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Abstract

Since the European Commission prohibited the use of bisphenol A (BPA) in the production of polycarbonate (PC) baby bottles, many other materials have replaced PC for the manufacture of this type of food contact materials. In the present study, the potential migration risks associated with these alternative materials were investigated. A distinction was made between migrants listed in Annex I of European Regulation 10/2011 and the unlisted substances (e.g. non-intentionally added substances (NIAS)). For the listed substances, concentrations in the migration solutions were compared to their respective specific migration limits (SML) (when applicable). Migration of all substances was shown to be below their SML. The unlisted substances were evaluated using the Threshold of Toxicological Concern (TTC) approach. The estimated exposure of some unlisted substances exceeded the human exposure threshold determined by the TTC concept. For these substances, a more in-depth risk assessment was performed. In addition, all substances were also evaluated for endocrine disruptive (ED) activity by using different existing lists of (suspected) endocrine disrupting chemicals. Based on the results of the (refined) TTC approach and the information on ED activity, five baby bottles were considered of high concern because of the potential toxicity of compounds migrating thereof.

1. Introduction

Bisphenol A (BPA) has been used for many years as a starting product to manufacture polycarbonate (PC) food contact materials (FCMs) including infant feeding (baby) bottles. Over the last years, studies identifying BPA as an endocrine disruptor (ED) have however been published (Alonso-Magdalena et al., 2012; Hass et al., 2016; Mandrup et al., 2016; Palanza et al., 2008; Talsness et al., 2009). Together with the observation that BPA can migrate into the food (Nam et al., 2010), these reports have raised worldwide concern about the application of BPA in FCMs. To address these concerns, the European Food Safety Authority (EFSA) re-evaluated BPA exposure and toxicity and concluded that BPA poses no health risk to consumers of any age group at current exposure levels (EFSA, 2015). Nevertheless, controversy over BPA remains. In 2011, the European Commission (EC) had already decided to prohibit the use of BPA in the manufacture of PC baby bottles in the European Union on the basis of the precautionary principle (European Union, 2011a). Consequently, PC has been replaced by a wide variety of other materials, such as polypropylene, polyamide, polyethersulfone, silicone, and glass. Compared to PC baby bottles, release of substances from replacement products has been relatively poorly studied. Recently, results of migration studies with baby bottles used as substitutes for PC have however become available (Onghena et al., 2014 and 2015; Simoneau et al., 2012). These studies showed that only part of the substances migrating from PC replacement products are included in the positive list (Annex I) of commission regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food. In Europe, only substances included in this Annex I of Regulation 10/2011 can be used as starting product for the manufacture of plastic FCMs and migration should be below the specific migration limit (SML), if available (European Union, 2011b). Other substances that were found to migrate from PC replacement products included non-intentionally added substances (NIAS) migrating from plastics (e.g. degradation and reaction products with unknown chemical identity) or

substances migrating from non-plastic FCMs, such as silicones. Although no specific regulation exists for these substances, they should be in accordance with Regulation (EC) No 1935/2004 stating that migration of FCM constituents should not negatively affect consumer health (European Union, 2004). Furthermore, for substances migrating from plastic FCM, any potential health risk should be assessed by the manufacturer in accordance with internationally recognized scientific principles (European Union, 2011b).

One possibility to investigate the potential risks associated with the migration of substances not included in Annex I of Regulation 10/2011 is to use the threshold of toxicological concern (TTC) approach (EFSA, 2016). Within the TTC approach, a threshold value is identified for a chemical below which there is a very low probability of adverse effects to human health following daily ingestion. Since this approach is solely based on the structural chemical characteristics and estimated exposure, it can be used to assess health concerns of chemicals with limited or no specific toxicity data (EFSA, 2012). Both in the US and Europe, the usefulness of the TTC approach as a pragmatic risk assessment or prioritisation tool has been established in different domains, including that of FCMs (US FDA, 1993 and EFSA, 2016). Importantly, the TTC approach cannot be applied when there is a requirement to submit toxicity data or when the available toxicity data allow a chemical-specific hazard assessment (Brüschweiler, 2014). So whereas the TTC approach might be an interesting tool to preliminary assess the risks associated with NIAS migrating from FCMs, it cannot be used for starting products for the manufacture of plastic FCMs.

In the present study, a strategy was developed to evaluate the potential health risks associated with substances for which migration from PC replacement products has been quantified (Onghena et al, 2016). Depending whether or not a substance is present in Annex I of Regulation 10/2011, a different approach was used. Indeed, for substances included in Annex

I of Regulation 10/2011, a risk assessment has already been performed by the EFSA or by its predecessor, the Scientific Committee on Food (SCF), based on the toxicological information submitted in the application dossier (Barlow, 2009 and EFSA, 2008). For these substances, migration values were compared with the corresponding SML, if available. For substances not included in Annex I of Regulation 10/2011, the TTC approach was applied to evaluate whether the estimated exposure to these substances remains below the respective TTC values. Finally, all substances were also investigated for their potential endocrine disrupting activity. Effectively, due to the lack of consensus in the scientific community regarding the existence and/or relevance of low-dose effects for endocrine disrupting chemicals, these effects are currently not considered in the TTC approach (EFSA/WHO, 2016). However, suspected endocrine disrupting activity at low doses was in fact the reason why BPA was prohibited to be used in PC baby bottles. Consequently, it was evaluated whether substances which have been reported to migrate from PC replacement baby bottles (Onghena et al. 2016) are included in lists of (suspected) EDs.

2. Materials and methods

2.1. Chemicals

An overview of the substances selected for the current study is included in Table 2 and 3. The substances were selected based on the publication of Onghena and colleagues (2016). For the 17 substances, migration was shown to be above the detection limit in the third migration solution of at least one of the 24 PC replacement baby bottles. An overview of the 24 baby bottles included in the present study is given in Table 1.

2.2. Safety assessment of substances included in Annex I of Regulation 10/2011

Four out of the 17 substances are included in Annex I of Regulation 10/2011. For all four substances, an SML is available and consequently, the concentration detected in the third

migration solution was compared to its respective SML for all 24 baby bottles. The SML indicates the maximum amount of a substance allowed to migrate into food and varies between "not detectable" to 60 mg/kg. An overview of the substances included in Annex I of Regulation 10/2011, their SML and the concentration detected in the third migration solution of all 24 baby bottles is presented in Table 2.

2.3. Evaluation of substances not included in Annex I of Regulation 10/2011

2.3.1. Identification of the TTC values

The TTC approach is designed as a decision tree based on structural alerts (SAs) for genotoxicity, neurotoxicity and Cramer classification (Cramer et al., 1978). Depending on the absence or presence of these SAs, different human exposure threshold values have been established below which there is considered to be a very low probability of an appreciable risk to human health. The TTC values proposed by EFSA are the following:

(i) 0.15 µg/person/day for substances with SA(s) for genotoxicity,

(ii) 18 µg/person/day for organophosphates and carbamates with anti-cholinesterase activity,

(iii) 90 µg/person/day for Cramer Class III and Cramer Class II substances,

(iv) 1800 µg/person/day for Cramer Class I substances (EFSA, 2012),

with Cramer Class I being substances with a low level of oral toxicity, Cramer Class II being substances with less innocuous structures than Class I but without structural features for toxicity as in Class III, and Cramer Class III being substances with complicated structures which show no strong initial impression of safety and may even suggest a significant toxicity.

Because these TTC values were established for adults with a body weight of 60 kg, they first had to be translated into values for infants. In the present study, exposure scenarios were investigated (see 2.3.2) for both infants of 3 and 7 kg, and consequently, values were calculated for these two weight groups (Table 3).

Importantly, the TTC approach cannot be applied for certain structural groups of substances, such as high potency carcinogens (i.e. aflatoxin-like, azoxy- or N-nitroso-compounds, benzidines, hydrazines), inorganic substances, metals and organometallics, proteins, steroids, substances that are known to bioaccumulate, nanomaterials, and radioactive substances. Therefore, before applying the TTC approach, each of these exclusion criteria was verified for the 13 substances not included in Annex I of Regulation 10/2011.

