Dietary exposure to acrylamide: A critical appraisal on the conversion of disregarded intermediates into acrylamide and possible reactions during digestion

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ABSTRACT

The amount of acrylamide in asparagine rich thermally processed foods has been broadly monitored over the past two decades. Acrylamide exposure can be estimated by using the concentration of acrylamide found in foods and alternatively, biomarkers of exposure are correlated. A better estimation of dietary acrylamide exposure is crucial for a proper food safety assessment, regulations, and public health research. This review addresses the importance of the presence of neglected Maillard reaction intermediates found in foods, that may convert into acrylamide during digestion and the fate of acrylamide in the gastrointestinal tract as a reactive compound. Therefore, it is questioned in this review whether acrylamide concentration in ingested foods is directly correlated with the dietary exposure to acrylamide.

1. Introduction

Acrylamide is an α,β-unsaturated carbonyl compound and thus it reacts with nucleophiles (Fig. 1) (Khaneghah et al., 2020; Mogol et al., 2021). It is a highly water-soluble, colorless and odorless compound with a low molecular mass (71.08 g/mol). Polyacrylamide, the polymerized form of acrylamide, had been used in several industrial applications such as paper and textile industry, water and sewage treatment, cosmetics, tunnel construction and ore for almost 50 years while it was discovered in foods in 2002 (Mogol et al., 2021).

In 1994, the International Agency for Research on Cancer announced that acrylamide has been classified as a "probable human carcinogen" in Group 2A (IARC, 1994). In 2000, researchers found that acrylamide was a food contaminant after determining high amounts of the acrylamide-hemoglobin adduct in rats fed with fried feed (Tareke et al., 2000). In 2002, the researchers in Stockholm University and Swedish National Food Authority revealed that acrylamide was present in foods processed at temperatures greater than 120 °C such as bread, cereals, coffee, french fries and potato chips (Tareke et al., 2002). According to the studies, cytochrome P450 2E1 mainly metabolized acrylamide to form glycidamide which is a highly reactive epoxide compound (Friedman, 2003). The alkylation of DNA by glycidamide results in

stable adducts to DNA and causes carcinogenesis through its genotoxic properties (Friedman, 2003). Since then, researchers have been mainly focused on understanding the formation mechanism of acrylamide in foods, the toxicity in human body, improving the analytical techniques on the detection, and developing the mitigation strategies, with a great effort. The health institutions and food authorities including European Food Safety Authority (EFSA), U.S. Food and Drug Administration (FDA), World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO) developed and updated the databases of acrylamide considering the scientific and market reports. In addition to these databases, the toolboxes were built for highlighting the ways to reduce the acrylamide levels in each defined food groups by controlling the parameters such as raw material selection, recipe formation or process design. To date, an extensive data about acrylamide levels in industrially produced foods or in model food systems have been generated and more precise and accurate analytical techniques to determine the acrylamide levels have been developed by the researchers. Besides, the detailed information on the toxicity of acrylamide have been provided and the proposed strategies have been served to reduce the acrylamide in foods. Nevertheless, few studies have been published about the fate of acrylamide during digestion (Badoud et al., 2020; Hamzalıoğlu and Gökmen, 2015; Kim et al., 2007; Sansano et al.,

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2017; Schabacker et al., 2004).

Formation of acrylamide in the gastrointestinal tract might pose an additional risk for the exposure to acrylamide via foods. On the other hand, elimination of acrylamide in gastrointestinal tract could be positive in terms of exposure. Therefore, the information about acrylamide levels during digestion of different foods and the role of neglected Maillard reaction intermediates and interactions in acrylamide formation and elimination is of importance. For this purpose, this review aimed to (i) draw an attention to the importance of disregarded intermediates and interactions in acrylamide formation and elimination during digestion, (ii) understand the fate of acrylamide during digestion and (iii) compare the dietary exposure to acrylamide from foods with exposure during digestion process in order to carry out a realistic risk assessment. From this point of view, this review suggests further research on the role of the intermediates on the fate of acrylamide starting from food to digestion.

