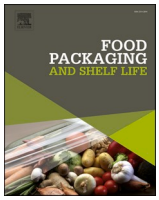
Food Packaging and Shelf Life 40 (2023) 101196

Contents lists available at ScienceDirect

Food Packaging and Shelf Life

journal homepage: www.elsevier.com/locate/fpsl



Determination of volatile migrants from breast milk storage bags

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ARTICLE INFO

Keywords:
Food packaging
Migration
Breastmilk
Polyethylene
Printing inks
NIAS

ABSTRACT

Breast milk storage bags are commonly used to facilitate extended periods of breastfeeding. These bags must meet the necessary safety standards for infant food and comply with current regulations. As they are typically made from polyethylene and feature printing inks on their surface, there is a potential for the transfer of polymer and ink additives, as well as non-intentionally added substances (NIAS), into the milk. An initial study was conducted using two breast milk bags to identify the primary migrants that could be released from this particular food packaging. Migration tests were conducted in both milk and the corresponding food simulant D1 (50% ethanol/water, v/v) under conditions mimicking typical breast milk storage conditions (4–5ºC, 7 days) and defrosting conditions (40ºC, 2 h). The results showed the presence of volatile migrants in both situations, whether long storage periods at refrigerated conditions or brief periods if the temperature is not under control. The outcomes also highlighted that the primary migrants were breakdown products from Irgafos 168, a widely used trisarylphosphite-based antioxidant. These included 2,4-ditertbutylphenol (2,4-dtBP), 1,3-di-tert-butylbenzene (1,3-dtBB), and 2,6-di-tert-butyl-1,4-benzoquinone (2,6-dtBBQ). A subsequent study was carried out involving eight breast milk bags to evaluate the migration of these compounds and to conduct a comprehensive risk assessment of the materials used, ensuring the safety of infants' health is not compromised. Results showed that 1,3-dtBB exceeded the maximum recommended migration values in two of the studied bags. Nevertheless, further toxicity tests are necessary to ensure the safety of these materials in relation to food.

1. Introduction

Food packaging offers numerous advantages to food, including safeguarding it against external elements, preserving its quality, extending its shelf life, and displaying essential information. However, it is crucial to regulate the transfer of substances from the packaging to the food (known as migration processes) that may occur during food storage to ensure food safety (Castle, 2007). If the compounds transferred possess toxic properties, they can pose a health risk to consumers and if they are odorous in nature, they can alter the sensory quality of the food. To prevent such issues, it is essential that all packaging materials used for food contact comply with Regulation (EC) 1935/2004 that establishes the framework to ensure the safety of food packaging materials (European-Commission, 2004). Its fundamental principle is that any material or article designed for direct or indirect contact with food should be chemically inert enough to prevent the transfer of substances that could endanger human health or cause undesirable alterations in the composition or sensory properties of the food. Furthermore, plastic materials intended for food contact must comply with Regulation EU/10/2011 and next amendments (European Comission, 2011). This regulation outlines a comprehensive list of compounds approved for use in the production of these materials, along with specific migration limits (SMLs) that restrict the amount of substances allowed to migrate from the packaging to the food. Additionally, the regulation specifies the time-temperature conditions to be employed during migration assessments to ensure the safety and suitability of the plastic materials used in food packaging.

This study focused on a specific type of food packaging, breast milk storage bags. Breastfeeding is one of the most effective ways to ensure children health, since it is safe, clean and contains antibodies which help protect against many common childhood illnesses (Boix-Amorós et al., 2019). The World Health Organization recommends breastfeed infants at least for 6 months (World Health Organization, 2017). Unfortunately, many mothers find difficulties for breastfeeding due to job incompatibilities or, in some cases, to specific illness. In these cases, the possibility of store breast milk can help to solve the problem. The ABM (Academy of Breastfeeding Medicine) establishes the optimum storage conditions to guarantee the correct maintenance of breast milk

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https://doi.org/10.1016/j.fpsl.2023.101196
Received 6 July 2023; Received in revised form 22 September 2023; Accepted 1 October 2023
Available online 7 October 2023
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biological and nutritional properties (Eglash et al., 2010). The maximum recommended storage duration for breast milk varies depending on the storage temperature. At room temperature (16 – 29 ºC), the optimal maximum storage duration is 3–4 h, while under very clean conditions, an acceptable storage duration of 6–8 h can be maintained. The optimal maximum duration in the refrigerator ($\leq$ 4ºC) is 72 h, while under very clean conditions, it can be stored for 5–8 days. In the freezer (< -4ºC), the ideal maximum storage duration is 6 months, although it remains acceptable for up to 12 months. When thawing frozen milk, it is recommended to defrost it gradually, either by placing it in the refrigerator overnight, running it under warm water, or immersing the container in a container of warm water. Using a microwave for heating breast milk is not recommended due to difficulties in controlling the temperature, resulting in uneven heating of the milk (Eglash et al., 2010). During the storage of breast milk, in addition to preserving its properties, it is crucial to ensure that the packaging used does not transfer any substances that could pose a risk to the health of infants. and to determine the main factors affecting the migration process.

Migration occurs due to two primary processes: diffusion and partition, both influenced by various factors, including the properties of the migrants (boiling point, polarity, molecular weight, spatial conformation), as well as the properties of both the food and the polymer (Ji et al., 2020). Furthermore, temperature plays a significant role in migration, as it has a positive correlation with the migration process. The increased temperature in high polymer materials leads to an increase in the freedom energy of polymer chain segments, resulting in greater flexibility and the creation of small gaps or holes through which small migrants can escape (Gladysz & Chawla, 2015). Additionally, small molecules experience additional free energy, aiding their movement through the polymer The mobility of migrants can also be influenced by the thickness of the polymer material. Experiments conducted by Liu et al. demonstrated reduced mobility in thicker PE materials when oil was used as a simulant, (Liu et al., 2020).