Next, the presence of SAs for genotoxic carcinogenicity was assessed by using the carcinogenicity (genotox and nongenotox) and mutagenicity rulebase by Instituto Superiore di Sanità (ISS) of the *in silico* rule-based program Toxtree (Benigni et al., 2008). An outcome of 'Yes' was considered as a positive prediction, whereas the outcome of 'No' was regarded as negative. Substances with SAs for genotoxic carcinogenicity were assigned the TTC value of 0.0075 µg/day or 0.0175 µg/day for infants of 3 kg and 7 kg, respectively. In case no SAs for genotoxic carcinogenicity were detected, the chemical structures of the substances were analysed in order to decide whether they belonged to the groups of organophosphates or carbamates. These neurotoxic substance groups are associated with a TTC value of 0.9 µg/day or 2.1 µg/day for infants of 3 kg and 7 kg, respectively. In case the substance was not an organophosphate nor a carbamate, the Cramer rules (with extensions) of the *in silico* software Toxtree was used to assign the substance to one of the 3 Cramer Classes. Substances of Cramer Class II and III are associated with a TTC value of 4.5 µg/day or 10.5 µg/day for infants of 3 kg and 7 kg, respectively, whereas substances of Cramer Class I had a TTC value of 90 µg/day or 210 µg/day for infants of 3 kg and 7 kg, respectively.

2.3.2. Calculation of the estimated exposure

For all 24 baby bottles, the exposure to each of the 13 substances was calculated based on the concentration detected in the third migration solution and the consumption values. First,

consumption for the Belgian infants was estimated using the data of "Kind en Gezin", a Flemish agency focusing on preventive treatment and guidance of young children (Kind en Gezin, 2016). Two exposure scenarios were selected:

Exposure scenario 1 (= 'worst-case exposure scenario'): Infants of 3 kg drinking a volume of 100 ml 6-7 times per day. This results in a maximal consumption of 233 mL kg^{-1} body weight (bw) day^{-1} or 700 ml day^{-1}.

Exposure scenario 2: Infants of 7 kg drinking a volume of 240 ml 5 times per day. This results in a maximal consumption of 171 mL kg^{-1} bw day^{-1} or 1200 ml day^{-1}.

Second, exposure was also calculated based on the consumption value for infants recently proposed by EFSA, i.e. 150 g kg^{-1} bw day^{-1} (EFSA, 2016), resulting in a third exposure scenario:

Exposure scenario 3: Infants of 3 kg drinking 150 g kg^{-1} bw day^{-1}. This results in a consumption of 450 ml day^{-1}.

2.3.3. Comparison of the estimated exposure to the TTC value

For all 24 baby bottles, the estimated exposure to each of the 13 substances was compared to its respective TTC value in the different exposure scenarios.

2.3.4. Refinement of the TTC approach

For the substances exceeding the TTC value in at least one of the 24 baby bottles, a more in-depth evaluation using available toxicity data was performed. In order to further investigate SAs for genotoxicity, information collected from the database of the European CHemicals Agency (ECHA), an additional *in silico* rule-based program (i.e. Derek Nexus™) and the *in vitro* genotoxicity test (Vitotox®) was used. A detailed description on how the information was collected and analysed is provided in Mertens et al, 2016. For the non-genotoxic

substances with exceeded TTC values, data were also collected in the database of ECHA and in literature by using PubMed and TOXNET.

2.4. Evaluation of the potential endocrine disrupting activity of all substances

For all 17 selected substances, the presence in different existing lists of (suspected) endocrine disrupting chemicals was verified.

EU Priority list: The EU priority list has been assembled by DG Environment of the EC. In a first step, a 'candidate' list was compiled containing 553 substances identified as 'suspected' ED. Based on scientific literature and quantitative structure-activity relationship (QSAR) tools substances included in this list were given a first score (I, II or III). In a second step, the substances of the candidate list were prioritized based on their persistence in the environment and on the production volume. This resulted in a new list with 146 'suspected' EDs being either persistent or produced in high volumes. Next, a more in depth analysis of the 146 compounds was performed in order to allocate them to one of the three following categories:

- Category 1: evidence of ED activity in at least one species using intact animals (# 66)
- Category 2: at least some *in vitro* evidence of biological activity related to ED activity (# 52)
- Category 3: no evidence of ED activity or no data available (# 28)

Most of the substances of category 1 and 2 (109 out of 118) were already subject to bans or restrictions or were being addressed under existing Community legislation although for reasons not necessarily related to endocrine disruption. For nine substances which were neither restricted nor addressed under existing Community legislation, an in-depth study was performed. Thus, for 118 out of the 553 substances of the candidate list, sufficient data to assess (potential) endocrine disruption were available. After 2000, a more detailed evaluation was done for the remaining 435 substances of the candidate list. Again, priority was assigned

to substances of high production volume, high persistence in the environment or high concern for exposure. After exclusion of substance groups, mixtures or polymers and duplicates (# 58), 204 (out of 435) substances were identified to be produced in high volumes and/or persistent and/or high exposure. These 204 substances were assigned to 1 of the 3 categories. The criteria of these categories slightly differed from the previous and are summarized below (RPS-BKH, 2002):

- Category 1: at least one study providing evidence of endocrine disruption in an intact organism. Not a formal weight of evidence approach (# 94).
- Category 2: potential for endocrine disruption. *In vitro* data indicating potential for endocrine disruption in intact organisms. Also includes effects *in vivo* that may, or may not, be ED-mediated. May include structural analyses and metabolic considerations (# 53).
- Category 3: this category was subdivided in (3a) No scientific basis for inclusion in list (ED studies available but no indications on ED effects) and (3b) Substances with no or insufficient data gathered (# 57).

Finally, the remaining 173 (out of 435) substances of the candidate list were evaluated in 2006. After the addition of some new substances and deletion of those not included in the ESIS database or without CAS number, 107 substances were retained for evaluation of which 34 were allocated in Category 1 (DHI, 2007). In total, 194 (66 + 94+ 34) substances were allocated to Category 1.

TEDX-list: The TEDX list contains about thousand compounds for which at least one verified, accessible, primary scientific publication is available describing endocrine disrupting effects *in vivo* and/or *in vitro* (TEDX list 2015). The database was set up and is maintained by the EndocrineDisruption Exchange, Paonia, CO, USA (Geueke, 2014).

SIN-list: The SIN (Substitute It Now!)-list 2.1 contains 844 substances and substance groups that were identified by the International Chemical Secretariat (ChemSec, Gothenburg, Sweden) to be of 'very high concern' based on the criteria established in article 57 of Regulation (EC) No. 1907/2006 (European Union, 2006). In addition to chemicals characterized as carcinogenic, mutagenic or toxic to reproduction (CMR), persistent, bioaccumulative and toxic (PBT), very persistent and very bioaccumulative (vPvB), the list contains a category of chemicals posing an 'equivalent environmental or health threat'. The latter includes besides chemicals that are less toxic, but highly bioaccumulative and/or persistent, also chemicals with endocrine disrupting properties (article 57(f), Regulation (EC) No. 1907/2006). Identification of chemicals as EDs by ChemSec was based on the criteria specified by the Danish Centre on Endocrine Disrupters (2012) (Geueke, 2014).

3. Results and discussion

Recent studies have shown that both substances included and substances not included in Annex I of Regulation 10/2011 can migrate from PC replacement baby bottles. More information on the potential impact of this migration on the health of infants is urgently needed. For the 17 substances selected based on the publication of Onghena et al. (2016), the potential health risks associated with their migration were investigated by applying a dual strategy depending on whether or not the substance is included in Annex I of Regulation 10/2011.

3.1. Evaluation of the potential health risks of substances included in Annex I of Regulation 10/2011

In all 24 baby bottles, migration of the 4 (out of 17) substances included in Annex I of Regulation 10/2011 was below their respective SML in the 3rd migration solution.

Consequently, no adverse health effects are expected due to migration of these substances from PC-replacement products (Table 2).