2. The role of intermediates and interactions in acrylamide formation and elimination during heating

After the discovery of acrylamide in foods, several researchers have stated that the Maillard reaction, the reaction between amino acids and reducing sugars, was mainly responsible for the formation of acrylamide in certain foods, such as potato chips, french fries, cereal products (Mottram et al., 2002; Stadler et al., 2002; Tareke et al., 2002). Stadler et al. (2002) and Mottram et al. (2002) indicated that acrylamide can be released by the thermal treatment of certain amino acids such as asparagine. Further experiments performed by Zyzak et al. (2003) using labeled carbon and nitrogen asparagine supported with those that the key precursor of the formation of acrylamide was asparagine. Despite the fact that asparagine was revealed as the main source, the conversion of asparagine itself to acrylamide was found in a limited extent (Yaylayan et al., 2003). Indeed, Yaylayan et al. (2003) have found that asparagine was rapidly degraded to acrylamide in the presence of carbonyl compounds such as reducing sugars. Several studies have supported that the reaction between carbonyl compounds and asparagine yields acrylamide (Hamzalıoğlu and Gökmen, 2012; Stadler et al., 2002, 2004).

The main acrylamide formation pathway is given in Fig. 1. According to this mechanism, α-amino group of asparagine first reacts with the carbonyl group of a carbonyl compound such as reducing sugars and a Schiff base is formed (Stadler et al., 2002; Tareke et al., 2002; Zyzak et al., 2003). Most of the Schiff base rearranges to an Amadori or a Heyns compound, which are not direct intermediates of acrylamide formation (Ledl and Schleicher, 1990; Stadler et al., 2004), however they take part in the formation of acrylamide in the later stages through their degradation to α-dicarbonyl compounds. Secondly in the formation of acrylamide, decarboxylation of Schiff base produces an azomethine ylide. The azomethine ylide degrades into imine I or II (Yaylayan et al., 2003; Zyzak et al., 2003). Then, imine I is hydrolyzed to a Strecker aldehyde (3-oxopropanamide) which can be a precursor of the acrylamide formation but in trace amounts (Blank, 2005; Stadler et al., 2004). On the
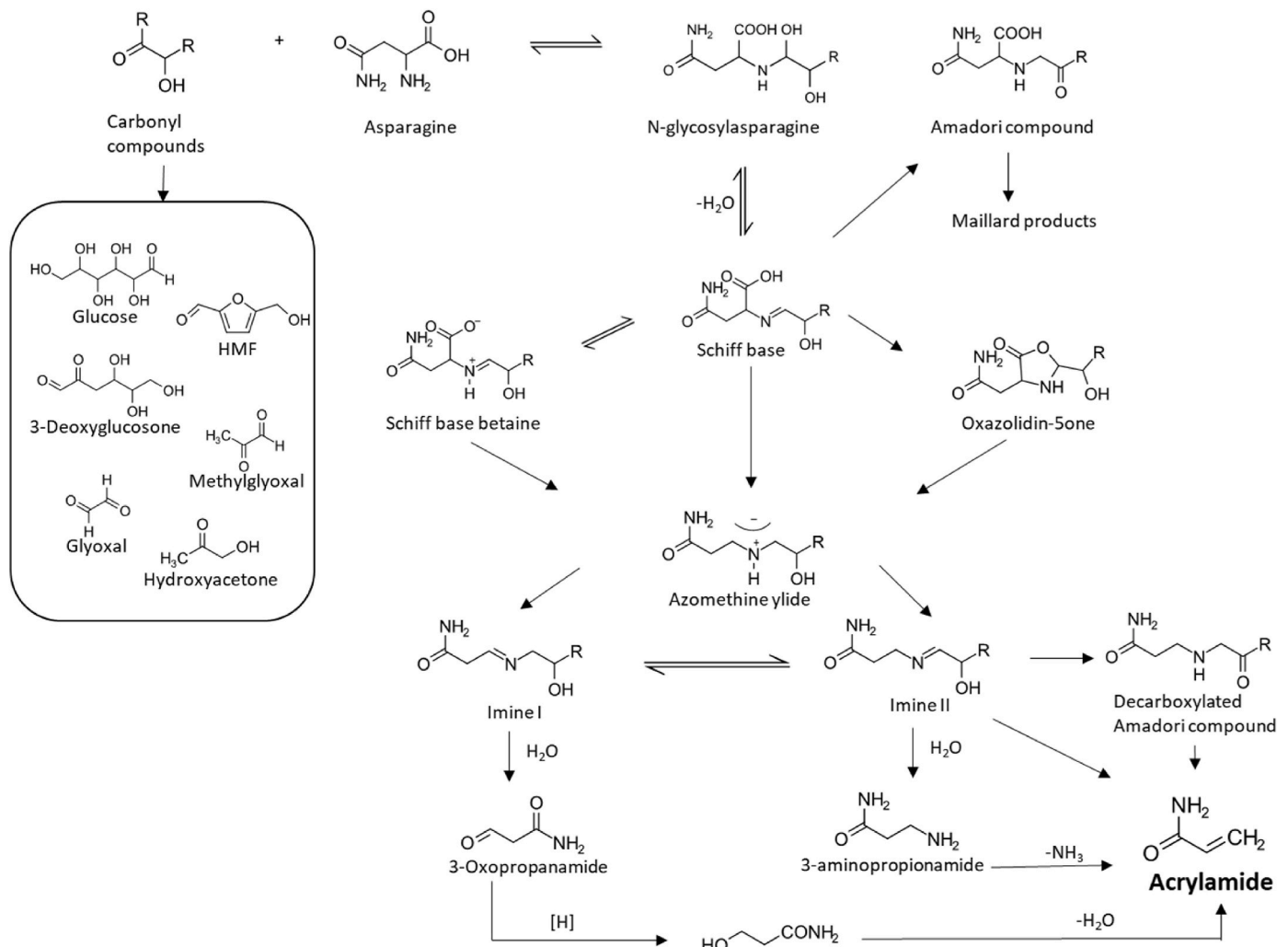

