Journal of Food and Nutrition Research, 2019, Vol. 7, No. 1, 33-40
Available online at http://pubs.sciepub.com/jfnr/7/1/5
Published by Science and Education Publishing
DOI:10.12691/jfnr-7-1-5

The Maillard Reaction in Powdered Infant Formula

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Received December 04, 2018; Revised January 08, 2019; Accepted January 23, 2019

Abstract Powdered infant formulas are manufactured by dissolving dried ingredients in water or skimmed milk, which is then followed by pasteurization, homogenization, concentration in a vacuum evaporator and drying in spray dryer. Due to this large number of thermal processes, the formulas are subject to a series of reactions that can negatively impact their quality, among them the Maillard reaction. It is the result of chemical reactions between a carbonyl group of the reducing sugar and a free amino group of the protein or amino acid. During prolonged heating or storage of the powdered infant formula, a wide variety of reactive compounds are formed, which can then polymerize with protein residues and form dark pigments or melanoidins. The Maillard reaction is affected by several factors including pH, temperature, water activity, type of reducing sugar and presence of metals. It can result in numerous consequences, such as: an unavailability of amino acids, solubility loss, increase the allergenicity of certain proteins, and even impediment of mineral absorption. Much research is still needed to understand the consequences of the Maillard reaction in powdered infant formulas in order to find solutions that provide foods with high nutritional properties and are safe for the consumer.

Keywords: *breast milk, cow milk, heat treatments, infants, nutrients*

Cite This Article: Lauane Nunes, Evandro Martins, Ítalo Tuler Perrone, and Antônio Fernandes de Carvalho, “The Maillard Reaction in Powdered Infant Formula.” *Journal of Food and Nutrition Research*, vol. 7, no. 1 (2019): 33-40. doi: 10.12691/jfnr-7-1-5.

1. Introduction

The World Health Organization (WHO) recommends exclusive breastfeeding up to 6 months of age, with continued breastfeeding along with appropriate complementary foods up to two years of age or beyond [1].

However, in certain circumstances, mothers may choose not to breastfeed or not to do so exclusively. These circumstances can include insufficient milk syndrome, breastfeeding failure, social factors (working mothers), medical reasons, such as when breastfeeding is contraindicated in infants who have metabolic issues or are born premature and/or have low birth-weight. It is then necessary to substitute or supplement breastfeeding with infant formulas [2,3,4].

The Codex Alimentarius Committee (Codex), the primary international infant formula regulatory agency, defines infant formula as a specially manufactured substitute for breast milk that satisfies, by itself, the nutritional requirements of infants during the first months of life up to the introduction of appropriate complementary feeding.

In most cases, powdered infant formulas are produced using cow’s milk with the addition of other components such as lactose, long-chain polyunsaturated fatty acids, vitamins and minerals to mimic breast milk [5]. All ingredients are mixed together and undergo successive heating treatments (pasteurization, concentration, drying) to guarantee their microbiological safety while, at the same time, promote undesirable reactions between the constituents [6,7,8].

Powdered infant formulas are especially predisposed to the initiation and propagation of the Maillard reaction due to their unique composition, their exposure to high temperatures, and their prolonged storage period [9,10]. Due to the nutritional importance of powdered infant formula and the negative effects the Maillard reaction has been shown to have on them, the purpose of this overview is to evaluate the consequences of Maillard reaction occurrence in powdered infant formulas.

2. Infant Formulas

2.1. Composition of Infant Formulas

Because infant formulas are the primary substitute for or supplement of breast milk and are often the only source of nutrients during a significant period of rapid growth and development, it is crucial that the infant formula manufacturing industry provide safe and nutritionally adequate products to meet infants’ needs [3]. It is essential that these products deliver sufficient amounts of all nutrients in appropriate ways, because the inclusion of unnecessary components or in inappropriate amounts of nutrients may overload an infant’s physiological and metabolic functions [11].

