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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 $bw^{-1}.d^{-1}$. The temporary tolerable daily intake of the European Food Safety Authority (EFSA), set at 4 μg.kg $bw^{-1}.d^{-1}$, 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

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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 endpoints than those considered to set specific migration limits by risk managers (i.e. European Commission in Europe). The best-known example of these controversies is bisphenol A (BPA), suspected of triggering toxicological effects *via* endocrine disrupting mechanisms at concentrations much lower than those tested in the studies supporting marketing authorization. BPA is the starting monomer to produce a polycarbonate that has a wide variety of applications for food contact materials (baby bottles) or epoxy resins used for canned foods. At the European level, the specific migration limit for BPA is 0.6 $mg.kg^{-1}$ of food. It was established on the basis of the temporary tolerable daily intake (t-TDI) set by the European food safety authority (EFSA) in 2015 at 4 $\mu g.kg\ bw^{-1}.d^{-1}$, based on the effect of BPA on the mean relative kidney weight in a two-generation study in mice (EFSA 2015). On the other hand, ANSES established different reference values, among which the lowest at 0.083 $\mu g.kg\ bw^{-1}.d^{-1}$ (ANSES 2013). This value was based on a dose of 25 $\mu g.kg\ bw^{-1}.d^{-1}$ with no effects observed in rats on the mammary glands of the female offspring exposed *in utero* (Moral et al. 2008), to which an uncertainty factor of 300 was applied.

In addition to BPA, this study focused specifically on bisphenol A diglycidyl ether (BADGE), and its derivatives, some phthalates, and ink photoinitiators, for several reasons. First, questions have been raised about their adverse effects, of a general nature or specific to the population considered. Moreover, very few data on food contamination were available, like for phthalates, which are plasticizers, in spite of their wide range of uses as food contact materials, resulting in limited risk assessments for these substances.

BADGE is an organic compound derived from BPA and epichlorohydrin, mainly used as a starting substance in the manufacture of can coatings for food-contact applications, for the stabilization of vinyl organosol coatings. BADGE is used as an additive to trap HCl released by polyvinyl chloride during varnish curing. This process can form chlorinated or hydroxylated derivatives (BADGE.H_2O, BADGE·$2H_2O$, BADGE.HCl, BADGE.2HCl, BADGE·$2H_2$·O2HCl) that can also migrate into foodstuffs. Migration in food is limited to 9 $mg.kg^{-1}$ for BADGE and its hydrolysis products, and to 1 $mg.kg^{-1}$ for BADGE chlorohydrin (Regulation (EC) No 1895/2005).

Ink photoinitiators are chemical compounds initiating the polymerization of a material under the effect of light. They are particularly present in UV-curable inks and coatings and can migrate through different packaging to the food (Koivikko et al. 2010). They can also be found in paper and board from the recycling process. In 2009, an alert was raised through the Rapid Alert System for Food and Feed (RASFF) due to high concentrations of benzophenone in infant cereals. Following this alert, EFSA concluded that, according to exposure assessment, the presence of this substance is unlikely to pose a health concern (EFSA, 2009a). However, for children, based on the highly conservative scenario (high consumption of breakfast cereals, highest concentration of 4-methylbenzophenone), a health concern could not be ruled out.

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 records 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 regarding their market shares (SECODIP-TNS 2005, Worldpanel 2009, SECODIP-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 grouped, 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·H_2O, BADGE·$2H_2O$, BADGE·HCl, BADGE·2HCl, BADGE·$2H_2O$·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-D_{16}). The detection limits (LODs) and quantification limits (LOQs) were dependent on the nature of the matrix: 2 $\mu g.kg^{-1}$ and 10 $\mu g.kg^{-1}$ for cereals, and 0.2 $\mu g.kg^{-1}$ and 1.0 $\mu g.kg^{-1}$ 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 $\mu g.kg^{-1}$ and 10 $\mu g.kg^{-1}$, 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), di-isobutyl 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-isodecyl phthalate (DIDP, CAS No 26761-40-0, EC No 247-977-1), di-isononyl phthalate (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 using 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 carried out by isotopic dilution using deuterated standards. In the case of mixtures of isomers such as DINP and DIDP (unresolved chromatographically), the quantification was ensured by isotopic dilution of a close linear form (D_4-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 $\mu g.kg^{-1}$. For other phthalates (DIBP, DIDP, and DEHP), LOR was calculated with the median of blanks plus three standard deviations and ranged from 1.57 to 2.67 $\mu g.kg^{-1}$. Bottled water samples were analyzed with a multi-residue analytical method by gas chromatography coupled mass spectrometry, and after solid phase micro-extraction (SPE off line).