Fig. 1. Formation pathway of acrylamide (Mottram et al., 2002; Stadler et al., 2002; Yaylayan et al., 2003).

other hand, imine II may produce acrylamide in two ways; (i) β-elimination of imine II to directly to form acrylamide, (ii) the formation of 3-aminopropionamide (3-APA) through the hydrolysis of imine II and then the deamination of 3-APA results in the formation of acrylamide (Stadler et al., 2004; Zyzak et al., 2003). As a minor pathway, acrylamide can be formed from acrolein which is formed from oils by heating at elevated temperatures (Granvogl et al., 2004; Yasuhara et al., 2003). In addition, 3-APA can be the precursor of more efficient acrylamide formation in the presence of carbonyl compounds (Granvogl et al., 2004; Granvogl and Schieberle, 2007).

Apart from reducing sugars, intermediates formed during thermal processing can also trigger acrylamide formation from asparagine under suitable conditions as they bear carbonyl groups (Amrein et al., 2006). Gökmen, Kocadağlı, Göncüoğlu, and Mogol (2012) showed that HMF was more efficient than glucose in the formation of acrylamide from asparagine at elevated temperatures. Then, Cai et al. (2014) have stated that higher amounts of HMF in the presence of chlorogenic acid might promote the acrylamide formation in the model system. Hamzalıoğlu and Gökmen (2020) showed that among other precursors such as glucose and 3-deoxyglucosone, HMF played a critical role on acrylamide formation in coffee during roasting by using multiresponse kinetic modeling. Berk, Hamzalıoğlu, and Gökmen (2020) supported this finding in sesame seeds during roasting.

The other reactive intermediates formed during Maillard reaction and/or caramelization, α-dicarbonyl compounds such as methylglyoxal and glyoxal took attention as they promote acrylamide formation as very reactive carbonyls. Amrein et al. (2006) stated that, the α-dicarbonyl compounds, glyoxal, methylglyoxal, and diacetyl were much more efficient compared to glucose or fructose in converting asparagine into acrylamide in model systems under mild conditions (heating at 120 °C for 10 min). In agreement with these findings, Koutsidis et al. (2008) have indicated that glyoxal played a significant role in acrylamide formation in model systems heated at various temperatures. Contrarily, Stadler et al. (2004) indicated that methylglyoxal and glyoxal had minor contribution to the formation of acrylamide in low-moisture Maillard reaction model systems based on asparagine, reducing sugars, Maillard reaction intermediates, and sugar degradation products heated at 180 °C for 5 min. Constantinou and Koutsidis (2016) also showed that more acrylamide was formed in asparagine-glucose model system than in asparagine-glyoxal model system under wet-to-dry conditions containing 0.2% moisture, heated for 15 min at 160 °C. To the limited studies on the contribution of C-6 skeletal α-dicarbonyl compounds to acrylamide formation, Hamzalıoğlu and Gökmen (2020) and Berk et al. (2020) have indicated that 3-deoxyglucosone route was not a quantitatively important pathway in acrylamide formation.