Polyethylene, a polyolefin commonly used in the production of breast milk storage bags, exhibits high diffusivity, making it prone to transferring compounds to food (Dole et al., 2006). Numerous studies have investigated migration from food packaging made with this polymer, both as a monolayer material and as part of multilayer packaging structures. Different kind of compounds have been found in migration: antioxidants such as Irganox 3114 (Bodai et al., 2015), Irganox 1010 and Irganox 1076 (Sungur & Tunur, 2020), Ethanox 330 and Irgafos 168 (Dopico-García et al., 2003); fluorescent whitening agents (FWAs) (Ji et al., 2020); UV-ink photoinitiators such as Irgacure 819 or Darocure 1173 (Zhang et al., 2016); and plasticizers such as diisobutyl phthalate (DIBP) and dibutyl phthalate (DBP) (Liu et al., 2020)(Di Bella et al., 2014). Other authors have specifically studied the migration of non-intentionally added substances (NIAS) from polyethylene and other polyolefins such as polypropylene (Su et al., 2020) (Vera et al., 2019) (Vera et al., 2020)(Chen et al., 2021). The studies conducted by Vera et al. highlights the importance of the analysis of NIAS in polyethylene since a total of 17 different NIAS were identified in migration of 18 polyethylene films, including degradation products of Irganox 1010 and Irganox 1076, breakdown products such as hexa-heptadecanamide; impurity reaction products and compounds of unknown origin like phosphine oxide (Vera et al., 2019) and also compounds responsible for off-odors that could impact the sensory quality of the packaged food (Vera et al., 2020).

Breast milk storage bags also contain printing inks on its surface that help to measure the volume of the stored milk. Several studies have confirmed that printing inks are a possible source of migrants and therefore must be considered in the evaluation of the studied materials (Aznar et al., 2015; Clemente et al., 2016).

The aim of this study was to examine the potential transfer of volatile compounds from polyethylene-based breast milk bags to the stored milk and to perform a thorough risk assessment of the materials employed, guaranteeing the preservation of infants' health and safety. The analyses were performed by solid phase microextraction coupled to gas chromatography-mass spectrometry (SPME-GC-MS).

2. Material and methods

2.1. Samples

Eight breast milk bags with capacity between 180 and 250 mL were purchased in supermarkets or pharmacies for this study (BMB01 to BMB08). All of them were made of polyethylene and had been partially printed in the front side with different colors with the aim of providing information about the brand or capacity. It is estimated that the printed surface area of the bag was in all cases below 5%. Additional information about the bags, such as price, material thickness, capacity, and printing inks colors, is shown in Supplementary Material 1.

2.2. Reagents and SPME fibers

Limonene (CAS: 138–86–3); 1,3-Di-tert-butylbenzene (CAS: 1014–60–4); 2,6-Di-tert-butylbenzoquinone (CAS: 719–22–2); 2,4-Di-tert-butylphenol (CAS: 96–76–4); Undecane (CAS: 1120–21–4); Dodecane (CAS: 112–40–3); Tetradecane (CAS: 629–59–4); Pentadecane (CAS: 629–62–9); Hexadecane (CAS: 544–76–3); Heptadecane (CAS: 629–78–7); Octadecane (CAS: 593–45–3); Phenol, 2,4-di-t-butyl-6-nitro- (DBNP) (CAS: 20039–94–5); 3,3′,5,5′-tetramethylbiphenyl (CAS: 25570–02–9) and 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TXIB) (CAS: 6846–50–0) were bought from Sigma-Aldrich (Barcelona, Spain).

Panreac (Barcelona, Spain) provided dichloromethane, Scharlau (Setmenat, Spain) supplied HPLC-grade absolute ethanol and ultra-pure water was obtained from a Millipore Milli-Q system (Billerica, MA, USA).

Whole cow milk for the migration test was bought in a local supermarket (Composition in 100 mL of milk: 3.6 g fat, 4.6 g carbohydrate, 3.1 g protein 3.1 g and 0.1 g salt).

SPME fibers (DVD/CAR/PDMS) were provided by Supelco (Bellefonte, PA, USA).

2.3. Analysis of breast milk storage bags

Two kinds of sample treatment protocols were tested over the milk bag samples to select the best methodology for the determination of the main volatile compounds present in the bags: liquid extraction and direct analysis by HS-SPME.

In both cases, 0.5 g of bag samples were cut in small cut-offs (< 0.5 cm^2) for the analyses. The analysis distinguished between sections of the bag with printing inks on their surfaces (portions had a minimum of 50% printed surface) and sections without any printed surface. For the liquid extraction experiment, two consecutive extractions with 4 mL of dichloromethane were performed during 1 h in an ultrasounds bath. Afterwards, the extracts were mixed, and an aliquot was analyzed by GC-MS (Injection volume 1 μL).

To perform a thorough analysis of the samples, the sample cut-offs were carefully placed into a sealed 20 mL glass vial. Subsequently, the analysis was conducted using HS-SPME-GC-MS.

All the samples were analyzed in triplicate by each methodology.

2.4. Migration assays

Migration assays were performed in the first place in food simulant D1 (50% ethanol/water, v/v), identified in the Regulation EU/10/2011 as the most appropriate option for mimic migration to milk (European Comission, 2011). Subsequently, migration assays were carried out in whole cow milk.

Following the procedures of the Academy of Breastfeeding Medicine (ABM) (Eglash et al., 2010), the bags were filled with 60 mL of food simulant/milk, since it is the estimated milk dose for newborn babies.

According to ABM procedures, breast milk can be stored a maximum of 5–8 days under refrigerated conditions (4–5ºC) in order to preserve its nutritional and biological properties. Alternatively, breast milk can be frozen for up to 12 months. When defrosting frozen breast milk, it is recommended to either defrost it overnight in the refrigerator or warm it in a water bath (maximum temperature 40 ºC). Migration conditions tested in this study were:

- 7 days under refrigerated conditions (4–5 ºC)
- 40 ºC for 2 h (in order to assess potential migration during the defrosting step under a worst-case scenario).

After this time, migration samples were analyzed by SPME-GC-MS, either by analyzing their headspace (HS) or by direct immersion in the solution (DI). Milk samples were analyzed by HS-SPME-GC-MS, which was conducted using 3 mL aliquots.Ethanol 50% samples were diluted five-fold with water prior to be analyzed by DI-HS-SPME, which was conducted using 15 mL aliquots. DI was selected in this matrix since it provided slightly higher peaks than HS (Supplementary material 2).

All the migration assays were performed in triplicate.

2.5. Analysis by SPME-GC-MS

In both cases, DI-SPME-GC-MS and HS-SPME-GC-S, the samples were subjected to equilibration at 70ºC for 1 min, followed by SPME performed at 70ºC for 15 min with agitation at 500 rpm. The SPME fiber was desorbed in splitless mode at 250ºC for 2 min.

