Polímeros
ISSN 1678-5169 (Online)

https://doi.org/10.1590/0104-1428.20220081

REVIEW ARTICLE

Potential antioxidant migration from polyethylene packaging to food: a systematic review

Mayara de Simas Mesquita[1]* and Shirley de Mello Pereira Abrantes[1]

[1]Laboratório de Contaminantes, Departamento de Química, Instituto Nacional de Controle de Qualidade em Saúde, Fundação Oswaldo Cruz – FIOCRUZ, Rio de Janeiro, RJ, Brasil

**mayarasimas@yahoo.com.br*

Abstract

This systematic review investigates evidence concerning antioxidant migration from polyethylene packaging to food. The review protocol was based on the Preferred Reporting Items for Systematic Reviews guidelines. Several electronic databases were consulted for relevant studies, as well as references in eligible studies. Of the 44 eligible studies, only two did not indicate antioxidant migration. The reported migrations were influenced by numerous factors, the most important comprising the fatty contents of food and/or fat simulants, with higher fat amounts resulting in higher migration rates. Migrated antioxidant values ranged from 3.42 mg kg^{-1} to 231.70 mg kg^{-1}, far above the maximum permissible amounts established by the current legislation regarding foods in contact with plastic resins.

Keywords: *antioxidants, health surveillance, migration, polyethylene.*

How to cite: Mesquita, M. S., & Abrantes, S. M. P. (2022). Potential antioxidant migration from polyethylene packaging to food: a systematic review. *Polímeros: Ciência e Tecnologia*, *32*(4), e2022042. https://doi.org/10.1590/0104-1428.20220081

1. Introduction

Plastic packaging significantly contributes to human chemical exposure, as numerous chemicals are employed in the manufacturing of plastic food packagings[1]. In this regard, health surveillance plays a role in essential public health actions to ensure the necessary safety for human populations always seeking to control the health risks assigned in the manufacture and consumption of products and services[2]. Concerning health safety associated to plastic packagings, Brazilian legislation presents a list of permitted compounds, such as polymers, resins and additives, and certain restrictions concerning these compounds, such as specific migration limits (SML) for additives[3].

Plastics comprise the packaging class that most interacts with food, due to their permability, although barrier properties vary between different materials, potentially leading to the presence of harmful substances in food[4]. These may, in turn, damage organismal health, depending on the food concentration, ingestion frequency and absorbed dose, among others[5].

In this context, the aim of this study was to carry out a systematic literature review to address evidence on the migration of certain antioxidants established by Brazilian Resolution of the Collegiate Board of Directors (RDC) No. 326/2019[6] present in high density polyethylene (HDPE), low density polyethylene (LDPE) and linear low density polyethylene (LLDPE) packagings. These antioxidants include butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, octyl gallate (OR 3,4,5-trihydroxybenzoic acid octyl ester OR octyl gallate dihydrate), lauryl gallate (OR dodecyl gallate OR antioxidant E-312), methyl 4-hydroxybenzoate, propyl 4-hydroxybenzoate; hydroquinone (OR 1,4-dihydroxybenzene), irganox 1076 (octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate) and 4-sec-butyl-2,6-di-tert-butyl-phenol. Several food simulants associated with these antioxidants, namely 8, 10, 50, 95 and 100% ethanol, olive oil, 3% acetic acid, distilled water, water; poly (2,6-diphenyl-p-phenylene oxide) (PPPO or TENAX); α-tocopherol; sunflower oil and iso-octane and HB 307 (mixture of synthetic triglycerides, primarily C10, C12 and C14 - Fatty food simulant) will also be discussed.

Determining antioxidant levels in plastic furthers information on the migration potential of these compounds and on plastic quality. However, a need for a systematic analysis to assess the consequences of antioxidant migration in polyethylene packaging is noted. Therefore, the purpose of this review is to support an adequate and updated antioxidant migration potential analysis, providing data on the safety of antioxidant use in different polyethylene packagings to ensure human health safety and further Sanitary Surveillance and Public Health actions.

2. Material and Methods

2.1 Research method

This study was guided by Center for Reviews and Dissemination recommendations[7], *Cochrane Collaboration*[8] and structured in five steps, as follows: (a) The elaboration of the study guiding question; (b) a search for primary studies on the migration potential of antioxidants present

in polyethylene packaging for food/food simulant; (c) the identification and selection of studies associated to antioxidants according to established inclusion and exclusion criteria; (d) data extraction followed by the analysis, description and evaluation of the parameters and outcomes of each selected study; in addition, the bibliographic references of eligible studies were consulted (manual search), which could contain citations of articles that met the inclusion criteria proposed by this work and that eventually had not been located in the databases. Finally, an electronic search of the gray literature was performed using the Google Scholar database; (e) a critical opinion on the methodological quality of the selected studies.

The searches covered all studies on the subject up to September 4, 2020. All searches were carried out employing Medical Subject Headings Terms (MeSH), PUBMED and Health Sciences (DeCS) descriptors, from BIREME (Latin American and Caribbean Center on Health Sciences Information), as well as author-selected keywords, later adapted to the other searched databases, namely: *# 1. Migration; # 2. Diffusion; # 3. Antioxidants; # 4. Polyethylene packaging; # 5. Low density polyethylene; # 6. High density polyethylene; # 7. Food; # 8. Food simulants.*

To further detail the searches, the following antioxidants and other descriptors were also used: *#9. Butylated hydroxytoluene (BHT); # 10. Butylated hydroxyanisole (BHA) # 11. Propyl gallate; # 12. Octyl gallate (OR 3,4,5-trihydroxybenzoic acid octyl ester OR octyl gallate dihydrate) # 13. Lauryl gallate (OR dodecyl gallate OR E-312 antioxidant); # 14. Methyl 4-hydroxybenzoate # 15. Propyl 4-hydroxybenzoate; # 16. Hydroquinone (OR 1,4-dihydroxybenzene); # 17. Irganox 1076 Octadecyl (3-(3,5-di-tert- butyl-4-hydroxiphenyl) propionate)*; *# 18. 4-sec- butyl-2,6-di-tert- butyl- phenol*; *AND # 19. Food packaging (OR food containers OR food-contact plastics OR food contact materials).*

Table 1. Eligible study methodological quality assessment.

1. Is the research design well defined with a focus on antioxidant migration?
2. Is a description of the methodology used to evaluate the antioxidant migration test available?
3. Is the migration test based on any regulations?
4. Is a description of the employed reagents available?
5. Was antioxidant characterization carried out in the tested packaging?
6. Was antioxidant characterization performed employing at least three techniques?
7. Is a description of the type of evaluated packaging available?
8. Does the article report how the antioxidant was incorporated into the packaging?
9. Is antioxidant quantification described in the study?
10. Does the article determine which antioxidant is present in the tested packaging and in the food?
11. Does the article use an antioxidant reference standard?
12. Are the employed methods validated?
13. Does the study include a statistical analysis?