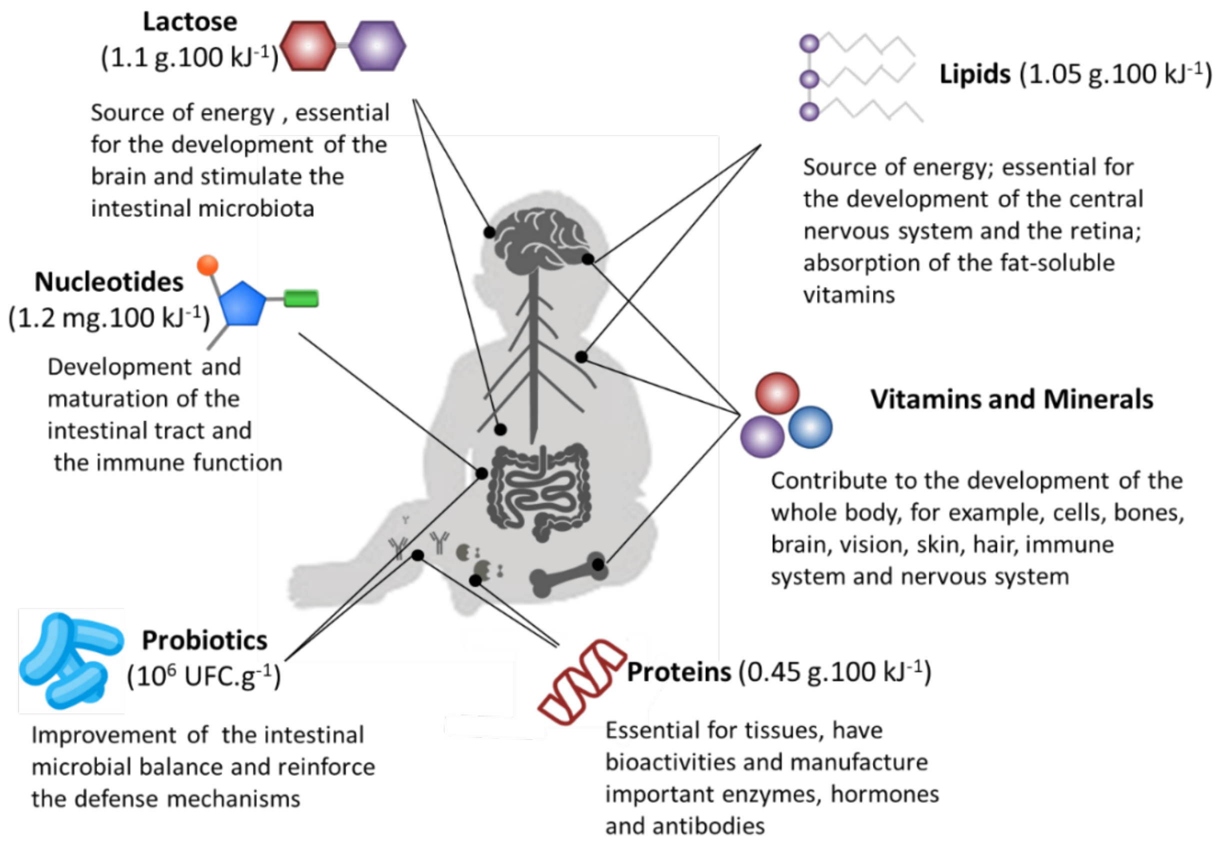

Figure 1. Importance of primary nutrients and minimum recommendations for infants [6,13,16]

Recommendations for nutrient limits have been given by FAO and WHO [12], in addition to other authors [6,11,13]. They are presented in Figure 1 along with the importance of the primary nutrients.

The main proteins used in powdered infant formulas are cow's milk protein, soy protein and goat milk protein isolates. Formulas made using cow's milk should be enriched with essential amino acids and present reduced protein content to 0.7 g.100 kJ^{-1} with a ratio of whey protein to casein of 60:40 [12].

Non-protein nitrogen is derived from a number of components, such as free amino acids, peptides, creatine and creatinine, nucleic acids and nucleotides, urea, uric acid, ammonia, amino sugars, polyamines, carnitine, and other compounds [14]. A number of these components have important functions for infants. Some studies suggest that nucleotides improve the development and maturation of the intestinal tract, as well as boost immune function, for example [3,15].

