Infant total diet study in France: Exposure to substances migrating from food contact materials

Véronique Sirot, Gilles Rivière, Stéphane Leconte, Jean-Charles Leblanc, Martine Kolf-Clauw, Paule Vasseur, Jean Pierre J. P. Cravedi, Marion Hulin

To cite this version:
Véronique Sirot, Gilles Rivière, Stéphane Leconte, Jean-Charles Leblanc, Martine Kolf-Clauw, et al.. Infant total diet study in France: Exposure to substances migrating from food contact materials. Environment International, 2021, 149, pp.106393. 10.1016/j.envint.2021.106393 . hal-03136921

HAL Id: hal-03136921
https://hal.inrae.fr/hal-03136921
Submitted on 10 Feb 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives| 4.0 International License
Infant total diet study in France: Exposure to substances migrating from food contact materials

Véronique Sirot\textsuperscript{a, *}, Gilles Rivière\textsuperscript{a}, Stéphane Leconte\textsuperscript{a}, Jean-Charles Leblanc\textsuperscript{a}, Martine Kolf-Clauw\textsuperscript{b}, Paule Vasseur\textsuperscript{c}, Jean-Pierre Cravedi\textsuperscript{d}, Marion Hulin\textsuperscript{a}

\textsuperscript{a} ANSES, Risk Assessment Department, Maisons-Alfort, France
\textsuperscript{b} CREFRE, Toulouse University, INSERM, Toulouse Veterinary School, 23 Chemin des Capelles, BP 87614, 310176 Toulouse Cedex 3, France
\textsuperscript{c} University of Lorraine, CNRS, LIEC, 57070 Metz, France
\textsuperscript{d} Toxalim (Research Center in Food Toxicology), University of Toulouse, INRAE, ENVT, INP-Purpan, UPS, Toulouse, France

\textbf{ARTICLE INFO}

Handling Editor: Adrian Covaci

Keywords: Total diet study, Children, Bisphenol A, Phthalates, Food contact materials, Exposure assessment

\textbf{ABSTRACT}

A total diet study (TDS) was conducted in France to assess the health risks related to the chemicals in food of non-breastfed children under three years of age (Infant TDS). For the first time, substances coming from food contact materials, such as bisphenol A (BPA), bisphenol A diglycidyl ether (BADGE) and its derivatives, some phthalates, and some ink photoinitiators, were targeted because of growing interest in these substances. Food samples were collected to be representative of the whole diet of non-breastfed children aged 1–36 months, and prepared as consumed prior to analysis. Dietary exposure was assessed for 705 representative children under three years of age. Generally, the substances from food contact materials were detected in few samples: 38% for BPA, 0% for BADGE and its derivatives, 0–35% for phthalates, 1.9% for benzophenone, and 0% for the other ink photoinitiators. Regarding exposure levels, the situation was deemed tolerable for BADGE and its hydrolysis products, di-isodecyl phthalate, dibutyl phthalate, butyl benzyl phthalate, bis(2-ethylhexyl) phthalate, and di-isononyl phthalate, benzophenone, and 4-methylbenzophenone. Only for BPA, the exposure levels of some children exceeded the lowest toxicological value established by the French Agency for Food, Environmental and Occupational Health & Safety at 0.083 μg kg\(^{-1}\) d\(^{-1}\). The temporary tolerable daily intake of the European Food Safety Authority (EFSA), set at 4 μg kg\(^{-1}\) d\(^{-1}\), was never exceeded. However, actual exposure to BPA was probably overestimated, as well as the associated risk, because the foods were sampled prior to the recent regulations banning BPA in food packaging. This study is the first worldwide to provide an estimate of infant food contamination levels and exposures of children under 3 years of age, based on a TDS approach. It therefore provides key data on the exposure of this particularly sensitive population to substances released from food contact materials, and presents useful data for studies evaluating exposure to mixtures or aggregated exposure.

1. Introduction

Food is a source of a large number of nutrients but also a vector of a number of chemical substances. These include contaminants, substances migrating from food contact materials, food additives, and pesticide residues. Dietary exposure of the population to these substances may raise health concerns; therefore, an assessment of the corresponding daily exposure is required. The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) conducted the first infant Total Diet Study (TDS) focusing on children under 3 years old (Hulin et al., 2014). This study aimed at evaluating exposure to potentially harmful substances in infants and young children in France, a population known to be more susceptible to pollutants (Landrigan et al. 2003). TDSs have the advantage of assessing the occurrence of chemicals of interest in foods “as consumed” and are representative of the whole diet, and therefore estimate dietary exposure for different population groups in an efficient, cost-effective, and accurate way (WHO 1968a,b). Beyond the substances analyzed in previous studies (Leblanc et al. 2005, Arnich et al. 2012, Nougadere et al. 2012, Sirot et al. 2012, Sirot et al. 2013, Veyrand et al. 2013, Riviere et al. 2014), new substances were considered. In particular, substances released from food contact materials have been the focus of growing interest in recent years, especially those for...
which food has been identified as a major route of exposure (Wittassek et al., 2011, Blanchard et al., 2013).

Before being consumed, food comes into contact with many materials and articles during production, processing, storage, preparation, and serving. To ensure that these materials are not a source of health risks, various regulations have been issued at the national and European levels (especially framework Regulation (EC) No 1935/2004 and plastic Commission Regulation (EU) No 10/2011). The basis of the framework regulation is the inertia principle, as specified in article 3 of Regulation (EC) No 1935/2004, according to which the material must not transfer to food any constituents in amounts that may represent a risk to the consumer, or that may change the organoleptic qualities, or composition of the food. Several studies have shown that some substances authorized in food contact materials can be found in infant food (Yano et al., 2005, Wormuth et al., 2006, Rothenbacher et al., 2007, Pandelova et al., 2011) and have triggered controversy when taking into account other toxicological effects (EC) No 1935/2004, according to which the material must not transfer and serving. To ensure that these materials are not a source of health risks.