Score: High (10 to 14 points); Average (6 to 9 points); Low (0 to 5 points).

Table 2. Search strategy results from the selected databases after eliminating duplicate studies and total number of articles identified on antioxidant migration assays.

Database	(1)	(2)
PubMed	45	14
Taylor & Francis	332	09
Science Direct	18	02
Embase	80	00
Scielo	00	00
Google	06	02
Total	480	27

(1) Step 1: Studies retrieved from the database searches; (2) Step 2: Eligible studies.

2.2 Coding of the eligible articles

An alphanumeric coding was assigned to each article, with studies coded by the letter (E) followed by a sequential number (E1, for example). After extracting the relevant information, qualitative analyses were critically carried out for data synthesis and interpretation.

After including the eligible articles, a Methodological Quality Assessment was performed following the criteria described in Table 1, attributing one point for each obtained criterion. Total points ranks high from 10 to 14 points, average from 6 to 9 points, and low from 0 to 5 points.

3. Results and Discussion

The search process for primary studies carried out at the electronic databases retrieved a total of 491 references, with an extensive screening carried out in order to reach a significant number of studies. Of this total, eleven duplicates were discarded. Table 2 depicts the result of the search strategy and the total number of eligible studies.

Several studies are usually excluded from systematic reviews, especially those employing wide searches, whose aim is to prevent any important and pertinent article from not being reached by this screening method[9]. After analyzing all studies, a manual search was performed on all eligible articles. A total of 468 studies were obtained, 17 of which were eligible and included in this review, as well as the 27 studies displayed in Table 3. Thus, a total of 44 studies were included herein to answer this review's question.

3.1 Risk of bias assessment

The applied Methodological Quality Assessment indicated 42 of the 44 eligible studies as presenting high quality (10 to 14 points) and only two of medium quality (6 to 9 points). None were categorized as low quality (0 to 5 points).

3.2 Antioxidant migration assessments

Migration studies are carried out to identify the best simulants for food product evaluation assays and to define the test conditions (temperature/contact time) that best simulate real product packaging situations[10].

The mass transfer or migration phenomenon involves the diffusion of substances from materials in contact with food. Several parameters can influence this process, such

Table 3. Eligible studies employed in this systematic review and their alphanumeric coding.

Article/ Code	Author(s)	Article/ Code	Author(s)
E1	Figge et al.[10]	E23	Dopico-García et al.[11]
E2	Till et al.[12]	E24	Han et al.[13]
E3	Figge and Freytag[14]	E25	Stoffers et al.[15]
E4	Bieber et al.[16]	E26	Stoffers et al.[17]
E5	Bieber et al.[18]	E27	Begley et al.[19]
E6	Schwope et al.[20]	E28	Dopico-García et al.[21]
E7	Gandek et al.[22]	E28	Torres-Arreola et al.[23]
E8	Goydan et al.[24]	E30	Jeon et al.[25]
E9	Ho et al.[26]	E31	Vitrac et al.[27]
E10	Limm and Hollifield[28]	E32	Cruz et al.[29]
E11	Yam et al.[30]	E33	Soto-Cantú et al.[31]
E12	O'Brien et al.[32]	E34	Machado et al.[33]
E13	Wessling et al.[34]	E35	Mauricio-Iglesias et al.[35]
E14	Cooper et al.[36]	E36	Coltro and Machado[37]
E15	Linssen et al.[38]	E37	Beldí et al.[39]
E16	Bailey et al.[40]	E38	Reinas et al.[41]
E17	O'Brien et al.[42]	E39	Jakubowska et al.[43]
E18	Wessling et al.[44]	E40	Haitao et al.[45]
E19	O'Brien and Cooper[46]	E41	García-Ibarra et al.[47]
E20	Brandsch et al.[48]	E42	Rubio et al.[49]
E21	Feigenbaum et al.[50]	E43	Vera et al.[51]
E22	Helmroth et al.[52]	E44	Liang et al.[53]

as type of food, fat content, temperature, contact duration, migrant packaging concentration, polymer morphology, migrant density and molecular size and physical state[47], as well as pH and alcohol content, among others[16].

In addition, Specific Migration Limits (SML) have been established, comprising the "maximum admissible amount of a specific component of the material in contact with food transferred to simulants under the rehearsal conditions"[54:28].

Of the 44 primary eligible articles, 20 reported no evidence of antioxidant migration above the LME, while the other 24 reported evidence of migration above the LME (Table 4).

3.3 Migration assessment by type of simulant and/or food

Fat is a significant migration enhancer, and the higher the fat content of the food or simulant, the greater the antioxidant packaging migration. For example, one study reported migration values of various fatty foods (pork sausage, liver sausage, yogurt, fresh, hard and processed cheese, and margarine) above the LME in LDPE packaging, and antioxidant migration below the LME in all HDPE packaging[18], indicating that LDPE seems to be unsuitable for fatty food packaging.

Concerning food simulants, studies E41[47] and E13[34] reported that the antioxidant BHT migrated to a lesser extent in the food simulant in 50% ethanol when compared to 95% ethanol, especially as this compound displayed a lower

Table 4. Studies evidencing and not evidencing antioxidant migration.

Studies evidencing antioxidant migration and SML above permissible values	Studies evidencing antioxidant migration and SML below permissible values
E1, E4, E5, E6, E7, E9, E10, E11, E12, E14, E16, E18, E19, E20, E22, E27, E29, E32, E33, E35, E37, E39, E41, E43.	E2, E3, E8, E13, E15, E17, E21, E23, E24, E25, E26, E28, E30, E31, E34, E36, E38, E40, E42, E44.

Specific Migration Limits (SML).

affinity for 50% ethanol at all test temperatures. However, migrations were of 90% even in 50% ethanol tested at 20 °C and 40 °C, with a migration value of 821.97 mg kg^{-1} reported from an initial antioxidant polymer concentration of 913.30 mg kg^{-1}.

Similarly to E40[45],E41 and E6[20] reported a fast BHT migration of 1 hour at similar temperatures (49 °C and 21 °C), also using 50% ethanol, exceeding the established LME of 3 mg kg^{-1}. However, the same was not observed in 8% ethanol and water, and migration results were lower than in water when employing 3% acetic acid, increasing the migrated amount only with increasing exposure times.

In aqueous solutions, part of the BHT migrates and then decomposes into unknown substances. The accepted hypothesis is that BHT migrates by diffusion from the polymer to the surface of the food or simulant, and an equilibrium takes place after BHT increases, reducing migration rates, although migration continues, as BHT is simultaneously decomposed[20]. Furthermore, BHT decomposition rates seem to be much lower in acidic solutions than in aqueous ones.

The simulant favoring the highest rate of antioxidant migration is olive oil used in the primary studies is olive oil, due to its high fat content (100%), as reported by E1[10], E4[16], E12[42], E14[36], E19[46], E22[52], E27[19], E35[35] and E37[39]. This compound is considered the official simulant for fatty foods[50]. However, the migration test for olive oil is not only somewhat imprecise but also very time consuming and, therefore, expensive[15].

