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COMPREHENSIVE REVIEWS IN FOOD SCIENCE AND FOOD SAFETY

Dietary advanced glycation end-products, 2-monochloropropane-1,3-diol esters and 3-monochloropropane-1,2-diol esters and glycidyl esters in infant formulas: Occurrence, formulation and processing effects, mitigation strategies

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Abstract

Infant formula contains thermal processing contaminants, such as dietary advanced glycation end-products (dAGEs), glycidyl esters (GEs), 2-monochloropropane-1,3-diol esters and 3-monochloropropane-1,2-diol esters (MCPDEs). This systematic review aimed to gain insights into the occurrence of these contaminants in different types of infant formula, to understand potential effects of the formulation and processing of infant formulas on these contaminants, as well as into possible mitigation strategies. The occurrence of dAGEs in infant formula depends on the recipes and processing conditions. Hydrolyzed protein formulations promote dAGEs formation in infant formula since peptides are more prone to glycation than intact proteins, which is reflected in high dAGEs concentration in hypoallergenic infant formula. Different carbohydrates in recipes result into different glycation extents of infant formula: maltodextrin containing formulas contained less dAGEs than those with lactose. Concerning mitigation strategies, applying ultra-high-temperature (UHT) treatment during milk processing leads to less dAGEs formation than using in-bottle sterilization. Although data are limited, evidence showed that encapsulation of raw ingredients or the use of antioxidants or enzymes in recipes is promising. The occurrence of MCPDEs and GEs in infant formula fully depends on the vegetable oils used in the recipe. High levels of these contaminants can be found when relatively high amounts of palm oils or fats are

Abbreviations: 1-DG, 1-deoxyglucosone; 2-MCPDEs, 2-monochloropropane-1,3-diol esters; 3-DG, 3-deoxyglucosone; 3-DGal, 3-deoxygalactosone; 3-DPs, 3-deoxypentosone; 3-MCPDEs, 3-monochloropropane-1,2-diol esters; CEL, Nε-(carboxyethyl)lysine; CML, Nε-(carboxymethyl)lysine; dAGEs, dietary advanced glycation end-products; EFSA, European Food Safety Authority; ELISA, enzyme-linked immunosorbent assay; GC-MS, gas chromatography-mass spectrometry; GEs, glycidyl esters; G-H, glyoxal hydroimidazolones; GO, glyoxal; GOS, galacto-oligosaccharides; LC-MS/MS, liquid chromatography with tandem mass spectrometry; MG-H, methylglyoxal hydroimidazolones; MGO, methylglyoxal; ML, maximum limit; MR, Maillard reaction; TDI, tolerable daily intake; UHT, ultra high temperature; WHO, World Health Organization

used. The mitigation of MCPDEs and GEs should therefore be performed on fats and oils before their application to infant formula recipes. Data and knowledge gaps identified in this review can be useful to guide future studies.

KEYWORDS
dAGEs database, Maillard reaction, milk product, mitigation strategies, thermal processing contaminants

1 | INTRODUCTION

The World Health Organization (WHO) recommends exclusive breastfeeding for babies until the age of six months. However, for various reasons such as lactation failure, more than 50% of babies over the world receive infant formula before the age of three months (UNICEF, 2020). This percentage increases up to nearly 60% for babies at the age of six months. Infant formula is a substitute for human milk, in which the composition is adjusted to mimic the nutrient profile of human milk and provide the equivalent nutrition to babies.

Infant formula undergoes a series of thermal processing steps (Figure 1), including pre-heating, sterilization, evaporation, and spray drying (for powdered infant formula), to meet product quality and safety as well as consumer demands (Ferrer et al., 2000; Jiang & Guo, 2014). During these processing steps, various undesirable chemical compounds, named thermal processing contaminants, can be formed as well (Chávez-Servín et al., 2015; Contreras-Calderón et al., 2009; Van Asselt et al., 2017). Moreover, the ingredients used for preparation of infant formula may also contain processing contaminants, resulting from thermal treatment to meet ingredient quality, safety, and infant formula producer demands. The occurrence of these processing contaminants in infant formula poses a potential risk to infant health. Hence, it is necessary to investigate their concentrations and develop appropriate mitigation strategies to reduce the occurrence of these contaminants in infant formula to guarantee the safety of babies, while still meeting their nutritional demands.

Thermal processing contaminants in infant formula can be classified as water-soluble contaminants and lipophilic contaminants. A group of water-soluble contaminants is the Maillard reaction (MR) products, formed during heat processing of infant formula. The MR has been studied for many decades by food scientists because of its sensory and nutritional consequences. During the early stages of the MR, amino acids bearing amino group in the lateral chain incorporates the carbonyl group to form Amadori products, followed by the formation of advanced glycation end-products (AGEs), furan, acrylamide, and so on. Because the presence of furan and acrylamide in infant formula is relatively low (Altaki et al., 2017; Lambert et al., 2018), we do not cover these contaminants in this review. AGEs are recognized as the intermediate markers of MR, comprising Nε-(carboxymethyl)lysine (CML), Nε-(carboxyethyl)lysine (CEL), pyrraline, and other lysine and arginine derivatives. To distinguish endogenous AGEs and AGEs from foods in the human body, scientists named the latter dietary advanced glycation end-products (dAGEs) (Delgado-Andrade & Fogliano, 2018). dAGEs are regarded as a group of thermal processing contaminants, and their formation is facilitated when the food items undergo heat treatment.

For safety and technological reasons, a severe thermal treatment is mandatory during infant formula production. As a consequence, the occurrence of dAGEs is relatively high in infant formula. The basic formulation includes milk proteins, lactose, fatty acids, vitamins, and minerals. Compared to cow's milk, the concentration of lactose is adjusted from 4.6% to 7.1% in infant formula; the higher concentration of reducing carbohydrate is one of the factors responsible for the high occurrence of dAGEs in infant formula (Pischetsrieder & Henle, 2012). The whey to casein ratio is usually high in infant formula in order to mimic the human milk protein profile and to improve the milk digestibility by babies (Birlouez-Aragon et al., 2004). However, whey proteins are more prone to glycation reaction also because they contain more lysine residues than caseins. Besides macronutrient composition, ascorbic acid and iron are often fortified in infant formula that facilitates the occurrence of glycation and increases the likeliness for dAGEs formation (Nguyen et al., 2016; Schwarzenbolz et al., 2016). The formation of dAGEs lowers the nutritional value of the final product. It has been reported that around 20% of lysine residues in milk product will be lactosylated during glycation: lactulosyllysine is not digested by infant thus glycation caused the reduction of available lysine in recipe and the decrease of milk protein digestibility (Contreras-Calderón et al., 2009; Henle et al., 1991; Mauron, 1990). Moreover, several cross-sectional studies have proposed that the consumption of dAGEs can increase the risk especially for those

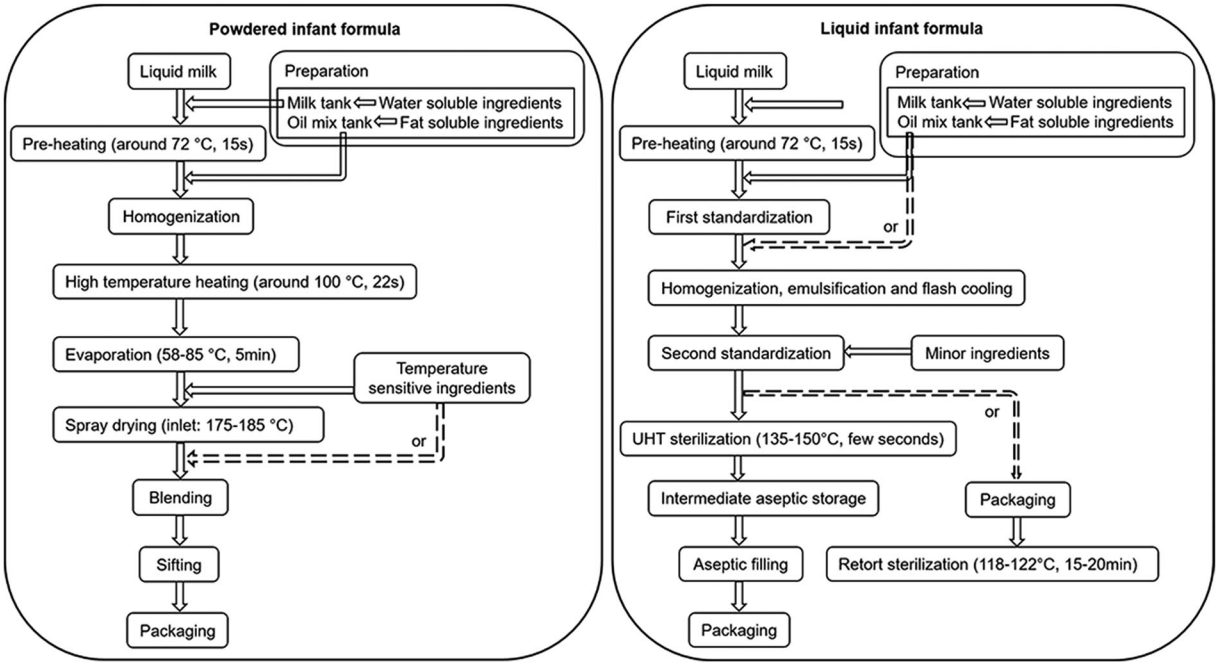

FIGURE 1 Flow chart of a general overview on the processing of the standard powdered infant formula and liquid infant formula. The process of powdered infant formula is a combination of the dry blending and the wet mixing-spray drying process

suffering from chronic kidney disease or having pathologies related to an altered intestinal permeability (Birlouez-Aragon et al., 2010; Snelson et al., 2021). Interestingly, some of the biological effects exerted by dAGEs can be reverted by limiting their dietary intake (van Dongen et al., 2021). Mounting evidence recently suggests an impact of AGEs on human microbiota (Graf von Armansperg et al., 2021; Mastrocola et al., 2020). This can be particularly relevant for bottle-fed infants and therefore for infant formula manufacturers. From the nutritional and health aspects, the occurrence of dAGEs in infant formula still raises concerns. Therefore, it is worth to investigate the strategies that can be used to mitigate dAGEs concentration so as to guarantee milk quality.

