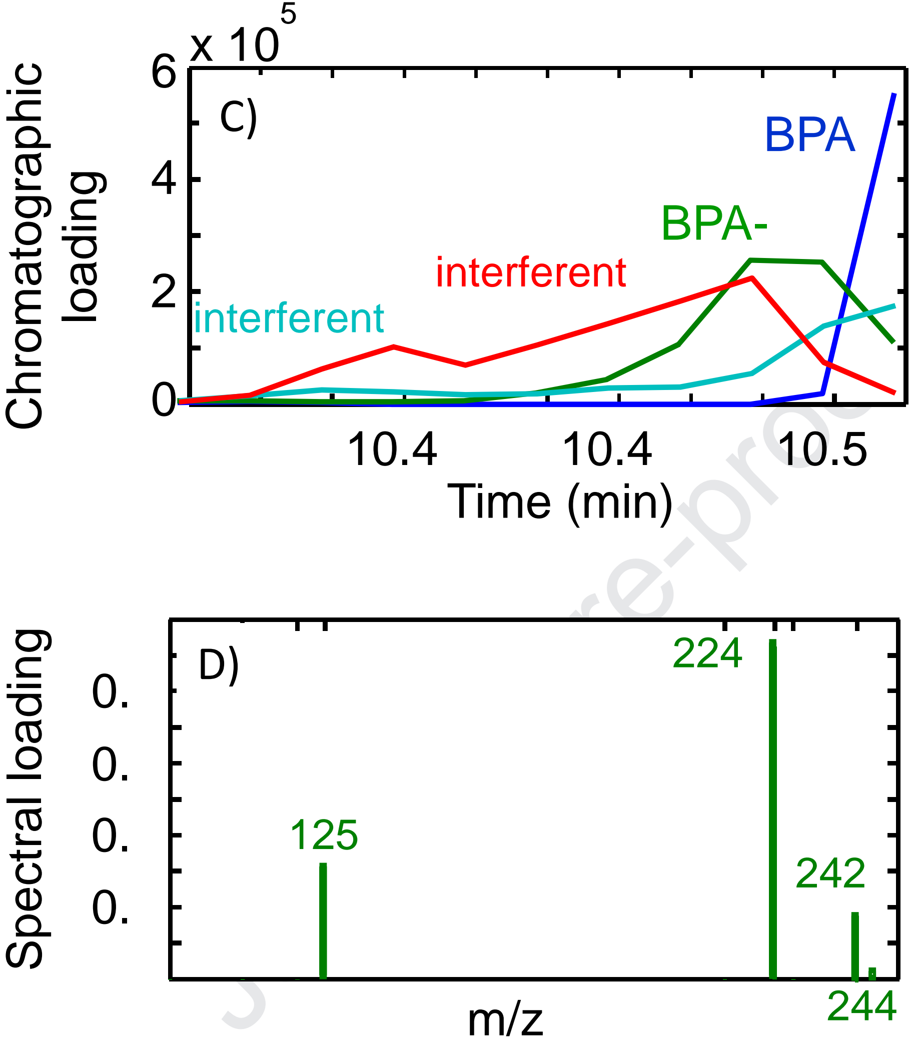

Figure 4 (C-D)