Most studies clearly identify lower antioxidant migration rates in acidic and non-acidic aqueous simulants, especially irganox 1076. For example, E37 and E60 reported no measurable migration of this compound when determining antioxidant migration in LDPE using 3% acetic acid, distilled water and 10% ethanol as simulants, due to hydrophobic antioxidant behavior.

Solubility, comprising the maximum amount that a substance can dissolve in a liquid, on the other hand, depends on antioxidant molecular dimensions[55]. Increasing molecular sizes result in increased solubility, leading to higher migration rate. In this regard, even BHT and irganox 1076, which display some insolubility in water, have been reported as exhibiting high migration levels, and some studies report that complete extraction may take place [20]. In addition, BHT solubility in water in LDPE packaging increases with temperature[12], in contrast with HDPE, where this does not occur.

Regarding fatty food simulants, ranging from 8% to 100% ethanol, the higher the ethanol concentration, the

greater the antioxidant migration rate[27]. This also applies to temperature, where higher temperatures lead to greater migration rates for greasy simulants.

Some contradictory data are noteworthy, such as, for example, no migration detected in fat and migration observed in water or aqueous simulants. Study E21[50], for example, analyzed BHT migration from LLDPE packaging (2 mm thickness) to 95% ethanol and olive oil, and detected this antioxidant at trace levels only. Polyethylene thickness could explain this fact, as thick samples are unlikely to present migration[32]. On the other hand, olive oil can lead to higher migration values than most fatty foods, so it is unusual not to detect at least residual migrated levels in this simulant. Furthermore, E9[26], E10[28], E11[30], E28[23], E30[25], E34[33] and E44[53] reported antioxidant migration in water or aqueous simulants, all above the LME for BHT and irganox 1076. E9[26], which evaluated BHT migration to LDPE water at 38 ºC, reported 6.26 mg kg^{-1} of migrated antioxidants more than double the LME for BHT, of 3 mg kg^{-1}.

E6[20] presented evidence of migration in water when compared to acetic acid, with BHT migrating less to 3% acetic acid solutions than to water, probably due to the fact that BHT decomposition rates are much lower in acidic solutions. Studies E10[28], E28[23], E30[25] and E44[53] also evaluated antioxidant migration in water or aqueous simulants, all detecting antioxidant migration, albeit below the LMEs. However, determinations concerning overall migration to water may contain significant errors, as the applied method gravimetrically measures the migrated amounts as residue following complete water evaporation[56].

In addition, migration takes place even though in dry food (*e.g.,* rice, milk powder, soup mixes). The results reported by E6[20] and E2[12], for example, indicate that BHT migrated at a considerable rate and that differences were particularly noticeable in the case of dry solid foods, with much lower differences for simulants. E39[43] tested BHT migration in a dry food simulant, poly (2,6-diphenyl-p-phenylene oxide) (PPPO or Tenax) (1 g), in LDPE containing 300 mg kg^{-1} of the antioxidant at 60ºC for 10 days. The obtained data indicated that BHT is very sensitive to the tested simulant, with a migrated value of 15.61 mg kg^{-1}, comprising 5.20% of the BHT value added to the polymer and 5-fold higher than the LME.

Studies E38[41] and E42[49] also evaluated migration in PPPO, which has been used as a simulant for the specific migration concerning dry foods, according to Commission Regulation (EU) 10/2011[57]. Both studies reported migration values, although below the LME of the evaluated antioxidants. E42[49] detected BHT in all PPPO samples, averaging 4.7 x 10^{-5} mg kg^{1}. The study, however, did not specify the type of evaluated polyethylene. E38[41] compared LDPE migration in rice and in PPPO, noting that migration to PPPO is faster and higher compared to rice. Furthermore, temperature effects are more significant concerning migration to PPPO compared to rice, regardless of the migrant. Therefore, this food simulant tends to overestimate migration values and can, therefore, be safely used to assess material conformity. In addition, the results indicate that PPPO is a more severe simulant for rice. This must be considered when assessing material compliance under EU Regulation 10/2011, which mentions that the "results of specific migration tests obtained in food shall take precedence over results obtained in food simulants"[57:12].

Irganox 1076 equilibrium in PPPO at 70 °C was reached after 15 days and at 40 °C, after 10 days, in contrast to rice, where the antioxidant did not reach an equilibrium at any of the tested temperatures. These behavior differences can be explained mainly by PPPO's high porosity and adsorption capacity[41]. It is important to note, as mentioned previously, that migration results obtained in the food prevail over results obtained with simulants.

E16[40] was the only study that did not mention the type of analyzed simulant, but demonstrated that over 95% of BHT was lost from the assessed film in 36 h at 40 °C, in 5 days at 30°C and in 16 days at 23°C. BHT can be depleted from films in short periods of time and may, therefore, not be effective as an antioxidant during packaged product shelf lives.

Food simulant standardization is required considering the importance of food simulants. Furthermore, it is essential that antioxidant packaging concentrations are determined experimentally prior to migration tests, in order to correlate measured values to real sample values, as in the case reported by E12, so results may truly express antioxidant behavior, and, therefore, accurately evaluate their safety as packaging additives[32].

Migration experiments endorse the importance of physicochemical food matrix properties, that is, combinations of high temperature and high fat content greatly aid antioxidant migration, increasing with increasing temperatures, while fat content alone has also been proven a determining migration parameter, as mentioned previously. Finally, antioxidant migration levels in simulants were reported by all studies as higher than in foods at all evaluated temperatures. Our assessment of all eligible studies confirms that the use of simulants in migration studies provides a good safety margin and that the transfer of low molecular weight hydrophobic components from plastic packaging material to food is governed by the fat releasing properties of the investigated food, *i.e.,* the amount of fat available on the food surface.

3.4 Migration assessments according to polymer type

Antioxidant migration was assessed by the studies included in this systematic review in three types of polyethylene, LDPE, HDPE and LLDPE. Of the 44 studies, only one (2%) did not specify the type of investigated polyethylene (E42)[49], while 39% evaluated LDPE, 30% analyzed LDPE and HDPE, 18% only HDPE, 9% LLDPE and 2% analyzed the three types.

LDPE is the most widely employed food packaging material, used as coating in food containers, especially in bakery products, milk, margarine, water and poultry[12,20,51].