Photoinitiators analyzed 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 204-337-6), 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-D_{10}) and dicyclohexylphthalate-3,4,5,6-d4, (DCHP-D_4)). The procedure concerned concentrations between 20 and 500 $\mu g.kg^{-1}$ of sample. The LOD and LOQ were equal to 5 $\mu g.kg^{-1}$ and 20 $\mu g.kg^{-1}$, 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 below the LOD were equal to the LOD, and those between the LOD and the LOQ were equal to the LOQ.

The study protocol was not specifically designed to determine how the container could influence the concentrations of substances potentially migrating from food contact materials. However, Wilcoxon Mann-Whitney tests were performed to determine whether differences could be observed in contamination depending on the type of packaging in which the foods were contained, when at least 3 samples were available in each group.

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:

$$E_{i,j} = \frac{\sum_{k=1}^{n} C_{i,k} \times L_{k,j}}{BW_i}$$

where $E_{i,j}$ is the mean daily exposure to contaminant j of individual i, n the number of foods in the diet of the individual i, $C_{i,k}$ the daily consumption of food k by individual i, $L_{k,j}$ 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 (CI95%). 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·2H$_2$O and BADGE·H$_2$0·HCl were quantified in the same food groups, with levels ranging for individual samples from 25 to 93 μg.kg^{-1} and from 190 to 540 μg.kg^{-1}, respectively. As already observed (Yonekubo et al., 2008), BADGE·2H$_2$O and BADGE·HCl·H$_2$O 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, 2009a), 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 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 $bw^{-1}.d^{-1}$) (Bemrah 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 constructed 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 gland, these changes being related to the estrogenic activity of BPA and indicative of breast cancer susceptibility later in life. On the other hand, EFSA's temporary TDI set at 4 µg.kg $bw^{-1}.d^{-1}$ was not exceeded, even when considering the UB hypothesis. This t-TDI was based on a benchmark dose limit derived from a two generation study by Tyl et al (2008): a $BMDL_{10}$ of 8960 µg.kg $bw^{-1}.d^{-1}$ for an adverse effect on the male mouse kidney weight, corresponding to a dose of 609 µg.kg $bw^{-1}.d^{-1}$ in humans, to which an uncertainty factor of 150 was applied (EFSA 2015). In terms of risk assessment for the children subpopulation, the EFSA health-based guidance value based on a study covering both pre- and postnatal exposures might be more appropriate compared with the protective value established by ANSES on the basis of an exposure period occurring prenatally only.

In children who exceeded the ANSES toxicological value under the LB hypothesis, consumption of canned foods explained 90% of the exposure (data not presented) whereas 2–28% of children (depending on the age group) who do not consume canned foods exceeded this value, and only under the UB hypothesis (Table 2). With regard to EFSA's temporary TDI, the health risk associated with dietary exposure to BPA can be ruled out, whereas it cannot be excluded for certain consumers on the basis of the values proposed by ANSES. However, considering the methodology to establish a health-based guidance value intended to protect the entire population including the most sensitive individuals (especially the use of uncertainty factors), an exceedance of the value does not necessarily trigger adverse effects. Occurrence of adverse effects will depend on the extent and duration of exceedance, if exposure covers specific time windows of sensitivity. External health-based guidance values can hardly predict health effects; however, they allow to trigger risk management measures. Instead, an internal health-based guidance value, which corresponds to a critical concentration in blood or tissues above which a risk for the health cannot be excluded, would be more appropriate to predict the impact of all external inputs (Pruvost-Couvreur et al 2020). It would be useful to build an internal health-based guidance value of BPA accounting on sensitive populations.