For the analysis, an Agilent Technologies gas chromatograph system (6840 GC) coupled with a mass spectrometer (5975 MSD) was used. The autosampler employed was a Combi PAL from CTC Analytics in Zwingen, Switzerland.

The column used was an Agilent HP-5MS with dimensions of 30 m x 0.25 mm × 0.25 μm film thickness. The oven temperature was programmed as follows: initially held at 50ºC for 5 min, followed by a ramp of 10ºC per minute up to 300 ºC. Mass spectrometry analysis was conducted in SCAN mode, covering the *m/z* range of 40–450.

2.6. Identification of volatile compounds

Initially, the identification of a detected compound was carried out by comparing its mass spectrum with those of the NIST library. Only identifications with match values exceeding 800 were considered. Subsequently, the candidates were further confirmed using retention index (RI). In order to accomplish this, the experimental RI (RI_{exp}) was compared to the bibliographic RI (RI_{bib}) obtained from databases such as [www.flavornet.org] or [www.chemspider.com].

In cases where feasible, the candidate was further validated by injecting a commercial standard. Confirmation was achieved if the observed pattern (retention time and mass spectra) matched that of the standard. Those compounds for which the standard was not available were considered as *tentatively* identified.

2.7. Quantification of migrants

Quantification was conducted using an external calibration method. Calibration curves were prepared using as matrix 10% ethanol/water (v/v) or milk. The calibration curves were then subjected to analysis using HS-SPME-GC-MS, in milk samples, or DI- SPME-GC-MS, in ethanol 10% samples. The analysis method was the same employed for the analysis of migration samples. The limit of detection (LOD) and the limit of quantification (LOQ) were calculated as the smallest concentration of the analyte that provided a signal (heigh) three times and ten times the blank respectively.

3. Results and discussion

3.1. Volatile compounds present in breast milk bags

In the initial phase, breast milk bags (BMB01 and BMB02) were subjected to analysis to identify the primary categories of migrants that might be transferred from this kind of food packaging to the breast milk during the storage period.

Table 1 shows the compounds detected in the analysis of BMB01 and BMB02 by HS-SPME-GC-MS, along with their respective intensity ranges. The three intensity categories were established according to the relative percentage of counts of the chromatographic peak (related to the counts of the largest peak in the chromatogram): Low (L) < 10%;

Table 1
Compounds identified in BMB01 and BMB02 by HS-SPME-GC-MS, its retention time (t_R), experimental retention index (RI) and its intensity level according to the relative percentage of chromatogram peak counts: Low (L) < 10%; Medium (M) 10–50%; High (H) > 50%).

	t_R	RI	Compound	CAS	BMB01	BMB02
1	3.74	< 800	Toluene	108–88–3		1
2	4.38	800	Octane *✓	111–65–9		1
3	9.53	1000	Decane *✓	124–18–5		2
4	10.24	1036	Alkane RI1036			1
5	11.13	1082	Alkane RI1082			1
6	11.27	1090	Alkane RI1090			1
7	11.39	1096	Alkane RI1096			1
8	11.47	1100	Undecane*✓	1120–21–4		1
9	11.51	1102	Alkane RI1102			2
10	11.59	1110	Nonanal*	124–19–6	1	
11	11.72	1115	Alkane RI1115			2
12	11.77	1118	Alkane RI1118			2
13	11.95	1129	Alkane RI 1129			2
14	12.05	1134	Alkanes RI1134			2
15	12.11	1138	Alkanes RI1138			2
16	12.59	1167	Alkane RI 1167			1
17	12.67	1171	Undecane, 3-methyl*	1002–43–3		2
18	13.05	1198	ni (mz 128.2)		1	
19	13.14	1200	Dodecane*✓✓	112–40–3	2	2
20	13.36	1214	Alkane RI1214			1
21	13.56	1232	2-Phenoxyethanol*	122–99–6	1	
22	13.99	1256	1,3-Di-tert-butylbenzene (1,3-dtBB)*✓	1014–60–4	2	3
23	14.55	1299	ni (mz 83.2)		1	
24	14.63	1300	Tridecane *	629–50–5		1
25	15.13	1334	Alkane RI1334			1
26	15.17	1336	Alkane RI1336			1
27	15.53	1362	Alkane RI1362			1
28	15.60	1367	Tridecane, 3-methyl-*	6418–41–3	L	M
29	15.89	1388	1-Tetradecene*	1120–36–1		L
30	15.95	1399	ni (mz 84.1)		L	
31	16.00	1400	Tetradecane*✓	629–59–4	M	M
32	16.08	1403	Alkane RI1403			L
33	16.65	1446	Alkyl alcohol RI1446			L
34	16.94	1469	2,6-Di-tert-butylbenzoquinone (2,6-dtBBQ)*✓	719–22–2		L
35	17.20	1490	Alkane RI1490			L
36	17.34	1500	Pentadecane*✓	629–62–9	L	
37	17.43	1507	2,4-Di-tert-butylphenol (2,4-dtBP)*✓	96–76–4	H	H
38	18.13	1566	Pentadecane, 3-methyl*	2882–96–4		L
39	18.46	1600	Hexadecane *✓	544–76–3	M	L
40	18.97	1638	ni (mz 173)	1654–86–0		M
41	19.69	1700	Heptadecane*✓	629–78–7	L	
42	20.77	1800	Octadecane*✓	593–45–3	L	

ni: non identified
*Confirmed by retention index✓Confirmed by standard

Medium (M) 10–50%; High (H) > 50%. A total of 14 compounds were detected in BMB01 analysis, and the corresponding peaks can be observed in Fig. 1a. Among these compounds, 2,4-ditertbutylphenol (2,4-dtBP) exhibited the highest intensity. This particular compound is a degradation product of Irgafos 168, a commonly used trisarylphosphite-based antioxidant (Ta & Bones, 2017)(Kim et al., 2023). Additionally, four compounds were observed at medium intensities: 1,3-di-tert-butylbenzene (1,3-dtBB), which is also a by-product of Irgafos 168; as well as three alkanes (dodecane, tetradecane and hexadecane). Considering that the milk bags were manufactured using polyethylene, alkanes with different carbon units were expected to be present in the samples (Biedermann-Brem et al., 2012).

When comparing the chromatograms obtained from the analysis of the bag cut-offs containing printed inks to those with no printed surface, no additional compounds were observed. This could be due to the diffusion processes that the volatile compounds (present initially only in the printing inks) can suffer during the bags storage. At the end of the storage period, printing ink compounds will be equally present in all the bag surface. This would explain why when comparing chromatograms, no discernible distinctions between both kind of cut-offs were identified.