Although many studies have focused on the determination of dAGEs in dairy products, the knowledge gaps related to the occurrence of dAGEs in infant formula remains. Most of the available studies on dAGEs occurrence focus on CML; however, many other dAGEs molecules (e.g., CEL, methylglyoxal hydroimidazolones (MG-H), and pyrraline) are simultaneously formed during heat treatment (Hellwig & Henle, 2019). Since the formation of other dAGEs is not linearly related to the formation of CML, expressing dAGEs concentration in CML-equivalents is not a correct procedure. More insights into the occurrence of specific dAGEs compounds in infant formula are necessary. Unfortunately, comparing the concentrations of dAGEs in infant formula across studies is not easy due to the inconsistent use of units, different analytical techniques, and the lack of detailed information on infant formula samples as well as their processing conditions. This leads to the challenge of proposing a systematic and handy dAGEs database obtained with reliable analytical techniques. Many studies measured dAGEs in food products with enzyme-linked immunosorbent assay (ELISA) method (Dittrich et al., 2006; Goldberg et al., 2004; Prosser et al., 2019; Uribarri et al., 2010). The ELISA method does not provide reliable data for dAGEs in infant formula and it was amply demonstrated that it overestimates CML concentration in foods with high fat content and underestimates the concentration in foods that are rich in carbohydrates (Charissou et al., 2007; Niquet-Léridon et al., 2015).

In addition to dAGEs from the MR, infant formula can also contain another class of thermal processing contaminants, namely the so-called glycidyl esters (GEs), and 2-monochloropropane-1,3-diol esters and 3-monochloropropane-1,2-diol esters (2- and 3-MCPDEs, all of them are further on collectively named as "MCPDEs"). GEs and MCPDEs are formed in vegetable oils during the deodorization step of oil refining (Oey et al., 2019). Thus, these contaminants are only present in infant formula (and other dairy products) to which refined vegetable oils have been added. During oil refining, 3-MCPDEs are predominantly found from triacylglycerols (Hrncirik & van Duijn, 2011; Stadler, 2015), while GEs are formed through the scavenging of free fatty acids of diacylglycerols or the dehydration of monoacylglycerols (Cheng et al., 2017;

Craft et al., 2012; Destaillats et al., 2012). The formation of 2-MCPDEs comes alongside the formation of 3-MCPDEs and GEs, at a concentration that is about the half of 3-MCPDEs (Kuhlmann, 2011). Both GEs and MCPDEs can be hydrolyzed by intestinal lipase once being ingested, releasing free glycidol, 2- and 3-MCPD, and resulting into adverse effects on human health (Andres et al., 2013; Arisseto et al., 2018). The International Agency for Research on Cancer recognized glycidol as "potential carcinogenic to humans" (group 2A) in 2000 (IARC, 2000). Glycidol has been identified as having carcinogenicity, genotoxicity, and reproductive toxicity in animal tests using rats or mice (EFSA, 2016). Consumption of 3-MCPD contributes to renal and reproductive problems in mature male rat, while the consumption of 2-MCPD may result muscle, heart, renal, and liver disease in rat (ESFA, 2018; Schilter et al., 2011). To this end, the European Food Safety Authority (EFSA) established a tolerable daily intake (TDI) of 2 μg/kg bw/day for 3-MCPD (EFSA, 2016, 2018).

To date, a limited number of studies on the occurrence of GEs and 2- and 3-MCPDEs in infant formula have been conducted, conceivably by the challenges of extracting esters from complicated food matrix (Leigh & MacMahon, 2017). Notably, many available data showed that exposure of infants to 3-MCPDEs exceeds the TDI, implying that high attention should be paid to investigate the concentration of MCPDEs in infant formula (Arisseto et al., 2017; Jędrkiewicz et al., 2016; Wang et al., 2016; Zelinková et al., 2009). Since these contaminants in infant formula are contributed by the raw ingredients instead of being formed from the milk processing, its mitigation should be focused on refined vegetable oils, which is out of the scope of this review. The detailed information about this matter was already introduced in another paper recently published by our groups (Oey et al., 2019).

In conclusion, dAGEs, GEs, and MCPDEs are thermal processing contaminants and their presence in infant formula lowers milk digestibility and potentially causes human health risks. To this end, this review aims to obtain insights into the occurrence of these contaminants in infant formula and to highlight the possible mitigation strategies, as well as the current knowledge gaps. Based on the available data, possible relations between the occurrence of these contaminants and the types of infant formulas, with different recipes and processing conditions, were qualitatively investigated.

2 | MATERIALS AND METHODS

A systematic literature review was performed in the first half of January 2020 using the online databases Scopus and Web of Science, and focusing on scientific papers published in the English language in the 20-year period 1999–2019. The literature search covered the two subjects of occurrence data and mitigation strategies for dAGEs in infant formula, named as dAGEs_ocr search and dAGEs_mt search, respectively. To ensure high quality of data, we only included dAGEs data collected by chromatographic methods. Background information on the reaction pathway of dAGEs was collected from the selected relevant papers. References on dAGEs occurrence and mitigation in infant formula were selected by using the following predefined search strings applied to title, abstract, and/or keywords:

("infant formula*" OR milk OR dairy) AND (glycat* OR *carboxymethyl* OR *carboxyethyl* OR MG-H OR G-H OR pyrraline) AND (occurren* OR presen* OR concentrat* OR content OR level OR analysis OR determination OR quantification) AND NOT (ELISA OR metaboli* OR color OR *cellul?se OR furfural OR blood OR pH OR digest* OR allerg* OR bacteri* OR emulsion OR cell OR oxidation OR antioxidant OR immuno*).

("infant formula*" OR milk OR dairy) AND (glycat* OR *carboxymethyl* OR *carboxyethyl* OR MG-H OR G-H OR pyrraline) AND (mitigat* OR prevent* OR control* OR reduc* OR inhibi* OR decreas*) AND NOT (ELISA OR digestion OR rat OR blood OR cellulose OR inflammation OR tissue OR gene OR foam* OR cell OR furfural OR cheese).

These search terms were arranged together to cover a selection of dAGEs (CML, CEL, MG-H, glyoxal hydroimidazolones (G-H), pyrraline) concentration/mitigation in different types of infant formula.

Similarly to the procedure for dAGEs, a systematic literature search was conducted with regarding to the occurrence of MCPDEs/GEs in infant formula (named as GEs_ocr search), as follows:

("infant formula*" OR milk OR dairy) AND (monochloro* OR MCPD* OR glycid*l) AND (occurren* OR presen* OR concentrat* OR content OR level OR analysis OR determination OR quantification) AND NOT (rat or toxicological).

For all dAGEs_ocr, dAGEs_mt, and GEs_ocr search, the retrieved references from the two databases were combined into one Endnote database, after which duplicate references (resulting from using two databases) were removed. By screening the titles, keywords and abstracts, irrelevant papers were removed from the Endnote database. Additional relevant references were retrieved from the resulting selected papers, applying the

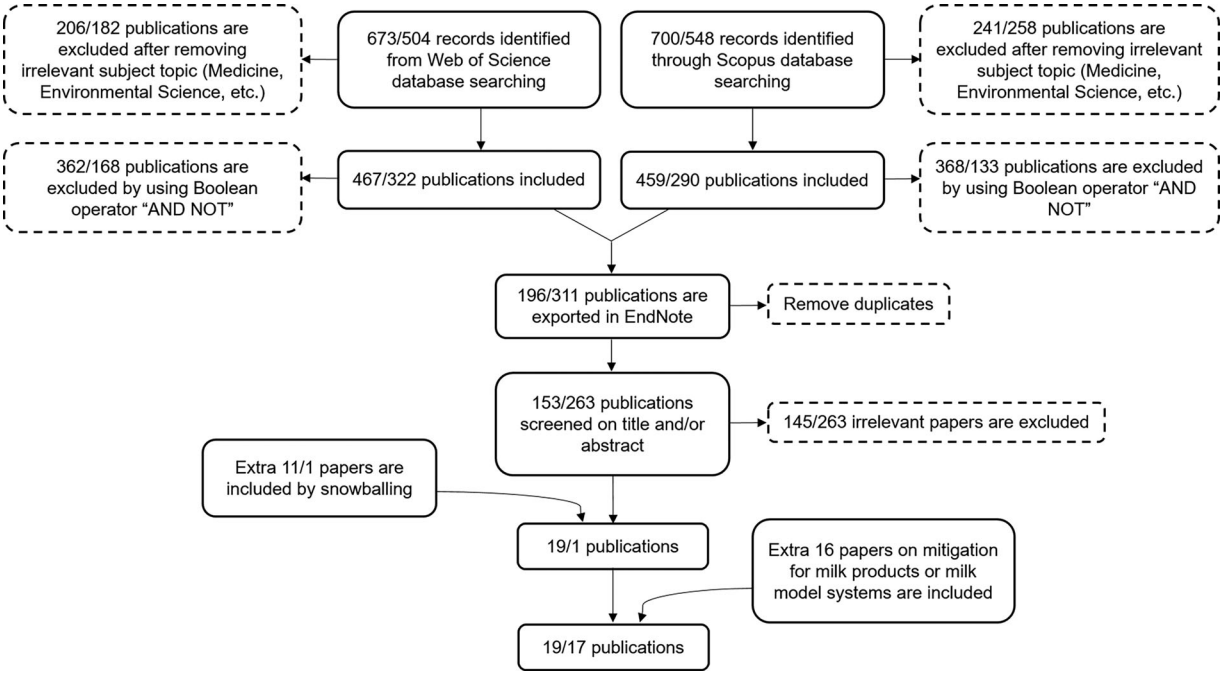

FIGURE 2 Flow chart of search strategy and results of the two literature searches on dAGEs occurrence and dAGEs mitigation. Left-hand number (separated by the /) shows the number of papers on occurrence and the right-hand number shows the number of papers on mitigation

snowballing method. The snowballing implies identifying additional papers relevant to our study aims by using the citation of the retrieved papers and by searching the recent articles that have cited the retrieved papers. Two independent investigators did the paper selection, after which the selected relevant papers were compared and—in case of differences—discussed between the two investigators to derived at a final set of selected papers.

2.1 | Data extraction and processing

From the relevant publications following the dAGEs_ocr search, the reported dAGEs data were collected. Due to the different sample pretreatment methods applied, the units used to express dAGEs concentration varied across studies. To facilitate the reviewing of data, concentration data were made comparable by normalizing the values on protein basis. If the protein concentration was not provided in the article, we estimated that per 100 g of powdered adapted infant formula for 0–6 months of age and powdered follow-on formula for the baby over 6 months obtain 9.6 g and 11 g protein, respectively; per 100 ml of liquid formula containing 2.0 g protein. The lysine content in liquid formula was assessed to be 81 g/kg protein by the mean value of the lysine data that is summarized in this review. As an example for data conversion, a CML content of 0.25 mg per 100 ml liquid formula equals to 0.125 mg CML in 1.0 gram of protein in the liquid formula, which equals to 125 mg CML per kilogram protein.

Occurrence data on GEs and MCPDEs in infant formula were extracted from the set of relevant papers resulting from the GEs_ocr search. All data were converted to "mg/kg of lipids," if needed. The recalculation method was similar to the one applied to dAGEs, with an estimation of lipid concentration as follows: powdered adapted formula contains 26 g fat/100 g powder (or 3.5 g fat/100 ml milk); powdered follow-on formula contains 22.3 g fat/100 g powder (or 3 g fat/100 ml milk); liquid formula (i.e., concentrated formula and ready-to-used formula) contains 3.6 g fat/100 ml milk. In the case that the paper did not mention the stage of powdered infant formula used, an average value of 24 g fat/100 g powder (or 3.3 g fat/100 ml milk) was applied.