A different scenario was reported by E33[31], which evaluated a solid and fatty food (cheese), indicating different losses from films, which contained 8 mg kg^{-1} and 14 mg kg^{-1} of BHT per kilogram of plastic. BHT losses from resins containing 8 and 14 mg kg^{-1} tested at 5 °C in 3 days corresponded to over 69 and 75%, respectively, while

losses were much higher in 20 days, corresponding to over 82 and 88%, respectively. Therefore, migration was higher during longer storage periods, and both migration results were above the BHT LME. It should be noted that most of the migrated BHT may have been deposited on the cheese surface, where antioxidants are more necessary, due to light exposure effects. E33, however, did not quantify BHT in the cheese samples as, once the antioxidant reaches the product, it can be consumed by reactions with free radicals. Most of the BHT was diffused from the LDPE layer to the cheese during the first 20 d of storage at 5°C. The release of BHT from the film added with 8 mg/g of the antioxidant in the LDPE layer complied with the legal limit in the cheese. However, the film added with 14 mg/g of the antioxidant in the LDPE layer could exceed that limit if all the BHT is released to the cheese. Thus, LDPE monolayer films are not suitable for cheese packaging, due to their high oxygen transmission rates, accelerating oxidation reactions.

LLDPE films are widely used in situations requiring flexibility and strength[25]. Studies investigating LLDPE only (E15[38], E21[50], E30[25] and E35[35]) reported no significant migration values above the LME. All studies employed mostly the same temperature (up to 40 °C) and fat simulants, although thickness differences were noted, with the thinnest package measuring 0.05 mm and the thickest, 2 mm, a 40-fold increase. This high variation, however, does not seem to have contributed to greater or lesser migration.

E11[30] evaluated the effect of resin type on BHT migration, determining the extent of HDPE odor and off-flavor release. A sensory study indicated that the BHT-free resin led to less off-flavor compared to the BHT-containing resin. In addition, resin containing a natural antioxidant (vitamin E) produced less off-flavor compared to the resin containing BHT. One study limitation, however, was that only one processing condition was applied to all evaluated resins, although each resin is likely to require a unique processing condition.

Among articles assessing antioxidant migration potential in more than one type of plastic packaging, E7[22] was the only one to evaluate the three main polyethylene types (LDPE, HDPE, LLDPE) in water, reporting that only 40% of BHT was extracted from the resins after three months, while 10% of BHT migrated in less than one day. Articles evaluating LDPE and HDPE, comprising E3[14], E8[24], E24[13], E25[15], E26[17], E28[21] E43[51], and E36[37] did not report migration values above the LME. However, E3, despite having detected a migration value below the irganox 1076 LME of 6 mg kg^{-1} reported a value very close to the limit, of 5.82 mg kg^{-1} in HDPE tested at 40 ºC in 10 days.

E3 also reported greater fatty food simulant migration in LDPE when compared to HDPE. However, the study did not determine irganox 1076 concentrations prior to the migration test and after the plastic formation process. The ideal scenario would be to test the amount of additive before and after processing.

Studies E1[10] and E27[19] evaluated HDPE (0.3 mm and 0.5 mm thick, respectively) and irganox 1076, with the former reporting no antioxidant migration and the latter, a migrated value exceeding the LME by 62.26%. Both studies evaluated migration in olive oil at the same temperatures (40 ºC), with only film thickness as the differing variable. However, no migration was reported for the thinner HDPE.

Studies E12[42] and E14[36] also evaluated irganox 1076 HDPE olive oil migration at 40 ºC for 10 days, reporting the same migrated value of 6.2 mg kg^{-1}. At 121º C for 2 hours, values were reported as 58 mg kg^{-1} and 55.9 mg kg^{-1} in E12 and E14, respectively.

A temperature of 121ºC was used to simulate HDPE autoclave for sterilization conditions, considered adequate for this polymer and covering the most rigorous use conditions. However, E14[36], which investigated a thicker film compared to E1[10] (2 mm), reported a migrated value above the LME. The packaging thickness used by E12[42] resembles the packaging thickness studied by E27[19], with antioxidant migrated values above the LME.

Comparing these studies with E25[15], which also employed HDPE, olive oil and a similar temperature (100 ºC for 2 h), no irganox 1076 migration above the LME was noted. Similarly to E12[42], E25[15] reported a significant amount of antioxidant present in the resin prior to the migration test (896 mg kg^{-1} or 0.09%) and the film thickness was significant (1.043 mm) which may explain the reason for the reported low antioxidant migration (0.437 mg kg^{-1}).

For polyolefin samples (HDPE), specific migration values obtained with 95% ethanol under the same exposure conditions agreed with the values obtained with olive oil, in line with FDA recommendations[58].

3.5 Migration assessments concerning type of antioxidant

Regarding antioxidants, the most studied was irganox 1076. According to Beldì et al.[39], this compound is commonly used as a migrant model as it is a typical antioxidant in food packaging polymers, as well as stable and available as a certified reference material. It protects plastic materials against thermo-oxidative degradation, presents low volatility and high extraction strength, and is not present naturally or as a food additive in foods.

BHT is one of the most commonly employed antioxidants used to protect plastics against oxidation due to heat and light exposure, also used in other applications as a food additive and in cosmetics, pharmaceuticals and petroleum products[47]. It is a fat-soluble and synthetic antioxidant, widely used in the food industry, with a legal limit for addition to most foods of 200 mg kg^{-1} of fat, increasing to 500 mg kg^{-1} in packaging. During film processing, part of the antioxidant is lost due to its ability to function as a free radical scavenger, also lost to the environment due to high volatility at processing temperatures[31].

Study E7[22] evaluated both BHT and irganox 1076 migration from LLDPE to water, reporting that irganox 1076 migration was slower than BHT under similar conditions, probably due to the fact that it is a much larger molecule than BHT, with a much lower diffusivity and slower oxidation compared to BHT. In addition, BHT solubility in the polymer and in water increased with temperature, all leading to faster and more significant BHT migration compared to irganox 1076 to water.

Study E23[11] demonstrated undetectable irganox 1076 migration to water in LDPE, similarly to results reported for butylated hydroxyanisole *(*BHA), considered one of the best antioxidants and preservatives employed by the industry, widely used in bulk oils and oil-in-water emulsions, as well as in packaging materials, aiming at food protection, as well as in many cosmetic products, alongside BHT[59].

Study E18[44] also compared BHT with vitamin E, as did E9[26], but with a dry food (oatmeal). The BHT content of the LDPE film became depleted much faster than vitamin E content, possibly due to diffusion to the surface of the film and evaporation, as BHT is a volatile molecule. After evaporation, it is likely that the BHT was either absorbed into the oatmeal or lost to the environment. Unfortunately the article does not mention the amount of BHT remaining in the oatmeal.

BHT is known to inhibit oxidation processes in food products and polymers. However, due to its migratory nature, a growing interest in the use of vitamin E as an alternative antioxidant for polymer stabilization has been noted. This vitamin has been reported as more effective at levels lower than those required for other antioxidants in reducing aftertaste, especially concerning resins used to store water, as noted by E18[44], E7[22], E9[26]. Directive 90/128/EC recommends a migration vitamin E limit of 60 mg kg^{-1}[60].