Codex recommends a minimum total carbohydrate content in infant formulas of 2.2 g.100 kJ^{-1}. Carbohydrates in infant formulas can theoretically contribute between 28% and 56% of energy. Fifty percent of the carbohydrates present in the formulas must be lactose; however, glucose and fructose cannot be added due to effects on osmolarity, the Maillard reaction, and hereditary fructose intolerance [17].

Infant formulas are fortified with lactose in order to simulate lactose concentrations present in breast milk, so a minimum addition of 1.1 g.100 kJ^{-1} is required, with no maximum limit [17]. Lactose acts as a source of energy and is essential for the development of the infant brain. Lactose also stimulates the development of intestinal microbiota [13,14].

Oligosaccharides like galactooligosaccharides (GOS), fructooligosaccharides (FOS), and inulin are added for the purpose of mimicking the biological benefits of oligosaccharides present in breast milk [6].

Lipids provide about 50 % of an infant's daily caloric intake and their addition is allowed up to 1.4 g.100 kJ^{-1} [12,14]. The majority of lipids (98 %) are in the form of triglycerides; the rest consist of diglycerides, monoglycerides, free fatty acids, cholesterol and phospholipids [18].

Long-chain polyunsaturated fatty acids are added to infant formulas because they are essential for the development of an infant's central nervous system and retinas [5].

Trans-fatty acid content in infant formulas should be as low as possible. According to Codex, the maximum level of trans-fatty acids must not surpass 3 % of total fatty acids [13].

Six elements (K, Na, Ca, Mg, P and Cl) are referred to as minerals and are present in mg.100 kJ^{-1}, while trace elements (Fe, Cu, Zn, Se, Mn and I) are present in µg or less than 100 kJ^{-1} [19]. These compounds should also be fortified in infant formulas in order to resemble breast milk more closely and maintain optimal osmotic pressure for the infant [12].

Infant formulas provide liposoluble and hydrosoluble vitamins to ensure an infant is able to grow and develop normally without running the risk of malnutrition [13].

However, liposoluble vitamin absorption from infant formulas is linked to the efficacy of the formula's lipid absorption, though an excess intake of hydrosoluble vitamins can easily eliminated from the body as compared to the former [19].

The most commonly studied and used species of probiotics belong to genera *Lactobacillus*, *Bifidobacterium* and *Saccharomyces* [20]. When added to infant formula, these microorganisms improve the intestinal microbial balance and strengthen the infant body's defense mechanisms, through antagonistic, competition and immunological effects [13].

Although there is a current trend to add nucleotides, prebiotics, probiotics, arachidonic acid (ARA) and docosahexaenoic acid (DHA) to infant formulas, further research is needed to define daily use recommendations and to determine the health effect on infant nutrition [5].

2.2. Production of Powdered Infant Formula

Infant formulas are currently available in powdered or concentrated liquid forms. Due to the advantages of powdered infant formula (lower production and transport costs, longer storage time at ambient temperature, practicality, among others), it has shown greater acceptance by global consumers.

The first dehydrated infant formulas were produced using a dry mixing process in which the powdered ingredients were purchased separately and mixed in large batches. The microbiological safety of this process has been put into question by cases of contamination with pathogens such as *Enterobacter sakazakii* and *Salmonella enterica* [3,7].

Dry mixing has been replaced by a wet mixing process, shown in Figure 2, which consists in dissolving the dried ingredients in preheated water or skimmed milk, then pasteurizing and homogenizing the mixture. The preparation is first concentrated in a vacuum evaporator in order to reduce the energy costs associated with spray drying [6,7].

Spray drying of the concentrated preparation is characterized by the atomization of the liquid into small droplets whose water molecules are evaporated by a flow of heated air. The hot air stream temperature varies between 140 and 200 °C but, due to the relatively brief exposure time of the particles to heating, their core temperature does not exceed 45 ºC [21,22].

After passing through a cyclone, the resulting powder is collected and packed in large bags or stored in silos during quality control analysis [23]. Subsequently, it is canned on an aseptic packaging line in a modified atmosphere such as nitrogen, to prevent possible oxidation of the product [7].

The product must then be packed in suitable containers that block out light, prevent water and O_2 transmission, and resist impact and stacking damage. The packages must then be stored in ideal humidity and temperature conditions [24]. Even when all these conditions are met, powdered infant formulas are still subject to a series of reactions that can cause a reduction in quality, such as the Maillard reaction.