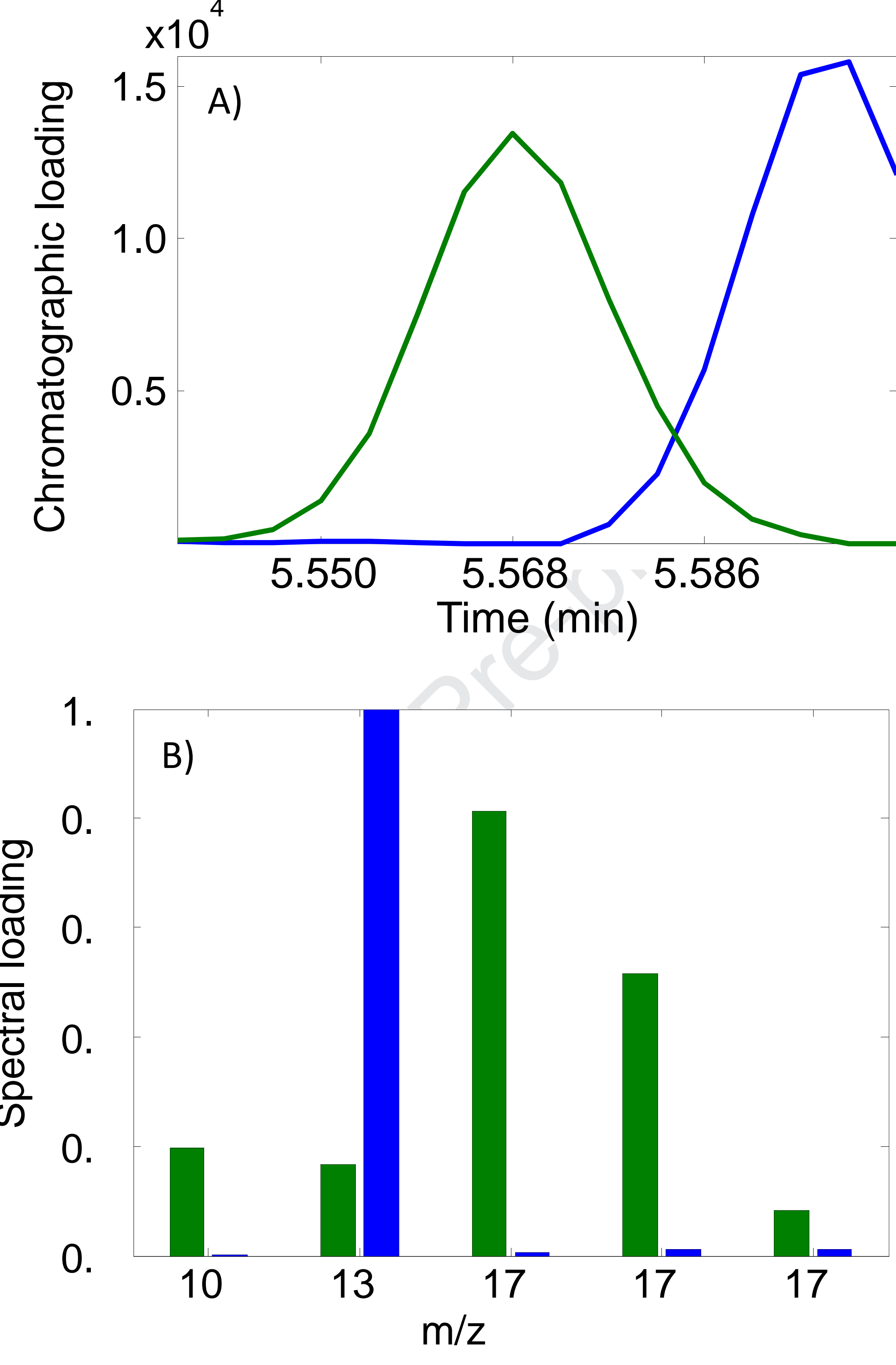

Figure 5