Both agencies consider that their toxicological values are liable to change following the conclusions of the long-term Clarity-BPA studies currently being analyzed by different health authorities (NTP 2018, 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 (Santé 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

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.

Age group	n	Mean exposure (ng.kg $bw^{-1}.d^{-1}$)		P90 exposure (ng.kg $bw^{-1}.d^{-1}$)		% children exceeding the value of 0.083 µg.kg $bw^{-1}.d^{-1}$ (ANSES 2013) (%)		% canned food consumers among children exceeding the value of 0.083 µg.kg $bw^{-1}.d^{-1}$ (ANSES 2013) (%)	% children exceeding the value of 4 µg.kg $bw^{-1}.d^{-1}$ (EFSA 2015) (%)
		LB	UB	LB	UB	LB	UB		LB = UB
1–4 months	124	10 ± 26	67 ± 52	35	173	NC	24.6 [15.1; 34.1]	2	0
5–6 months	127	28 ± 44	68 ± 47	49	125	6.6 [0; 14.3]	29.2 [15.0; 43.3]	8	0
7–12 months	195	46 ± 74	81 ± 76	97	137	11.9 [6.00; 17.7]	26.8 [18.8; 34.8]	47	0
13–36 months	259	74 ± 133	99 ± 133	189	203	26.6 [22.6; 30.6]	38.2 [33.8; 42.6]	97	0

n, number of subjects; LB, lower bound; NC, not calculated because of an insufficient number of subjects; TDS, total diet study; UB, upper bound.

Table 2
Estimated daily dietary exposure to bisphenol A (BPA) in the four age groups of the Infant TDS population in France according to the consumption of canned foods, and risk assessment. Exposure values are mean (±standard deviation) expressed in ng.kg $bw^{-1}.d^{-1}$. Percentages of children exceeding the reference values are given with a 95% confidence interval.

Population group regarding consumption of canned food	N	Mean exposure		% children exceeding the value of 0.083 µg.kg $bw^{-1}.d^{-1}$ (ANSES 2013)		% children exceeding the value of 4 µg.kg $bw^{-1}.d^{-1}$ (EFSA 2015) (%)
		LB	UB	LB	UB	LB = UB
Non consumers						
1–4 months	123	8 ± 12	65 ± 47	NC	24.3 [14.8; 33.8]	0
5–6 months	123	18 ± 14	59 ± 21	4.29 [0; 10.7]	27.6 [13.5; 41.8]	0
7–12 months	166	20 ± 16	55 ± 23	1.51 [0; 3.92]	16.7 [9.34; 24.1]	0
13–36 months	125	16 ± 17	43 ± 23	1.51 [0; 3.92]	2.37 [0.38; 4.35]	0
Consumers						
7–12 months	29	185 ± 147	219 ± 149	12.6 [6.03; 19.1]	15.1 [8.00; 22.1]	0
13–36 months	134	128 ± 152	152 ± 153	55.3 [48.8; 61.8]	77.1 [71.6; 82.5]	0

Consumers<6 months old are not presented because of a low number of subjects (1 for 1–4 months, 4 for 5–6 months). 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_2O and BADGE·$2H_2O$ 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 exposures 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 exposures ranged from 2.39 ± 1.03 to 3.28 ± 0.62 $\mu g_{DEHP\ eq}$.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}.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 358 ± 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

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).