In studies comparing natural and synthetic antioxidants, BHT is rapidly lost from resins, especially LDPE, within a few days of storage at all tested temperatures, due to its small size, volatile and migratory nature[22,26,44,45]. Both E32[29] and E33[31] emphasize that the highest migration rates occur in polyolefins, especially in LDPE films, and BHT, as it is one of the smallest phenolic antioxidants, passes more easily from the resin to the food or food simulant, especially those rich in fat. Both E13[34] and E41[47] evaluated migration to 95% ethanol and observed that the relative amount of BHT migrated from LDPE to the simulant food was almost total, migrating to a lesser extent to 50% ethanol, considering that BHT exhibits a lower affinity for this simulant.

An evaluation carried out in fatty food simulants demonstrated that a BHT-containing film exhibited rapid BHT decreases soon after contact with the two simulants. After one week of storage at 4 °C, BHT levels in the film dropped below the limit of detection, with an even faster decay observed at 20°C, with only one day of storage enough to reduce BHT levels to undetectable in films in contact with sunflower oil and ethanol, thus indicating rapid BHT polymer migration[34,45].

Regarding irganox 1076, most analyzed samples contained several antioxidants at the same time, especially high molecular weight compounds, with irganox 1076 detected in almost 50% of the samples. In addition, most studies mentioned the importance of plastic film thickness and antioxidant concentration concerning migration. Furthermore, irganox 1076 results are very similar to the BHT results reported by the eligible studies included in this systematic review. One of the most mentioned issues for both is associated to antioxidant fat exposure, in turn associated with most of the migration that occurs from the packaging to the material. irganox 1076 migration was also reported as much higher in oil than in aqueous simulants, explained by its hydrophobic properties, *i.e.,* insolubility in water, therefore dissolving in other organic compounds. Olive oil, isooctane and 95% ethanol are, thus, routinely used as simulants, as described by Directive 82/711/EEC (European Commission 1982) due to a higher affinity with irganox 1076[39].

Study E8[24] demonstrated similar migrations for two aqueous simulants, water and 8% ethanol, at 135 ºC in HDPE and LDPE and, higher, albeit comparable, rates for two non-aqueous simulants for 95% ethanol and corn oil. For the non-aqueous simulants, migration was faster in LDPE and slower in HDPE. Study E43[51] also indicated higher migration values for the 95% ethanol simulant, as expected, as this antioxidant is more soluble in ethanol than in acidic or aqueous simulants.

Study E28[21] reported the marked presence of irganox 1076 in different commercial packages, and migration to permitted food simulants, such as distilled water, 3% acetic acid, 10% ethanol and olive oil, were observed in most samples (RDC No. 51, 2010)[61].

Study E25[15] reported migration values for sunflower oil, a very good choice for a certified reference material, relevant to compliance testing, where over 35% of the irganox 1076 was transferred to the simulant.

As foods are complex matrices, different protocols comprising different extraction times and modes, as well as temperature, must be adapted for each food matrix. High-fat matrices contained higher antioxidant concentrations, due to the difficulty of extracting irganox 1076 from fatty foods. High irganox 1076 migration rates have generally been detected in high-fat, low-water foods. The physical state of the food is also an important factor in the migration process. The results for 95% ethanol and olive oil indicated comparable migration levels at all temperatures Irganox 1076 migration in iso-octane was always the highest at all study temperatures and times. The maximum migration level achieved in food applying the same time and temperature conditions, was, in all cases, lower than that obtained with the corresponding simulants.

Fat food content seems to significantly influence additive migration. Study E5[18] also analyzed several food matrices, but compared low-calorie and low-fat foods under normal storage conditions and, in most cases, demonstrated equivalent migration to more caloric and higher fat content foods. Migration from polyolefins to the fat food simulant HB 307 is higher than for real foods, except for margarine and hard cheese under normal storage conditions.

Furthermore, temperature changes display a dramatic influence on antioxidant migration. At 100 ºC, irganox 1076 migration in 8% ethanol was higher in LDPE than HDPE, while migration in 95% ethanol at 100 ºC reached 100% of the irganox 1076 content in LDPE and around 70% in HDPE. At all temperatures, the highest migration for the aqueous simulant was from LDPE, followed by HDPE. For non-aqueous simulants such as olive oil, HDPE migration is minimal. In most cases, most antioxidant content was lost from LDPE packaging after a few hours.

4. Conclusions

This systematic review study assessed primary studies investigating the migration capacity of antioxidants from polyethylene packaging to food. Studies addressing the issue of antioxidant migration have been published since the 1970's, increasing up to the 2010's, when a slight drop from 2011 to the present date is noted. Of the 44 primary articles included in this systematic review, only two (E21 and E23) did not report antioxidant migration, with E21 detecting only traces of BHT and E23, no detection. This demonstrates that most studies report migration of the evaluated additives to foods and/or food simulants, and this exposure to synthetic substances, thus, takes place daily, via food, at minimum and sometimes maximum doses, with long still unknown-term health consequences.

Regarding migration assessments, one of the most important observations concerns BHT motility. BHT is considered an extremely mobile antioxidant in LDPE films, especially compared to natural antioxidants such as vitamin E, a harmless substance with a comparatively low food migration rate. Thus, vitamin E comprises a suitable BHT substitute as an antioxidant in plastic and more beneficial for use in food films, especially LDPE.

Concerning the different types of packaging evaluated in the eligible articles, LDPE promotes the highest antioxidant migration rate, followed by HDPE. Several packaging factors can influence migration, such as packaging density and thickness and contact time between the packaging and the food, among others.

With regard to type of simulant, antioxidant migration rates in simulants were higher than those in foods at all evaluated temperatures, indicating that the use of simulants in migration studies provides a good safety margin.

A higher trend for antioxidant migration in food/fatty simulants is noteworthy, as all the articles analyzing antioxidant migration in these cases reported higher migration rates in the presence of food or simulant containing higher fat content, with gradual migration increases with increasing contact time and temperature.

The eligible studies evaluated only the antioxidants BHT and irganox 1076, with no research on other antioxidants included in the search method applied to this review obtained, indicating that research on a wider range of antioxidants is paramount.

The growing application of antioxidants, especially in the food packaging industry, proves that human exposure to these substances is extremely relevant and the lack of further research on the subject represents a major challenge for the scientific community.

The findings reported here are conclusive regarding antioxidant migration, as the included studies evaluated wide time and temperature ranges, several simulants and food matrices, and employed several techniques to verify migrated amounts. In addition, values migrating above the LME ranged from 3.42 mg kg^{-1} to 231.7 mg kg^{-1}, much higher than the maximum permissible amounts regarding foods in contact with plastic resins, potentially leading to harmful human health effects.

Part II of this article intends to present the toxicological results regarding the antioxidant migration research presented herein.