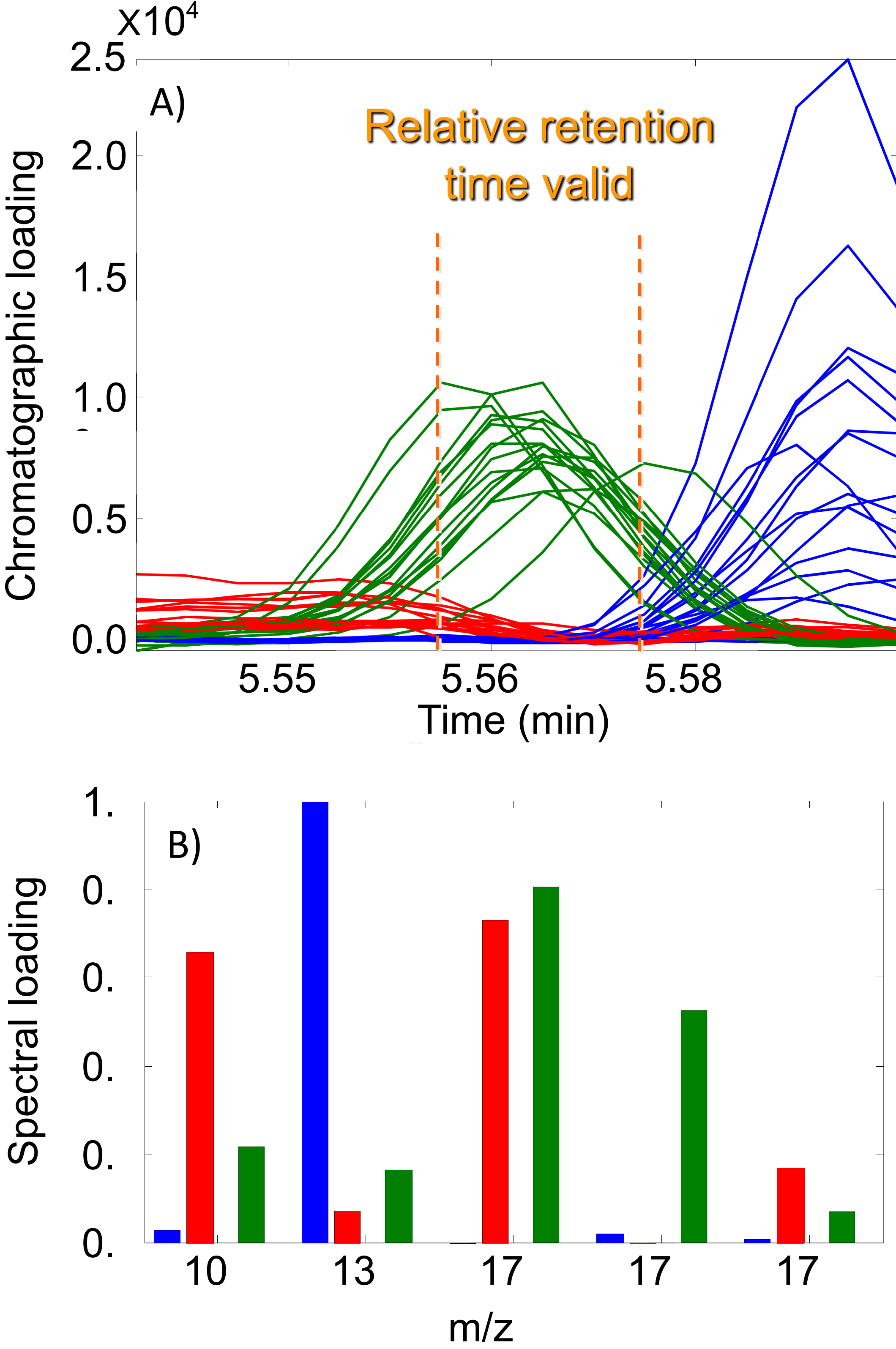

Figure 6

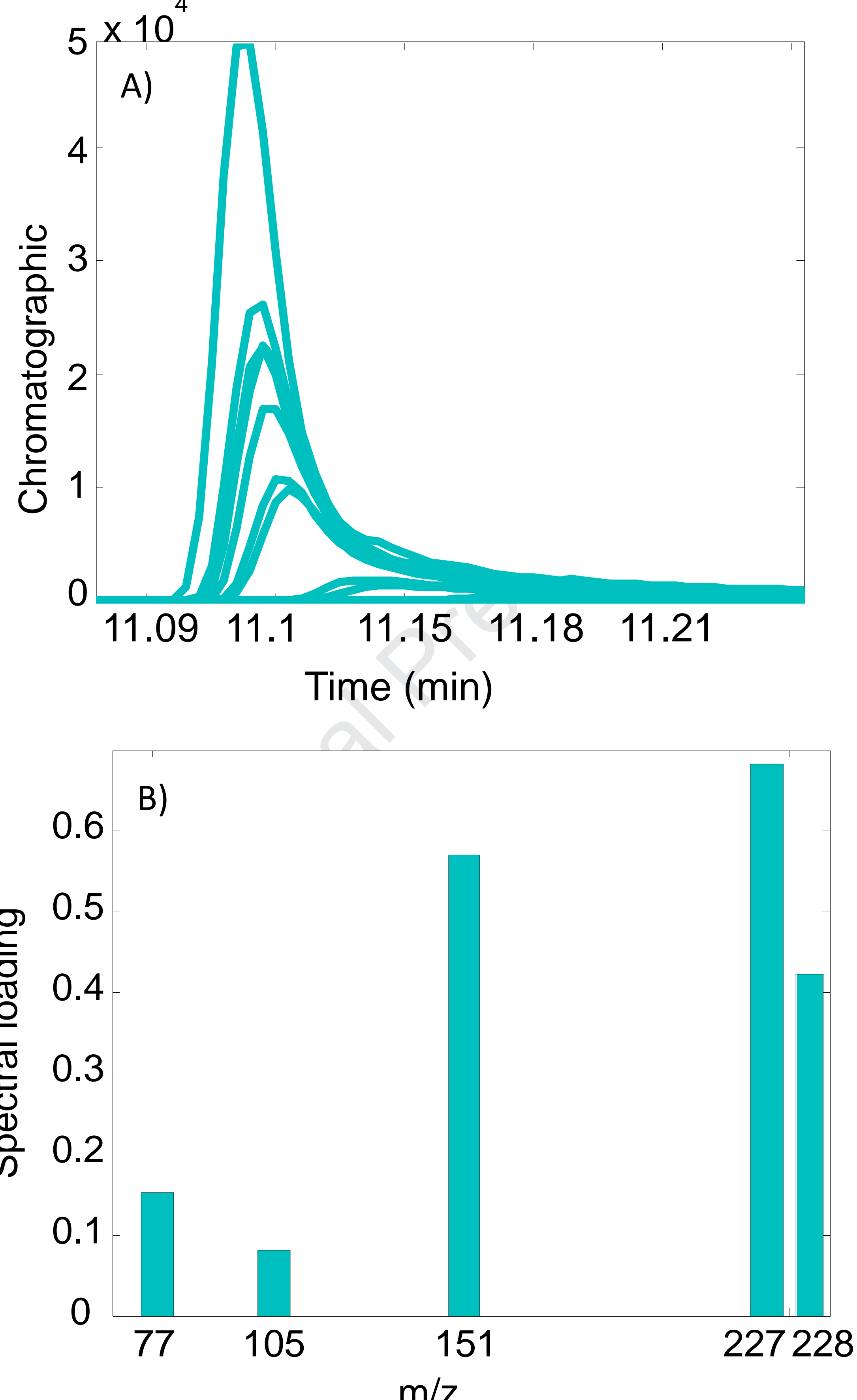