In the present manuscript, we report the concentrations of these substances measured in the samples collected during the Infant TDS in France and the resulting dietary exposure with the corresponding health risk assessment. The type of packaging was accounted for in most cases, to detect a possible influence on contamination results.

2. Materials and methods

2.1. Consumption data and food samples

Consumption data were used from the cross-sectional survey on individual dietary consumption in children under 3 years conducted by the Syndicat Français des Aliments de l’Enfance et de la Nutrition Clinique, © “Etude SOFRES 2005 / Université de Bourgogne – Pr M. Fantino pour le Syndicat Français des Aliments de l’Enfance” (Fantino 2005, Fantino and Gourmet 2008). In this survey, a representative sample of 705 children living in France aged from 1 month to 3 years was recruited based on proportionate quota sampling according to the previous French census taking into account the age, the occupation of the mother, and the family’s socioeconomic category. Totally or partially breastfed infants (during the survey period) were excluded from the study for practical reasons. People who took care of the children filled in individual 3-day weight food recall in order to list all their food consumptions and characteristics including brands, quantities, and portion sizes. Information on body weight was also recorded on the child’s health record.

A list of foods to be sampled was selected among the foods recorded on the basis of two criteria: (i) the most consumed foods by the children in terms of quantity and/or consumer rates in order to cover more than 95% of the whole diet of the population, and (ii) the foods less consumed but known to contribute significantly to exposure to one or more chemicals of interest. Foods were divided into 11 so-called “infant food” groups and 38 “common food” groups. The infant foods consisted of foods specifically dedicated to young children and that follow specific regulations for marketing and monitoring of chemicals with legal limits to ensure their safety: infant formulae, infant cereals, babyfood jars, etc. The common foods corresponded to foods that are not dedicated to young children such as fruits, vegetables, meat, or fish.

To take into account the potential variability of contamination arising from the use of different food contact materials, specific food items were stratified according to their possible types of packaging according to their market shares (SECOIDIP-TNS 2005, Worldpanel 2009, SECOIDIP-TNS 2010, Hulin et al., 2014).

Food samples were composite, in accordance with the general TDS methodology (WHO 1968a,b, IPCS 2009), i.e. made up of 12 pooled samples of the same food item and with common characteristics, in order to be representative of the food habits of the population. Between 2011 and 2012, every month for one year, one subsample of each food item was bought and prepared “as consumed”, according to the results of a specific 2011 online survey on common parental practices for home food preparation (Hulin et al., 2014, Hulin et al., 2019). This survey was conducted on a representative sample of 429 households with at least one child under 3 years of age. It included questions on containers used during processing or cooking, in order to take into account the potential migration of substances from the food contact materials. For each food item, the percentage of each type of preparation/cooking and heating process was applied to the distribution of the 12 subsamples to be prepared, according to each practice. After collection and preparation, the 12 subsamples were homogenized, and frozen (−18°C) prior to analysis. Containers used for sampling were tested beforehand for the different selected substances in order to avoid potential contamination during storage.

2.2. Sample analyses and contamination data

Analytical methods are briefly described below, more details are available in supplementary material. Analyses of chemicals migrating from food contact materials were performed on food items identified as potential contributors to exposure, specifically regarding the type of...
packaging in relation to the requirements of the regulation on food contact materials (EC 2004). In this way, BPA (CAS No 80-05-7, EC No 201-245-8) was analyzed in 309 food samples packaged in all materials, i.e. glass, plastic, metal (canned food), paper, and cardboard, except in bricks. These samples included several infant foods: milk (including reconstituted powered milks), fruits, vegetables (including vegetables mixed with meat or fish) and cereals. BADGE, its hydrolysis products and chlorohydrin derivatives (BADGE-H₂O, BADGE-2H₂O, BADGE-HCl, BADGE-2HCl, BADGE-2H₂O-2HCl), were analyzed in foods canned in metal only (n = 74). BPA was extracted from food samples by liquid-phase extraction techniques. Samples were injected into a reverse phase HPLC C18 column (SPE on line) using a gradient elution with acetonitrile and water. Quantification by liquid chromatography–tandem mass spectrometry (LC-MS/MS) was carried out using an internal deuterated standard (bisphenol A-D₄). The detection limits (LODs) and quantification limits (LOQs) were dependent on the nature of the matrix: 2 µg.kg⁻¹ and 10 µg.kg⁻¹ for cereals, and 0.2 µg.kg⁻¹ and 1.0 µg.kg⁻¹ for the other matrices, respectively.

The analytical method to measure the concentrations of BADGE and its derivatives was based on an extraction followed by LC/MS/MS analysis. Briefly, food samples were extracted with solvent (ethanol, acetic acid or acetonitrile), filtered and then injected to a LC/MS/MS equipment. The quantities of sample needed for the analysis were 5.0 ± 0.05 g for milks, fruit mixes and vegetable mixes and 2.0 ± 0.02 g for infant cereals. Extracts were then injected to a reverse phase HPLC C18 column using a methanol:water gradient elution. Quantification was performed by an external calibration. The LOD and LOQ were 3 µg.kg⁻¹ and 10 µg.kg⁻¹, respectively.