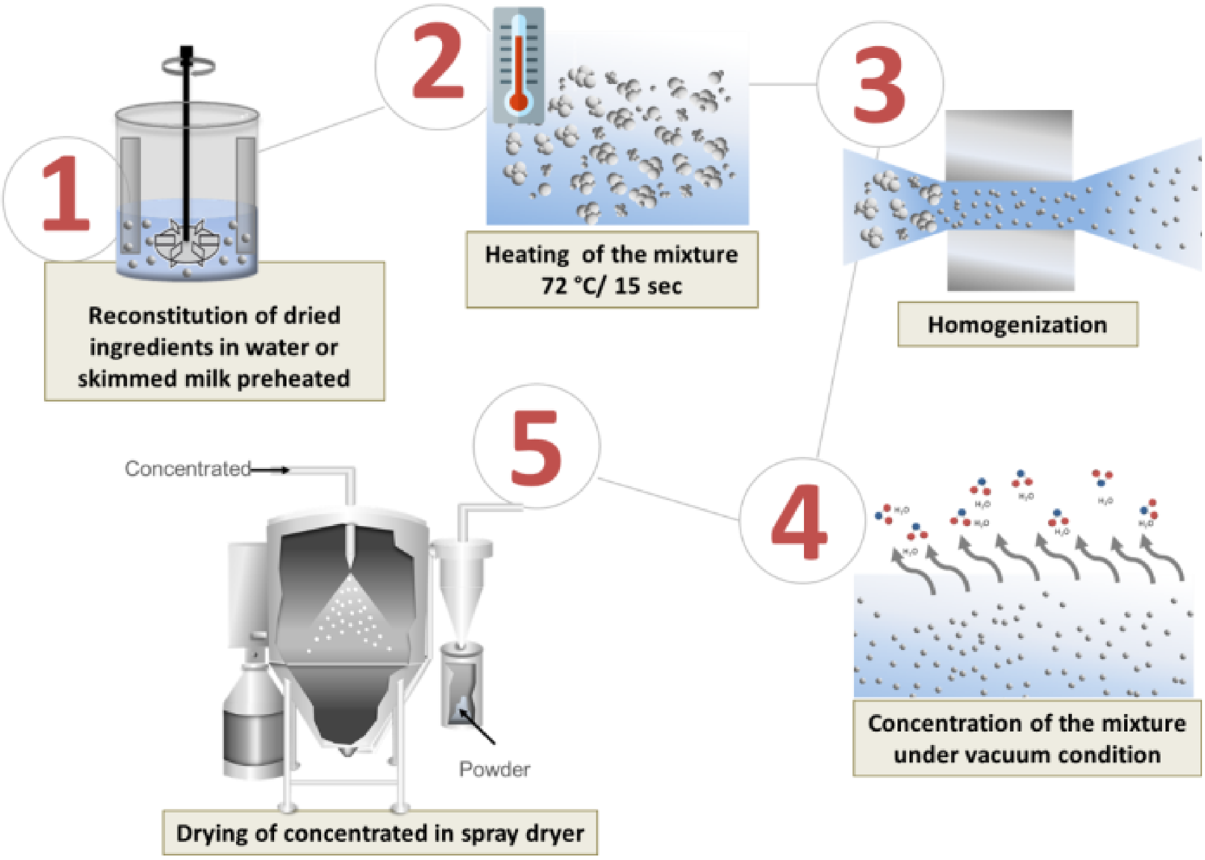

Figure 2. Production of powdered infant formulas [6,7,21]

3. The Maillard Reaction

The Maillard reaction is the result of chemical reactions between a carbonyl group of the reducing sugar present and a free amino group of the protein or amino acid, which forms a lactosyl-lysine, also known as Schiff's base [25].

In the vast majority of infant formulas, lactose is the main reducing sugar present while proteins are found as casein and whey proteins [17,18]. Due to high lactose (7.0-7.5 % $w.v^{-1}$) and protein (1.2-1.55 % $w.v^{-1}$) content, infant formulas are prone to initiating the Maillard reaction conducive to the formation of Schiff's bases when exposed to high temperatures. As previously described, powdered infant formulas are subjected to successive heating treatments during the manufacturing process. These heat treatments favor the initiation of Maillard reaction.