To explore the possibility of detecting new potential migrants, liquid extraction of BMB01 using dichloromethane was also tested. The main compounds identified through this method were 2,4-dtBP (previously detected by HS-SPME), as well as oleamide and erucamide, which are commonly used plasticizers in flexible packaging (Supplementary Material 2). Both plasticizers are listed in Regulation EU/10/2011 without any specific migration limit (SML) restrictions (European Comission, 2011). Interestingly, the analysis of dichloromethane extracts also did not reveal any differences between cut-offs with and without printing, despite the extracts displaying distinct colors.

The analysis of BMB02 exhibited the presence of a total of 34 compounds, which is 20 more than those found in BMB01. Fig. 1b illustrates a chromatogram of the analysis. Similar to BMB01, the compounds resulting from Irgafos 168 degradation, namely 1,3-dtBB and 2,4-dtBP, exhibited the highest intensity values. In BMB02, a higher proportion of acyclic saturated hydrocarbons (alkanes) was discovered, particularly within the 10–13-minute timeframe, where a minor hump was observed in the chromatogram. These compounds, named as POH (polyolefin oligomeric hydrocarbons), primarily encompass saturated hydrocarbons (POSH) and varying quantities of monounsaturated ones (POMH). Due to the inability to precisely identify them, they were encoded based on their retention index. The presence of POH is associated with the polyethylene manufacturing process, including the monomer used and the catalyst involved (PlasticsEurope, 2018).

3.2. Migration study from breast milk bags

This research was conducted in BMB01 and BMB02. It was focused on studying migration in two different mediums: food simulant D1 (EtOH 50%) and cow milk. Two distinct time/temperature conditions were employed: 7 days at 5ºC to simulate refrigeration conditions, and 2 h at 40 ºC to simulate defrosting conditions. The findings for BMB01 are presented in Table 2, while those for BMB02 can be found in Table 3. The quantification process was carried out using external calibration and the analytical parameters characterizing the calibration curves as well as the quantification standards used (QS) are displayed in Table 4.

In the migration analysis of BMB01, 12 different compounds were detected and their details are provided in Table 2. Supplementary Material 2 includes chromatograms of the migration solutions obtained after 7 days at 4–5ºC in milk (a) and simulant D1 (b). Two of the identified compounds, 1,3-dtBB and 2,4-dtBP, had been previously identified in the direct analysis of the bags. Other compounds detected were 2,6-di-tert-butyl-1,4-benzoquinone (2,6-dtBBQ) and several diethylbiphenyl isomers. These compounds were not readily apparent upon visual inspection of the chromatograms obtained in the analysis of the bags. Nevertheless, they became evident upon drawing the chromatograms using exclusively the main ions associated with them.

The compounds 1,3-dtBB, 2,4-dtBP and 2,6-dtBBQ were identified as degradation products of Irgafos 168, a commonly used antioxidant in polyethylene films (Ta & Bones, 2017). These compounds are considered NIAS, as they are not deliberately added but originate from the degradation of additives used in polymer manufacturing. Other compounds that were detected included various isomers of diethylbiphenyl and TXIB (2,2,4-Trimethyl-1,3-pentanediol diisobutyrate). Both, alkylated biphenyls and isobutyrates have been suggested as potential polymer plasticizers (Wypych, 2017). Among the detected migrants, only TXIB was listed in EU/10/2011, with a specific migration limit (SML) of 8 mg kg^{-1}. Values found in migration, both in ethanol 50% and milk, were well below this value.

For compounds that are not included in the authorized list, such as the NIAS, a new approach is required to conduct a risk assessment. In this particular case, the initial step involved reviewing the existing literature for toxicity studies in order to obtain relevant toxicity values such as the no-observed-adverse-effect level (NOAEL) or low-observed-adverse-effect level (LOAEL). A study conducted by Hirata-Koizumi et al. (Hirata-Koizumi et al., 2005) established a NOAEL value of 5 mg kg^{-1}/day for 2,4-dtBP, based on its hepatic and renal toxicity observed in newborn rats. According to the EFSA guidance an uncertainty factor of 100 should be applied to calculate the tolerable daily intake (TDI) of a compound (EFSA Scientific Committee, 2012b). Therefore, the TDI for 2,4-dtBP would be 0.05 mg kg^{-1} bw per day. To determine a safe maximum migration level for consumers, we need to consider both the average weight of consumers and their daily consumption of the packaged food. According to the EFSA Guidance (EFSA Scientific Committee, 2012a), an average weight of 5 kg can be considered for infants (aged 0–12 months). The guidance also establishes that the highest daily intake occurs between 3 and 6 months at a rate of approximately 132.4 g/kg bw per day, equating to approximately 0.6 kg per day for this age group. To ensure the safety of infants in a worst-case scenario, a daily intake of 0.8 kg per day was considered. Based on these estimations, migration levels of 2,4-dtBP should not exceed 312.5 μg kg^{-1}. None of the migration studies conducted in BMB01 exceeded this threshold. The study by Hirata-Koizumi also determined that newborn rats were 4–5 times more susceptible to 2, 4-dtBP compared to young rats, which underscores the importance of prioritizing neonatal consumers in future toxicological investigations involving this compound.

Regarding tert-butylbenzene, there is a provisional peer-reviewed toxicity assessment available, which establishes a NOAEL of 812 mg kg^{-1}-day based on the absence of toxicity at this dose (Epa & Health Risk Technical Support Center, n.d.). However, no studies have been found regarding di-tert-butylbenzenes.