Widely used phthalates were searched for in 294 samples of food packaged in all materials, except in metal, but also in water samples and in the most consumed infant formulae. Phthalates studied were: bis(2-ethylhexyl) phthalate (DEHP, CAS No 117-81-7, EC No 204-211-0), dibutyl phthalate (DBP, CAS No 84-74-2, EC No 201-557-4), diisobutyl phthalate (DIBP, CAS No 84-69-5, EC No 201-553-2), benzyl butyl phthalate (BBP, CAS No 85-68-7, EC No 201-622-7), di-isodicyclosiphthalate (DIDP, CAS No 26761-40-0, EC No 247-977-1), di-isononylphthalate (DINP, CAS No 28553-12-0, EC No 249-079-5), diethyl phthalate (DEP, CAS No 84-66-2, EC No 201-550-6), dicyclohexyl phthalate (DCHP, CAS No 84-61-7, EC No 201-545-9), dioctyl phthalate (DOP, CAS No 117-81-7, EC No 204-211-0), dibutyl sebacate (DBS, CAS No 109-43-3, EC No 203-672-5), and bis(2-ethylhexyl) adipate (DEHA, CAS No 103-23-1, EC No 203-090-1); DBS and DEHA being two alternative products for phthalates. Phthalates were extracted from food samples with isohexane for matrices containing fat or dairy products, or with a refined 3% olive oil solution in isohexane. Samples were analyzed by gas-chromatography tandem mass spectrometry (GC/MS-MS) (triple quadrupole, electronic impact). The quantification was performed by using a calibration curve. The LOD and LOQ were equal to 5 µg.kg⁻¹ and 20 µg.kg⁻¹, respectively.

Censored data, corresponding to the results below the LOD or LOQ, were processed according to a substitution method that involved framing the actual level using the lowest (lower-bound (LB)) and highest (upper-bound (UB)) values possible. The LB was calculated by assuming that all values below the LOD were equal to zero, and those between the LOD and the LOQ were equal to the LOD. The UB was calculated by assuming that all values above the LOD were equal to the LOQ, and those between the LOD and the LOQ were equal to the LOQ.

For BPA, additional data were used, generated from the campaigns (unresolved chromatographically), the quantification was ensured by isotopic dilution of a close linear form (D₃-DnOP). These two compounds (DINP and DIDP) were dosed as a “group”. Due to the variability of the blanks, the concentrations of the phthalate diesters were measured in the samples by using a reporting limit (LOR). LOR corresponded to the mean of analytical blanks plus three standard deviations for DEP, BBP, DEHA, DBP, DCHP, DBS, DOP, and DINP, and ranged from 0.83 to 15.8 µg.kg⁻¹. For other phthalates (DBBP, DIDIP, and DEHP), LOR was calculated with the mean of blanks plus three standard deviations and ranged from 1.57 to 2.67 µg.kg⁻¹. Bottled water samples were analyzed by a multi-residue analytical method by gas chromatography coupled mass spectrometry, and after solid phase micro-extraction (SPME off line).

Photoinitiated analyzes were the five substances usually targeted by the European network of laboratories analyzing food contact materials: benzophenone (BP, CAS No 119-61-9, EC No 204-237-6), 4-methylbenzophenone (4-MBP, CAS No 134-84-9, EC No 205-159-1), 4-hydroxybenzophenone (4-HBP, CAS No 1137-42-4, EC No 214-507-1), 4-phenylbenzophenone (PBZ, CAS No 2128-93-0, EC No 218-345-2), and 2-isopropylthioxanthone (ITX, CAS No 5495-84-1, EC No 226-827-9). They were analyzed in 212 samples of food packed into plastic, paper and cardboard, including mixtures based on fruits, vegetables, fish or meat with vegetables, milks (including reconstituted powered milks), and cereals. Samples were extracted with ethyl acetate, then analyzed on an apolar column by gas chromatography coupled with tandem mass spectrometry (GC-MS/MS) (triple quadrupole). Quantification was performed in the presence of two internal standards (deuterated benzophenone (BP-D₁₀) and dicyclohexylphthalate-3,4,5,6-d₄, (DCHP-D₄)). The procedure concerned concentrations between 20 and 500 µg.kg⁻¹ of sample. The LOD and LOQ were equal to 5 µg.kg⁻¹ and 20 µg.kg⁻¹, respectively.

2.3. Exposure calculation and risk assessment

According to WHO recommendations, exposure data were estimated following the LB and UB approaches. In the present article, exposure as well as health risk are presented considering the worst-case scenario, i.e., considering the UB hypothesis, except for BPA as a difference was observed in the percentage of children exceeding the reference values between both hypotheses (see section 3.2.1).

For each subject in the consumption survey, dietary exposure was assessed according to the following formula:

\[ E_{ij} = \sum_{k} C_{ik} \times L_{kj} / BW_i \]

where \( E_{ij} \) is the mean daily exposure to contaminant \( j \) of individual \( i \), \( n \) the number of foods in the diet of the individual \( i \), \( C_{ik} \) the daily consumption of food \( k \) by individual \( i \), \( L_{kj} \) the concentration of contaminant \( j \) in food \( k \), and \( BW_i \) the body weight of individual \( i \).

The consumption study did not always record the packaging material in which the consumed product was packaged. When the information was not available in order to affect contamination data, a random draw was conducted for each child and each food, based on household purchase data (Worldpanel, 2009, SECODIP-TNS 2005, 2010, not published). If the child consumed the same food for the three consecutive days of the investigation, the same packaging was assumed.

For BPA, additional data were used, generated from the campaigns carried out by the Nancy Laboratory for Hydrology for the General Health Directorate in the context of monitoring plans of tap and bottled water. Contamination data were randomly allocated to each consumption of each child having consumed water. Distribution of type and brand of water used for diluting powdered formula was based on the results of the 2011 online survey (Hulin et al., 2014, Hulin et al., 2019). For tap water, contamination data from the department or region of the child’s place of residence were considered for allocation.

To take into account dietary diversification periods for the exposure and risk assessment, the population was divided into four age groups: 1–4 months, 5–6 months, 7–12 months and, 13–36 months. Arithmetic
mean, standard deviation, and 90th percentile (P90) of exposure were calculated for all groups.

The health risk associated with dietary exposure to each chemical was assessed by calculating, for each age group, the percentage of children having an estimated exposure higher than the chronic health-based guidance value and its 95% confidence interval (C95%). The relevance to apply each health-based guidance value to the specific population of children under 3 years old was studied, for example the inclusion of reprotoxicity, developmental, or multigenerational data, or the existence of a comprehensive expert appraisal of the toxicological data corpus (ANSES 2016). This methodology was considered appropriate to assess the risk at the population scale, in that the population sample is representative of the less than 3-years-old children in France, and the use of a multiple-day dietary survey provides a proxy of the chronic exposure of the subjects (IPCS, 2020).