3 | RESULTS AND DISCUSSION

3.1 | Paper selection results

The dAGEs_ocr search (Figure 2, left-hand number separated by the /) resulted into 19 relevant papers on the occurrence of dAGEs in infant formulas, including two review papers. In the evaluation process, the two scientists came up with the same set of selected relevant papers. Ten out of 19 studies involve dAGEs data, from which six papers

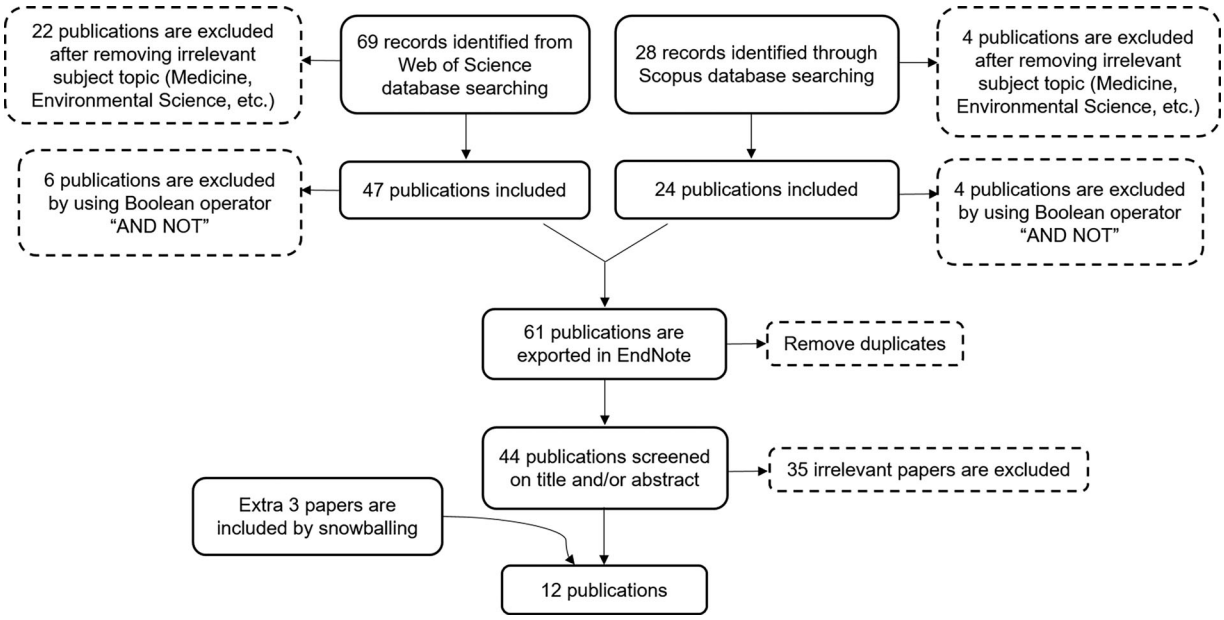

FIGURE 3 Flow chart of literature search for the occurrence of MCPDEs and GEs in infant formula

used CML as the only indicator to dAGEs, three papers also included data on CEL, one paper reported pyrraline concentration, and data on the other dAGEs, such as MG-H and G-H, have not been reported so far. Most of the papers reported dAGEs concentrations in different types of processed food items; only eight papers specifically focused on those concentrations in infant formulas. From the latter eight studies which focused on dAGEs occurrence in infant formulas, seven papers reported dAGEs and/or furosine data in hydrolyzed protein infant formulas, two papers reported such data in infant formula containing different carbohydrates, and one paper focused on furosine variation in adapted infant formula and follow-on infant formula during their storage.

The dAGEs_mt search (Figure 2, right-hand number separated by the /) resulted in only one paper that investigated dAGEs mitigation in infant formula specifically, and 16 other papers focused on milk or milk model systems. Out of these 17 studies, 14 of them focused on dAGEs mitigation strategies in milk products using recipes, either by limiting the participation or reactivity of precursors of glycation reaction in the recipe, or by adding dAGEs inhibitors into the recipe. The remaining three papers focused on dAGEs mitigation through milk processing techniques.

In total, twelve papers on the occurrence of MCPDEs and/or GEs in infant formula were selected as relevant (Figure 3), of which three are review papers. Only three papers reported the occurrence of all three compounds (2-MCPDE, 3-MCPDE, and GEs) in infant formula. Three studies focused on the effect of using palm oils in the recipe on the presence of MCPDEs/GEs in infant formulas, as the presence of these contaminants in infant formula originates from using vegetable oils in the recipe, and palm oils are more susceptible to formation of these contaminants during the refining step compared to the other vegetable oils.

3.2 | dAGEs

3.2.1 | dAGEs formation pathways in infant formula

The pathway for the formation of dAGEs (Figure 4) consists of several parallel reactions that simultaneously occur during high temperature processing, with carbohydrates, ascorbic acid, and amino acids as key precursors, with Amadori products and dicarbonyls as the initial markers, and with iron as the catalyst of glycation reaction. In the early stage of glycation, carbohydrates can either react with amino groups to yield Amadori/Heyns products, or produce dicarbonyls after oxidation. Amadori products, including lactulosyllysine, fructoselysine, tagatoselysine, are the first stable markers during the glycation that can be quantified by analyzing the furosine concentration after acid hydrolysis (Nguyen et al., 2014). The dicarbonyls are a group of compounds comprising C6 fragments (e.g., 1-deoxyglucosone (1-DG), 3-deoxyglucosone (3-DG), 3-deoxygalactosone (3-DGal), 3-deoxypentosone (3-DPs), glucosone, and galactosone) and breakdown products (e.g., glyoxal (GO), methylglyoxal (MGO), and diacetyl). Both Amadori products and dicarbonyls are reactive compounds, followed by several reactions to form dAGEs. In

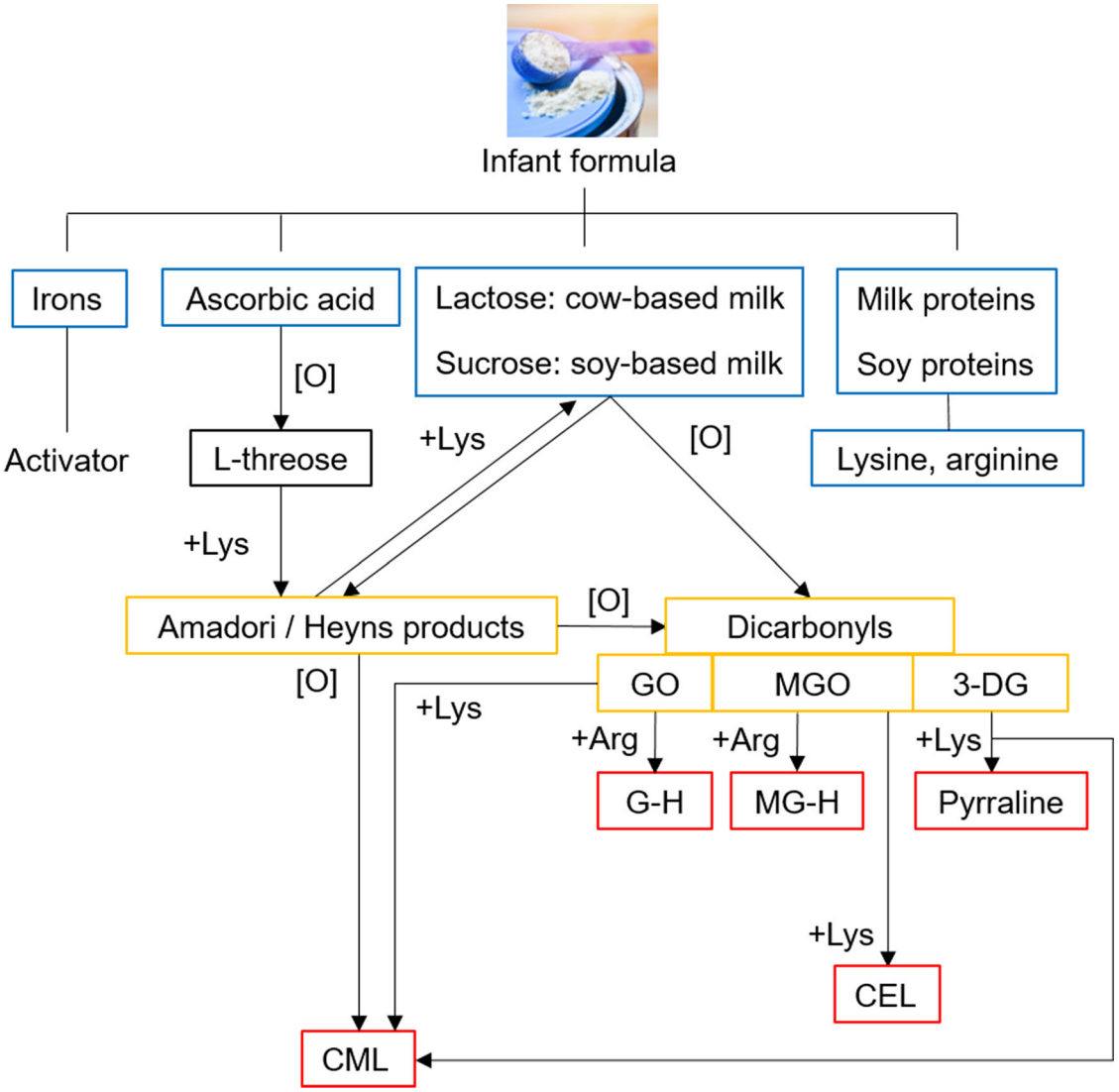

FIGURE 4 Reaction pathways for the formation of dAGEs in infant formula. The compounds marked as blue are the precursors of glycation reaction, and those marked as yellow and red are the initial markers and intermediate markers of Maillard reaction, respectively. [O]: oxidizing agents; Lys: lysine; Arg: arginine

the advanced stage of glycation, CML is formed through Amadori products directly or through the Namiki-pathway that refers to the indirect reaction pathway from Amadori products to dAGEs via the formation of dicarbonyls (Hayashi & Namiki, 1986). GO modifies the side chain of lysine and arginine, and produces CML and G-H, respectively (Vistoli et al., 2013). Similarly, MGO reacts with lysine and arginine residues to generate CEL and MG-H, respectively. CML can also be formed, together with pyrraline, when the side chain of lysine is modified by 3-DG (Hellwig & Henle, 2019).