For compounds that are not listed in EU/10/2011 and do not have a NOAEL or LOAEL value, a "*read-across*" approach was employed to determine their theoretical toxicity and estimate a *threshold of toxicological concern* (TTC). The TTC is determined based on the Cramer rules, which classify the toxicity of a compound according to its molecular structure. Toxtree software version 3.1.0.1851, developed by Ideaconsult Ltd, enables the classification of a compound into a Cramer class upon entering its chemical identifier. Class I is assigned to compounds with low toxicity, Class II to compounds with medium toxicity, and Class III to compounds with high toxicity. Each Cramer class corresponds to a maximum recommended daily intake: 30 μg/kg bodyweight-day for Class I, 9 μg/kg bodyweight-day for Class II and 1.5 μg/ kg bodyweight-day for Class III. Assuming an average weight of 5 kg for infants (aged 0–12 months) according to EFSA (EFSA Scientific Committe, 2012a), and a daily intake of breast milk of 0.8 kg, migration values should not exceed 187.5 μg kg^{-1} for Class I, 56.2 μg kg^{-1} for Class II, and 9.4 μg kg^{-1} for Class III. Some Class III compounds, such as 2,4-di-t-butyl-6-nitro-phenol (DBNP) and 1,1,3-trimethyl-3-phenylindan, slightly exceeded the recommended maximum migration value. However, it should be noted that these compounds were semi-quantified using a

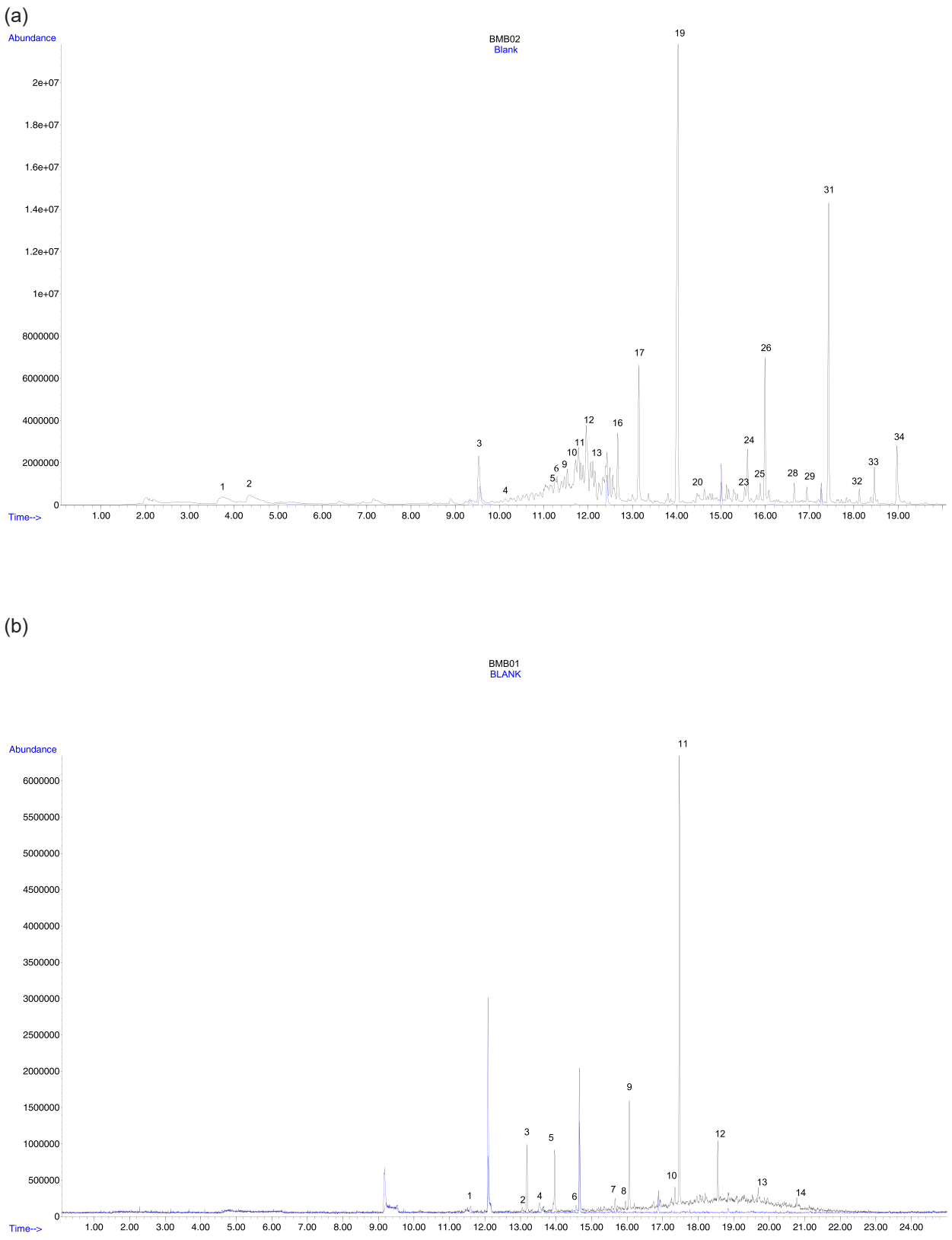

Fig. 1. **a**. HS-SPME-GM-MS chromatogram of BMB01 sample: (1) Nonanal, (2) ni (mz 128.2), (3) Dodecane, (4) 2-Phenoxyethanol, (5) 1,3-Di-tert-butylbenzene (1,3-dtBB), (6) ni (mz 83.2), (7) Tridecane, (8) 3-methyl-, (9) ni (mz 84.1), (10) Tetradecane, (11) Tetradecane, (13) 2,4-Di-tert-butylphenol (2,4-dtBP), (14) Hexadecane, (15) Heptadecane, (16) Octadecane. **b**. HS-SPME-GM-MS chromatogram of BMB02 sample: (1) Toluene, (2) Octane, (3) Decane (4−7) alkanes RI1036–1096, (8) Undecane, (9−15) alkanes RI1102–1167, (16) Undecane, 3-methyl, (17) Dodecane, (18) Alkane RI1214, (19) 1,3-Di-tert-butylbenzene (1,3-dtBB), (20) Tridecane, (21−23) alkanes RI1334–1362, (24) Tridecane, 3-methyl-, (25) 1-Tetradecene, (26) Tetradecane, (27) Alkane RI1403.

Table 2
Compounds identified in migration from BMB01, retention time (t_R), experimental retention index (RI_{exp}), quantification standard (QS), migration values in food simulant D1 (Ethanol 50%) and milk after 7 days storage at 5ºC and 2 h at 40ºC and specific migration limit (SML) values according to EU/10/2011 or Cramer Class.