However, some important remarks need to be made. Specific European legislation exists only for plastic materials and articles in contact with food (i.e. EU Regulation 10/2011). As a result, the silicone baby bottle BB10 is not covered by a specific regulation, but only by the general provisions of European Regulation 1935/2004 which apply to all FCMs. However, the Council of Europe (CoE) has established general recommendations for various types of materials such as coatings (CoE, 2004a), inks (CoE, 2005), paper and board (CoE, 2002), rubber (CoE, 2004b), etc. These recommendations contain 'inventory lists' mentioning monomers, additives, solvents and other starting products, together with their toxicological evaluation - whenever this information is available. Such a Resolution is available for silicones in which 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (TXIB) is included in List 2 of the inventory list, meaning that the substance is not approved for the manufacture of materials and articles intended to come into contact with food (CoE, 2004c). However, two other substances included in Annex I of Regulation 10/2011 (i.e. dibutyl phthalate and benzophenone) were also found in the silicone baby bottle BB10. Although these substances are allowed to be used for the manufacture of plastic FCM, they are not present in the CoE Resolution on silicones (CoE, 2004c). One explanation for this discrepancy might be that the last update of the Resolution ResAP(2004)5 on silicones dates back to 2004. Since a Resolution of the CoE is a recommendation and thus not legally binding, the compliance of the silicone bottle cannot be evaluated. However, the results of this baby bottle were interpreted using EU Regulation 10/2011 as a reference.

According to EU Regulation 10/2011, the SML of TXIB is 5000 µg kg^{-1} with a restricted use to single-use gloves. Therefore, TXIB should not be present in the migration solution of the

plastic baby bottles. As illustrated in Table 2, TXIB has only been detected in BB10 made of silicone, with a concentration of 348 µg kg^{-1}. However, the restriction 'only to be used in single-use gloves' is the consequence of how the dossier of TXIB has been submitted to the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) of EFSA. Indeed, manufacturers need to make an official request to obtain a (re)-evaluation of a substance for the purpose of introducing it or changing its restriction in the respective European legislation. In the dossier of TXIB, the petitioner stated that TXIB would be used in plasticized PVC single use gloves for contact with food. Since the migration data in the dossier supported the use of TXIB in single use gloves, no interpretation could be made regarding other potential uses of the substance and thus a restricted use was proposed. However, toxicity data for TXIB could be found, both in the Scientific Opinion of the AFC panel (EFSA, 2006), and in a report of the Danish competent authority for the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (DEPA, 2011), and therefore, a (preliminary) assessment of the potential risks associated with migration of TXIB from the silicone baby bottle could be made. The lowest No Observed Adverse Effect level (NOAEL) reported by the Danish competent authority for REACH was 276 mg kg^{-1} bw day^{-1} based on the reproductive effects observed in a reproductive screening toxicity study in rats. In the Scientific Opinion of the AFC panel, a NOAEL of 150 mg kg^{-1} bw day^{-1} was determined in a 90 day oral feeding study in rats due to the presence of statistically significant increases in relative liver weights at the higher dose. For the present risk assessment, the lowest NOAEL was used, i.e. 150 mg kg^{-1} bw day^{-1}. Next, the exposure to TXIB due to migration from the silicone baby bottle was estimated. When applying the worst-case exposure scenario (scenario 1), the estimated exposure is 244 µg day^{-1} or 81 µg kg^{-1} bw day^{-1}. A margin of safety (MOS) of about 1850 between the NOAEL and the estimated exposure can be derived, which is thus much larger than the normally accepted MOS of 300. The latter consists of (i) a factor 10 to correct for interspecies differences, (ii) a factor 10 to correct for

intraspecies differences and (iii) a factor 3 to correct for gaps in toxicological knowledge (in this case the lack of a long-term toxicity studies and the limited (screening) data for fertility). Consequently, migration of TXIB from the silicone baby bottles is unlikely to cause adverse health effects.

Dibutyl phthalate is included in Annex I of EU Regulation 10/2011 with an SML expressed as the sum of many other plasticizers and a use that is restricted to plasticizers in repeated use materials and articles contacting non-fatty foods. The latter include food for which in migration testing only food simulants other than food simulants D1 (50% EtOH in water) or D2 (vegetable oil) are laid down in Table 2 of Annex V of EU Regulation 10/2011. The restricted use for dibutyl phthalate originates from an evaluation made by the AFC Panel of EFSA (EFSA, 2005). In its opinion, the AFC Panel had set a tolerable daily intake (TDI) of 0.01 mg kg^{-1} bw for dibutyl phthalate and estimated that the human exposure is in the same range as the TDI. Therefore, the EC considered it appropriate to restrict its use to those applications which do not significantly contribute to the total exposure. As a result, the use of dibutyl phthalate was restricted to non-fatty foods and therefore, this substances is not allowed to migrate from baby bottles since these FCM are intended to be in contact with milk which is simulated by simulant D1 (50% EtOH in water). In EU Regulation 10/2011, it is mentioned that for substances with an SML 'non-detectable', a detection limit of 10 µg kg^{-1} is applicable. The concentration of dibutyl phthalate detected in the 3rd migration solution, i.e. 5 ± 1.3 µg kg^{-1}, is lower than the above detection limit. However, in order to verify the compliance of the baby bottle with Regulation 10/2011, the migration of dibutyl phthalate in the 1st migration solution should be evaluated.

3.2. Evaluation of substances not included in Annex I of Regulation 10/2011

3.2.1. Application of the TTC approach

Substances not included in Annex I of EU Regulation 10/2011 should be assessed in accordance with internationally recognized scientific principles on risk assessment (Art. 19 of EU Regulation 10/2011) like the TTC approach. Therefore, the decision tree as proposed by EFSA was applied to allocate the appropriate TTC values to each of the 13 substances not included in Annex I of EU Regulation 10/2011. First the exclusion criteria were verified and it was concluded that the TTC decision tree was applicable to all substances. An overview of the information needed to apply the TTC decision tree, together with the corresponding TTC values is presented in Table 3.

Next, the TTC approach was applied using different exposure scenarios. A complete overview of the estimated daily intakes for all baby bottles according to the different exposure scenarios is given in the supplementary data. First, the results of the worst-case exposure scenario (scenario 1) are discussed. It is however important to note that for five baby bottles (i.e. BB03, BB04, BB13, BB23 and BB24), the 3rd migration solutions did not contain substances not included in Annex I of EU Regulation 10/2011. These baby bottles are thus considered to be of no concern for the substances investigated in this part of the study. An overview of the estimated daily intake for the migrating substances of the remaining 19 baby bottles according to the worst-case exposure scenario is presented in Table 4.

When applying the worst-case exposure scenario, exposure to all substances was estimated to be below their respective TTC value only for two baby bottles (i.e. BB01 and BB19). Like the five baby bottles for which the 3rd migration solution did not contain substances not included in Annex I of EU Regulation 10/2011, these two baby bottles are thus considered to be of no concern for the substances investigated in this part of the study. For the other 17 baby bottles,

the TTC value of at least one substance was exceeded implying that the safety of these baby bottles cannot be guaranteed.

3.2.2. Refinement of the TTC approach

It is important to note that the TTC approach is a rather conservative method and the TTC values may thus be much lower than the actual TDI. Furthermore, exposure scenario 1 was based on worst-case conditions, and consequently, exposure estimates could be further refined. For these reasons, the risks associated with the migration of the substances not included in Annex I of Regulation 10/2011 were investigated using both refined TTC values and estimated exposures.

Refinement of the TTC values

For the 8 substances exceeding their TTC value in the worst-case exposure scenario, more toxicological information was collected to investigate whether the TTC value is appropriate.