Apart from the pathways described above, ascorbic acid is another precursor for dAGEs formation in infant formula. It participates in the reaction after being oxidized into L-threose (Dunn et al., 1990). L-threose reacts with amino groups and forms Amadori products, followed by a series of reactions like those described above. dAGEs can also be formed independently of Amadori products. The presence of carbohydrates in the recipe of infant formula can lead to the formation of dicarbonyls directly by its oxidation, and dAGEs are formed subsequently (Hidalgo & Zamora, 2005).

3.2.2 | Occurrence of dAGEs indicators in infant formula

In this section, reported data on dAGEs as well as their precursors, initial markers, and intermediate markers for infant formula, presented in the selected relevant articles are described. Table 1 presents reported data on the concentration of dAGEs, including CML, CEL, and pyrraline

TABLE 1 Reported data on concentrations of dAGEs in different types of powdered and liquid infant formulas

Category	Infant formula	Compound	No. samples	No. positive samples	LOQ	LOD	Mean value in positive samples (mg/kg protein)	Range in positive samples (mg/kg protein)	Analytical method	Reference
Powder	Infant formula (n.s.)	CML	4	4	5 ng/ml	0.5 ng/ml	111	82.2–148	LC-ESI MS/MS	(Troise et al., 2015)
		CEL	4	4	5 ng/ml	1 ng/ml	9.9	7.1–13.1		
	Infant formula (n.s.)	CML	6	6	7 ng/ml	2 ng/ml	453	323–572	LC-ESI MS/MS	(Zhou et al., 2015)
		CEL	6	–	7 ng/ml	2 ng/ml	10.5	4.5–18.4		
	Infant formula (n.s.)	CML	4	–	–	–	–	68.8–190[b]	LC-ESI MS/MS	(Aalaei et al., 2019)
	Standard infant formula	CML	7	7	27 mg/kg protein	8 mg/kg protein	75.6	–	LC-ESI MS/MS	(Delatour et al., 2009)
	Standard infant formula	CML	8	8	–	–	60.1	25.6–140	LC-ESI MS/MS	(Fenaille et al., 2006)
	Standard infant formula	CML	–	–	1 mg/kg protein	0.1 mg/kg protein	–	9.0–12.0	GC-MS	(Charissou et al., 2007)
	Standard infant formula	Pyrraline	1	0	–	–	nd	–	HPLC-DAD	(Contreras-Calderón et al., 2009)
	Standard infant formula (adapted)	CML	3	3	1 ng/ml	–	36.3	28.0–45.0	LC-ESI MS/MS	(Chen et al., 2019)
	Hydrolyzed infant formula	CML	9	–	27 mg/kg protein	8 mg/kg protein	184	–	LC-ESI MS/MS	(Delatour et al., 2009)
	Hydrolyzed infant formula	CML	1	1	1 mg/kg protein	0.1 mg/kg protein	54.0	–	GC-MS	(Charissou et al., 2007)
	Partially hydrolyzed infant formula	Pyrraline	1	0	–	–	nd	–	HPLC-DAD	(Contreras-Calderón et al., 2009)
	Hypoallergenic infant formula	CML	5	5	–	–	212	135–322	LC-ESI MS/MS	(Fenaille et al., 2006)
	Hypoallergenic infant formula (adapted)	CML	1	1	1 ng/ml	–	81.0	–	LC-ESI MS/MS	(Chen et al., 2019)
	Hydrolyzed lactose-free infant formula	CML	2	–	27 mg/kg protein	8 mg/kg protein	50.9	–	LC-ESI MS/MS	(Delatour et al., 2009)
	Lactose-free infant formula	Pyrraline	1	0	–	–	nd	–	HPLC-DAD	(Contreras-Calderón et al., 2009)

(Continues)

TABLE 1 (Continued)

Category	Infant formula	Compound	No. samples	No. positive samples	LOQ	LOD	Mean value in positive samples (mg/kg protein)	Range in positive samples (mg/kg protein)	Analytical method	Reference
Liquid	Infant formula (n.s.)	CML	6	–	–	–	–	160[b]–508	LC-ESI MS/MS	(Aalaei et al., 2019)
	Infant formula (adapted)	CML	3	–	0.03 mmol/mol lysine	0.009 mmol/mol lysine	174[a]	–	LC-ESI MS/MS	(Assar et al., 2009)
	Infant formula (follow-on)	CML	3	–	0.03 mmol/mol lysine	0.009 mmol/mol lysine	120[a]	–	LC-ESI MS/MS	(Assar et al., 2009)
	UHT infant milk (follow-on)	CML	–	–	–	–	–	Up to 88.2	LC-ESI MS/MS	(Aktag et al., 2019)
		CEL	–	–	–	–	–	Up to 30.7		
	Standard infant formula	CML	3	3	27 mg/kg protein	8 mg/kg protein	153	–	LC-ESI MS/MS	(Delatour et al., 2009)
	Standard infant formula	CML	2	2	–	–	62.9	53.8–71.9	LC-ESI MS/MS	(Fenaille et al., 2006)
	Standard infant formula	CML	–	–	1 mg/kg protein	0.1 mg/kg protein	–	5.0–25.0	GC-MS	(Charissou et al., 2007)
	Hydrolysed infant formula	CML	7	–	27 mg/kg protein	8 mg/kg protein	405	–	LC-ESI MS/MS	(Delatour et al., 2009)
	Hydrolysed infant formula	CML	1	1	1 mg/kg protein	0.1 mg/kg protein	31.0	–	GC-MS	(Charissou et al., 2007)
	Hydrolysed lactose-free infant formula	CML	5	–	27 mg/kg protein	8 mg/kg protein	58.6	–	LC-ESI MS/MS	(Delatour et al., 2009)

No., number of; –, not available; LOQ, limit of quantification; LOD, limit of detection; n.s., not specified; nd, not detected; UHT, ultra-high temperature treatment; LC-ESI MS/MS, liquid chromatography electrospray ionization tandem mass spectrometry; GC-MS, gas chromatography-mass spectrometry; HPLC-DAD, high performance liquid chromatography with diode array detector; CML, Nε-(carboxymethyl)lysine; CEL, Nε-(carboxyethyl)lysine.

[a]Value was recalculated to reach the same unit of mg/kg protein.

[b]Value was not given by the author but estimated from the figure.

in various infant formulas. The investigation of dAGEs molecules should be contextualized to the chemical nature of precursors. When the amino moiety of the key precursor is lysine, the lysine-derived dAGEs should be the main target to study, while the arginine-derived dAGEs should be the main research target when the amino moiety of the key precursor in food proteins is arginine. There is a reasonable knowledge base on CML, but the available data on CEL and pyrraline is limited. The concentration of CML in hydrolyzed protein infant formula is more than 120% higher than this level in standard infant formula containing intact proteins. The reason could be that peptides are more prone to be modified than proteins (Fenaille et al., 2006). Delatour et al. (2009) found concentrations of CML significantly lower in lactose-free infant formula as compared to other types of infant formula, but they did not mention possible reasons. It is possible that the lactose-free infant formula used in this study was produced by mixing milk protein isolate and maltodextrin in the recipe instead of by using skimmed milk as a raw ingredient and enzymatically hydrolyzing the endogenous lactose to reach a lactose-free level. Since maltodextrin has less glycation power than lactose, the CML concentration is expected to be low in this case. The reported CML concentrations in powdered infant formula (9.0–572 mg/kg protein) are comparable with the CML concentrations in liquid infant formula (5.0–508 mg/kg protein). Although few studies observed differences in CML concentrations between liquid infant formula and powdered infant formula, results were not statistically different (Charissou et al., 2007; Delatour et al., 2009; Fenaille et al., 2006). Pyrraline is generally absent in infant formula (Contreras-Calderón et al., 2009).

Based on the dAGEs data presented in Table 1, CML was analyzed most frequently and it is the dominant intermediate marker of MR in cow-based infant formula with a significantly higher concentration than the other dAGEs compounds. To the best of our knowledge, there is no information on other dAGEs such as G-H and MG-H in infant formulas.

Table 2 presents the reported concentrations of lysine in infant formulas. These concentrations are either equivalent to or above the minimum requirement for infants, as recommended by Commission Directive 91/321/EEC (67 g/kg protein for adapted infant formula, 64.8 g/kg protein for follow-on infant formula). The available lysine concentration ranges from 54.1 g/kg protein to 131 g/kg protein, and no difference was found between different types of infant formulas within the same study.

The Amadori products are quantified as furosine concentration (Table 3). A proper conversion factor is needed to further calculate the concentration of individual Amadori product from furosine concentration (Krause et al., 2003). From this table, it appears furosine concentrations in infant formulas are scattered across studies, ranging from 214 mg/kg protein to 19,370 mg/kg protein. It has been reported that the presence of furosine in infant formula originates from the raw ingredients, sharply increases in concentration during the spray-drying step, and exponentially increases in concentration during storage (Contreras-Calderón et al., 2009; Ferrer et al., 2003). The comparison of furosine concentration between hydrolyzed infant formula and standard infant formula is inconsistent across studies. Several studies showed that hydrolyzed infant formula had a higher furosine concentration than standard infant formula (Chen et al., 2019; Penndorf et al., 2007). As possible explanation, the authors speculated that N-terminal hydrophobic amino acids are more prone to be glycated and form Amadori products, while the main hydrolyzed site in milk protein—when industrially producing hydrolyzed infant formula—is in its hydrophobic regions (Penndorf et al., 2007). However, Fenaille et al. (2006) found an opposite result: the concentration of furosine in hydrolyzed infant formula was significantly lower than in infant formula with intact protein. The authors assumed this might be the case because the Amadori products in hydrolyzed infant formula converted into advanced products already, as the hydrolyzed proteins are more prone to MR. Another explanation is due to the possible different carbohydrate compositions in hydrolyzed infant formulas and standard infant formulas. Amadori products formed from different carbohydrates yield different degrees of furosine after acid hydrolysis. Ferrer et al. (2003) evaluated the concentrations of furosine in adapted infant formulas and follow-on infant formulas that were produced from similar quality of raw cow's milk and underwent the same thermal conditions during the whole processing. Results indicated that the per kilogram of follow-on infant formula had a significant higher furosine concentration than per kilogram of adapted infant formula, which is caused by the higher total protein content in the recipe of follow-on infant formula. Baptista and Carvalho (2004) and Contreras-Calderón et al. (2009) used different sources of carbohydrates in the recipes to study the MR in infant formula and found that lactose is more reactive to glycation than maltodextrin. Different processing conditions applied to infant formula resulted to different degrees of furosine occurrence. As compared to ultra-high-temperature (UHT) treated infant formula, the formation of furosine was boosted when the infant formula undergoes in-bottle sterilization (Birlouez-Aragon et al., 2004). From the Table 3, powdered infant formulas (4860 mg/kg protein on average) appear to present more furosine as compared to liquid infant formulas (2215 mg/kg protein on average). The reason could be due to the low water activity in powdered infant formula, and the high concentrations of reactants resulting from the spray dry-

TABLE 2 Reported data on concentrations of lysine in different types of powdered and liquid infant formulas