Figure 7

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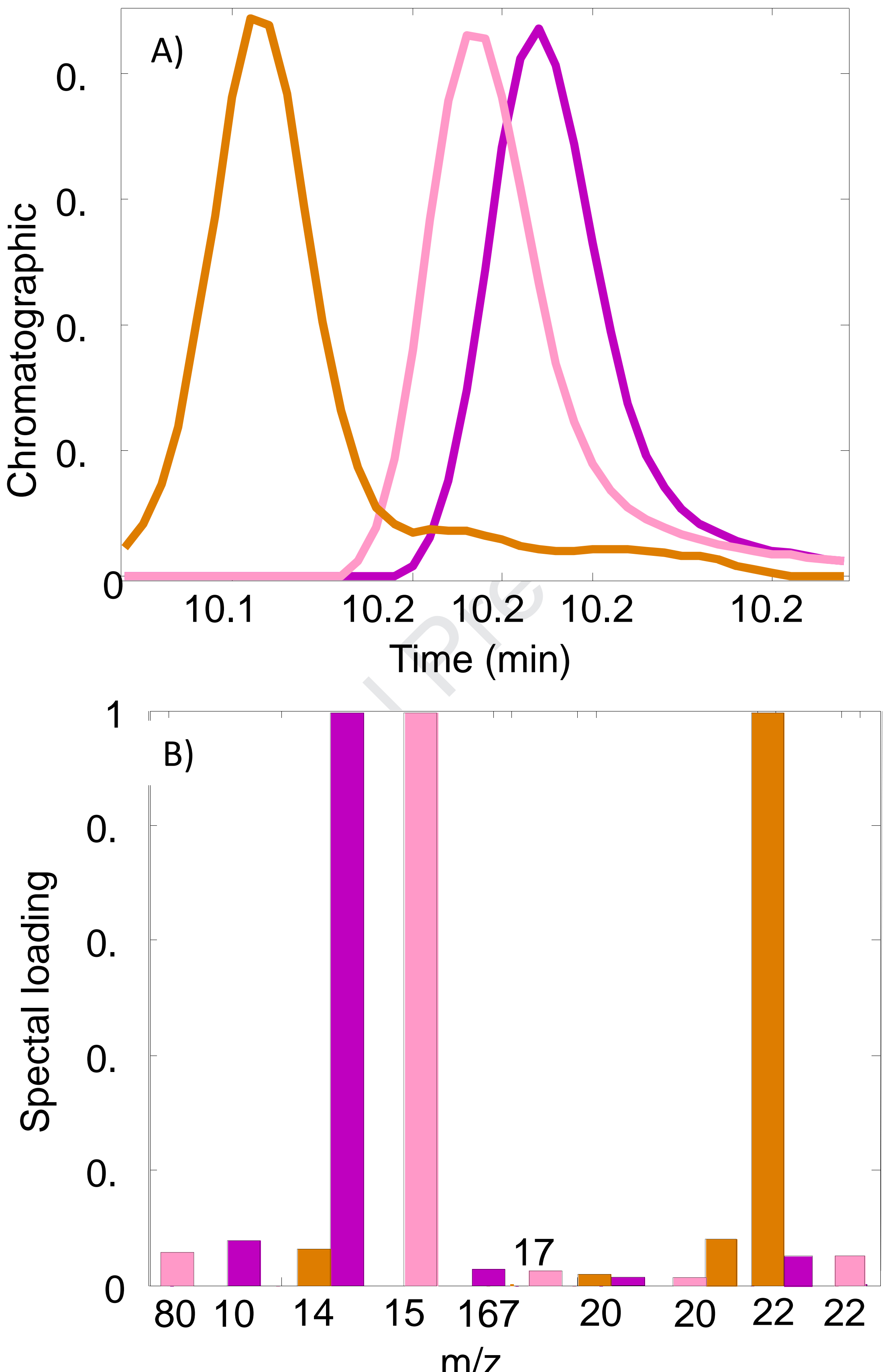