Nº	t_R	RI_{exp}	Compound	CAS nº	QS	Migration concentration (μg kg^{-1})				SML /Cramer Class
						5ºC 7 days		40ºC 2 h		
						EtOH 50%	Milk	EtOH 50%	Milk	
1	10.13	1035	Limonene*✓	138–86–3	Q1	<LOQ	0.72 ± 0.18	<LOD	<LOD	I
2	13.99	1256	1,3-Di-tert-butylbenzene (1,3-dtBB)*✓	1014–60–4	Q2	<LOQ	<LOQ	<LOQ	<LOQ	I
3	15.26	1343	1-Cyclohexylheptane*	5617–41–4	Q3	<LOQ	<LOD	<LOD	<LOD	I
4	16.65	1446	Alkyl Alcohol	575–41–7	Q3	<LOQ	<LOD	<LOD	<LOD	I
5	16.93	1469	2,6-di-tert-Butyl-1,4-benzoquinone (2,6-dtBBQ)*✓	719–22–2	Q4	14.05 ± 1.14	<LOD	15.7 ± 0.69	<LOD	II
6	17.41	1508	2,4-Di-tert-butylphenol (2,4-dtBP)*✓	96–76–4	Q5	90.4 ± 16.8	27.7 ± 2.66	3.63 ± 0.22	29.1 ± 2.07	I
7	18.52	1592	TXIB*✓	6846–50–0	Q6	23.9 ± 3.66	23.1 ± 6.50	4.33 ± 0.86	20.8 ± 0.79	8 mg kg^{-1}
8	19.27	1677	Diethylbiphenyl	-	Q7	<LOQ	<LOD	<LOD	<LOD	III
9	19.49	1696	3,4-Diethylbiphenyl*	61141–66–0	Q7	<LOQ	<LOD	<LOD	<LOD	III
10	19.56	1696	2,4-di-t-butyl-6-nitro-phenol (DBNP)	20039–94–5 728–40–5	Q5	19.4 ± 3.8	<LOD	<LOD	<LOD	III
11	19.81	1727	Diethylbiphenyl	-	Q7	9.63 ± 1.92	<LOD	<LOD	<LOD	III
12	19.95	1729	1,1,3-Trimethyl-3-phenylindan*	3910–35–8	Q7	14.8 ± 2.39	<LOD	<LOD	<LOD	III

*Confirmed by retention index. ✓Confirmed by standard. QS description presented in Table 4

Table 3
Compounds identified in migration from BMB02, retention time (t_R), experimental retention index (RI_{exp}), quantification standard (QS), their migration values in food simulant D1 (Ethanol 50%) and milk after 7 days storage at 5ºC and 2 h at 40ºC and Cramer Class.

Nº	t_R	RI exp	Compound	CAS nº	QS	Migration concentration (μg kg^{-1})				Cramer Class
						5ºC 7 days		40ºC 2 h		
						EtOH	Milk	EtOH	Milk	
1	10.24	1036	Alkane RI1036		Q3	4.91 ± 0.98	<LOQ	3.93 ± 0.69	<LOQ	I
2	10.40	1043	Alkane RI1043		Q3	5.20 ± 0.31	<LOQ	4.46 ± 0.66	<LOD	I
3	11.13	1082	Alkane RI1082		Q3	<LOD	<LOD	4.59 ± 0.65	<LOD	I
4	11.27	1090	Alkane RI1090		Q3	7.20 ± 1.43	<LOQ	4.62 ± 0.51	<LOD	I
5	11.39	1096	Alkane RI1096		Q3	4.94 ± 0.99	<LOD	4.57 ± 0.52	<LOD	I
6	11.51	1102	Alkane RI1102		Q3	4.91 ± 0.98	<LOD	4.22 ± 0.84	<LOD	I
7	11.72	1115	Alkane RI1115		Q3	6.75 ± 1.30	<LOQ	4.74 ± 0.80	<LOD	I
8	11.77	1118	Alkane RI1118		Q3	7.99 ± 1.0	<LOQ	5.45 ± 0.75	<LOD	I
9	11.95	1129	Alkane RI 1129		Q3	6.49 ± 1.59	<LOQ	4.82 ± 0.89	<LOD	I
10	12.59	1167	Alkane RI 1167		Q3	<LOD	<LOD	3.75 ± 0.74	<LOD	I
11	12.67	1171	Undecane, 3-methyl*	1002–43–3	Q3	4.92 ± 0.98	<LOQ	4.24 ± 0.36	<LOD	I
12	13.36	1214	Alkane RI1214		Q3	<LOD	<LOD	3.71 ± 0.43	<LOD	I
13	13.99	1256	1,3-Di-tert-butylbenzene*✓	1014–60–4	Q2	92.8 ± 10.8	553.0 ± 28.6	101.1 ± 15.2	215.5 ± 32.3	I
14	15.60	1367	Tridecane, 3-methyl*	6418–41–3	Q8	<LOQ	<LOD	<LOQ	<LOD	I
15	16.08	1403	Alkane RI1403		Q8	<LOQ	<LOD	<LOQ	<LOD	I
16	16.65	1446	Alkyl Alcohol RI1446		Q8	<LOQ	<LOD	<LOQ	<LOD	I
17	16.94	1469	2,6-Di-tert-butylbenzoquinone*✓	719–22–2	Q4	47.2 ± 7.1	<LOD	20.6 ± 2.6	<LOD	II
18	17.41	1508	2,4-Di-tert-butylphenol*✓	96–76–4	Q5	139.6 ± 13.9	224.4 ± 33.6	257.7 ± 28.6	90.6 ± 13.6	I
19	18.13	1566	Pentadecane, 3-methyl*		Q8	<LOQ	<LOD	<LOQ	<LOD	I

*Confirmed by retention index. ✓Confirmed by standard. QS description presented in Table 4

standard with a similar structure due to the unavailability of the pure standard.

The migration experiments conducted in 50% ethanol at 5 ºC for 7 days yielded the highest migration values, potentially attributed to the swelling effect on the polymer, often associated with increased migration. Several studies have demonstrated a strong correlation between migration and swelling for certain plastic additives when fatty simulants such as 95% ethanol and isooctane were employed, such as those performed by Kirchkeszner et al. (Kirchkeszner et al., 2022) or Bodai et al. (Bodai et al., 2015). In the first study migration tests were conducted on polypropylene and PLA while in the second one they were conducted on HDPE. The results obtained by Bodai et al. (Bodai et al., 2015)showed that using the food simulant ethanol 50% for modelling the migration of Irganox 3114 from HDPE into milk gave an overestimation with a factor of minimum 3.5.

However, this effect was not observed when the experiments were conducted for a duration of 2 h at 40ºC, likely because the shorter migration times did not induce the swelling of the polymer to the same extent.

In the case of this particular sample, migration to ethanol 50% at 5ºC for 7 days resulted in higher migration values compared to heating the milk bag at 40ºC for 2 h while the migration to milk displayed nearly identical values in both conditions.