Benzaldehyde-related compounds

Four out of the eight substances for which the TTC value was exceeded in the worst-case exposure scenario, were benzaldehyde-related compounds i.e. 2,4,6-trimethylbenzaldehyde, 4-methylbenzaldehyde, 4-propylbenzaldehyde, and 3,4-dimethylbenzaldehyde. All four substances showed the same SA for genotoxic carcinogenicity in ToxTree, resulting in a TTC value of 0.0075 µg day^{-1}. In 16 baby bottles, this TTC value was exceeded for at least one benzaldehyde. Since the TTC value was based on a SA for genotoxicity, the genotoxic potential of the four substances was further investigated using additional information collected from the ECHA database, a second *in silico* rule-based program (i.e. Derek Nexus^{TM}) and an *in vitro* genotoxicity test (Vitotox$^{®}$). Based on these data and as discussed in detail in Mertens et al. (2016), *in vivo* genotoxicity of benzaldehydes is considered to be

rather unlikely and the TTC value for benzaldehydes of 0.0075 µg day^{-1} is thus probably too low. If benzaldehydes are considered not genotoxic in the TTC decision tree, the TTC value of all four substances increases to 90 µg day^{-1}. Indeed, the four benzaldehydes are not included in the neurotoxic groups of organophosphates or carbamates and are all assigned to Cramer class I. For all 16 baby bottles, the estimated exposure to one or more of the benzaldehydes is now below the TTC value of 90 µg day^{-1}. Migration of benzaldehydes from the 16 baby bottles for which the initial TTC value was exceeded will thus probably not result in an adverse health effect. However, since more data are needed to confirm the lack of genotoxicity of the four benzaldehydes, the baby bottles for which the estimated exposure to benzaldehydes was above the TTC value are still considered of concern.

3,5-Di-tert-butylbenzoquinone

For one baby bottle, the exposure to the substance 3,5-di-tert-butylbenzoquinone estimated in the worst-case exposure scenario exceeded the TTC value. Like the benzaldehyde-related compounds, this substance showed an SA for genotoxic carcinogenicity in ToxTree and consequently, its genotoxic potential was also further investigated. The substance also showed an SA for the endpoint '*in vitro* chromosome damage' in Derek Nexus™, but was negative in the Vitotox® test. Since the substance has not yet been registered under REACH, no genotoxicity data were found in the ECHA database (Mertens et al., 2016). A broader literature search did not yield any additional information on the genotoxic potential of the substance. At present, there are thus no data available that could justify an increase of the TTC value of 3,5-di-tert-butylbenzoquinone. In order to investigate the safety of the baby bottle from which 3,5-di-tert-butylbenzoquinone is released, more genotoxicity data on this substance are urgently needed, in particular data on chromosome damage, and therefore, the baby bottle is considered to be of high concern.

Dicyclopentyl(dimethoxy)silane and 4-phenylbenzophenone

Dicyclopentyl(dimethoxy)silane and 4-phenylbenzophenone did not show any SAs for genotoxic carcinogenicity or carbamate/organophosphate-induced neurotoxicity and were both assigned to Cramer Class III, resulting in a TTC value of 4.5 µg day^{-1}. For dicyclopentyl(dimethoxy)silane, the estimated exposure was above this value in five baby bottles. Dicyclopentyl(dimethoxy)silane has been registered under REACH, and consequently, toxicity data on the substance are available in the ECHA database. In a 28 day oral subchronic toxicity study in rats, no adverse effects were observed at the highest dose tested, and consequently a NOAEL of 1000 mg kg^{-1} bw day^{-1} was derived. The same NOAEL value was found in an oral prenatal developmental toxicity study in rats. Again, no adverse effects were observed at the highest dose tested, neither for maternal nor for developmental toxicity (ECHA, 2015). The MOS between the lowest NOAEL value of these toxicity studies (i.e. 1000 mg kg^{-1} bw day^{-1}), and the highest estimated exposure resulting from migration of dicyclopentyl(dimethoxy)silane from the tested baby bottles (i.e. 81.9 µg day^{-1} or 27.3 µg kg^{-1} bw day^{-1}), is 36630. This MOS is thus much larger than the generally accepted safety factor of 300. It is however important to note that information from the ECHA database should be interpreted with caution as the data are introduced by the registrant. Indeed, ECHA may examine any registration dossier to verify if the information submitted by registrants is compliant with the legal requirements, but these compliance checks are only required for 5% of the registration dossiers of each tonnage band. Additionally, an evaluation of certain substances is performed by the European Member States in order to clarify whether their use poses a risk to human health or the environment. Only for these substances, a thorough and critical study of the provided toxicity data is performed. Consequently, for most of the substances, including dicyclopentyl(dimethoxy)silane, the data provided by the registrant have not been evaluated independently. Although the MOS between the lowest NOAEL value of dicyclopentyl(dimethoxy)silane and the estimated exposure due to migration from each of

the five baby bottles is large, an independent evaluation of the toxicity data for dicyclopentyl(dimethoxy)silane is needed. Baby bottles for which the TTC value of dicylopentyl(dimethoxy)silane is exceeded are therefore considered still to be of concern.

For 4-phenylbenzophenone, the TTC value was exceeded only in 1 baby bottle. In contrast to dicyclopentyl(dimethoxy)silane, this substance has not been registered under REACH and toxicity data could thus not be found on the ECHA website. Furthermore, a broader literature search did not result in any toxicity data on the substance. Consequently, more toxicity data are needed to investigate whether migration of 4-phenylbenzophenone from the baby bottle is potentially associated with adverse health effects. The baby bottle for which the estimated exposure to 4-phenylbenzophenone was above the TTC value is thus considered of high concern.

2-Butoxyethyl acetate

2-Butoxyethyl acetate did not show any SAs for genotoxic carcinogenicity or carbamate/organophosphate-induced neurotoxicity either but, compared to the two previous substances, it was assigned to Cramer Class I. The substance thus received the highest TTC value, i.e. 90 µg day^{-1}. This high threshold was nevertheless exceeded for one baby bottle. 2-Butoxyethyl acetate has been registered under REACH and therefore, toxicity data are included in the ECHA database. These toxicity data are based on read-across with 2-butoxyethanol since 2-butoxyethyl acetate is rapidly metabolized in the body. Importantly, no NOAEL could be established for 2-butoxyethanol in a 90 day oral subchronic toxicity study due to cystoplasmic alterations observed in liver histopathology of both males and females rats at the lowest dose tested. Benchmark analysis of the results indicated a benchmark dose level 10 (BMDL10) of 27 and 20 mg kg^{-1} bw day^{-1} in males and females, respectively. In an oral two-generation study in mice, effects of 2-butoxyethanol on fertility were only observed at doses which were severely toxic to the animals (1340 and 2050 mg kg^{-1} bw day^{-1}). A

NOAEL of 720 mg kg^{-1} bw day^{-1} was identified for reproductive toxicity by oral route in mice. For developmental toxicity, effects were observed at all doses tested. However, since at the lowest dose studied, the only effect was a marginal statistically significant reduction in pup weight which was not repeated in the second generation, the NOAEL for developmental toxicity was also set at 720 mg kg^{-1} bw day^{-1}. Finally, in a prenatal developmental toxicity study in rats, the NOAEL for developmental toxicity was set at 100 mg kg^{-1} for 2-butoxyethanol. However, the developmental toxicity was considered to be secondary to the marked maternal toxicity observed at doses of 100 mg kg^{-1} including body weight gain reductions, organ weight changes and severe haemotoxicity. These toxicity data were used to evaluate the potential health risks associated with migration of 2-butoxyethyl acetate from the baby bottle. Since in the subchronic toxicity study no NOAEL could be established for 2-butoxyethanol, the BMDL10 was used. On a molar basis, the BMDL10 for 2-butoxyethanol needed to be increased by a factor of 1.36 in order to derive the BMDL10 for 2-butoxyethyl acetate resulting in values of 36.72 and 27.4 mg kg^{-1} bw day^{-1} for males and females respectively. Exposure to 2-butoxyethyl acetate due to migration from the baby bottle was compared to the lowest BMDL10 value in order to calculate the margin of exposure (MOE). This resulted in a MOE of 125 indicating that the daily exposure to 2-butoxyethyl acetate is 125 times lower than the dose associated with a 10% increased incidence of the effect over background (or control data). The MOE is thus smaller than the generally accepted factor of 300. In the present study, a baby bottle for which the estimated exposure to 2-butoxyethyl acetate was above the TTC value is therefore considered of high concern.