5. Author's Contribution

- **Conceptualization** – Mayara de Simas Mesquita.
- **Data curation** – Mayara de Simas Mesquita.
- **Formal analysis** – Mayara de Simas Mesquita.
- **Funding acquisition –** Shirley Pereira Abrantes.
- **Investigation** – Mayara de Simas Mesquita.
- **Methodology** – Mayara de Simas Mesquita.
- **Project administration** – Shirley Pereira Abrantes.
- **Resources** – Shirley Pereira Abrantes.
- **Software** – Mayara de Simas Mesquita.
- **Supervision** – Shirley Pereira Abrantes.
- **Validation** – Shirley Pereira Abrantes.
- **Visualization** – Shirley Pereira Abrantes.
- **Writing – original draft** – Mayara de Simas Mesquita.
- **Writing – review & editing** – Shirley Pereira Abrantes.

6. Acknowledgements

This article is part of a doctoral thesis defended at the Instituto Nacional de Controle de Qualidade e Saúde (INCQS) and was financed in part by the Coordenação Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001. Funding acquisition by Shirley Pereira Abrantes.

7. References

1. Groh, K. J., Backhaus, T., Carney-Almroth, B., Geueke, B., Inostroza, P. A., Lennquist, A., Leslie, H. A., Maffini, M., Slunge, D., Trasande, L., Warhurst, A. M., & Muncke, J. (2019). Overview of known plastic packaging-associated chemicals and their hazards. *The Science of the Total Environment*, *651*(Pt 2), 3253-3268. http://dx.doi.org/10.1016/j.scitotenv.2018.10.015. PMid:30463173.
2. Lucchese, G. (2001). *Globalização e regulação sanitária: os rumos da vigilância sanitária no Brasil* (Doctoral thesis). Fundação Oswaldo Cruz, Escola Nacional de Saúde Pública, Rio de Janeiro.
3. Fabris, S., Freire, M. T. A., & Reyes, F. G. R. (2006). Embalagens plásticas: tipos de materiais, contaminação de alimentos e aspectos de legislação. *Revista Brasileira de Toxicologia*, *19*(2), 59-70.
4. Oliveira, W. S. (2013). *Estudo do potencial de migração de materiais plásticos utilizados para fabricação de mamadeiras* (Master's dissertation). Universidade Estadual de Campinas, Faculdade de Engenharia de Alimentos, Campinas.
5. Barros, S. B. M., & Davino, S. C. (2003). *Avaliação da toxicidade*. In S. Oga (Ed.), *Fundamentos de toxicologia* (pp. 57-68). Rio de Janeiro: Editora Atheneu.
6. Brasil. *Resolução da Diretoria Colegiada - RDC Nº 326/2019*. (2019, December 4). Estabelece a lista positiva de aditivos destinados à elaboração de materiais plásticos e revestimentos poliméricos em contato com alimentos e dá outras providências. Diário Oficial da República Federativa do Brasil, Brasília.