Despite the evidence of important contribution of these intermediates to the acrylamide formation at least as much as reducing sugars, there is lack of comprehensive studies on the model and/or real food systems including various α-dicarbonyl compounds or other carbonyl compounds at different heating and moisture conditions. In addition to this, acrylamide formation is well known to accelerate at temperatures higher than 120 °C and also in dry or semi-dry systems, thus most studies on understanding the formation mechanism of acrylamide have been performed in dry systems at elevated temperatures. However, there are few studies reporting acrylamide formation under mild conditions (Becalski et al., 2011; Constantin et al., 2019; Napolitano et al., 2008; Yaylayan et al., 2003). There is a need to understand the role of α-dicarbonyl compounds on acrylamide formation in foods subjected to mild conditions.

The possible reactions of Maillard reaction intermediates and acrylamide with nucleophilic compounds might be important on the final amounts of acrylamide in foods. There are studies which confirmed these reactions of acrylamide in the literature (Adams et al., 2010; Claeys et al., 2005; Hidalgo et al., 2011; Zamora et al., 2010). Due to the electrophilic nature of acrylamide, nucleophilic amino and thiol compounds react with acrylamide in foods through Michael addition. Claeys et al. (2005) indicated that simultaneous formation and elimination of acrylamide specified the final acrylamide concentration in model systems. In this regard, Adams et al. (2010) have shown that the presence of amino acids with a nucleophilic side chain considerably decreased acrylamide in model systems, containing lysine, *n*-butylamine, cysteine, *N*-acetylcysteine, arginine, ascorbic acid or serine. Among these nucleophiles, they found that cysteine had the highest reactivity leading to the formation of a mono-addition product (cysteine-*S*-β-propionamide) as well as to a double addition product. Then, Zamora et al. (2010) studied the role of amino compounds such as amines, amino acids, and polypeptides on the fate of acrylamide in model systems. They showed that amino compounds were added to acrylamide through Michael addition that resulted in the production of 3-(alkylamino)propionamides. Additionally, they investigated the activation energies of the adduct formation and elimination considering the unstable nature of 3-(alkylamino)propionamides and found that conversion of acrylamide into its Michael adduct had a lower activation energy than the elimination of the Michael adducts. Similarly, Hidalgo et al. (2011) investigated the formation of Michael adducts of acrylamide with amino and sulfhydryl groups of different nucleophiles such as glutamic acid, *N*-acetylcysteine, glutamic acid/*N*-acetylcysteine mixture, glutathione and cysteine. It was reported that acrylamide disappearance was inversely correlated to the activation energy of the reaction. In addition, the researchers discovered that acrylamide always reacts with nucleophile when amino and sulfhydryl groups were simultaneously present in the same molecule. Furthermore, they suggested that the closer the position of both groups in the same molecule the higher the positive interaction. Recently, Michael adduct of acrylamide with 6 different amino acids, most abundantly with γ-aminobutyric acid, was confirmed and quantified in different food products (Li et al., 2022).