Safety assessment of the baby bottles according to the worst-case exposure scenario

A final call on the safety of the PC replacement baby bottles was made by combining the assessment results of the different substances detected in the 3rd migration solution which were not included in Annex I of the Regulation 10/2011. An overview is given in Table 5. For

each baby bottle, the final call was determined by the substance that received the highest level of concern for that baby bottle. For example, for BB25, five substances not included in Annex I of Regulation 10/2011 were detected in the 3rd migration solution. According to the worst-case exposure scenario, the TTC value of four of these substances was exceeded. After a more detailed evaluation, migration of three of these substances was considered to be of concern. However, as migration of the fourth substance could be of high concern, the baby bottle was considered to be of high concern.

Refinement of the exposure calculations

Up till now, the estimated daily intake has been determined according to the worst-case exposure scenario (i.e. exposure scenario 1: infants of 3 kg drinking 700 mL day-1 according to "Kind en Gezin"). However, other exposure scenarios could be considered. For example, according to "Kind en Gezin", an infant of 7 kg consumes 1200 mL day^{-1} (i.e. exposure scenario 2) or the guidelines of EFSA, i.e. 150 g kg^{-1} bw day-1 (EFSA, 2016) for infants of 3 kg, resulting in a consumption of 450 mL day^{-1} for infants of 3 kg (i.e. exposure scenario 3). For exposure scenario 2 including infants of 7 kg, similar results were found to those of the worst-case exposure scenario. Indeed, TTC values were exceeded in the same 17 baby bottles for the same substance(s). However, compared to the worst-case exposure scenario, the ratio between the estimated daily intake and the TTC value was lower as infants of 7 kg consume relatively less food per kg bw than infants of 3 kg. In exposure scenario 3, the TTC value for dicyclopentyl(dimethoxy)silane was only exceeded for 4 instead of 5 baby bottles. Furthermore, the daily estimated intake of 4-phenylbenzophenone was now below the TTC value for all baby bottles. Compared to the worst-case exposure scenario, the ratio between the estimated daily intake and the TTC value was again lower due to the fact that according to the EFSA opinion, consumption in infants of 3 kg is estimated to be lower than the data of 'Kind en Gezin'. Again, a final call on the safety of the PC replacement baby bottles was

made by combining the assessment results of the different substances detected in the 3rd migration solution which were not included in Annex I of the Regulation 10/2011. As a result, one additional baby bottle (BB21) was no longer of high concern since the exposure of 4-phenylbenzophenone no longer exceeded the corresponding TTC value. All other baby bottles remained at the same level of concern compared to the worst case exposure scenario (e.i. scenario 1).

Strengths and limitations

By applying the TTC approach, three baby bottles of high concern could be identified in the worst-case exposure scenario. For these baby bottles, more data on the substances for which the TTC value was exceeded are urgently needed. It is however important to note that in the present study, extrapolation of the TTC values of adults weighing 60 kg to infants weighing 3 and 7 kg was solely based on a linear calculation taking into account the change in body weight. Ideally, differences in toxicokinetic parameters between adults and young children should be considered as well. Very young infants might be a particularly sensitive subgroup because their metabolic capacities are not yet fully developed (WHO, 2011). However, toxicokinetic differences between young infants and children or adults are transient and generally not more than 2- to 5-fold. Particularly when exposures are low, there is thus capacity in the first weeks of life to metabolize and eliminate chemicals. Therefore, the EFSA concluded that the TTC approach can be applied to assess exposures in young infants although additional consideration needs to be given in cases where the estimated exposure is in the range of the TTC values (EFSA/WHO, 2016). Furthermore, the TTC values for non-genotoxic and non-neurotoxic Cramer class I and Cramer classes II and III substances are based on NOAEL values from repeated dose toxicity studies. In most cases, the NOAEL for chronic toxicity was derived by applying a conversion factor to the NOAEL obtained in subchronic toxicity studies (EFSA, 2012). Exposure to substances migrating from PC

replacement baby bottles will only occur during a limited period of human life. The TTC values may thus contain an additional safety factor when applying the TTC approach for the preliminary safety assessment of baby bottles. However, baby bottles are used in a very early life stage during which organs and tissues are still in full development. Consequently, exposure to the substances migrating from baby bottles occurs during a limited but critical period of human life. At present, no toxicity studies that have been specifically designed to evaluate adverse health effects of substances during these life stages, are yet available. Consequently, these effects – if present – cannot be taken into account. Finally, it should be noted that in the present study, the TTC approach was applied on the individual substances and not on the complete 'mixture' of substances migrating from PC replacement baby bottles. The different substances in this mixture had diverse structures and characteristics, and consequently a dose addition approach could not be applied (EFSA/WHO, 2016). Additional methodological refinements are required to evaluate these mixture effects but these fell outside of the scope of the present study.

3.3. Evaluation of the potential endocrine disrupting activity of all substances

Importantly, the TTC approach does not take into account possible low-dose effects for EDs due to the lack of consensus in the scientific community regarding the existence and/or relevance of this type of effects. Since the use of BPA in PC baby bottles was forbidden based on its endocrine disrupting characteristics, all substances for which migration had been quantified in at least one baby bottle were also evaluated for endocrine disruptive activity by using different existing lists of (suspected) endocrine disrupting chemicals. Two out of the 17 substances, i.e. 4-tert-octylphenol and dibutyl phthalate, were found in category 1 of the EU priority list, indicating that there is evidence of endocrine disrupting activity in at least one species using intact animals. Dibutyl phthalate has been shown to migrate from two baby bottles, whereas for 4-tert-octylphenol migration was only observed for one baby bottle.

Although there is still an ongoing debate on low-dose effects of EDs, these three baby bottles are considered of high concern as they release substances which have, like BPA, recognized endocrine disruptive properties.

In addition, two of the 17 substances can be considered as 'suspected' EDs, i.e. benzophenone and diisobutyl phthalate. Both substances were not identified as (suspected) EDs by the EC in 2000 (RPS-BKH, 2002) but were nevertheless included in the TEDX-list and the SIN-list. Later, the EC allocated benzophenone to category 3 in 2000 and in 3b in 2002, meaning that insufficient data were available. Diisobutyl phthalate was evaluated in 2006 as the substance was not produced in high volumes (HPV), not persistent and no high exposure was expected. Based on this evaluation, diisobutyl phthalate was classified in category 2, thus being a potential ED. Benzophenone was shown to migrate from four baby bottles, whereas diisobutyl phthalate only migrated from one. Although the indications for endocrine disrupting activity of benzophenone and diisobutyl phthalate appear to be weaker than those for 4-tert-octylphenol and dibutyl phthalate, baby bottles showing migration of these substances should also be further investigated and are therefore considered of concern.

Safety assessment of the baby bottles based on the migration of (suspected) EDs

A final call on the safety of the PC replacement baby bottles was made based on the potential endocrine activity of substances that were detected in the 3rd migration solution. An overview is given in Table 6. For each baby bottle, the final call was determined by the substance that received the highest level of concern for that baby bottle. For example, for BB10, two (suspected) EDs were detected in the 3rd migration solution. Migration of one substance was considered to be of concern, whereas migration of the other was considered to be of high concern. Therefore, the baby bottle received a final call of 'high concern'.

4. Conclusions

The information obtained within the different parts of the study [comparison with SML, application of (refined) TTC approach and inclusion in lists of (suspected) EDs] was combined in order to evaluate the potential risks associated with the 24 baby bottles collected on the Belgian Market. Six baby bottles were considered of no concern for the substances investigated as exposure to all substances was estimated to be below their respective TTC value and they did not release recognized or potential EDs. Five out of these 24 baby bottles were considered of high concern (Table 7). For two of them, the high level of concern was based on the lack of toxicity data to show that the exceeding of the TTC value was not associated with adverse health effects. For two other baby bottles, the high level of concern was triggered by the presence of substances that are recognized EDs. The fifth baby bottle of high concern released both a genotoxic compound for which the TTC value was exceeded and a recognized ED. For these five baby bottles, additional toxicological data are thus urgently needed in order to further investigate their safety. Migration from the remaining 13 baby bottles will probably not result in adverse health effects, but since additional data are needed to confirm the safety of the baby bottles, they were considered to be of concern.