Substances	Age group	Mean exposure		P90 exposure	
		LB	UB	LB	UB
BADGE	1–4 months	0	462 ± 123	0	617
	5–6 months	0	245 ± 78.2	0	416
	7–12 months	0	109 ± 80.7	0	250
	13–36 months	0	10.7 ± 25.8	0	30
BADGE and its hydrolysis products	1–4 months	16.0 ± 198	1402 ± 404	0	1870
	5–6 months	116 ± 474	851 ± 493	0	1283
	7–12 months	298 ± 828	623 ± 875	694	1064
	13–36 months	617 ± 1240	644 ± 1258	1760	1792
BBP	1–4 months	0.64 ± 3.70	334 ± 60.9	0	425
	5–6 months	10.9 ± 10.5	268 ± 31.0	45.9	343
	7–12 months	11.7 ± 12.4	235 ± 46.6	31.6	297
	13–36 months	6.30 ± 13.8	166 ± 71.6	15.2	240
DBP	1–4 months	0.20 ± 1.10	335 ± 61.5	0	425
	5–6 months	1.90 ± 2.60	267 ± 30.6	9.78	336
	7–12 months	3.50 ± 4.70	233 ± 44.3	12.3	291
	13–36 months	9.90 ± 18.9	172 ± 68.1	22.3	238
DEHP	1–4 months	10.5 ± 36.6	678 ± 132	19.3	849
	5–6 months	88.1 ± 84.2	603 ± 104	274	820
	7–12 months	241 ± 200	682 ± 221	539	1005
	13–36 months	536 ± 588	830 ± 590	961	1265
DIDP	1–4 months	0	3333 ± 611	0	4245
	5–6 months	0	2568 ± 296	0	3132
	7–12 months	4.90 ± 20.1	2213 ± 426	0	2795
	13–36 months	3.50 ± 29.1	1636 ± 662	0	2285
DINP	1–4 months	9.40 ± 51.5	3344 ± 605	0	4245
	5–6 months	86.8 ± 122	2654 ± 318	338	3425
	7–12 months	368 ± 321	2553 ± 548	941	3544
	13–36 months	687 ± 668	2275 ± 928	1266	3116
DIDP + DINP	1–4 months	9.40 ± 51.5	6677 ± 1214	0	8490
	5–6 months	86.8 ± 122	5222 ± 603	338	6500
	7–12 months	373 ± 326	4766 ± 940	972	6200
	13–36 months	691 ± 670	3911 ± 1486	1266	5194
DBP, BBP, DEHP and DINP as a group	1–4 months	14.3 ± 45.0	3389 ± 623	19.3	4289
	5–6 months	125 ± 118	2760 ± 332	395	3554
	7–12 months	371 ± 273	2638 ± 544	784	3574
	13–36 months	792 ± 785	2387 ± 1030	1397	3282
Benzophenone	1–4 months	0	60.3 ± 170	0	82.4
	5–6 months	0.25 ± 1.34	197 ± 107	0	515
	7–12 months	1.42 ± 4.82	321 ± 132	2.72	542
	13–36 months	3.64 ± 9.94	358 ± 145	11.3	495
4-MBP	1–4 months	0	60.3 ± 170	0	82.4
	5–6 months	0	196 ± 107	0	515
	7–12 months	0	317 ± 130	0	537
	13–36 months	0	348 ± 143	0	485

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

values considered applicable for children under three years of age. Importantly, no individual exceeded the TDI of 0.03 mg benzophenone. kg $bw^{-1}.d^{-1}$ derived from a $BMDL_{10}$ of 3.1 mg.kg $bw^{-1}.d^{-1}$ established on non-neoplasic effects on male rats kidney (EFSA, 2009b). Multi-generational studies have shown adverse effects of benzophenone 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 benzophenone 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 effects *via* an endocrine disruptor mechanism 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 photo-initiators (i.e. PBZ, 4-HBP and ITX). These phthalates, depending on the compound, 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.

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 tTDI 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. submitted for publication). An analysis of exposure to mixtures of these substances integrating the different routes of exposure would therefore be necessary. This is particularly important as several of these substances have endocrine disrupting effects. The data collected in this study, with the need to update BPA food concentrations, could provide input for studies on the potential associations between mixtures of substances and health effects, as well as population whole-life exposure to chemicals.

CRediT authorship contribution statement

Véronique Sirot: Methodology, Formal analysis, Project administration, Writing - original draft. **Gilles Rivière:** Formal analysis, Writing - original draft. **Stéphane Leconte:** Data curation, Writing - original draft. **Jean-Charles Leblanc:** Conceptualization, Funding acquisition, Writing - review & editing. **Martine Kolf-Clauw:** Formal analysis, Writing - review & editing. **Paule Vasseur:** Formal analysis, Writing - review & editing. **Jean-Pierre Cravedi:** Formal analysis, Writing - review & editing. **Marion Hulin:** Methodology, Formal analysis, Project administration, Writing - original draft.

Declaration of Competing Interest

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

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Appendix A. Supplementary material

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