7. National Health Service Centre for Reviews and Dissemination. (1996). *Undertaking systematic reviews of research on effectiveness. CRD guidelines for those carrying out or commissioning reviews*. York: University of York.
8. Higgins, J. P. T., & Green, S. (2011). *Cochrane handbook for systematic reviews of interventions*. London: The Cochrane Collaboration. Retrieved in 2023, January 25, from https://handbook-5-1.cochrane.org/
9. Morais, L. O. (2018). *Embalagens para alimentos contendo nanopartículas de prata representam perigo para a população humana? Uma revisão sistemática como subsídio para ações de vigilância sanitária* (Doctoral thesis). Programa de Pós-graduação em Vigilância Sanitária, Instituto Nacional de Controle de Qualidade em Saúde, Fundação Oswaldo Cruz, Rio de Janeiro.
10. Figge, K., Koch, J., & Freytag, W. (1978). The suitability of simulants for foodstuffs, cosmetics and pharmaceutical products in migration studies. *Food and Cosmetics Toxicology*, *16*(2), 135-142. http://dx.doi.org/10.1016/S0015-6264(78)80193-X. PMid:669510.
11. Dopico-García, M. S., López-Vilariño, J. M., & González-Rodríguez, M. V. (2003). Determination of antioxidant migration levels from low-density polyethylene films into food simulants. *Journal of Chromatography. A*, *1018*(1), 53-62. http://dx.doi.org/10.1016/j.chroma.2003.08.025. PMid:14582626.
12. Till, D. E., Ehnlholt, D. J., Reid, R. C., Schwartz, P. S., Sidman, K. R., Schwope, A. D., & Whelan, R. H. (1982). Migration of BHT antioxidant from high density polyethylene to foods and food simulants. *Industrial & Engineering Chemistry Product Research and Development*, *21*(1), 106-113.
13. Han, J.-K., Selke, S. E., Downes, T. W., & Harte, B. R. (2003). Application of a computer model to evaluate the ability of plastics to act as functional barriers. *Packaging Technology & Science*, *16*(3), 107-118. http://dx.doi.org/10.1002/pts.618.
14. Figge, K., & Freytag, W. (1984). Additive migration from various plastics with different processing or properties into test fat HB 307. *Food Additives and Contaminants*, *1*(4), 337-347. http://dx.doi.org/10.1080/02652038409385864. PMid:6537356.
15. Stoffers, N. H., Störmer, A., Bradley, E. L., Brandsch, R., Cooper, I., Linssen, J. P. H., & Franz, R. (2004). Feasibility study for the development of certified reference materials for specific migration testing. Part 1: initial migrant concentration and specific migration. *Food Additives and Contaminants*, *21*(12), 1203-1216. http://dx.doi.org/10.1080/02652030400023911. PMid:15799565.
16. Bieber, W.-D., Freytag, W., Figge, K., Vom Bruck, C. G., & Rossi, L. (1984). Transfer of aditives from plastics material sinto foodstuffs and into food simulants: a comparison. *Food and Chemical Toxicology*, *22*(9), 737-742. http://dx.doi.org/10.1016/0278-6915(84)90202-3. PMid:6541627.
17. Stoffers, N. H., Brandsch, R., Bradley, E. L., Cooper, I., Dekker, M., Störmer, A., & Franz, R. (2005). Feasibility study for the development of certified reference materials for specific migration testing. Part 2: estimation of diffusion parameters and comparison of experimental and predicted data. *Food Additives and Contaminants*, *22*(2), 173-184. http://dx.doi.org/10.1080/02652030400028076. PMid:15864868.
18. Bieber, W.-D., Figge, K., & Koch, J. (1985). Interaction between plastics packaging materials and foodstuffs with different fat content and fat release properties. *Food Additives and Contaminants*, *2*(2), 113-124. http://dx.doi.org/10.1080/02652038509373533. PMid:4018317.
19. Begley, T., Castle, L., Feigenbaum, A., Franz, R., Hinrichs, K., Lickly, T., Mercea, P., Milana, M., O' Brien, A., Rebre, S., Rijk, R., & Piringer, O. (2005). Evaluation of migration models that might be used in support of regulation for food-contact Plastics. *Food Additives and Contaminants*, *22*(1), 73-90. http://dx.doi.org/10.1080/02652030400028035. PMid:15895614.
20. Schwope, A. D., Till, D. E., Ehntholt, D. J., Sidman, K. R., Whelan, R. H., Schwartz, P. S., & Reid, R. C. (1987). Migration of BHT AND irganox 1010 from low-density polyethylene (LDPE) to foods and food-simulating liquids. *Food and Chemical Toxicology*, *25*(4), 317-326. http://dx.doi.org/10.1016/0278-6915(87)90129-3. PMid:3583158.
21. Dopico-García, M. S., López-Vilarino, J. M., & González-Rodríguez, M. V. (2007). Antioxidant content of and migration from commercial polyethylene, polypropylene, and polyvinyl chloride packages. *Journal of Agricultural and Food Chemistry*, *55*(8), 3225-3231. http://dx.doi.org/10.1021/jf070102+. PMid:17381127.
22. Gandek, T. P., Hatton, T. A., & Reid, R. C. (1989). Batch extraction with reaction: phenolic antioxidant migration from polyolefins to water. 2. Experimental results and discussion. *Industrial & Engineering Chemistry Research*, *28*(7), 1036-1045. http://dx.doi.org/10.1021/ie00091a024.
23. Torres-Arreola, W., Soto-Valdez, H., Peralta, E., Cardenas-Lopéz, J. L., & Ezquerra-Brauer, J. M. (2007). Effect of a low-density polyethylene film containing butylated hydroxytoluene on lipid oxidation and protein quality of Sierra fish (*Scomberomorus sierra*) muscle during frozen storage. *Journal of Agricultural and Food Chemistry*, *55*(15), 6140-6146. http://dx.doi.org/10.1021/jf070418h. PMid:17595103.
24. Goydan, R., Schwope, A. D., Reid, R. C., & Cramer, G. (1990). High-temperature migration of antioxidants from polyolefins. *Food Additives and Contaminants*, *7*(3), 323-337. http://dx.doi.org/10.1080/02652039009373897. PMid:2379650.
25. Jeon, D. H., Park, G. Y., Kwak, I. S., Lee, K. H. L., & Park, H. J. (2007). Antioxidants and their migration into food simulants on irradiated LLDPE film. *Lebensmittel-Wissenschaft + Technologie*, *40*(1), 151-156. http://dx.doi.org/10.1016/j.lwt.2005.05.017.
26. Ho, Y. C., Yam, K. L., Young, S. S., & Zambetti, P. F. (1994). Comparison of vitamin E, Irganox 1010 and Bht as antioxidants on release of off-flavor from Hdpe bottles. *Journal of Plastic Film & Sheeting*, *10*(3), 194-212. http://dx.doi.org/10.1177/875608799401000303.
27. Vitrac, O., Mougharbel, A., & Feigenbaum, A. (2007). Interfacial mass transport properties which control the migration of packaging constituents into foodstuffs. *Journal of Food Engineering*, *79*(3), 1048-1064. http://dx.doi.org/10.1016/j.jfoodeng.2006.03.030.
28. Limm, W., & Hollifield, H. C. (1995). Effects of temperature and mixing on polymer adjuvant migration to corn oil and water. *Food Additives and Contaminants*, *12*(4), 609-624. http://dx.doi.org/10.1080/02652039509374349. PMid:7589724.
29. Cruz, J. M., Silva, A. S., García, R. S., Franz, R., & Losada, P. P. (2008). Studies of mass transport of model chemicals from packaging into and within cheeses. *Journal of Food Engineering*, *87*(1), 107-115. http://dx.doi.org/10.1016/j.jfoodeng.2007.11.022.
30. Yam, K. L., Ho, Y. C., Young, S. S., & Zambetti, P. F. (1996). Effect of resin types and antioxidants on release of off-flavor from HDPE bottles. *Polymer-Plastics Technology and Engineering*, *35*(5), 727-755. http://dx.doi.org/10.1080/03602559608004057.
31. Soto-Cantú, C. D., Graciano-Verdugo, A. Z., Peralta, E., Islas-Rubio, A. R., González-Córdova, A., González-León, A., & Soto-Valdez, H. (2008). Release of butylated hydroxytoluene from an active film packaging to Asadero cheese and Its effect on oxidation and odor stability. *Journal of Dairy Science*, *91*(1), 11-19. PMid:18096920.
32. O'Brien, A. P., Cooper, I., & Tice, P. A. (1997). Correlation of specific migration (Cf) of plastics additives with their

initial concentration in the polymer (Cp). *Food Additives and Contaminants*, *14*(6-7), 705-719. http://dx.doi.org/10.1080/02652039709374582. PMid:9373534.