The results of the present study indicate that the TTC approach, in particular in combination with additional toxicological information, can be an important tool to assign priority to baby bottles of potential concern. Importantly, the presented approach might also have applications in other domains, including those outside the field of FCMs.

5. Conflict of Interest

The authors declare that there are no conflicts of interest.

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Table captions

Table 1
Overview of the baby bottles selected for the migration experiments and their corresponding material.

Table 2

Overview of the substances included in Annex I of Regulation 10/2011, their corresponding SML for baby bottles and the concentration detected in the 3rd migration solution. Only the information of baby bottles for which at least one substance included in Annex I of EU Regulation 10/2011 was detected in the 3rd migration solution is shown.

Table 3

Application of the TTC decision tree on the substances not included in Annex I of EU Regulation 10/2011 and their corresponding TTC values for infants of 3 and 7 kg.

Table 4

Overview of the substances not included in Annex I of EU Regulation 10/2011, their corresponding TTC value and estimated daily intake according to the worst-case exposure scenario (exposure scenario 1). Only the baby bottles for which at least one of the substances was present in the 3rd migration solutions are included.
Bold: Substance exceeding the TTC value.

Table 5

Final call on the safety of the PC replacement baby bottles obtained by combining the results of the (refined) TTC approach for the substances not included in Annex I of Regulation 10/2011 that were detected in the 3rd migration solution (worst-case exposure scenario).

Table 6

Final call on the safety of the PC replacement baby bottles based on the potential endocrine activity of substances that were detected in the 3rd migration solution.

Table 7

Overview of the baby bottles of high concern.

Table 1

Material	Baby bottle
PP	BB02, BB05, BB07, BB08, BB09, BB11, BB12, BB17, BB18, BB19, BB20, BB21, BB22, BB24, BB25, BB26, BB27
PA	BB03, BB23
Silicone	BB10
Tritan™	BB06
PES	BB01, BB04
Stainless Steel	BB13

Table 2

Name	CAS-number	SML (µg kg^{-1})	Concentration detected in the 3rd migration solution (µg kg^{-1}) (Onghena et al., 2016)						
			BB03 (PA)	**BB05** (PP)	**BB10** (Silicone)	**BB12** (PP)	**BB18** (PP)	**BB19** (PP)	**BB23** (PA)
azacyclotridecan-2-one	947-04-6	5000	924±93	-	-	-	-	-	1091± 109
TXIB	6846-50-0	5000[a]	-	-	348*	-	-	-	-
Benzophenone	119-61-9	600	-	14±3	9±2	97±23	35±8	-	-
Dibutyl phthalate	84-74-2	300[b]	-	-	11±3	-	-	5±1.3	-

[a] Only to be used in single-use gloves.
[b] Only to be used as plasticizer in repeated use materials and articles contacting non-fatty foods.

Table 3

Substance	Application of the TTC decision tree			Allocated TTC values (µg day^{-1})	
	SA for genotoxic carcinogenicity?	Organophosphate or carbamate?	Cramer classification	Infants – 3kg	Infants – 7 kg
Acetophenone	No	No	I	90	210
2-Butoxyethyl acetate	No	No	I	90	210
Dicyclopentyl(dimethoxy)silane	No	No	III	4.5	10.5
Diisobutyl phthalate	No	No	I	90	210
3,4-Dimethylbenzaldehyde	Yes	No	I	0.0075	0.0175
2,4-Di-tert-butylphenol	No	No	I	90	210
3,5-Di-tert-butylbenzoquinone	Yes	No	II	0.0075	0.0175
4-Methylbenzaldehyde	Yes	No	I	0.0075	0.0175
Methyl oleate	No	No	I	90	210
4-Phenylbenzophenone	No	No	III	4.5	10.5
4-Propylbenzaldehyde	Yes	No	I	0.0075	0.0175
4-tert-Octylphenol	No	No	I	90	210
2,4,6-Trimethylbenzaldehyde	Yes	No	I	0.0075	0.0175

Table 4

Name	CAS-number	Estimated daily intake (µg day^{-1})																			
		TTC (µg day^{-1})	**BB01** (PES)	**BB02** (PP)	**BB05** (PP)	**BB06** (Tritan™)	**BB07** (PP)	**BB08** (PP)	**BB09** (PP)	**BB10** (Silicone)	**BB11** (PP)	**BB12** (PP)	**BB17** (PP)	**BB18** (PP)	**BB19** (PP)	**BB20** (PP)	**BB21** (PP)	**BB22** (PP)	**BB25** (PP)	**BB26** (PP)	**BB27** (PP)
Acetophenone	98-86-2	90	2.1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2.1	-	-
2-Butoxyethyl acetate	112-07-2	90	-	10.5	15.4	-	-	-	-	-	-	-	-	-	31.5	-	-	-	**662**	-	-
Dicyclopentyl(dimethoxy)silane	126990-35-0	4.5	-	-	-	**7**	**21.7**	**81.9**	-	-	-	-	0.7	-	-	**6.3**	-	-	**9.1**	3.5	0.7
Diisobutyl phthalate	84-69-5	90	-	-	-	-	-	-	-	10.5	-	-	-	-	-	-	-	-	-	-	-
3,4-Dimethylbenzaldehyde	5973-71-7	0.0075	-	**41.3**	-	-	-	-	**7.7**	**10.5**	-	-	**9.1**	-	-	**9.1**	-	**4.2**	**37.1**	**4.2**	**4.2**
2,4-Di-tert-butylphenol	96-76-4	90	-	8.4	-	5.6	50.4	-	-	-	8.4	-	-	-	-	82.6	-	-	-	-	-
3,5-Di-tert-butylbenzoquinone	719-22-2	0.0075	-	-	-	-	-	-	-	**5.6**	-	-	-	-	-	-	-	-	-	-	-
4-Methylbenzaldehyde	104-87-0	0.0075	-	-	**22.4**	-	-	-	-	-	-	-	**2.8**	-	-	-	-	-	**18.2**	-	-
Methyl oleate	112-62-9	90	-	-	-	-	-	-	-	-	-	-	23.8	-	-	-	-	-	-	-	-
4-Phenylbenzophenone	2128-93-0	4.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**4.9**	-	-	-	-
4-Propylbenzaldehyde	28785-06-0	0.0075	-	-	**14**	**18.9**	**8.4**	**7.7**	-	**0.7**	**11.9**	**7.7**	-	**2.1**	-	-	-	-	-	-	-
4-tert-Octylphenol	140-66-9	90	-	-	-	-	4.9	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2,4,6-Trimethylbenzaldehyde	487-68-3	0.0075	-	-	**3.5**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 5

Level of concern	Baby bottle	Reason of concern
No concern	BB03, BB04, BB13, BB23, BB24	No migration of substances not included in Annex I of EU Regulation 10/2011 detected in the 3rd migration solution.
	BB01, BB19	TTC value was not exceeded for any of the substances not included in Annex I of EU Regulation 10/2011 and detected in the 3rd migration solution.
Concern	BB02, BB05, BB06, BB07, BB08, BB09, BB11, BB12, BB17, BB18, BB20, BB22, BB26, BB27	TTC value was exceeded for at least one of the substances not included in Annex I of EU Regulation 10/2011 and detected in the 3rd migration solution AND Data available indicating that estimated exposure is not associated with potential adverse health effects.
High concern	BB10, BB21, BB25	TTC value was exceeded for at least one of the substances not included in Annex I of EU Regulation 10/2011 and detected in the 3rd migration solution AND Insufficient data available to guarantee that estimated exposure is not associated with adverse health effects.

Table 6

Level of concern	Baby bottle	Reason of concern
No concern	BB01, BB02, BB03, BB04, BB06, BB08, BB09, BB11, BB13, BB17, BB20, BB21, BB22, BB23, BB24, BB25, BB26, BB27	No migration of substances included in any of the lists of suspected EDs detected in the 3rd migration solution.
Concern	BB05, BB12, BB18	Migration of 'suspected' ED detected in the 3rd migration solution.
High concern	BB07, BB10, BB19	Migration of recognized ED detected in the 3rd migration solution.