Category	Infant formula	Compound	No. samples	No. positive samples	LOQ	LOD	Mean value in positive samples (g/kg protein)	Range in positive samples (g/kg protein)	Analytical method	Reference
Powder	Infant formula (n.s.)	lysine	4	4	5 ng/ml	0.5 ng/ml	114	98.9–131	LC-ESI MS/MS	(Troise et al., 2015)
	Infant formula (adapted)	lysine	4	–	–	–	62.3	54.1–72.1	–	(Martysiak-Zurowska and Stolyhwo, 2007)
	Infant formula (follow-on)	lysine	4	–	–	–	65.2	62.1–68.3	–	(Martysiak-Zurowska and Stolyhwo, 2007)
	Standard infant formula	lysine	1	1	0.024 g/kg protein	0.0073 g/kg protein	52.4	–	HPLC-UV	(Contreras-Calderón et al., 2009)
	Partially hydrolyzed infant formula	lysine	1	1	0.024 g/kg protein	0.0073 g/kg protein	55.8	–	HPLC-UV	(Contreras-Calderón et al., 2009)
	Lactose-free infant formula	lysine	1	1	0.024 g/kg protein	0.0073 g/kg protein	48.8	–	HPLC-UV	(Contreras-Calderón et al., 2009)
Liquid	UHT infant milk (follow-on)	lysine	–	–	–	–	–	71.1–128	LC-MS/MS	(Aktag et al., 2019)

No., number of; –, not available; LOQ, limit of quantification; LOD, limit of detection; n.s., not specified; UHT, ultra-high temperature treatment; LC-ESI MS/MS, liquid chromatography electrospray ionization tandem mass spectrometry; HPLC-UV, high performance liquid chromatography with ultraviolet detector.

TABLE 3 Reported data on concentrations of furosine in different types of powdered and liquid infant formulas

Category	Infant formula	Compound	No. samples	No. positive samples	LOQ	LOD	Mean value in positive samples (mg/kg protein)	Range in positive samples (mg/kg protein)	Analytical method	Reference
Powder	Infant formula (n.s.)	Furosine	17	–	–	–	–	1750[b]–3750[b]	HPLC	(Birlouez-Aragon et al., 2004)
	Infant formula (n.s.)	Furosine	4	4	9 ng/ml	3 ng/ml	5571	4719–6394	LC-ESI MS/MS	(Troise et al., 2015)
	Infant formula (n.s.)	Furosine	8	8	–	–	5600	2300–14,600	LC-ESI MS/MS	(Fenaille et al., 2006)
	Infant formula (adapted)	Furosine	4	4	–	60 mg/kg protein	14,235	13,200–15,509	HPLC-UV	(Martysiak-Zurowska and Stolyhwo, 2007)
	Infant formula (adapted)	Furosine	1	–	–	4.7 mg/kg sample	1615[a,c]	–	HPLC-UV	(Ferrer et al., 2003)
	Infant formula (follow-on)	Furosine	1	–	–	4.7 mg/kg sample	1407[a,c]	–	HPLC-UV	(Ferrer et al., 2003)
	Infant formula (follow-on)	Furosine	4	4	–	60 mg/kg protein	10,376	9319–11,567	HPLC-UV	(Martysiak-Zurowska & Stolyhwo, 2007)
	Standard infant formula	Furosine	4	–	–	0.03 μmol/L	–	2750–3710	HPLC-UV	(Penndorf et al., 2007)
	Standard infant formula	Furosine	1	1	3.5 mg/kg protein	1.05 mg/kg protein	8000	–	HPLC-UV	(Contreras-Calderón et al., 2009)
	Standard infant formula	Furosine	4	–	–	–	644	508–812	LC-ELSD/UV	(Baptista & Carvalho, 2004)
	Standard infant formula (adapted)	Furosine	3	3	1 ng/ml	–	2333	1700–2800	LC-ESI MS/MS	(Chen et al., 2019)
	Hypoallergenic infant formula	Furosine	5	5	–	–	2400	1300–8700	LC-ESI MS/MS	(Fenaille et al., 2006)
	Hypoallergenic infant formula	Furosine	7	–	–	0.03 μmol/L	–	3590–6130	HPLC-UV	(Penndorf et al., 2007)
	Hypoallergenic infant formula (adapted)	Furosine	1	1	1 ng/ml	–	3500	–	LC-ESI MS/MS	(Chen et al., 2019)
	Hydrolyzed infant formula	Furosine	3	–	–	–	616	516–815	LC-ELSD/UV	(Baptista & Carvalho, 2004)
	Partially hydrolyzed infant formula	Furosine	1	1	3.5 mg/kg protein	1.05 mg/kg protein	2560	–	HPLC-UV	(Contreras-Calderón et al., 2009)

(Continues)

TABLE 3 (Continued)

Category	Infant formula	Compound	No. samples	No. positive samples	LOQ	LOD	Mean value in positive samples (mg/kg protein)	Range in positive samples (mg/kg protein)	Analytical method	Reference
	Lactose-free infant formula	Furosine	1	1	3.5 mg/kg protein	1.05 mg/kg protein	19,370	–	HPLC-UV	(Contreras-Calderón et al., 2009)
	Lactose-free infant formula	Furosine	2	–	–	–	268	214–321	LC-ELSD/UV	(Baptista & Carvalho, 2004)
	Infant formula (skimmed milk, maltodextrin)	Furosine	4	–	–	–	371	267–458	LC-ELSD/UV	(Baptista & Carvalho, 2004)
Liquid	Infant formula (n.s.)	Furosine	2	2	–	–	1900	1600–2100	LC-ESI MS/MS	(Fenaille et al., 2006)
	Infant formula (n.s.)	Furosine	2	–	–	–	7708	6615–8800	HPLC-VWD	(Guerra-Hernandez et al., 2002)
	In-bottle sterilized infant formula	Furosine	5	–	–	–	2520	–	HPLC	(Birlouez-Aragon et al., 2004)
	UHT infant formula	Furosine	19	–	–	–	1590	–	HPLC	(Birlouez-Aragon et al., 2004)
	UHT infant milk (follow-on)	Furosine	–	–	–	–	–	1910–9740	HPLC-UV	(Aktag et al., 2019)

No., number of; LOQ, limit of quantification; LOD, limit of detection; n.s., not specified; –, not available; UHT, ultra-high temperature treatment; HPLC, high-performance liquid chromatography; LC-ESI MS/MS, liquid chromatography electrospray ionization tandem mass spectrometry; HPLC-UV, high performance liquid chromatography with ultraviolet detector; LC-ELSD/UV, high performance liquid chromatography with evaporative light scattering/ultraviolet detector; HPLC-VWD, high performance liquid chromatography with variable wavelength detector.

[a]Value has been recalculated to reach the same unit of mg/kg protein.

[b]Value was not given by the author but estimated from the figure.

[c]We assume the original data from this study were based on mg/kg protein instead of g/kg protein that the author stated.

TABLE 4 Reported data on concentrations of dicarbonyls in different types of liquid infant formulas

Category	Infant formula	Compound	Mean value in positive samples (mg/kg protein)	Range in positive samples (mg/kg protein)	Analytical method	Reference
Liquid	UHT infant milk (follow-on)	1-DG	–	Up to 5.2[a]	LC-ESI MS/MS	(Aktag et al., 2019)
		3-DG	–	76.5–673[a]		
		3-DGal	–	7.5–44.8[a]		
		diacetyl	–	Up to 4.2[a]		
		galactosone	–	Up to 2.2[a]		
		glucosone	–	Up to 111[a]		
		GO	–	14.7–31.7[a]		
		MGO	–	Up to 20.0[a]		
	Micronutrients fortified infant milk	3-DG	850[a]	–	HPLC-UV	(Hellwig et al., 2010)
		3-DGal	nd	–		
		3-DPs	nd	–		
		GO	nd	–		
		MGO	30.0[a]	–		

–, not available; UHT, ultra-high temperature treatment; 1-DG, 1-deoxyglucosone; 3-DG, 3-deoxyglucosone; 3-DGal, 3-deoxygalactosone; GO, glyoxal; MGO, methylglyoxal; 3-DPs, 3-deoxypentosone; nd, not detected; LC-ESI MS/MS, liquid chromatography electrospray ionization tandem mass spectrometry; HPLC-UV, high performance liquid chromatography with ultraviolet detector.

[a]The value has been recalculated with an estimation of 6.0 g protein per 100 ml milk.

ing step (Van Boekel, 1998). However, there is currently no sufficient evidence to prove this assumption due to the lack of furosine data for liquid formulas. It should be noticed that Fenaille et al. (2006) found no direct relations between the concentration of furosine and the concentration of CML in infant formula as the high concentration of furosine did not simultaneously present in the infant formula containing high concentration of CML. This is possible because the formation of CML in infant formula is not solely attributed by Amadori products.

Table 4 presents the reported concentrations of dicarbonyls in infant formulas. 3-DG and 3-DGal are the most abundant dicarbonyls in infant formula, followed by GO and MGO (Aktag et al., 2019). As indicated from Table 4, the occurrence of 3-DG in infant milk is significantly higher than 3-DGal, and this difference could reach up to 90%. Infant formulas from the same manufacturer but from different batches showed different levels of dicarbonyls. Interestingly, this difference was mainly seen in the 3-DGal concentration and not in the concentration of 3-DG, which might be caused by the stronger stability of 3-DG as compared to 3-DGal (Hellwig et al., 2010). 3-DPs were not detected in the infant formula investigated.

Overall, the reported data illustrate that the types of protein and carbohydrates, and the amount of iron in the recipe affect dAGEs formation in the process of producing infant formula. Under similar thermal treatments, hydrolyzed protein (i.e., peptides) is more prone to glycation than intact protein. Maltodextrin has relatively low reactivity towards glycation reaction. When the lactose in the recipe is partly or fully replaced by maltodextrin, the glycation degree in the final product will be lower. Iron is a trigger of the glycation reaction and its higher amount in the recipe promotes the occurrence of dAGEs. Processing conditions, particularly of the sterilization step and the spray drying step, also determine the glycation degree in the final infant formula product. Traditional in-bottled sterilization facilitates glycation during milk processing as compared to UHT treatment. Spray-drying may facilitate the formation of early MR product, not only because of the applied high temperature but also due to the low water activity in the final product that promotes the occurrence of glycation. This process concentrates the reactive ingredients of infant formula, such as protein, carbohydrates, ascorbic acid, and iron, and therefore speeds up the glycation and results into more glycation products at the end. Another assumption for the reported higher presence of furosine in powdered infant formulas is that the spray-dried infant formulas may be more prone to glycation during their storage than liquid infant formulas. This assumption needs further investigation by evaluating dAGEs formation as a function of processing step and throughout their entire storage time.