In the migration sample from **BMB02,** a total of 19 compounds were detected and their details can be found in Table 3. Supplementary Material 3 includes chromatograms of the migration solutions obtained after 7 days at 4–5ºC in milk (a) and simulant D1 (b). The majority of the detected compounds were acyclic saturated hydrocarbons (alkanes), which had been previously detected in the bag analysis. The concentration of the detected hydrocarbons was consistently below 10 μg kg^{-1}. If all the alkanes from 10.20 to 12.60 min were combined as a single peak, the total concentration for migration performed at 5ºC during 1

Table 4
Analytical parameters for the quantification by SPME-GC-MS.

	Compound	QI	Matrix	Equation	R^2	Linear range (μg kg^{-1})	LOD (μg kg^{-1})	LOQ (μg kg^{-1})
Q1	Limonene	68.0	EtOH	y = 38762x + 461.3	0.997	0.35–25.2	0.12	0.35
	CAS 138–86–3		Milk	y = 22701x - 6772.4	0.999	0.45 – 29.0	0.15	0.45
Q2	1,3-Di-tert-butylbenzene (1,3dtBB)	175.1	EtOH	y = 205195x + 118579	0.991	0.18–37.9	0.06	0.18
	CAS 1014–60–4		Milk	y = 16002x + 21664	0.995	0.30–99.8	0.10	0.30
Q3	Undecane	57.1	EtOH	y = 145059x + 28241	0.986	0.15–25.2	0.05	0.15
	CAS 1120–21–4		Milk	y = 9785x − 7310.7	0.995	7.5–58.9	2.5	7.5
Q4	2,6-di-tert-Butyl-1,4-benzoquinone	177.1	EtOH	y = 308.11x-1009.6	0.998	0.36–38.4	0.12	0.36
	(2,6-dtBBQ)CAS 719–22–2		Milk	y = 447.63x − 301.18	0.988	0.60–22.1	0.20	0.60
Q5	2,4-Di-tert-butylphenol (2,4 dtBP)	191.2	EtOH	y = 1216.8x - 40.695	0.990	1.5–84.1	0.5	1.5
	CAS 96–76–4		Milk	y = 342.04x - 690.84	0.957	1.05–62.4	0.35	1.05
Q6	TXIB	71.1	EtOH	y = 1337.5x + 2648.2	0.991	3.6–47.9	1.2	3.6
	CAS 6846–50–0		Milk	y = 330.7x - 2564	0.980	21.0–100.7	7	21
Q7	Tetramethylbiphenyl	195.1	EtOH	y = 4143x - 12486	0.983	7.0 – 51.0	2	7.0
	CAS 25570–02–9		Milk*	—				
Q8	Tridecane	57.1	EtOH	y = 194138x − 55013	0.999	0.30–34.1	0.10	0.30
	CAS 629–50–5		Milk	y = 2299x - 8958.5	0.996	21.0 − 158.1	7.0	21.0

Compound not detected below 150 ng g^{-1}

week would be 70.6 μg kg^{-1} (in ethanol 50%) and 16.6 μg kg^{-1} (in milk). For migration carried out at 40ºC for 2 h, the total concentration was calculated as 30 μg kg^{-1} (in Ethanol 50%) and 7.5 μg kg^{-1} (in milk).

In this case, there was no distinct trend observed in the impact of using either milk or food simulant D1 on migration from BMB02. The materials used for the manufacturing of this bag seemed not to be highly affected by the swelling effect of ethanol. Variation in effect for the different compounds can likely be attributed to the chemical structure and properties of the migratory substance, which influence its interaction with the migration matrix.

In addition to the previously mentioned compounds, three degradation products of Irgafos 168 were also detected (1,3-dtBB, 2,6-dtBBQ, and 2,4-dtBP). Among them, 2,4-dtBP and 1,3-dtBB exhibited the highest migration values, exceeding the recommended thresholds in certain instances. On the other hand, 2,6-dtBBQ demonstrated lower migration values compared to the other Irgafos 168 compounds, falling below the recommended maximum concentration for Class II compounds.

3.3. Migration of NIAS coming from Irgafos168 degradation

The compounds coming from the degradation of Irgafos 168 (2,4-dtBP, 1,3-dtBB and 2,6-dtBBQ) showed the highest migration values in BMB01 and BMB02 and therefore were pointed as the compounds of greatest concern to the consumers. For this reason, the research was expanded to encompass a larger sample of bags and ascertain the presence of these compounds in migration to milk and food simulant D1. Migration tests were performed in 6 additional commercially available breast milk bags. These tests were carried out at 5ºC during 7 days to replicate typical usage conditions. The results obtained from these tests are presented in Table 5. The table also includes information regarding the thickness of the bags.

As mentioned earlier, the maximum recommended limits on the migration values for these compounds were determined as 312.5 μg kg^{-1} for 2,4-dtBP (based on the NOAEL value), 187.5 μg kg^{-1} for 1,3-dtBB (classified as class I according to Cramer) and 56.2 μg kg^{-1} for 2,6-dtBBQ (classified as class II according to Cramer).

The recommended migration values were exceeded for 1,3-dtBB in the milk migration tests conducted on BMB02 and BMB07. However, it should be noted that the recommended values were calculated using a "read-across" approach based on theoretical toxicities. It was curious to observe that higher-priced milk bags did not necessarily guarantee lower migration values. In fact, BMB02 and BMB07, were two of the most expensive bags (the price per unit of the bags can be consulted on supplementary material 1). The elevated migration levels of this compound underscore the imperative need for conducting toxicity tests to ensure accurate risk assessment and guarantee consumer safety.

In a Pearson correlation analysis conducted between the target compounds, the results showed that both 1,3-dtBB and 2,4-dtBP exhibited strong correlations in 50% ethanol (Pearson coefficient: 0.76) as well as in milk (Pearson coefficient: 0.84). Bags exhibiting elevated migration values in 1,3-dtBB similarly demonstrated high migration values in 2,4-dtBP. When the Pearson correlation analysis was performed between material thickness and the total concentration of compounds coming from Irgafos 168, coefficients obtained were below 0.2. Therefore, no evidence that material thickness was related to the migration of these compounds was observed. It is necessary to consider that the presence of these compounds in the material will highly depend on the initial amount of Irgafos 168 added and the manufacturing and storage conditions.The disparities observed in migration values between ethanol 50% and milk can be primarily attributed to differences in polarities of both matrixes, due to the distinct chemical compositions. On the one hand, milk is a more complex mixture with varying polarities due to its diverse composition (3.22% proteins, 3.25% fat, etc) (Jenkins

Table 5
Migration values (μg kg^{-1}) of compounds coming from Irganos168 degradation. Experiments performed at 4–5ºC during 1 week.