Moreover, Schiff's bases are chemically unstable and can be subject to additional isomerization, a reaction known as the Amadori rearrangement, which leads to the production of lactoulosyl-lysine (Amadori product) and the loss of nutritional value due to essential amino acid blockage [10,25,26]. The Amadori rearrangement occur under slight acid conditions, which are reached when formic acid produced by parallel reactions between lactose molecules accumulates [27,28]. During prolonged heating or storage, Amadori products are degraded under neutral or acid conditions (1,2 enolisation) to form a wide variety of furfural compounds such as 5-hydroxymethylfurfural (HMF), 2-*furaldehyde (F),* 2-furyl-methyl ketone (FMC) and 5-methyl-2-furaldehyde (MF). As powdered infant formulas are slightly acidic or neutral, these compounds take precedence in formation [29,30].

If powdered infant formulas have a basic pH (variable according to the composition), Amadori products can also be degraded by other means (2,3 enolisation), to form reductones and a variety of fission products, including acetol, pyruvaldehyde and diacetyl. These carbonyl compounds are highly reactive and participate in other reactions such as the Strecker degradation. They can then react with amino acids to form aldehydes and aminoketones, compounds which contribute to aromas of foods such as chocolate, coffee, tea, honey and bread [28,31].

Reductones, furfurals, aldehydes and other intermediate products react readily with amines to give "polymeric" high molecular mass, dark pigments called melanoidins [10]. The positive and negative aspects of melanoidins will be discussed later.

3.1. Factors Which Affect the Maillard Reaction

A number of factors influence Maillard reaction speed. When the pH is above the isoelectric point of the involved amino acid, typically in alkaline conditions, favor amino group reactivity for the carbonyl group involved, in addition to favoring open chain sugar formation. Acidic environments, such as powdered infant formulas, favor the hydrolysis of non-reactive sugars, such as sucrose and promote amino-carbonyl interaction. In addition, pH affects the Amadori product degradation pathway. Acidic to neutral pH favors the formation of furfural as well. Alkaline conditions promote the formation of several products which contribute to the organoleptic properties of the product, as explained above [10,32,33].

The Maillard reaction rate is also influenced by temperature, which increases reactivity between the sugar and amino group present [25,34]. Because the Q_{10} of the reaction is 3-4, the reaction rate triples or even quadruples at each 10 °C increase in temperature [35].

Water activity (a_w) is another important factor, since condensation and dehydration reactions are part of the Maillard reaction pathways [36]. In a dilute system (excess water), there is a decrease in the Maillard reaction rate. The dilution of the reagents prevents the occurrence of many Maillard reaction stages. When water activity is reduced, reactants may begin to lose the mobility essential for the reaction to occur, resulting in a lower rate [37,38]. In this case, browning rates reach a maximum around intermediate values of 0.5 to 0.8 [39].

An increase in the Maillard reaction in dry dairy products is often attributed to reduced water activity, due to the increased concentration of reactants as a result of drying [32,40].

The type of reducing sugar or the amine in a product has a direct influence on the speed of the Maillard reaction. Pentoses are more reactive than hexoses and reducing monosaccharides are more reactive than disaccharides or reducing polysaccharides. Non-reducing sugars, however, require glycosidic bond hydrolysis to participate in the Maillard reaction. In most infant formulas, lactose is the main reducing sugar present, and it can positively influence reaction rates [10,41]. Lysine is one of the most reactive amino acids for the Maillard reaction. Beyond the α-amino group in the terminal amino acid, lysine contains a side chain with a free ε-amino group that also participates in the Maillard reaction [25,28]. Sugars also react with arginine, methionine, tryptophan, and histidine [42].

The Maillard reaction can also be catalyzed by metals such as copper, iron, calcium and magnesium, which are present in the composition of infant formulas. The mechanisms of metal ion action on Maillard browning are still unclear, but most studies involving polyvalent transition metals suggesting an unspecified contribution of redox processes in the observed browning [32,43].