3.2.3 | dAGEs mitigation

In the selected papers, several strategies have been proposed for mitigation of dAGE formation. As shown in Table 5, alternative processing techniques and optimization of processing parameters have been suggested as ways to modulate dAGEs occurrence in infant formula. Lee et al. (2019) used the response surface method to optimize the parameters of spray-drying, including the inlet temperature, pump rate, and aspirator rate, during the processing of powdered infant formula in order to inhibit the formation of CML while remaining a good powder quality. The study demonstrated that the inlet temperature and pump rate had the greatest effects on dAGEs formation during spray drying process. Aalaei et al. (2017) evaluated the effects of different drying techniques and storage conditions on the formation of CML in skim milk powders. The spray-dried powder had a significantly higher CML concentration than the freeze-dried powder, and this difference increased during the storage time. The storage conditions also influence the formation of CML. CML formation was inhibited by 68% when the storage temperature reduced from 30 to 20°C under 52% relative humidity and was inhibited by 90% when the relative humidity of storage decreased from 52% to 33% under 30°C. Gliguem and Birlouez-Aragon (2005) found that using UHT as sterilization technology during milk processing lowers furosine concentration than applying in-bottle sterilization, and this difference increased with longer storage duration.

Most mitigation strategies focused on milk recipes, by limiting the participation of precursors, by lowering the reactivity of precursors, or by adding dAGEs inhibitors into the recipe. Encapsulation has been highlighted as a potential tool to mitigate the formation of MR products by slowly releasing the reactive ingredient, such as ascorbic acid, Na^{+}, or Fe^{3+} (Troise & Fogliano, 2013). Troise et al. (2016) modulated the formation of dAGEs in UHT milk by encapsulating ascorbic acid and they found alleviation of lysine losses in this condition. With a heating time of maximum 4 min and with the usage of encapsulated ascorbic acid in milk, the authors significantly reduced the formation of furosine. Results revealed that encapsulating ascorbic acid in milk reduced the formation of CEL more than the formation of CML as it intervenes mostly with MGO that is directly related to the formation of CEL. Lactose-hydrolyzed milk has a high concentration of dAGEs since the sugar concentration doubles, and glucose and galactose are both more active Maillard reactants than lactose. Zhang et al. (2019) performed a series of experiments with lactose-hydrolyzed milk model systems and found that the application of commercial β-galactosidases in milk to release galactose from lactose and transfer galactose units onto lactose to form galacto-oligosaccharides (GOS) is a promising anti-dAGEs strategy. Interestingly, the GOS-containing milk model systems showed lower occurrence of CML, CEL, G-H, and MG-H as compared to the regular lactose-hydrolyzed milk model systems, but in the meantime the concentrations of 3-DG, 3-DGal, and pyrraline were relatively high when GOS presented in the model systems. The possible explanation is that the authors mimicked GOS-containing milk model systems by the usage of GOS powder into the model systems instead of by producing GOS from the addition of β-galactosidases. The GOS powder added into the model systems has β-D-Gal-$(1 \rightarrow 3)_n$-D-glucose as the main source of GOS; β-D-Gal-$(1 \rightarrow 3)_n$-D-glucose is prone to form 3-DG and 3-DGal in MR, which contributed to the higher pyrraline presence.

Brown fermented milk refers to the milk fermented by *Lactobacillus casei* and presented brown color that is contributed by the Maillard browning process. The conventional procedure of brown fermented milk needs around 5% glucose added as sweetener and these sugars undergo 3 h of high-temperature heating together with skimmed milk powder to get the milk brown. This prolonged thermal treatment leads to a high occurrence of MR products in the final milk. Han et al. (2019) found a solution to ease the formation of MR products in brown fermented milk by replacing the addition of glucose into the recipe with enzymatically hydrolyzing the original lactose in milk. Since the amount of the original lactose in milk is 5% which is the same as the amount of glucose added into recipe, hydrolyzing the original lactose in milk produced a comparable amount of glucose as needed, while at the same time giving a significant inhibition on the formation of 3-DG and the advanced MR product (hydroxymethylfurfural in this case). To explain these results, a series of model systems were further set up by the authors with lysine and different sources of carbohydrates, including glucose, galactose, and lactose. The authors observed that the glucose model system produced the highest amount of 3-DG during short-term heat treatment. However, when the heating duration was prolonged to 3 h, the highest 3-DG concentration was present in the lactose model system and the least 3-DG occurrence was in the galactose model system. This is probably the reason that hydrolyzing lactose in brown fermented milk formed less 3-DG and MR products as compared to the conventional processing of brown fermented milk.

Currently, most attempts for dAGEs mitigation in milk have been made by the use of dAGEs inhibitors, particularly focusing on natural compounds enriched with polyphenols. Olive mill wastewater phenolic powder, a byproduct from olive oil processing, effectively inhibited 47.7% of furosine, 55.9% of MGO, and 43.3% of GO in UHT milk (Troise et al., 2014). This treatment mitigated dAGEs

TABLE 5 Reported dAGEs mitigation strategies in dairy and soy milk products

Milk product	Mitigation strategy	Inhibitory effect	Reference
Powdered infant formula	Optimization of the spray drying parameters	–	(Lee et al., 2019)
Skim milk powder	Different drying techniques and storage conditions	Drying techniques: inhibitory effect of CML was up to 50% in freeze-dried samples as compared to that in spray-dried samples; Storage temperature: inhibitory effect of CML was 68% when the storage temperature decreased from 30 to 20 °C; Storage humidity: inhibitory effect of CML was 90% when the relative humidity decreased from 52% to 33%.	(Aalaei et al., 2017)
Fortified milk	Different sterilization techniques	Inhibitory effect of furosine was up to 29% in UHT milk as compared to that in in-bottle sterilized milk.	(Gliguem et al., 2005)
Lab-scale UHT milk	Ascorbic acid encapsulation	CML: 41% CEL: 53%	(Troise et al., 2016)
Milk model system	Transgalactosylate galactosidases	Furosine and pyrraline were reduced	(Zhang et al., 2019)
Brown fermented milk	Alter the conventional process with hydrolyzing endogenous lactose	3-DG: 54.5%	(Han et al., 2019)
Lab-scale UHT milk	0.1% olive mill wastewater phenolic powder	CML: 16.2% Furosine: 47.7% MGO: 55.9% GO: 43.3%	(Troise et al., 2014)
Milk model system (glucose, casein)	Baijiu vinasse extract	CML: 43.2%	(Wang et al., 2019)
Milk model system	300 μg/ml dried beetroot juice	CML: 17% Furosine: >30%	(Ieva Račkauskienė et al., 2015)
Milk model system	Lingonberry leaf extracts (0.3 mg/ml quinic acid and catechin)	CML: 51% Furosine: 40%	(Račkauskienė et al., 2019)
Milk model system (lactose, lysine)	1 mg/ml lotus seedpod oligomeric procyanidins	CML: 38.1%	(Wu et al., 2015)
UHT milk	1.12 mM catechin, 1.12 mM genistein, and 0.645 mM daidzein mixture	MGO: 64.9% GO: 46.6% 3-DG: 87.8%	(Kokkinidou & Peterson, 2013)
Model system (fructose, soy glycinin)	Soy isoflavone-rich extract (mixture of daidzein, glycitein, and genistein)	CML: >87% Heyns products: 20%	(Silvan et al., 2014)
Soy milk	2 mmol/L genistein	MGO: 42.7% GO: 45.6%	(Wang et al., 2017)
Model system (fructose, soy glycinin)	Ferulic acid	CML: 85%	(Silván et al., 2011)
Model system (lactose, lysine)	40 mmol/L sodium sulfite	CML: 84.3%	(Xu et al., 2013)
Low lactose milk	Fructosamine oxidase I	CML: 38.7% Furosine: 79.4%	(Troise et al., 2016)

–, not available; > , more than; UHT, ultra-high temperature treatment; CML, Nε-(carboxymethyl)lysine; CEL, Nε-(carboxyethyl)lysine ; 3-DG, 3-deoxyglucosone; GO, glyoxal; MGO, methylglyoxal.

mainly through inhibiting MGO and diacetyl. The effect of Baijiu vinasse extract on dAGEs mitigation was evaluated in a glucose and casein model system by Wang et al. (2019). Vinasse is a fermentation starter for Baijiu production, containing ten kinds of phenolic compounds. Its addition to the milk model system inhibited 43.2% of CML because phenolic acid compounds have the capacity to trap and scavenge GO. Beetroot juice showed mitigation effect on milk protein glycation, which influenced the formation of furosine (> 30%) more than of CML (17%) (Račkauskienė et al., 2015). The authors attributed the mitigation to the presence of compounds with phenolic ring structures in beetroot juice. The phenolic ring can trap dicarbonyls via aromatic electrophilic substitution when its structure contains vicinal hydroxyl groups, while it mainly occupies the available lysine via the formation of a quinone ring when its structure contains monohydroxyl group. Beetroot contains betalain whose structure of phenolic ring is monohydroxyl group rather than vicinal hydroxyl group, resulting into the higher inhibitory effect on the formation of furosine instead of on the formation of CML. Similarly, due to the presence of phenolic components, the extract of lingonberry leaf and the extract of lotus seedpod containing oligomeric procyanidins inhibited CML formation by 51% and 38.1%, respectively (Račkauskienė et al., 2019; Wu et al., 2015).

Compared to the extracts from natural plants rich in polyphenols, the addition of pure phenolic compounds in milk model system showed higher inhibitory effectiveness on dAGEs formation. A mixture of catechin, genistein, and daidzein had a good suppression on dicarbonyl compounds in UHT milk, particularly when the corresponding concentration was 1.12, 1.12, and 0.645 mM (Kokkinidou & Peterson, 2013). A mixture of daidzein, glycitein, and genistein used in soy milk model system showed 85% reduction in CML formation and 20% reduction in Heyns products formation (Silvan et al., 2014). It was hypothesized that flavonoids can trap dicarbonyl compounds; its antioxidant capacity may ease sugars oxidation and Amadori products oxidation, consequently mitigating the formation of CML. Another possible mechanism is that isoflavone can bind to soy glycinin and form glycinin-isoflavone adduct, which reduces the available protein contents in soy milk and decreases the occurrence of dAGEs formation. Among the flavonoid compounds, genistein and catechin displayed higher effectiveness on dAGEs mitigation (Wang et al., 2017). More than 40% of reduction on both MGO and GO were seen in soy milk when 2 mmol/L genistein was used. Ferulic acid has antioxidant activities that can inhibit sugars being converted into dicarbonyls, and it can react and bind to amino group to decrease the occurrence of protein glycation (Silván et al., 2011). Several studies have investigated the effects of chemical compounds or enzymes on protein glycation in milk model system. Research from Xu et al. (2013) indicated that sodium sulfite can significantly reduce dAGEs formation in a dairy model system by inhibiting the formation of Amadori product and by restraining the reaction between GO and lysine. Fructosamine oxidase is a type of enzyme that is isolated from *Aspergillus* spp. The addition of this enzyme during food processing can degrade the low-molecular-weight compounds (e.g., Amadori products) to deoxyglucosone and amino acids, leading to the reduction of the MR products. Troise et al. (2016) investigated the effect of this enzyme in low-lactose milk and found that the formation of Amadori product and CML in the milk containing fructosamine oxidase was delayed and significantly inhibited during the entire shelf life when compared to the milk without fructosamine oxidase.