2.4. Collective appraisal

The collective assessment of the risk linked to the exposure was conducted by the expert panel at ANSES dealing with chemical contaminants in food.

3. Results and discussion

3.1. Contamination data

All occurrence values in food samples are presented in supplementary results (Tables S1 to S4).

3.1.1. Bisphenol A (BPA)

BPA was detected in 38% of the food samples, and more specifically in 26% of infant food samples, whereas BADGE was not detected at all.

The detection rate varied from 0% (infant cereals, biscuits, some beverages, chocolate, fruits, milk, etc.) to 100% in infant fruit juices (n = 4), vegetables (n = 12), eggs (n = 1), fish (n = 2), and pasta (n = 2). Highest mean concentrations were found in vegetables (15.6 ± 18.3 μg kg⁻¹ under the UB hypothesis), and mixed dishes (18.0 ± 27.9 μg kg⁻¹ under the UB hypothesis). Highest values were observed in canned products, mainly canned vegetables (up to 53 μg kg⁻¹ for a leafy vegetable sample), but also ravioli-type stuffed pasta (49 μg kg⁻¹). However, most of the analyzed samples (97%) presented concentrations under 5 μg kg⁻¹, considered a background level of contamination in the most recent evaluation of dietary exposure to BPA in the French population (Bemrah et al. 2014). Nevertheless, it is important to note that the food samples were collected between 2011 and 2012. Taking into account the different regulations to ban BPA in food packaging, current environmental and food contamination is expected to be lower than during the sampling period.

When comparing, in a same food group, the average contamination of foods packaged in different materials, highest concentrations were measured in canned foods (data not shown), as previously observed (Bemrah et al. 2014, Sakhi et al. 2014): 35.0 ± 10.6 μg kg⁻¹ in canned vegetables compared to around 2 μg kg⁻¹ in frozen vegetables packaged in plastic bags (1.95 ± 2.93 under LB and 2.35 ± 2.63 under UB). Significantly higher concentrations were also observed in baby foods (vegetables, meat or fish and vegetables) packaged in glass jars compared to those packaged in plastic plates or cups: 0.62 ± 0.70 vs. 0.07 ± 0.10 μg kg⁻¹ in LB and 1.03 ± 0.51 vs. 0.47 ± 0.38 in UB, respectively (p < 0.0001, for both estimation hypotheses). These differences could be explained by the presence of BPA in the varnishes used in this type of packaging (cans and lids of small glass jars). However, concentrations of BPA measured in specific infant foods were low compared to those measured in common food products, regardless of the packaging. For infant formulae, the differences observed between metal and plastic canned formulae could not be confirmed due to the high percentage of samples in which the substances were not detected.

3.1.2. Bisphenol A diglycidyl ether (BADGE)

BADGE-2HCl was detected only in samples of vegetables and mixed dishes in canned form, and BADGE·2H₂O and BADGE·H₂O·HCl were quantified in the same food groups, with levels ranging for individual samples from 25 to 93 μg kg⁻¹ and from 190 to 540 μg kg⁻¹, respectively. As already observed (Yonekubo et al., 2008), BADGE·2H₂O and BADGE·H₂O·HCl appeared to be the major derivatives of BADGE in canned foods. These data reinforced the importance of searching for chlorinated or hydroxylated species in addition to BADGE in order not to underestimate consumer exposure (Hammarling et al. 2000, Muncke 2014). However, some studies have shown that adduct formation can also occur in foodstuffs with amino acids such as cysteine or methionine (Petersen et al. 2008, Coulier et al. 2010), that should also be analyzed and considered for the risk assessment.

3.1.3. Phthalates

Regarding phthalates, the detection rates were generally low, but also varied widely depending on the substance considered. Only DEHP, DINP and DIBP were detected in more than 10% of the samples.

For DEHP, which was detected in 35% of the samples, highest concentrations were found in baby biscuits (453 and 816 μg kg⁻¹ in two individual samples, data not shown). Next, butter (n = 3 samples) and chocolate (n = 1 sample of milk chocolate) were the most contaminated food groups, with an average of 275 ± 54.9 and 177 μg kg⁻¹, respectively. DINP was detected in 14% of samples, from 0 to 100% depending on the food group. The highest concentrations were observed once again in baby biscuits (472 and 497 μg kg⁻¹ in two individual samples, data not shown) and in one sample of chipolata sausages (434 μg kg⁻¹). Regarding DIBP (detected in 10% of the samples), highest concentrations were found in sugar (30 μg kg⁻¹) followed by infant breakfast cereals (19 μg kg⁻¹). Our results were generally consistent with those reported in previous studies, with higher concentrations of DEHP in fatty foods (Kappenstein et al. 2012, Sakhi et al. 2014), and also close to those reported in a Belgian study (Van Holderbeke et al. 2014).

Because of the low detection rates of phthalates, it was difficult to find a significant difference in concentrations according to the type of packaging, except for DEHP. For DEHP, significantly higher concentrations were found in dishes of vegetables with meat, or vegetables with fish packaged in plastic plates or bowls (respectively, 9.7 ± 11.2 and 13.1 ± 9.3 μg kg⁻¹ according to the LB and UB hypothesis), compared to those packaged in glass jars (2.47 ± 4.45 and 6.87 ± 4.02 μg kg⁻¹ (p < 0.01 for both LB and UB hypotheses, data not shown)). For other phthalates, higher detection rates were, however, observed for prepared baby dishes (dishes of vegetables, or dishes of vegetables with meat or vegetables with fish) packaged in plastic plates or bowls compared to those packaged in glass jars (for BBP), as well as for infant cereals presented in individual packaging (sachets) compared to those in cardboard packaging (for BBP and DEHP), in line with previous observations (Sakhi et al. 2014).