Table 7

Baby bottle	Substance(s) of concern	Reason of concern
BB07	4-tert-Octylphenol	Recognized ED
BB10	3,5-Di-tert-butylbenzoquinone	TTC value exceeded
	Dibutyl phthalate	Recognized ED
BB19	Dibutyl phthalate	Recognized ED
BB21	4-Phenylbenzophenone	TTC value exceeded
BB25	2-Butoxyethyl acetate	TTC value exceeded

Supplementary data

Table 1: Overview of the substances not included in Annex I of Regulation 10/2011, their corresponding TTC value and the estimated daily intake according to the 'worst case exposure scenario' (exposure scenario 1) for all baby bottles. **Bold**: Substance exceeding the TTC value.

Name	**CAS No.**	**TTC (µg day^{-1})**	**Estimated daily intake (µg day^{-1}) – Worst case scenario***											
			BB01 PES	**BB02** PP	**BB03** PA	**BB04** PES	**BB05** PP	**BB06** Tritan	**BB07** PP	**BB08** PP	**BB09** PP	**BB10** Silicone	**BB11** PP	**BB12** PP
Acetophenone	98-86-2	90	2.1	0	-	-	-	-	-	-	-	-	-	-
2-Butoxyethyl acetate	112-07-2	90	-	10.5	-	-	15.4	-	-	-	-	-	-	-
Dicyclopentyl(dimethoxy)silane	126990-35-0	4.5	-	-	-	-	-	**7**	**21.7**	**81.9**	-	-	-	-
Diisobutyl phthalate	84-69-5	90	-	-	-	-	-	-	-	-	-	10.5	-	-
3,4-dimethylbenzaldehyde	5973-71-7	0.0075	-	**41.3**	-	-	-	-	-	-	7.7	10.5	-	-
2,4-Di-tert-butylphenol	96-76-4	90	-	8.4	-	-	-	5.6	50.4	-	-	-	8.4	-
3,5-Di-tert-butylbenzoquinone	719-22-2	0.0075	-	-	-	-	-	-	-	-	-	**5.6**	-	-
4-Methylbenzaldehyde	104-87-0	0.0075	-	-	**-**	**-**	**22.4**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Methyl oleate	112-62-9	90	-	-	-	-	-	-	-	-	-	-	-	-
4-Phenylbenzophenone	2128-93-0	4.5	-	-	-	-	-	-	-	-	-	-	-	-
4-Propylbenzaldehyde	28785-06-0	0.0075	-	-	**-**	**-**	**14**	**18.9**	**8.4**	**7.7**	**-**	**0.7**	**11.9**	**7.7**
4-tert-octylphenol	140-66-9	90	-	-	-	-	-	-	4.9	-	-	-	-	-
2,4,6-trimethylbenzaldehyde	487-68-3	0.0075	-	-	**-**	**-**	**3.5**	**-**	**-**	**-**	**-**	**-**	**-**	**-**

* Worst case exposure scenario = Quantity and frequency that an infant of 3 kg should be fed according to Kind en Gezin.

Table 1 (continued): Overview of the substances not included in Annex I of Regulation 10/2011, their corresponding TTC value and the estimated daily intake according to the 'worst case exposure scenario' (exposure scenario 1) for all baby bottles. Bold: Substance exceeding the TTC value.

Name	**CAS No.**	**TTC (µg day^{-1})**	**Estimated daily intake (µg day^{-1}) – Worst case scenario***											
			BB13 Steel	**BB17** PP	**BB18** PP	**BB19** PP	**BB20** PP	**BB21** PP	**BB22** PP	**BB23** PA	**BB24** PP	**BB25** PP	**BB26** PP	**BB27** PP
Acetophenone	98-86-2	90	-	-	-	-	-	-	-	-	-	2.1	-	-
2-Butoxyethyl acetate	112-07-2	90	-	-	-	31.5	-	-	-	-	-	**666.2**	-	-
Dicyclopentyl(dimethoxy)silane	126990-35-0	4.5	-	0.7	-	-	**6.3**	-	**-**	**-**	-	**9.1**	3.5	**0.7**
Diisobutyl phthalate	84-69-5	90	-	-	-	-	-	-	-	-	-	-	-	-
3,4-dimethylbenzaldehyde	5973-71-7	0.0075	-	**9.1**	**-**	**-**	**9.1**	**-**	**4.2**	**-**	**-**	**37.1**	**4.2**	**4.2**
2,4-Di-tert-butylphenol	96-76-4	90	-	-	-	-	82.6	-	-	-	-	-	-	-
3,5-Di-tert-butylbenzoquinone	719-22-2	0.0075	-	-	-	-	-	-	-	-	-	-	-	-
4-Methylbenzaldehyde	104-87-0	0.0075	**-**	**2.8**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**18.2**	**-**	**-**
Methyl oleate	112-62-9	90	-	23.8	-	-	-	-	-	-	-	-	-	-
4-Phenylbenzophenone	2128-93-0	4.5	-	-	-	-	-	**4.9**	-	-	-	-	-	-
4-Propylbenzaldehyde	28785-06-0	0.0075	**-**	**-**	**2.1**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
4-tert-octylphenol	140-66-9	90	-	-	-	-	-	-	-	-	-	-	-	-
2,4,6-trimethylbenzaldehyde	487-68-3	0.0075	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**

* Worst case exposure scenario = Quantity and frequency that an infant of 3 kg should be fed according to Kind en Gezin.

Table 2: Overview of the substances not included in Annex I of Regulation 10/2011, their corresponding TTC value and the estimated daily intake according to exposure scenario 2 for all baby bottles. **Bold**: Substance exceeding the TTC value.

Name	**CAS No.**	**TTC ($\mu g\ day^{-1}$)**	**Estimated daily intake ($\mu g\ day^{-1}$) – Exposure scenario 2***											
			BB01 PES	**BB02** PP	**BB03** PA	**BB04** PES	**BB05** PP	**BB06** Tritan	**BB07** PP	**BB08** PP	**BB09** PP	**BB10** Silicone	**BB11** PP	**BB12** PP
Acetophenone	98-86-2	210	3.6	0	-	-	-	-	-	-	-	-	-	-
2-Butoxyethyl acetate	112-07-2	210	-	18	-	-	26.4	-	-	-	-	-	-	-
Dicyclopentyl(dimethoxy)silane	126990-35-0	10.5	-	-	-	-	-	**12**	**37.2**	**140.4**	-	-	-	-
Diisobutyl phthalate	84-69-5	10.5	-	-	-	-	-	-	-	-	-	18	-	-
3,4-dimethylbenzaldehyde	5973-71-7	0.0175	-	**70.8**	-	-	-	-	-	-	13.2	18	-	-
2,4-Di-tert-butylphenol	96-76-4	210	-	14.4	-	-	-	9.6	86.4	-	-	-	14.4	-
3,5-Di-tert-butylbenzoquinone	719-22-2	0.0175	-	-	-	-	-	-	-	-	-	**9.6**	-	-
4-Methylbenzaldehyde	104-87-0	0.0175	-	-	**-**	**-**	**38.4**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Methyl oleate	112-62-9	210	-	-	-	-	-	-	-	-	-	-	-	-
4-Phenylbenzophenone	2128-93-0	10.5	-	-	-	-	-	-	-	-	-	-	-	-
4-Propylbenzaldehyde	28785-06-0	0.0175	-	-	**-**	**-**	**24**	**32.4**	**14.4**	**13.2**	**-**	**1.2**	**20.4**	**13.2**
4-tert-octylphenol	140-66-9	210	-	-	-	-	-	-	8.4	-	-	-	-	-
2,4,6-trimethylbenzaldehyde	487-68-3	0.0175	-	-	**-**	**-**	**6.0**	**-**	**-**	**-**	**-**	**-**	**-**	**-**

* Exposure scenario 2 = Quantity and frequency that an infant of 7 kg should be fed according to Kind en Gezin.