Lipid oxidation products can also be a source of carbonyls in later stages of the Maillard reaction with behavior similar to carbohydrates. Specifically, the lipid oxidation product reactions with amines, amino acids, and proteins have long been related to the browning observed in many foods during processing and storage [32,44].

3.2. Consequences in Powdered Infant Formulas

The Maillard reaction contributes browning to most thermally-processed foods through melanoidin formation. Browning is undesirable, especially in certain dairy products [36,45].

The Maillard reaction also contributes to volatile compound formation, primarily aldehydes and aminoketones from the Strecker degradations that contribute to certain food aromas [28]. The cooked flavors mainly affect processed dairy products such as milk powder, UHT milk, pasteurized milk and infant formulas [10,39].

The reaction influences the texture of food via protein cross-linking during food processing. This is one of the main causes of changes to milk powders during storage [45]. A considerable amount of high-molecular-weight protein complexes that may be largely responsible for solubility loss in MPC 80 (milk protein concentrate), WMP (whole milk powder), and SMP (skim milk powder) via dicarbonyl compounds produced as advanced MRPs (Maillard reaction products), in addition to cross-links between molecules in casein micelles [46].

Amadori product degradation also forms acids, such as formic and acetic acid. These acids can cause a slight decrease in pH in stored dairy products [27,28].

The most apparent negative consequences of the Maillard reaction in food are decreased digestibility and destruction and/or biological inactivation of amino acids, particularly essential amino acids [28,47]. The quality and nutritional availability of proteins in dairy products is important as they are a main source of essential amino acids [10].

Furthermore, thermal processing can affect food protein allergies because it decreases protein solubility and promotes structural rearrangements and protein aggregation with sugar [47]. For example, the allergenicity of β-lactoglobulin may be enhanced by the Maillard reaction, since higher degrees of glycation lead to a higher resistance to proteolysis because the protein cleavage sites are masked [33,37,47].

Melanoidins have metal-chelating properties which may be undesirable when they affect nutritionally essential metals (Ca, Mg, Cu, Zn, Fe) and subsequently impede metabolism and mineral absorption [10,39]. Milk-processing conditions decrease calcium solubility which can result in significantly lower calcium absorption and retention values [48]. Other authors have also observed reduced iron and zinc bioavailability in bottle-sterilized infant formula compared to reconstituted powdered infant formula [49,50].

3.3. Potentially Harmful by-products of the Maillard Reaction

HMF is one of the intermediate compounds formed during the Maillard reaction. In general, HMF can be used as marker to determine both the extent of the thermal treatment applied and inadequate storage conditions [51]. There are reports of possible mutagenic, genotoxic and carcinogenic effects for HMF and subsequently prevent and its metabolites, mainly 5-sulfoxymethylfurfural (SMF), which can be metabolized *in vivo*. The interaction between this reactive intermediate and cellular nucleophiles (i.e., DNA, RNA, and proteins) may result in structural damage [52,53]. Special attention has been paid to HMF content in infant formulas and baby foods in general [51].

Acrylamide has been classified as a probable carcinogen. It is found in carbohydrate-rich foods that have been processed at a relatively high temperature. Acrylamide is formed during the Maillard reaction through the thermal degradation of free asparagine in the presence of sugars [41,54]. However, acrylamide levels in dairy products are relatively low (<100–1000 $\mu g.kg^{-1}$) [55]. The mean content of acrylamide in baby foods ranged from 2 to 516 $\mu g.kg^{-1}$ [56].

One group of non-volatile compounds, heterocyclic aromatic amines (HAAs), are highly mutagenic and have been found in protein-rich cooked foods subjected to high temperatures [54]. The Maillard reaction contributes to the formation of HAAs by generating crucial intermediates including aldehydes, pyridines and pyrazines through the Strecker degradation reaction [10]. These have been shown to be tumor inducers in long-term animal studies. HAAs may pose a carcinogenic risk for humans who are genetically susceptible and/or moderately to highly exposed to the compounds [31]. The presence of such mutagens has not yet been reported in dairy products [33].

In early 2004, the US Food and Drug Administration (FDA) expressed concern at the presence of furan, a possible human carcinogen, in a number of heat-treated foods [57]. Maillard reaction products such as furfural and furoic acid have been proposed as furan precursors but their levels in heated dairy products are considerably low (generally <20 $\mu g.kg^{-1}$ in infant formulas and evaporated milks) [33].