3.1.4. Ink photoinitiators

For ink photoinitiators, the detection rate was low. Only benzophenone was detected, but not quantified, in a sample of cheese, a sample of vegetables, a sample of rice and a sample of biscuits, i.e. 1.9% of samples. The other substances were not detected. The concentrations in the present study were lower than those reported in a 2006 Food Standards Agency (FSA) study, in which benzophenone was detected in 3.5% of the food samples and concentrations varied from 69 to 150 μg kg⁻¹ (FSA 2006). EFSA also noted high concentrations of 4-MBP in infant cereals, from 795 to 819 μg kg⁻¹ (EFSA 2009b), and levels of ITX reaching 305 μg kg⁻¹ in infant formulae and 445 μg kg⁻¹ in milk (EFSA 2005), i.e. far higher than in the present study (<5 μg kg⁻¹).
3.2. Exposure and risk assessment

3.2.1. Bisphenol A

Depending on the age group, mean daily exposure to BPA ranged from 10 ± 26 to 74 ± 133 ng.kg bw⁻¹.d⁻¹ under the LB hypothesis, and from 67 ± 52 to 99 ± 133 ng.kg bw⁻¹.d⁻¹ under the UB hypothesis (Table 1). The P90 reached 173 ng.kg bw⁻¹.d⁻¹ under UB in 1–4 month-old children, and 203 ng.kg bw⁻¹.d⁻¹ in 13–36 month-old children. Exposure tended to increase with age and varied by a factor of 3–10, under the UB, depending on whether or not the child consumed previously canned foods such as vegetables or filled pasta (ravioli) during the consumption survey period. These results are consistent with those from a previous study focusing on common foods, which assessed the mean daily exposure of 0–6 month-old children (between 62 and 78 ng.kg bw⁻¹.d⁻¹) and for 13–36 month-old children (between 156 and 182 ng.kg bw⁻¹.d⁻¹) (Semreh et al. 2014). The results are also in accordance with the latest EFSA assessment presenting a mean exposure of 36 ng.kg bw⁻¹.d⁻¹ for 0–6 month-old children consuming infant formulae, and 55–159 ng.kg bw⁻¹.d⁻¹ for 13–36 month-old children (EFSA 2015).

Many evaluations of BPA toxicity have been conducted in Europe and worldwide, and numerous adverse effects have been identified in animals, especially in terms of endocrine disruption. On one hand, the LB exposure of children aged 5–36 months and the UB exposure of all age groups significantly exceeded the lowest toxicological value of 0.083 µg.kg bw⁻¹.d⁻¹ proposed by ANSES (Table 1). This protective value was calculated based on a no observed adverse effect level (NOAEL) of 25 µg.kg bw⁻¹.d⁻¹ for an effect on the mammary glands in offspring rats exposed in utero (Moral et al. 2008), and considering an uncertainty factor of 300 (ANSES 2013). The study of Moral et al. (2008) revealed modifications in the morphology and the genomic profile of the mammary glands in the offspring rats exposed in utero, to which an uncertainty factor of 150 was applied (Camacho et al. 2019). However, effects of BPA at low doses (5 µg.kg bw⁻¹.d⁻¹ and below) were also observed and are still debated (Ziv-Gal et al., 2015, Heindel et al. 2020). Moreover, as the samples from the present study were collected in 2011–2012, i.e. before BPA was prohibited in food packaging at the European level (Commission Regulation (EU) No 10/2011 2011), the contamination and therefore the exposure reported in this study were most probably higher than those that would be measured today. In view of these recent restrictions on BPA migration limits in food containers, and considering recent results of monitoring BPA in human urine samples (Sante publique France 2019, Rolland et al. 2020), current exposure levels should be determined, i.e. after the introduction of these measures. Reassessing the risk would make it possible to evaluate the effects of the regulations on population exposure, and then assess the possible need for new recommendations. Moreover, in view of the increasing use of BPA substitutes, it is also important to consider other bisphenols, such as bisphenol F and bisphenol S, in the future assessments.

3.2.2. Bisphenol A diglycidyl ether (BADGE)

Exposure levels to BADGE and its hydroxylated species ranged under UB hypothesis from 623 ± 875 ng.kg bw⁻¹.d⁻¹ in 7–12 month-old children to 1402 ± 404 ng.kg bw⁻¹.d⁻¹ in 1–4 month-old children (Table 3). The P90 reached 1870 ng.kg bw⁻¹.d⁻¹ in the youngest group. For chlorinated species, mean UB exposure ranged from 156 ± 296 ng.kg bw⁻¹.d⁻¹ in the 13–36 month-old group and 1389 ± 368 ng.kg bw⁻¹.d⁻¹ in the 1–4 month-old group, with a P90 reaching 1850 ng.kg bw⁻¹.d⁻¹ in the same group (Supplementary results). These exposure levels were far below the TDI set by EFSA at 0.15 mg. kg bw⁻¹.d⁻¹ (EFSA 2004), considered to be applicable in children under 1.5 years of age.

### Table 1

Estimated daily dietary exposure to bisphenol A (BPA) in the four age groups of the Infant TDS population in France, and risk assessment. Exposure values are mean (±standard deviation) expressed in ng.kg bw⁻¹.d⁻¹, and 90th percentile (P90). Percentages of children exceeding the reference values are given with a 95% confidence interval.