Figure 8

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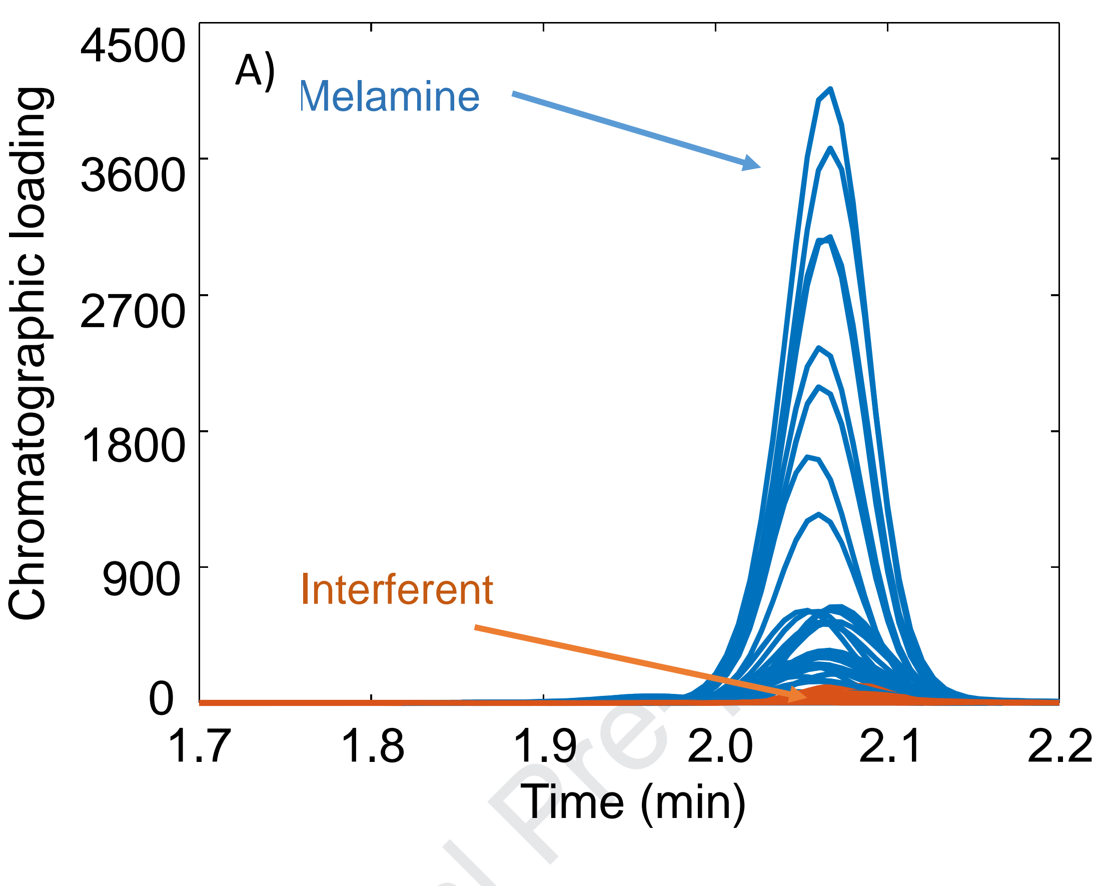