33. Machado, M. P., Coltro, L., Pissolato, C., & Favaro, M. A. (2009). *Determinação da migração específica de 3-(3,5-diter-butil-4-hidroxifenil) propionato de n-octadecila (Irganox 1076) em simulantes aquosos*. In *10° Congresso Brasileiro de Polímeros* (pp. 1-10). São Carlos: Associação Brasileira de Polímeros.
34. Wessling, C., Nielsen, T., Leufvén, A., & Jägerstad, M. (1998). Mobility of α-tocopherol and BHT in LDPE in contact with fatty food simulants. *Food Additives and Contaminants*, *15*(6), 709-715. http://dx.doi.org/10.1080/02652039809374701. PMid:10209582.
35. Mauricio-Iglesias, M., Jansana, S., Peyron, S., Gontard, N., & Guillard, V. (2010). Effect of high-pressure/temperature (HP/T) treatments of in-package food on additive migration from conventional and bio-sourced materials. *Food Additives and Contaminants*, *27*(1), 118-127. http://dx.doi.org/10.1080/19440040903268054. PMid:19809898.
36. Cooper, I., Goodson, A., & O'Brien, A. (1998). Specific migration testing with alternative fatty food simulants. *Food Additives and Contaminants*, *15*(1), 72-78. http://dx.doi.org/10.1080/02652039809374600. PMid:9534873.
37. Coltro, L., & Machado, M. P. (2011). Migração específica de antioxidante de embalagens plásticas para alimentos. *Polímeros*, *21*(5), 390-397. http://dx.doi.org/10.1590/S0104-14282011005000064.
38. Linssen, J. P. H., Reitsma, J. C. E., & Cozijnsen, J. L. (1998). Research note: migration of antioxidants from polyolefins into ethanolic simulants. *Packaging Technology & Science*, *11*(5), 241-245.
39. Beldì, G., Pastorelli, S., Franchini, F., & Simoneau, C. (2012). Time- and temperature-dependent migration studies of Irganox 1076 from plastics into foods and food simulants. *Food Additives & Contaminants: Part A*, *29*(5), 836-845. http://dx.doi.org/10.1080/19440049.2011.649304. PMid:22313384.
40. Bailey, L. A., Lin, J. F., & Giacin, J. R. (1999). The mass transfer of 3, 5-di-tertiary-butyl-4-hydroxy toluene and α-tocopherol from coextrusion film structures. *Polymer-Plastics Technology and Engineering*, *38*(2), 201-219.
41. Reinas, I., Oliveira, J., Pereira, J., Machado, F., & Poças, M. F. (2012). Migration of two antioxidants from packaging into a solid food and into Tenax. *Food Control*, *28*(2), 333-337. http://dx.doi.org/10.1016/j.foodcont.2012.05.023.
42. O'Brien, A., Goodson, A., & Cooper, I. (1999). Polymer additive migration to foods - a direct comparison of experimental data and values calculated from migration models for high density polyethylene (HDPE). *Food Additives and Contaminants*, *16*(9), 367-380. http://dx.doi.org/10.1080/026520399283858. PMid:10755128.
43. Jakubowska, N., Beldì, G., Bach, A. P., & Simoneau, C. (2014). Optimisation of an analytical method and results from the inter-laboratory comparison of the migration of regulated substances from food packaging into the new mandatory European Union simulant for dry foodstuffs. *Food Additives & Contaminants: Part A*, *31*(3), 546-555. http://dx.doi.org/10.1080/19440049.2013.874046. PMid:24409838.
44. Wessling, C., Nielsen, T., & Giacin, J. R. (2001). Antioxidant ability of BHT- and α-tocopherol-impregnated LDPE film in packaging of oatmeal. *Journal of the Science of Food and Agriculture*, *81*(2), 194-201. http://dx.doi.org/10.1002/1097-0010(20010115)81:2<194::AID-JSFA801>3.0.CO;2-R.
45. Haitao, C., Ying, L., Xia, G., Weili, L., & Yunjun, L. (2015). Antioxidant BHT modelling migration from food packaging of high density polyethylene plastics into the food simulant. *Journal of Food Science and Technology*, *9*(7), 534-538.
46. O'Brien, A., & Cooper, I. (2002). Practical experience in the use of mathematical models to predict migration of additives from food-contact polymers. *Food Additives and Contaminants*, *19*(Suppl. 1), 63-72. http://dx.doi.org/10.1080/10196780110082295. PMid:11962716.
47. García-Ibarra, V., Sendón, R., García-Fonte, X.-X., Losada, P. P., & Quirós, A. R. B. (2018). Migration studies of butylated hydroxytoluene, tributyl acetylcitrate and dibutyl phthalate into food simulants. *Journal of the Science of Food and Agriculture*, *99*(4), 1586-1595. http://dx.doi.org/10.1002/jsfa.9337. PMid:30151848.
48. Brandsch, J., Mercea, P., Rüter, M., Tosa, V., & Piringer, O. (2002). Migration modelling as a tool for quality assurance of food packaging. *Food Additives and Contaminants*, *19*(Suppl), 29-41. http://dx.doi.org/10.1080/02652030110058197. PMid:11962712.
49. Rubio, L., Valverde-Som, L., Sarabia, L. A., & Ortiz, M. C. (2019). The behaviour of Tenax as food simulant in the migration of polymer additives from food contact materials by means of gas chromatography/mass spectrometry and PARAFAC. *Journal of Chromatography. A*, *1589*, 18-29. http://dx.doi.org/10.1016/j.chroma.2018.12.054. PMid:30598289.
50. Feigenbaum, A., Scholler, D., Bouquant, J., Brigot, G., Ferrier, D., Franz, R., Lillemark, L., Riquet, A. M., Petersen, J. H., Van Lierop, B., & Yagoubi, N. (2002). Safety and quality of food contact materials. Part 1: evaluation of analytical strategies to introduce migration testing into good manufacturing practice. *Food Additives and Contaminants*, *19*(2), 184-201. http://dx.doi.org/10.1080/02652030110053002. PMid:11820501.
51. Vera, P., Canellas, E., Barknowitz, G., Goshawk, J., & Nerín, C. (2019). Ion-mobility quadrupole time-of-flight mass spectrometry: a novel technique applied to migration of nonintentionally added substances from polyethylene films intended for use as food packaging. *Analytical Chemistry*, *91*(20), 12741-12751. PMid:31502827.
52. Helmroth, I. E., Dekker, M., & Hankemeier, T. (2002). Influence of solvent absorption on the migration of Irganox 1076 from LDPE. *Food Additives and Contaminants*, *19*(2), 176-183. http://dx.doi.org/10.1080/02652030110066198. PMid:11820500.
53. Liang, R., Hu, Y., & Li, G. (2020). Monodisperse pillar[5]arene-based polymeric sub-microsphere for on-line extraction coupling with high-performance liquid chromatography to determine antioxidants in the migration of food contact materials. *Journal of Chromatography. A*, *1625*, 461276. http://dx.doi.org/10.1016/j.chroma.2020.461276. PMid:32709328.
54. Abrantes, S. M. P. (1998). *Uso da eletroforese capilar para a determinação da migração química em alimentos em contato com embalagens* (Doctoral thesis). Universidade Federal do Rio de Janeiro, Instituto de Química, Rio de Janeiro.
55. Gnanasekharan, V., Floros, J. D., & Glacin, J. R. (1997). Migration and sorption phenomena in packaged foods. *Critical Reviews in Food Science and Nutrition*, *37*(6), 519-559. http://dx.doi.org/10.1080/10408399709527788. PMid:9404993.
56. Baner, A., Bieber, W., Figge, K., Franz, R., & Piringer, O. (1992). Alternative fatty food simulants for migration testing of polymeric food contact materials. *Food Additives and Contaminants*, *9*(2), 137-148. http://dx.doi.org/10.1080/02652039209374056. PMid:1499771.
57. European Commission. (2011). *Commission Regulation (EU) no 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food Text with EEA relevance*. Luxembourg: Official Journal of the European Union.

58. U.S. Food and Drug Administration. (1995). *Recommendations for chemistry data for indirect food additive petitions*. Silver Spring: U.S. Food and Drug Administration.

59. Pop, A., Kiss, B., & Loghin, F. (2013). Endocrine disrupting effects of butylated hydroxyanisole (BHA - E320). *Clujul Medical*, *86*(1), 16-20. PMid:26527908.

60. Van Battum, D., Rijk, M. A. H., Verspoor, R., & Rossi, L. (1982). Draft eec method for the determination of the global migration of plastics constituents into fatty-food simulants: applicability to lacquers, plastics and laminates. *Food and Chemical Toxicology*, *20*(6), 955-959. http://dx.doi.org/10.1016/S0015-6264(82)80236-8. PMid:6891682.

61. Brasil. *Resolução da Diretoria Colegiada - RDC nº51/2010*. (2010, November 30). Dispõe sobre migração em materiais, embalagens e equipamentos plásticos destinados a entrar em contato com alimentos. Diário Oficial da República Federativa do Brasil, Brasília.

Received: Aug. 23, 2022
Revised: Jan. 24, 2023
Accepted: Jan. 25, 2023