<table>
<thead>
<tr>
<th>Age group</th>
<th>n</th>
<th>Mean exposure (ng.kg bw⁻¹.d⁻¹)</th>
<th>P90 exposure (ng.kg bw⁻¹.d⁻¹)</th>
<th>% children exceeding the value of 0.083 µg.kg bw⁻¹.d⁻¹ (ANSES 2013) (%)</th>
<th>% canned food consumers among children exceeding the value of 0.083 µg.kg bw⁻¹.d⁻¹ (ANSES 2013) (%)</th>
<th>% children exceeding the value of 4 µg.kg bw⁻¹.d⁻¹ (EFSA 2013) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LB</td>
<td>UB</td>
<td>LB</td>
<td>UB</td>
<td>LB</td>
<td>UB</td>
</tr>
<tr>
<td>1–4 months</td>
<td>124</td>
<td>10 ± 26</td>
<td>67 ± 52</td>
<td>35</td>
<td>24.6 (15.1; 34.1)</td>
<td>2</td>
</tr>
<tr>
<td>6–12 months</td>
<td>127</td>
<td>28 ± 44</td>
<td>68 ± 47</td>
<td>49</td>
<td>32.3 (15.0; 43.3)</td>
<td>8</td>
</tr>
<tr>
<td>7–12 months</td>
<td>195</td>
<td>46 ± 74</td>
<td>81 ± 76</td>
<td>97</td>
<td>37.8 (18.5; 48.8)</td>
<td>47</td>
</tr>
<tr>
<td>13–36 months</td>
<td>259</td>
<td>74 ± 133</td>
<td>99 ± 133</td>
<td>189</td>
<td>35.2 (33.5; 42.4)</td>
<td>97</td>
</tr>
</tbody>
</table>

n, number of subjects; LB, lower bound; NC, not calculated because of an insufficient number of subjects; TDS, total diet study; UB, upper bound.
three years of age. Indeed, the TDI was derived from a NOAEL of 15 mg kg bw\(^{-1}\)d\(^{-1}\) for BADGE coming from a 2-year oral carcinogenicity study on male rats. BADGE-H\(_2\)O and BADGE-2H\(_2\)O were included in the TDI insofar as BADGE is rapidly metabolized to its derivatives. The situation is therefore deemed tolerable for BADGE and its hydrolysis products. Given the absence of a toxicological point of departure, it is impossible to draw a conclusion as to the risk associated with dietary exposure to chlorohydrin-type derivatives.

### 3.2.3. Phthalates

The exposure levels are presented in Table 3 for the five individual phthalates for which a health-based guidance value was defined and in supplementary results for the other ones. Generally, the LB daily exposure increased with age, probably due to an increased proportion in the diet of common foods that are more highly contaminated. The trends in UB exposure cannot be interpreted because of the high censorship rate in the concentration data. Consequently, the exposure estimates were only explained by consumption.

In 2019, EFSA established a group TDI for DBP, BBP, DEHP and DINP, which are the most commonly used in the field of food contact materials (EFSA 2019). The TDI was set at 50 µg kg bw\(^{-1}\)d\(^{-1}\) expressed as DEHP equivalent, considering DEHP as the reference compound, and allocating potency factors to each of the four substances. This value was based on the effect of the phthalates on fetal testosterone, which is considered a plausible toxicological mechanism for this group of substances. Considering this group approach, the mean exposure ranged from 2.39 ± 1.03 to 3.28 ± 0.62 µg DEHP eq kg bw\(^{-1}\)d\(^{-1}\) when considering the UB hypothesis. These results are generally lower than those presented recently by EFSA. No individual exceeded the group TDI, even when considering the P90. Regarding DIDP, not included in the group-TDI, EFSA retained the TDI of 150 µg kg bw\(^{-1}\)d\(^{-1}\), previously set for the sum DINP + DIDP. Mean exposure to DIDP ranged from 1.63 ± 0.66 to 3.33 ± 0.61 µg kg bw\(^{-1}\)d\(^{-1}\) when considering the UB hypothesis. No individual exceeded the group TDI, even when considering the P90, reaching 4.09 µg DEHP eq kg bw\(^{-1}\)d\(^{-1}\) for the 1–6 month-old children under UB.

Exposure to DIDP, DBP, BBP, DEHP and DINP is therefore considered tolerable for these substances. However, even though the exposure levels are not considered to represent a public health problem, considering the fact that the latest evaluation is on a temporary basis, exposure monitoring should continue. This is particularly important in light of the increased consumption of ultra-processed foods, which have been shown to increase phthalate exposure (Buckley et al. 2019). In addition, analyses of phthalates in this study were performed in foods considered to be potential contributors to the exposure regarding the type of packaging. However, even though their detection is generally low, phthalates have been shown to be ubiquitous in food (Sakhi et al. 2014, Van Holderbeke et al. 2014). Although almost the entire diet was covered here for the youngest children consuming mainly industrial infant foods, it would be of interest to refine the exposure of the oldest children by integrating data on non-packaged common foods. The TDS approach appears to be a relevant way to assess exposure, in that foods are analyzed “as consumed”. Cooking at home has been shown to generally decrease phthalate concentrations in foods, and therefore clearly needs to be considered to correctly assess human dietary exposure to these contaminants (Fierens et al. 2012). Moreover, the present study dealt exclusively with exposure via food and did not incorporate exposure via other routes (respiratory, dermal, etc.) in the risk assessment approach. However, for phthalates, these other routes of exposure do exist and intakes via these non-dietary routes can be non-negligible in children (Schettler 2006, INSERM 2011, Beko et al. 2013). It would therefore be necessary to assess the whole risk by characterizing the other main routes of exposure and by considering them in an “aggregated” exposure approach, as has already been done for BPA (ANSES 2013, Vanacker et al. 2020).

Lastly, in the absence of robust health-based guidance values for DBS, DIBP, DEHA, DEP, DOP and DCHP, it is not possible to reach a conclusion as to the health risk associated with exposure to these phthalates. Toxicity studies should be conducted to establish health-based guidance values applicable to the general population and considering infant specificities.