Sample	Thickness (mm)	1,3-dtBB		2,6-dtBBQ		2,4-dtBP		Σ Degradation products of Irgafos 168	
		EtOH	Milk	EtOH	Milk	EtOH	Milk	EtOH	Milk
BMB01	0.0082 ± 0.0003	<LOQ	<LOQ	14.05 ± 1.14	<LOD	90.4 ± 16.8	27.7 ± 2.66	104.4 ± 16.8	27.7 ± 2.66
BMB02	0.0076 ± 0.0002	92.8 ± 10.8	**553.0±28.6**	47.2 ± 7.1	<LOD	139.6 ± 13.9	224.4 ± 33.6	279.6 ± 19.0	777.4 ± 44.1
BMB03	0.0076 ± 0.0002	<LOQ	<LOQ	<LOQ	<LOQ	5.07 ± 0.11	3.24 ± 1.07	5.07 ± 0.11	3.24 ± 1.07
BMB04	0.0081 ± 0.0001	5.55 ± 0.44	18.0 ± 0.26	1.26 ± 0.09	<LOQ	36.7 ± 0.76	77.5 ± 0.97	43.5 ± 0.88	95.5 ± 1.00
BMB05	0.0077 ± 0.0003	<LOQ	<LOQ	4.27 ± 0.36	4.07 ± 0.06	84.9 ± 2.8	138.3 ± 6.0	89.2 ± 2.82	142.4 ± 6.00
BMB06	0.0067 ± 0.0003	<LOQ	<LOQ	5.41 ± 0,09	4.32 ± 0.07	24.4 ± 1.03	27.8 ± 1.78	29.8 ± 1.03	32.1 ± 1.78
BMB07	0.0064 ± 0.0001	107.4 ± 0.83	**307.9±0.49**	4.00 ± 0.44	6.63 ± 0.08	106.8 ± 5.3	153.5 ± 3.5	218.2 ± 5.38	468.0 ± 3.53
BMB08	0.0084 ± 0.0001	103.6 ± 0.36	188.7 ± 16.5	5.44 ± 0.42	7.39 ± 0.14	268.6 ± 2.6	98.3 ± 7.3	377.6 ± 2.66	294.4 ± 18.0

Mark in bold characters those values above the recommended migration concentrations.

& McGuire, 2006), and on the other hand, ethanol is a pure substance whose polarity is primarily determined by the presence of an hydroxyl group. In many instances, 1,3-dtBB exhibited lower migration values in 50% ethanol than in milk. Among the three compounds, it was the one with the highest log P value (5.8), indicating lower polarity, which could explain its greater propensity for migration into milk. While the utilization of food simulants greatly aids in streamlining migration studies, there are scenarios where it is prudent to directly analyze the food product itself because, as in this case, results obtained from food simulants could potentially underestimate migration levels during the assessment. This observation has already been documented by previous authors in the bibliography (Blanco-Zubiaguirre et al., 2021; Sanches Silva et al., 2008).

For a more comprehensive understanding of migration processes from this specific packaging material to breast milk, conducting kinetic experiments during migration could provide valuable insights. This approach not only elucidates the migration dynamics but also helps identify shorter storage times that can enhance the overall food safety associated with these materials.

The migration test solutions from the additional 6 breast milk bags were also analyzed in SCAN mode to identify any other migrants present at higher levels compared to the degradation products of Irgafos 168. The obtained chromatograms revealed that 2,4-dtBP, and 1,3-dtBB were the primary migrants in all cases. Some additional compounds were found in the migration analysis, only a few exhibited intensities surpassing 5% of the main peak. This situation applied to: BHT (butylated hydroxytoluene, CAS No. 128–37–0), 2-tert-butyl-5-(2-methylprop-2-en-1-yl)cyclohexa-2,5-diene-1,4-dione and 2,6-di-tert-butyl-4-ethylphenol (2,6-DTBE) (CAS No: 4130–42–1)in BMB06; TXIB (2,2,4-trimethyl-1,3-pentanediol diisobutyrate, CAS No. 6846–50–0) in BMB05 and 4-tert-butyl-2,6-diisopropylphenol (4-TBDIP) (CAS No: 57354–65–1) in BMB08. BHT, 2,6-DTBE and 4-TBDIP can be used as polymer antioxidants, and TXIB is an intermediate compound in the production of resins and inks. BHT, 2,6-DTBE and TXIB are listed in the positive list of EU/10/2011 with specific migration limit (SML) values of 3 mg kg^{-1}, 4.8 mg $kg^{-1}$and 5 mg kg^{-1} respectively.

4. Conclusions

The use of breastmilk bags for long storage periods, whether in refrigerated conditions, or even for brief periods with inadequate temperature control, can result in the migration of volatile compounds that may pose health risk to infants. The degradation products of the antioxidant Irgafos 168 have been identified as the primary migrant compounds from breast milk bags made of polyethylene with printing inks. These findings highlight the importance of not only controlling the migration of intentionally added substances but also considering the migration of non-intentionally added substances (NIAS), such as degradation products, impurities, or reaction compounds. Experiments conducted under standard breast milk storage conditions (5ºC, 7 days) revealed that in some cases, 1,3-di-tert-butylbenzene (1,3-dtBB) migrated at concentrations exceeding the recommended limits, emphasizing the need for meticulous control of this procedure to safeguard infants' safety. However, additional toxicological tests are required to establish more accurate toxicity values for these compounds.

CRediT authorship contribution statement

Margarita Aznar: Design of the work, data collection, analysis and interpretation, writing. **Celia Domeño**: Conception, critical revision. **Cristina Nerín**: Critical revision, final approval.

Declaration of Competing Interest

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.

Data Availability

Data will be made available on request.

Acknowledgements

Grant PID2021128089OB-I00 funded by MCIN/AEI/ 10.13039/501100011033 and by the "European Union Next Generation EU/PRTR", financial help given to Grupo GUIA T53–20R by Gobierno de Aragón and European Social Funds. The authors want also acknowledge Dr. Ana Subirón for her information about breast milk storage protocols.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.fpsl.2023.101196.

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