3.4. Advanced Glycation End Products (AGEs)

The final products in biological systems resulting from the Maillard reaction occurs are referred to as AGEs. A large number of AGEs have been identified *in vivo* including carboxymethyllysine (CML), pentosidine and pyrraline and dietary MRPs. These all contribute to the AGES accumulation in the body [58,59].

AGEs can cause tissue damage generated by structure and protein changes; inter- or intramolecular cross-linking; free radical formation, and inflammation due to the interaction of these compounds with specific receptors [60,61].

As a result, excess AGE accumulation in body tissue seems to contribute to the development of chronic disorders such as diabetes, weight gain, cardiovascular diseases and neurodegenerative diseases, *i.e.,* Alzheimer, Parkinson and schizophrenia [62,65,66,67]. In addition, AGEs may contribute to the development of arthritis, bone mass loss, and disorders involving the function and/or structure of DNA and RNA molecules [45,58,60,67,68].

Young children have greater gastrointestinal/epithelial permeability, which been linked to the risk of atopic disease. Immune system immaturity might also make infants more susceptible to environmental/epigenetic influences [69].

The effects of the aforementioned compounds can be avoided or regulated by renal AGE elimination and antioxidant systems, but results depend on dietary intake, pathology presence and the amount and type of compounds ingested [45,47,58].

3.5. Benefits of the Maillard Reaction in Powdered Infant Formula

Some studies have evaluated the possible antioxidant, antihypertensive, prebiotic and antimicrobial activity of MRPs, found as melanoidins [45,60,70,71]. Higher antioxidant activity may be attributed the intermediate and (especially) final stage of the Maillard reaction in a system containing milk proteins and reducing sugars. Similar results were obtained for milk powder, sweetened condensed milk and "dulce de leche" [72]. Pre-heated milk protein and sugar mixtures effectively prevent lipid oxidation in dairy beverages. This prevention is probably due to Maillard reaction products generated at initial sterilization stages [73]. Other works also observed Maillard reaction product antioxidant activity in a system made up of milk proteins and sugars [74,75].

This antioxidant effect has been associated with intermediate reductone compounds that may break the radical chain through hydrogen atom donation. Others Maillard reaction products, such as melanoidins, have also been reported to be powerful scavengers of reactive oxygen species, peroxyl and 1,1-diphenyl-2-picryl-hydrazyl (DPPH) [41,76].

Some dietary AGEs may accumulate in body tissues. MRPs that are not absorbed can be metabolized by intestinal microbes and function as prebiotics [58].

3.6. Inhibition of Maillard Reaction in Powdered Infant Formula

Many sulphur compounds inhibit the Maillard reaction in milk systems by making carbonyl compounds unavailable for further reactions and browning [33].

Oxygen concentration may influence both the overall browning rate and the formation of low molecular weight oxidation products. Replacing air with nitrogen is efficient for reducing the rate of this and other deterioration reactions. This technique is already being used to inhibit the Maillard reaction in the powdered infant formula industry [33].

Replacing one carbohydrate with another, less reactive carbohydrate in powdered infant formula could also be a way to inhibit the Maillard reaction [77]. Yet another method, which is still being studied, would be optimizing microwave heating of a model infant formula to show that it is possible to produce a formula with a reduction in formed MRPs and in added spore deterioration [8,78].

Moreover, several authors recommend requiring milk, especially those that have been lactose-hydrolyzed, be stored at ≤ 4 ºC, in order to limit protein damage due to the Maillard reaction [79,80,81,82]. In addition, moisture content should be maintained below 30 % $w.w^{-1}$ to limit the molecule mobility in dairy powders [41].

4. Conclusions

Despite the importance of infant formulas for infant nutrition, there have been few studies published on the subject, particularly studies that clarify the effect of the Maillard reaction on infant formulas and any risk it may pose to infants. Understanding the chemical, nutritional and toxicological consequences of browning reactions and related transformations in infant formulas can help guide production strategies and result in safer and healthier powdered infant formula products.

Acknowledgements

The authors are grateful for the financial support provided by CAPES, CNPq and FAPEMIG to carry out this work.

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