#### 3.2.4. Ink photoinitiators

Under the UB hypothesis, the mean daily exposure to benzophenone was estimated to range from 60.3 ± 170 ng kg bw\(^{-1}\)d\(^{-1}\) in 1–4 month-old children to 558 ± 145 ng kg bw\(^{-1}\)d\(^{-1}\) in 13–36 month-old children (Table 3). The P90 reached 542 ng kg bw\(^{-1}\)d\(^{-1}\) in 7–12 month-old children. For 4-MBP, the exposure estimated was mainly driven by analytical limits due to the high level of censorship, and the UB exposure calculated was thus highly underestimated for all age groups. Nevertheless, these exposure levels for benzophenone and 4-MBP were deemed tolerable with regard to the selected health-based guidance
values considered applicable for children under three years of age. Importantly, no individual exceeded the TDI of 0.03 mg benzenophene/kg bw \(^{1}.d^{-1}\) derived from a BMDL\(_{10}\) of 3.1 mg/kg bw \(^{1}.d^{-1}\) established on non-neoplastic effects on male rats kidney (EFSA, 2009b). Multi-generational studies have shown adverse effects of benzenophene on reproduction and development, but only for exposure levels higher than those affecting the kidneys. Regarding 4-MBP, the margins of safety calculated based on the same BMDL\(_{10}\) ranged from 5769 in 7–12 month-old children to 38,000 in 1–4 month-old children, considering the P90 of exposure, i.e. much higher than the critical margin of 200 retained by EFSA to exclude the risk (EFSA, 2009b). Even though some in vitro studies showed that benzenophene and some of its derivatives might have endocrine disruption effects (Muncke 2011), these health-based guidance values cannot be called into question for the moment. Regarding PBZ, 4-HBP and ITX (Supplementary results), it was not possible to reach a decision in terms of the risk; they were not detected here, and no robust health-based guidance value is available.

4. Conclusion and recommendations

To our knowledge, this study is the first worldwide to provide an estimate of baby food contamination levels and exposures of children under 3 years of age, based on the Total Diet Study approach. On the one hand, our study provides key data on the exposure of this particularly sensitive population to substances that can migrate from food contact materials. These data made it possible to assess the risk for about ten substances or groups of substances, some of which are likely to trigger endocrine disruptor mechanisms of action. On the other hand, given the absence of health-based guidance values, it was not possible to reach a conclusion as to the risk associated with dietary exposure to chlorohydrin-type derivatives of BADGE, other phthalates (i.e. DBS, DIBP, DEHA, DEP, DOP and DCHP), and other ink photoinitiators (i.e. PBZ, 4-HBP and ITX). These phthalates, depending on the material, were detected in up to 10% of samples, whereas ink photoinitiators were never detected. These results underline the need to perform toxicological studies in order to produce health-based guidance values for the risk assessment of major substances migrating from food contact materials.

### Table 3

Estimated daily dietary exposure to bisphenol A diglycidyl ether (BADGE) and its hydroxylated derivatives, five phthalates, and ink photoinitiators in the four age groups of the Infant TDS population in France. Exposure values are mean (±standard deviation) expressed in ng/kg bw \(^{1}.d^{-1}\), and 90th percentile (P90).