Table 2 (Continued): Overview of the substances not included in Annex I of Regulation 10/2011, their corresponding TTC value and the estimated daily intake according to exposure scenario 2 for all baby bottles. **Bold**: Substance exceeding the TTC value (Continued)

Name	**CAS No.**	**TTC ($\mu g\ day^{-1}$)**	**Estimated daily intake ($\mu g\ day^{-1}$) – Exposure scenario 2***											
			BB13 Steel	**BB17** PP	**BB18** PP	**BB19** PP	**BB20** PP	**BB21** PP	**BB22** PP	**BB23** PA	**BB24** PP	**BB25** PP	**BB26** PP	**BB27** PP
Acetophenone	98-86-2	210	-	-	-	-	-	-	-	-	-	3.6	-	-
2-Butoxyethyl acetate	112-07-2	210	-	-	-	54	-	-	-	-	-	**1135.2**	-	-
Cedrol	77-53-2	10.5	-	-	-	-	-	-	-	-	-	-	-	-
Dicyclopentyl(dimethoxy)silane	126990-35-0	10.5	-	1.2	-	-	**10.8**	-	**-**	**-**	-	**15.6**	6.0	**1.2**
Diisobutyl phthalate	84-69-5	10.5	-	-	-	-	-	-	-	-	-	-	-	-
2,6-Diisopropylnaphthalene	24157-81-1	10.5	-	-	-	-	-	-	-	-	-	-	-	-
3,4-dimethylbenzaldehyde	5973-71-7	0.0175	-	**15.6**	**-**	**-**	**15.6**	**-**	**7.2**	**-**	**-**	**63.6**	**7.2**	**7.2**
2,4-Di-tert-butylphenol	96-76-4	210	-	-	-	-	141.6	-	-	-	-	-	-	-
3,5-di-tert-Butyl-4-hydroxybenzaldehyde	1620-98-0	0.0175	-	-	-	-	-	-	-	-	-	-	-	-
3,5-Di-tert-butylbenzoquinone	719-22-2	0.0175	-	-	-	-	-	-	-	-	-	-	-	-
4-Methylbenzaldehyde	104-87-0	0.0175	**-**	**4.8**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**31.2**	**-**	**-**
Methyl oleate	112-62-9	210	-	40.8	-	-	-	-	-	-	-	-	-	-
4-Phenylbenzophenone	2128-93-0	10.5	-	-	-	-	-	8.4	-	-	-	-	-	-
4-Propylbenzaldehyde	28785-06-0	0.0175	**-**	**-**	**3.6**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Oxacyclotridecan-2-one	947-05-7	210	-	-	-	-	-	-	-	-	-	-	-	-
4-tert-octylphenol	140-66-9	210	-	-	-	-	-	-	-	-	-	-	-	-
2,4,6-trimethylbenzaldehyde	487-68-3	0.0175	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
2-Undecanone	112-12-9	10.5	-	-	-	-	-	-	-	-	-	-	-	-
4-n-Nonylphenol	136-83-4	10.5	-	-	-	-	-	-	-	-	-	-	-	-

* Exposure scenario 2 = Quantity and frequency that an infant of 7 kg should be fed according to Kind en Gezin.

Table 3: Overview of the substances not included in Annex I of Regulation 10/2011, their corresponding TTC value and the estimated daily intake according to exposure scenario 3 for all baby bottles. **Bold**: Substance exceeding the TTC value.

Name	**CAS No.**	**TTC (µg day^{-1})**	**Estimated daily intake (µg day^{-1}) – Exposure scenario 3***											
			BB01 PES	**BB02** PP	**BB03** PA	**BB04** PES	**BB05** PP	**BB06** Tritan	**BB07** PP	**BB08** PP	**BB09** PP	**BB10** Silicone	**BB11** PP	**BB12** PP
Acetophenone	98-86-2	90	1.35	0	-	-	-	-	-	-	-	-	-	-
2-Butoxyethyl acetate	112-07-2	90	-	6.75	-	-	9.9	-	-	-	-	-	-	-
Dicyclopentyl(dimethoxy)silane	126990-35-0	4.5	-	-	-	-	-	**4.5**	**13.95**	**52.65**	-	-	-	-
Diisobutyl phthalate	84-69-5	4.5	-	-	-	-	-	-	-	-	-	6.75	-	-
3,4-dimethylbenzaldehyde	5973-71-7	0.0075	-	**26.55**	-	-	-	-	-	-	4.95	6.75	-	-
2,4-Di-tert-butylphenol	96-76-4	90	-	5.4	-	-	-	3.6	32.4	-	-	-	5.4	-
3,5-Di-tert-butylbenzoquinone	719-22-2	0.0075	-	-	-	-	-	-	-	-	-	**3.6**	-	-
4-Methylbenzaldehyde	104-87-0	0.0075	-	-	**-**	**-**	**14.4**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Methyl oleate	112-62-9	90	-	-	-	-	-	-	-	-	-	-	-	-
4-Phenylbenzophenone	2128-93-0	4.5	-	-	-	-	-	-	-	-	-	-	-	-
4-Propylbenzaldehyde	28785-06-0	0.0075	-	-	**-**	**-**	**9**	**12.15**	**5.4**	**4.95**	**-**	**0.45**	**7.65**	**4.95**
4-tert-octylphenol	140-66-9	90	-	-	-	-	-	-	3.15	-	-	-	-	-
2,4,6-trimethylbenzaldehyde	487-68-3	0.0075	-	-	**-**	**-**	**2.5**	**-**	**-**	**-**	**-**	**-**	**-**	**-**

* Exposure scenario 3 = Quantity and frequency that an infant of 3 kg should be fed according to EFSA (EFSA, 2016).

Table 3 (Continued): Overview of the substances not included in Annex I of Regulation 10/2011, their corresponding TTC value and the estimated daily intake according to exposure scenario 3 for all baby bottles. **Bold**: Substance exceeding the TTC value.

Name	**CAS No.**	**TTC (µg day^{-1})**	**Estimated daily intake (µg day^{-1}) – Exposure scenario 3***											
			BB13 Steel	**BB17** PP	**BB18** PP	**BB19** PP	**BB20** PP	**BB21** PP	**BB22** PP	**BB23** PA	**BB24** PP	**BB25** PP	**BB26** PP	**BB27** PP
Acetophenone	98-86-2	90	-	-	-	-	-	-	-	-	-	1.35	-	-
2-Butoxyethyl acetate	112-07-2	90	-	-	-	20.25	-	-	-	-	-	**425.7**	-	-
Dicyclopentyl(dimethoxy)silane	126990-35-0	4.5	-	0.45	-	-	**4.05**	-	**-**	**-**	-	**5.85**	2.25	**0.45**
Diisobutyl phthalate	84-69-5	90	-	-	-	-	-	-	-	-	-	-	-	-
3,4-dimethylbenzaldehyde	5973-71-7	0.0075	-	**5.85**	**-**	**-**	**5.85**	**-**	**2.7**	**-**	**-**	**23.85**	**2.7**	**2.7**
2,4-Di-tert-butylphenol	96-76-4	90	-	-	-	-	53.1	-	-	-	-	-	-	-
3,5-Di-tert-butylbenzoquinone	719-22-2	0.0075	-	-	-	-	-	-	-	-	-	-	-	-
4-Methylbenzaldehyde	104-87-0	0.0075	**-**	**1.8**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**11.7**	**-**	**-**
Methyl oleate	112-62-9	90	-	15.3	-	-	-	-	-	-	-	-	-	-
4-Phenylbenzophenone	2128-93-0	4.5	-	-	-	-	-	3.15	-	-	-	-	-	-
4-Propylbenzaldehyde	28785-06-0	0.0075	**-**	**-**	**1.35**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
4-tert-octylphenol	140-66-9	90	-	-	-	-	-	-	-	-	-	-	-	-
2,4,6-trimethylbenzaldehyde	487-68-3	0.0075	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**

* Exposure scenario 3 = Quantity and frequency that an infant of 3 kg should be fed according to EFSA (EFSA, 2016).