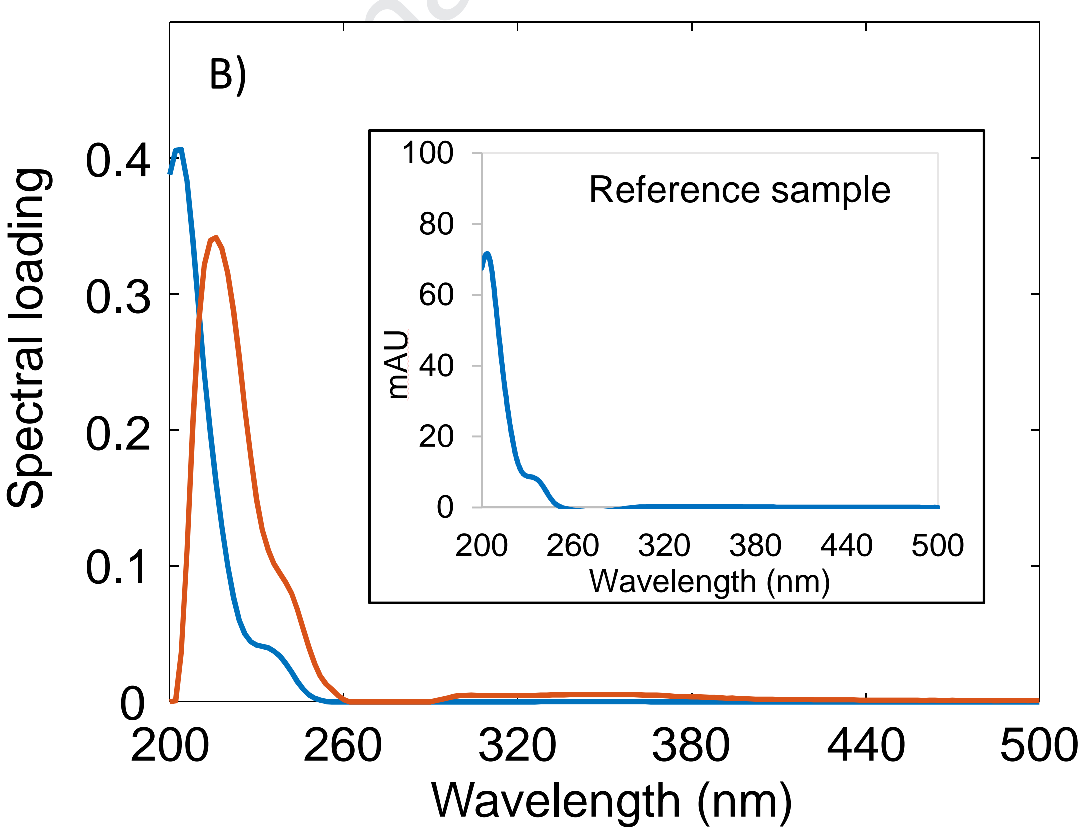

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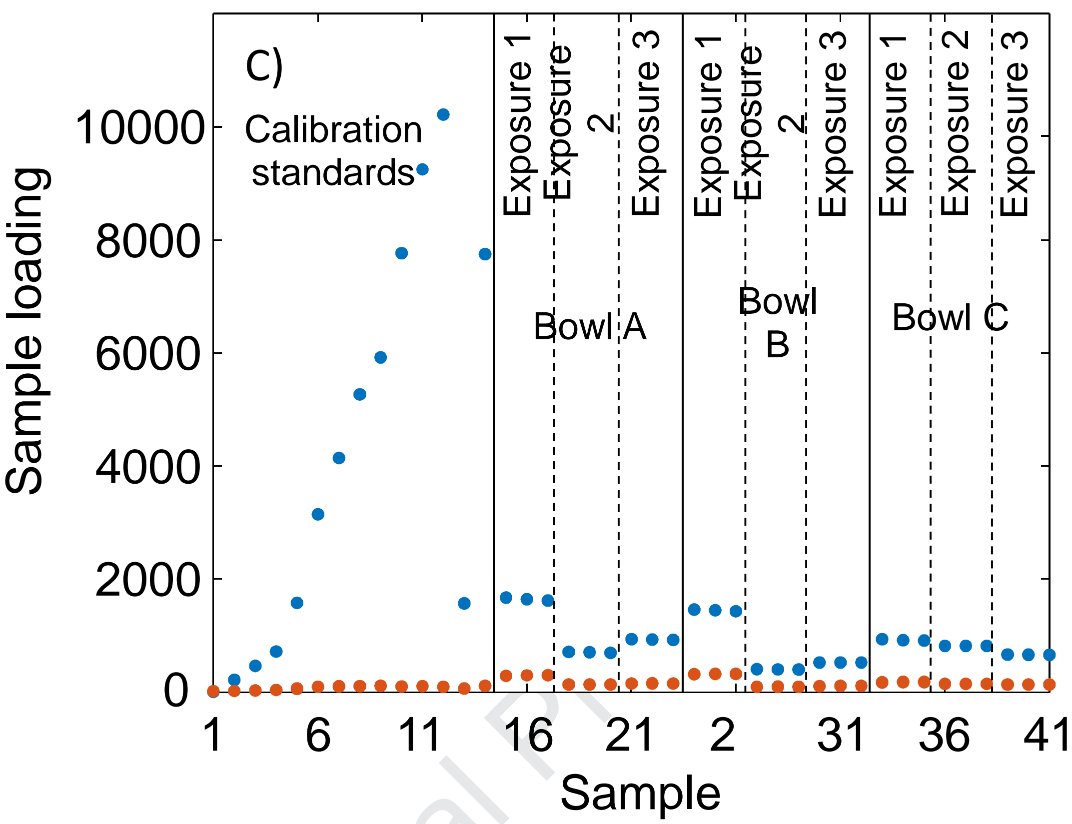

Figure 9

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Highlights

Unequivocal identification and quantification using PARAFAC and chromatographic data

Usefulness of multi-way techniques when there are legal requirements to comply with

Unequivocal identification of migrants in the presence of coeluents using PARAFAC

GC-MS and PARAFAC as useful tools in the identification of pesticides in foodstuffs

Use of PARAFAC in migration testing to avoid the overestimation of migrated melamine

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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