The selection of dAGEs mitigation strategies for infant formulas should consider the targeted infant formula types. For hydrolyzed protein infant formula, control and choice of reducing sugars are an important mitigation strategy. In this regard, the addition of fructosamine oxidase might be helpful for dAGEs reduction. However, infant formula with intact proteins may deserve mitigation during its production processes.

3.3 | Occurrence of MCPDEs and GEs in infant formula

MCPDEs are thermal contaminants that are primarily present in edible oils and foodstuffs with refined oils as ingredient (Andres et al., 2013). As can be seen from Tables 6, 7, and 8, infant formula containing palm oil or palm olein in the recipe usually has higher levels of MCPDEs and GEs (Becalski et al., 2015), unless certain effective strategies were taken by industries to lower the MPCDEs and GEs concentrations in palm oils before adding them into the recipe of infant formulas (Leigh & MacMahon, 2017). Indeed, palm oil has been reported to contain higher levels of MCPDEs and GEs than other types of vegetable oils (Kuhlmann, 2011; Weisshaar, 2011). It is still commonly chosen as an ingredient of infant formula because 20–25% of the total saturated fatty acids in human breast milk are palmitic acid (Mehrotra et al., 2019). Generally, the concentrations of 3-MCPDEs in infant formulas increased with the fat content in the recipe (Leigh & MacMahon, 2017; Zelinková et al., 2009). But this correlation does not exist when the mitigation strategies are applied in the refined vegetable oils before using the oils in the recipe to produce infant formulas (Arisseto et al., 2017). Leigh and MacMahon (2017) pointed on a potential bias in their results, due to a lack of analytical standards for quantification of all esters in their method. They stated

TABLE 6 Reported data on 3-MCPDE concentrations in different types of powdered and liquid infant formula

Infant formula	No. samples	No. positive samples	LOQ	LOD	Mean value of 3-MCPDE in positive samples (mg/kg fat)	3-MCPDE range in positive samples (mg/kg fat)	Analytical method	Reference
Infant formula (with palm oil)	73	73	0.001 mg/kg powder	–	1.92[a]	0.09–3.83[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
Infant formula (no palm oil)	25	25	0.001 mg/kg powder	–	0.53[a]	0.30–0.67[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
Powdered infant formula (with palm oil)	8	7	0.006 mg/kg milk	0.002 mg/kg milk	0.18[a]	0.03–0.36[a]	GC-MS	(Becalski et al., 2015)
Powdered infant formula (no palm oil)	2	2	0.006 mg/kg milk	0.002 mg/kg milk	0.07[a]	0.07–0.08[a]	GC-MS	(Becalski et al., 2015)
Powdered infant formula	24	–	–	–	–	Up to 3.8	GC-MS	(Jędrkiewicz et al., 2016)
Powdered infant formula	88	73	0.09 mg/kg powder	0.03 mg/kg powder	–	<1.32[a]	GC-MS	(Wang et al., 2016)
Powdered infant formula	5	3	0.05 mg/kg powder	0.01 mg/kg powder	0.53[a]	0.51–0.58[a]	GC-MS/MS	(Goh et al., 2019)
Powdered infant formula	2	2	0.004 mg/kg powder	–	0.33[a]	0.26–0.41[a]	GC-MS/MS	(Dubois et al., 2019)
Powdered infant formula (with palm oil)	33	14	0.16 mg/kg powder	0.08 mg/kg powder	1.18[a]	0.71–2.50[a]	GC-MS	(Arisseto et al., 2017)
Powdered infant formula (no palm oil)	7	1	0.16 mg/kg powder	0.08 mg/kg powder	0.71[a]	–	GC-MS	(Arisseto et al., 2017)
Powdered infant formula with exclusive lactose	7	7	0.19 mg/kg fat	0.06 mg/kg fat	0.39	0.25–0.49	GC-MS/MS	(Wöhrlin et al., 2015)
Powdered infant formula with additional carbohydrates	7	7	0.19 mg/kg fat	0.06 mg/kg fat	0.44	0.34–0.65	GC-MS/MS	(Wöhrlin et al., 2015)
Ready-to-use infant formula	1	1	0.006 mg/kg milk	0.002 mg/kg milk	0.39[a]	–	GC-MS	(Becalski et al., 2015)
Concentrated infant formula	4	3	0.006 mg/kg milk	0.002 mg/kg milk	1.50[a]	0.56–2.03[a]	GC-MS	(Becalski et al., 2015)
Concentrated soy based infant formula	1	1	0.006 mg/kg milk	0.002 mg/kg milk	0.39[a]	–	GC-MS	(Becalski et al., 2015)

(Continues)

TABLE 6 (Continued)

Infant formula	No. samples	No. positive samples	LOQ	LOD	Mean value of 3-MCPDE in positive samples (mg/kg fat)	3-MCPDE range in positive samples (mg/kg fat)	Analytical method	Reference
Premium infant formula (fully intact milk proteins)	31	31	0.001 mg/kg powder	–	1.88[a]	0.18–3.83[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
Hydrolyzed infant formula	15	15	0.001 mg/kg powder	–	1.71[a]	0.15–3.33[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
Extensively hydrolyzed infant formula	7	7	0.001 mg/kg powder	–	1.75[a]	0.46–3.46[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
Hypoallergenic infant formula	10	10	0.001 mg/kg powder	–	0.83[a]	0.27–2.58[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
"Special needs" infant formula	7	7	0.001 mg/kg powder	–	2.17[a]	0.58–3.71[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
Soy-based infant formula	16	16	0.001 mg/kg powder	–	1.54[a]	0.15–2.38[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
Adapted infant formula	6	6	0.3 mg/kg fat	0.1 mg/kg fat	1.39	1.04–2.03	GC-MS	(Zelinková et al., 2009)
Follow-on formula	5	3	0.3 mg/kg fat	0.1 mg/kg fat	1.78	1.51–2.06	GC-MS	(Zelinková et al., 2009)
Growing-up milk	3	3	0.3 mg/kg fat	0.1 mg/kg fat	0.71	0.33–1.46	GC-MS	(Zelinková et al., 2009)
Toddler formula	12	12	0.001 mg/kg powder	–	0.92[a]	0.10–1.83[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)

No., number of; LOQ, limit of quantification; LOD, limit of detection; –, not available; < , less than; 3-MCPDE, 3-monochloropropane-1,2-diol esters; LC-ESI MS/MS, liquid chromatography electrospray ionization tandem mass spectrometry; GC-MS/MS, gas chromatography-triple quadrupole mass spectrometer.

[a]The value has been re-calculated with estimated fat content. See Materials and Methods section for details of the used fat estimates.

TABLE 7 Reported data on 2-MCPDE concentrations in different types of powdered and liquid infant formula

Infant formula	No. samples	No. positive samples	LOQ	LOD	Mean value of 2-MCPDE in positive samples (mg/kg fat)	2-MCPDE range in positive samples (mg/kg fat)	Analytical method	Reference
Powdered infant formula (with palm oil)	8	7	0.002 mg/kg milk	–	0.07[a]	0.01–0.13[a]	GC-MS	(Becalski et al., 2015)
Powdered infant formula (no palm oil)	2	2	0.002 mg/kg milk	–	0.02[a]	0.02–0.03[a]	GC-MS	(Becalski et al., 2015)
Powdered infant formula	24	–	–	–	–	0.05–1.20	GC-MS	(Jędrkiewicz et al., 2016)
Powdered infant formula	88	0	0.09 mg/kg powder	0.03 mg/kg powder	<LOQ	–	GC-MS	(Wang et al., 2016)
Powdered infant formula	5	0	0.05 mg/kg powder	0.01 mg/kg powder	<LOQ	–	GC-MS/MS	(Goh et al., 2019)
Powdered infant formula	2	2	0.004 mg/kg powder	–	0.11[a]	0.08–0.13[a]	GC-MS/MS	(Dubois et al., 2019)
Powdered infant formula with exclusive lactose	7	5	0.13 mg/kg fat	0.04 mg/kg fat	0.21	0.16–0.26	GC-MS/MS	(Wöhrlin et al., 2015)
Powdered infant formula with additional carbohydrates	7	6	0.13 mg/kg fat	0.04 mg/kg fat	0.21	0.13–0.32	GC-MS/MS	(Wöhrlin et al., 2015)
Ready-to-use infant formula	1	1	0.002 mg/kg milk	–	0.14[a]	–	GC-MS	(Becalski et al., 2015)
Concentrated infant formula	4	4	0.002 mg/kg milk	–	0.48[a]	0.06–0.89[a]	GC-MS	(Becalski et al., 2015)
Concentrated soy based infant formula	1	1	0.003 mg/kg milk	–	0.14[a]	–	GC-MS	(Becalski et al., 2015)

No., number of; LOQ, limit of quantification; LOD, limit of detection; –, not available; <, less than; 2-MCPDE, 2-monochloropropane-1,2-diol esters; GC-MS, gas chromatography-mass spectrometry; GC-MS/MS, gas chromatography-triple quadrupole mass spectrometer.

[a]The value has been re-calculated with estimated fat content. See Materials and Methods section for details of the used fat estimates.