<table>
<thead>
<tr>
<th>Substances</th>
<th>Age group</th>
<th>Mean exposure LB (ng/kg bw (^{1}.d^{-1}))</th>
<th>P90 exposure UB (ng/kg bw (^{1}.d^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>BADGE</td>
<td>1–4 months</td>
<td>0</td>
<td>462 ± 123</td>
</tr>
<tr>
<td></td>
<td>5–6 months</td>
<td>0</td>
<td>245 ± 78.2</td>
</tr>
<tr>
<td></td>
<td>7–12 months</td>
<td>0</td>
<td>109 ± 80.7</td>
</tr>
<tr>
<td></td>
<td>13–36 months</td>
<td>0</td>
<td>10.7 ± 25.8</td>
</tr>
<tr>
<td>BADGE and its hydrolysis products</td>
<td>1–4 months</td>
<td>16.0 ± 198</td>
<td>1402 ± 404</td>
</tr>
<tr>
<td></td>
<td>5–6 months</td>
<td>116 ± 474</td>
<td>851 ± 493</td>
</tr>
<tr>
<td></td>
<td>7–12 months</td>
<td>298 ± 828</td>
<td>623 ± 875</td>
</tr>
<tr>
<td></td>
<td>13–36 months</td>
<td>617 ± 1240</td>
<td>644 ± 1258</td>
</tr>
<tr>
<td>BBP</td>
<td>1–4 months</td>
<td>0.64 ± 3.70</td>
<td>334 ± 60.9</td>
</tr>
<tr>
<td></td>
<td>5–6 months</td>
<td>10.9 ± 10.5</td>
<td>268 ± 31.0</td>
</tr>
<tr>
<td></td>
<td>7–12 months</td>
<td>11.7 ± 12.4</td>
<td>235 ± 46.6</td>
</tr>
<tr>
<td></td>
<td>13–36 months</td>
<td>6.30 ± 13.8</td>
<td>166 ± 71.6</td>
</tr>
<tr>
<td>DBP</td>
<td>1–4 months</td>
<td>0.20 ± 1.10</td>
<td>335 ± 61.5</td>
</tr>
<tr>
<td></td>
<td>5–6 months</td>
<td>1.90 ± 2.60</td>
<td>267 ± 30.6</td>
</tr>
<tr>
<td></td>
<td>7–12 months</td>
<td>3.50 ± 4.70</td>
<td>233 ± 44.3</td>
</tr>
<tr>
<td></td>
<td>13–36 months</td>
<td>9.90 ± 18.9</td>
<td>172 ± 68.1</td>
</tr>
<tr>
<td>DEHP</td>
<td>1–4 months</td>
<td>10.5 ± 36.6</td>
<td>678 ± 132</td>
</tr>
<tr>
<td></td>
<td>5–6 months</td>
<td>88.1 ± 84.2</td>
<td>603 ± 104</td>
</tr>
<tr>
<td></td>
<td>7–12 months</td>
<td>241 ± 200</td>
<td>682 ± 221</td>
</tr>
<tr>
<td></td>
<td>13–36 months</td>
<td>536 ± 588</td>
<td>830 ± 590</td>
</tr>
<tr>
<td>DIDP</td>
<td>1–4 months</td>
<td>0</td>
<td>3333 ± 611</td>
</tr>
<tr>
<td></td>
<td>5–6 months</td>
<td>0</td>
<td>2568 ± 296</td>
</tr>
<tr>
<td></td>
<td>7–12 months</td>
<td>4.90 ± 20.1</td>
<td>2213 ± 426</td>
</tr>
<tr>
<td></td>
<td>13–36 months</td>
<td>3.50 ± 29.1</td>
<td>1636 ± 662</td>
</tr>
<tr>
<td>DINP</td>
<td>1–4 months</td>
<td>9.40 ± 51.5</td>
<td>3344 ± 605</td>
</tr>
<tr>
<td></td>
<td>5–6 months</td>
<td>86.8 ± 122</td>
<td>2654 ± 318</td>
</tr>
<tr>
<td></td>
<td>7–12 months</td>
<td>368 ± 321</td>
<td>2553 ± 548</td>
</tr>
<tr>
<td></td>
<td>13–36 months</td>
<td>687 ± 668</td>
<td>2275 ± 928</td>
</tr>
<tr>
<td>DIDP + DINP</td>
<td>1–4 months</td>
<td>9.40 ± 51.5</td>
<td>6677 ± 1214</td>
</tr>
<tr>
<td></td>
<td>5–6 months</td>
<td>86.8 ± 122</td>
<td>5222 ± 663</td>
</tr>
<tr>
<td></td>
<td>7–12 months</td>
<td>373 ± 326</td>
<td>4766 ± 940</td>
</tr>
<tr>
<td></td>
<td>13–36 months</td>
<td>691 ± 670</td>
<td>3911 ± 1486</td>
</tr>
<tr>
<td>DBP, BBP, DEHP and DINP as a group</td>
<td>1–4 months</td>
<td>14.3 ± 45.0</td>
<td>3389 ± 623</td>
</tr>
<tr>
<td></td>
<td>5–6 months</td>
<td>125 ± 118</td>
<td>2760 ± 332</td>
</tr>
<tr>
<td></td>
<td>7–12 months</td>
<td>373 ± 273</td>
<td>2638 ± 544</td>
</tr>
<tr>
<td></td>
<td>13–36 months</td>
<td>792 ± 785</td>
<td>2387 ± 1030</td>
</tr>
<tr>
<td>Benzenophene</td>
<td>1–4 months</td>
<td>0</td>
<td>60.3 ± 170</td>
</tr>
<tr>
<td></td>
<td>5–6 months</td>
<td>0.25 ± 1.34</td>
<td>197 ± 107</td>
</tr>
<tr>
<td></td>
<td>7–12 months</td>
<td>1.42 ± 4.82</td>
<td>321 ± 132</td>
</tr>
<tr>
<td></td>
<td>13–36 months</td>
<td>3.64 ± 9.94</td>
<td>358 ± 145</td>
</tr>
<tr>
<td>4-MBP</td>
<td>1–4 months</td>
<td>0</td>
<td>60.3 ± 170</td>
</tr>
<tr>
<td></td>
<td>5–6 months</td>
<td>0</td>
<td>196 ± 107</td>
</tr>
<tr>
<td></td>
<td>7–12 months</td>
<td>0</td>
<td>317 ± 130</td>
</tr>
<tr>
<td></td>
<td>13–36 months</td>
<td>0</td>
<td>348 ± 143</td>
</tr>
</tbody>
</table>

4-MBP, 4-methylbenzenophene; BBP, benzyl butyl phthalate; DBP, dibutyl phthalate; DEHP, bis(2-ethylhexyl) phthalate; DIDP, di-isodecyl phthalate; DINP, diisononyl phthalate; n, number of subjects; LB, lower bound; TDS, total diet study; UB, upper bound.
contact materials.

Dietary exposure of children under 3 years of age to substances migrating from food contact material generally appeared to be tolerable, except for BPA, on the basis of the ANSES ITDI only. In addition, as the food sampling was performed before the latest European regulations banning BPA in food packaging, exposure to BPA should now be lower and not represent a public health concern, but this must now be verified. Moreover, it should be underlined that the assessment carried out in the present work was conducted only for dietary exposure, and on an individual basis, apart for the four phthalates. However, these substances are not present only in food, but also in different compartments of the environment. It would therefore also be of interest to consider the risk linked to exposure to multiple contaminants more generally. This requires first to identify mixtures of substances that are relevant from a public health point of view and consider population exposure (Traore et al. 2018), before assessing the risk through specific approaches to cumulate the risk under dose additivity (Crépet et al. 2018), before assessing the risk through specific approaches to cumulate the risk under dose additivity (Crépet et al. 2018), before assessing the risk through specific approaches to cumulate the risk under dose additivity (Crépet et al. 2018), before assessing the risk through specific approaches to cumulate the risk under dose additivity (Crépet et al. 2018).

The infant TDS was supported by the Ministry for food, agriculture and fisheries, the Ministry for health, the Ministry for ecology and sustainable development and the French Agency for Food, Environmental and Occupational Health & Safety (ANSES).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106393.

References


EFSA, 2004. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to 2,2-bis(4-hydroxyphenyl) propane bis(2,3-epoxypropyl)(ether) (bisphenol A diglycidyl ether, BADGE). In The EFSA journal, N. 113 (13), 2004-1109-IEC.

EFSA, 2005. Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to 2-isopropyl thioxanthone (ITX) and 2-ethyl-4-dimethylaminobenzylbenzene (EHDBA) in food contact materials.


Fantino, M., 2005. “Etude SFAE sur la consommation alimentaire des nourrissons et enfants en bas âge français de 1 mois à 36 mois - Analyse des données nutritionnelles (non publiées).”


V. Sirot et al.

Environment International 149 (2021) 106393
integration, analysis, and interpretation of eight academic CLARITY-BPA studies. Reprod. Toxicol.