TABLE 8 Reported data on GEs concentrations in different types of powdered and liquid infant formula

Infant formula	No. samples	No. positive samples	LOQ	LOD	Mean value of GEs in positive samples (mg/kg fat)	GEs range in positive samples (mg/kg fat)	Analytical method	Reference
Infant formula (with palm oil)	73	–	0.001 mg/kg powder	–	–	<1.67[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
Infant formula (no palm oil)	25	25	0.001 mg/kg powder	–	0.11[a]	0.02–0.63[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
Powdered infant formula (with palm oil)	8	7	0.01 mg/kg milk	–	0.08[a]	0.01–0.15[a]	LC-APCI MS/MS	(Becalski et al., 2015)
Powdered infant formula (no palm oil)	2	0	0.01 mg/kg milk	–	<LOQ	–	LC-APCI MS/MS	(Becalski et al., 2015)
Powdered infant formula	5	0	0.06 mg/kg powder	0.02 mg/kg powder	<LOQ	–	GC-MS/MS	(Goh et al., 2019)
Powdered infant formula (with palm oil)	33	16	0.20 mg/kg powder	0.10 mg/kg powder	1.48[a]	0.83–3.13[a]	GC-MS	(Arisseto et al., 2017)
Powdered infant formula (no palm oil)	7	1	0.20 mg/kg powder	0.10 mg/kg powder	3.0[a]	–	GC-MS	(Arisseto et al., 2017)
Powdered infant formula with exclusive lactose	35	33	0.15 mg/kg fat	0.05 mg/kg fat	0.37	0.16–0.81	GC-MS/MS	(Wöhrlin et al., 2015)
Powdered infant formula with additional carbohydrates	35	31	0.15 mg/kg fat	0.05 mg/kg fat	0.35	0.16–0.87	GC-MS/MS	(Wöhrlin et al., 2015)
Ready-to-use infant formula	1	0	0.01 mg/kg milk	–	<LOQ	–	LC-APCI MS/MS	(Becalski et al., 2015)
Concentrated infant formula	4	1	0.01 mg/kg milk	–	0.44[a]	–	LC-APCI MS/MS	(Becalski et al., 2015)
Concentrated soy based infant formula	1	0	0.01 mg/kg milk	–	<LOQ	–	LC-APCI MS/MS	(Becalski et al., 2015)
Premium infant formula (fully intact milk proteins)	31	31	0.001 mg/kg powder	–	0.42[a]	0.02–1.38[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
Hydrolyzed infant formula	15	15	0.001 mg/kg powder	–	0.36[a]	0.05–0.75[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
Extensively hydrolyzed infant formula	7	7	0.001 mg/kg powder	–	0.63[a]	0.05–1.67[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
Hypoallergenic infant formula	10	–	0.001 mg/kg powder	–	0.06[a]	<0.15[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
"Special needs" infant formula	7	7	0.001 mg/kg powder	–	0.30[a]	0.08–0.67[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
Soy-based infant formula	16	16	0.001 mg/kg powder	–	0.46[a]	0.19–1.04[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)
Toddler formula	12	12	0.001 mg/kg powder	–	0.24[a]	0.08–1.00[a]	LC-ESI MS/MS	(Leigh & MacMahon, 2017)

No., number of; LOQ, limit of quantification; LOD, limit of detection; –, not available; <, less than; GEs, glycidyl esters; LC-ESI MS/MS, liquid chromatography electrospray ionization tandem mass spectrometry; LC-APCI MS/MS, liquid chromatography with atmospheric pressure chemical ionization tandem mass spectrometry; GC-MS, gas chromatography-mass spectrometry; GC-MS/MS, gas chromatography-triple quadrupole mass spectrometer.

[a]The value has been re-calculated with estimated fat content. See Materials and Methods section for details of the used fat estimates.

that their 3-MCPDEs and/or GEs concentrations may be biased low for infant formulas containing high proportions of medium-chain triglyceride oils in their formulations. This plays a role in LC-MS/MS methods as they were using, but not in GC-MS(/MS) based methods as these focus on 2-MCPD, 3-MCPD, and glycidol as a basis for quantifying MCPDEs and GEs. Interestingly, the authors observed that medium-chain triglyceride oils tend to be used in the recipes of hypoallergenic infant formulas, and the relatively low concentrations of 3-MCPDEs and GEs were therefore seen in the hypoallergenic infant formulas in this study. Among the given three contaminants, 3-MCPDE seems to be the dominant contaminant in infant formula, with significantly higher concentrations than 2-MCPDE and GEs. A correlation was seen between the concentrations of 2-MCPDE and 3-MCPDE in infant formula: a high concentration of 2-MCPDE was usually present simultaneously with a high concentration of 3-MCPDE (Zelinková et al., 2009). Another study reported a ratio for concentrations of 2-MCPDE : 3-MCPDE of 0.45 ($p < .001$) (Wöhrlin et al., 2015). No significant correlation was found between the concentration of GEs and the concentration of 2-/3-MCPDEs in infant formula (Wöhrlin et al., 2015).

The above results confirmed that the occurrence of MCPDEs and GEs in infant formula fully depends on the vegetable oils in the recipe. Although MPCDEs and GEs are commonly present in all refined vegetable oils, the use of palm oil as ingredient or a relatively high fat content in recipe may have a risk to present higher concentrations of these contaminants in infant formula. In fact, in cases where palm oil was used in the infant formula (Table 6), several positive samples exceeded the current maximum limit (ML) for 3-MCPDEs (and 3-MCPD) of 0.50 mg/kg on fat basis (0.05 mg/kg in powder and 0.006 mg/kg in liquid) set by the European Commission in Commission Regulation 1881/2006 (European Commission, 2006), whereas the majority of the samples with explicitly no palm oil did not exceed this limit. Concerning GE levels, the ML for GEs is 0.75 mg/kg in a fat basis (0.125 mg/kg in powder, 0.015 mg/kg in liquid) and several samples both with and without palm oils exceeded this ML. To mitigate the levels of MCPDEs and GEs, the industries should pay more attention to reducing the occurrence of MCPDEs and GEs during refining of vegetable oils before application into the recipe of infant formula. It should be noted that industries are fully aware and currently address the topic of MCPDEs and GEs.

3.4 | Knowledge gaps

This review presents an overview of available data from scientific literature on the occurrence of dAGEs in infant formula. Results show that, to date, little attention has been paid to dAGEs beyond CML. This lack of information did not allow a comprehensive understanding of the glycation degree in infant formula. Thus, it is recommended to develop reliable analytical methods, and collect additional data on dAGEs other than CML, and on G-H, MG-H, pentosidine, argpyrimidine, etc. With the use of chromatographic method, sufficient protein extraction and protein hydrolysis are the prerequisite for an accurate dAGEs quantitation, which calls for an interlaboratory consensus. It has been found that recent studies using microwave assisted protein extraction improved the accuracy of dAGEs quantitation (Poojary et al., 2020; Zhang et al., 2019). However, a forthright comparison among different dAGEs extraction approaches is still missing.

It is important to note the limitations of the available data: the numbers of observations per infant formula type were low; infant formulas originated from different sources, with different starting materials and different heat treatments; and sample analysis was performed in different laboratories. This resulted into scattered data across studies, limiting the possibility to make good comparisons. As mentioned in the Materials and Methods section, in this paper the reported concentrations were recalculated to express the reported data in the same unit (on the basis of protein concentration). This facilitates the mutual comparison of the different studies and products providing a clear indication on the current state-of-knowledge.

From the data collected in this review, it can be noticed that cow's milk proteins are the main target for scientists to study the reactivity of milk proteins to glycation reaction under thermal treatment, however, very little is currently known about the reactivities of other sources of milk proteins to glycation reaction. With an increasing interest in producing goat milk infant formula and plant-based protein infant formula, the potential for dAGEs formation should be investigated in further studies. Moreover, studies on the role of free Amadori product are still lacking, and this is a very promising future research direction. It has been well established that different protein sources in milk recipe affect the occurrence of glycation differently. However, the effects of long chain polyunsaturated fatty acids (PUFA) in infant formula on dAGEs formation remains unclear. Oxidized PUFA can contribute to dAGEs formation through the entangled network of advanced lipoxidation end-products (ALEs), but it is a challenge to investigate this.

The concentrations of dAGEs in infant formula is not only recipe-dependent but also processing-dependent. One of the biggest challenges to the researchers who study on the glycation of infant formula is the lack of information on the processing conditions of each infant formula, for instance the intensity of heat treatment, the type of

sterilization (pasteurization or UHT sterilization), and the different heating techniques (direct UHT sterilization or indirect UHT sterilization). Unfortunately, this information is often confidential for the manufacturers and therefore only educated guesses can be performed to explain the differences in the occurrence of the dAGEs in commercial products.

A comprehensive understanding of dAGEs formation during the processing of infant formula is the foundation of designing promising dAGEs mitigation strategies. Kinetic modeling is a tool to deeply research the dynamic variation of the precursors, initial markers, and intermediate markers of MR, which can be applied to the processing of infant formula in later studies to give inspiration on further exploration of dAGEs mitigation strategies. Infant formula is the most regulated food item on the market. Therefore, the application of mitigation strategies needs further risk assessment considering the regulations on infant formula compositions, as well as taste acceptability.

A recent study demonstrated that both CML and hydroxymethylfurfural are largely formed during the storage of opened infant formula products (Condurso et al., 2020). This indicates the importance of controlling dAGEs formation during the secondary shelf-life of infant formula products. Hence, further research is required on mitigation of dAGEs formation via controlling storage conditions of opened infant formulas at the consumer stage. More work is also needed to identify mitigation strategies that prevent the dAGEs formation during the storage of infant formulas.

Regarding the dAGEs behaviors during the storage of infant formulas, a promising research direction is to link the processing technologies to the changes of dAGEs concentration during storage. It can be seen that the use of a spray drying step or the use of UHT treatment or pasteurization would have different effects on dAGEs variations during storage.

Regarding the occurrence of MCPDEs and GEs in infant formula, it should be noticed that four of the selected papers estimated the potential exposure of infants to 3-MCPD when they consume local infant formulas, and all these four papers showed that the estimation of daily intake value of 3-MCPDE to infants is higher than TDI. It is an attention point for infant formula manufacturers and they should be careful to select the vegetable oils with low MCPDEs and GEs to add as ingredients of infant formula. Nowadays, several toolboxes have been developed to accelerate the mitigation of MCPDEs and GEs in foods (BLL, 2016; Codex Alimentarius Commission, 2019). Therefore, occurrence data of MCPDEs and GEs in infant formulas should be updated to re-assess the exposure of infants to MCPDEs and GEs via infant formula products.

4 | CONCLUSION

The current review targets to provide insights into the occurrence of thermal processing contaminants, particularly dAGEs, MCPDEs, and GEs, in infant formula, revealing the potential effects of infant formula processing conditions and recipes, as well as into mitigation strategies on dAGEs in milk products. In conclusion, processing conditions and recipes play a crucial role in the formation of dAGEs in infant formula. Hydrolyzed protein is more prone to glycation as compared to intact protein. When partially or fully replacing lactose with maltodextrin in the recipe, or using UHT treatment as an alternative technique for in-bottle sterilization, the glycation degree in infant formula will decrease. Encapsulation of ascorbic acid in the recipe, and the addition of phenolic compounds or enzymes (e.g., β-galactosidases, fructosamine oxidase) into the recipe are both novel promising measures for the mitigation of dAGEs occurrence in infant formula. The occurrence of MCPDEs and GEs in infant formula originates from the vegetable oils used in the recipe and are not affected by infant formula processing. Therefore, limiting the occurrence of these compounds in infant formula fully relies on the type and concentration of vegetable oils added into recipe and the occurrence of MCPDEs and GEs already present in these oils. There is a trend promoting the use of dairy fat in the recipe of infant formulas instead of using vegetable oils as fat sources and this would surely eliminate the risk of MCPDEs and GEs presence.

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AUTHOR CONTRIBUTIONS

Yajing Xie: investigation; visualization; writing-original draft. **H. J. van der Fels-Klerx**: supervision; writing-review & editing. **Stefan P. J. van Leeuwen**: supervision; validation; writing-review & editing. **Vincenzo Fogliano**: supervision; writing-review & editing.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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