All these discoveries led the researchers to investigate nucleophiles as one of the acrylamide mitigation strategies. In addition to nucleophilic amino and thiol compounds, Rottmann et al. (2021) indicated that phenolic acids (ρ-coumaric acid, ferulic acid, caffeic acid and cinnamic acid) may react with acrylamide as a nucleophile in an oxa-Michael addition. The authors suggested that the reactions of polyphenols resulted in the formation of a Michael product mediated by a phenol ester formation rather than an ether formation. Most of the studies focused on the addition reactions of acrylamide and nucleophiles (Xiong et al., 2017; Zamora et al., 2016; Zhu, Luo, Sun, Wang, Hu, & Chen, 2020; Y. Zhu, Wang, Wang, Zhao, Hu and Chen, 2016). On the other hand, HMF, a significant precursor of acrylamide, was found to react effectively with amino and thiol groups of amino acids (cysteine, lysine and arginine) in high and low moisture model systems by Hamzalıoğlu and Gökmen (2018). Similarly, Nikolov and Yaylayan (2011) found that Schiff base adducts of HMF was generated in the presence of glycine. To date, the effect of the amino and thiol groups of amino acids on HMF elimination have been investigated in many model systems during heating at elevated temperatures. As acrylamide precursors, α-dicarbonyl compounds and another Maillard reaction intermediates have been also found to react with amino and thiol groups in model systems (Bruhns et al., 2019; Comert and Gokmen, 2019; Hamzalıoğlu and Gökmen, 2019b).

3. Acrylamide levels in foods

Acrylamide is mainly formed in carbohydrate and asparagine-rich but low protein and low moisture foods such as french fries, potato chips, breads, biscuits and coffee (Ahn et al., 2002; EFSA, 2015b). Thermal processes like baking, deep-fat frying, roasting lead formation of acrylamide in higher levels (150–4000 μg/kg) in certain foods (Mogol et al., 2021; Tareke et al., 2002). Authorities such as European Commission (EC), EFSA, WHO/FAO, and FDA have established international databases on acrylamide in individual foods and food groups (EC, 2017;

EFSA, 2015b; FDA, 2015; WHO/, 2002). Acrylamide levels of some food groups were summarized in Table 1, including the benchmark levels which can be used for the efficiency of acrylamide mitigation strategies of food industry. Potato based foods in particular fried potatoes contain very high levels of acrylamide. Potatoes contain high amounts of asparagine, and higher the amount of reducing sugars higher the formation of acrylamide during frying (Muttucumaru et al., 2017). Increased frying time and temperature also triggers the acrylamide formation in potatoes (Serpen and Gökmen, 2009). Pourmand, Ghaemi, and Alizadeh (2017) indicated that acrylamide formation in French fries was observed at frying temperatures above 120 °C and it also increased with increasing the time of frying. Several factors such as agricultural practices, processing techniques, and storage could affect the concentrations of acrylamide precursors, reducing sugars and asparagine (Haase et al., 2004; Khaneghah et al., 2020). It is suggested that as potatoes are well known to be highly rich in asparagine, selecting potato cultivars with low concentrations of reducing sugars could minimize acrylamide formation during processing (De Wilde et al., 2006). It was reported that storage at 4 °C led to the accumulation of high concentrations of reducing sugars and therefore cold storage of potatoes should be avoided (Haase et al., 2004). Herein, it should be also stated that the size and shape of food products are directly related to the acrylamide formation, since higher concentrations of acrylamide were mainly detected in the crust of food products (Acar and Gokmen, 2009).

Bakery products such as biscuits, crackers, and breads may also

Table 1
Acrylamide concentration (μg kg⁻¹) in foods (EC, 2017; FDA, 2015; WHO/, 2002).

Food product group	n	Median[a] (μg kg^{-1})	Mean[a] (μg kg^{-1})	P95[a] (μg kg^{-1})	Benchmark level [b] (μg kg^{-1})
Bakery Products					
Soft bread					
Wheat-based bread	302	15	38	120	50
Other breads	99	25	46	203	100
Biscuits and wafers	682	103	201	810	350
Crackers	162	183	231	590	400
Crisp bread	437	89	149	428	350
Ginger bread	693	155	407	1600	800
Coffee Products					
Roasted coffee	566	203	244	563	400
Instant coffee	116	620	674	1333	850
Coffee substitutes					
Based on cereals	20	522	510	–	500
Chicory	37	3100	2942	–	4000
Potato Products					
French fries	378	196	332	1115	500
Potato crisps and snacks	800	389	580	1841	750
Other Products					
Breakfast cereals					
Bran products and whole grain cereals	151	135	164	413	300
non-whole grain or non-bran based wheat and rye based products	33	140	142	–	300
non-whole grain or non-bran based maize, oat, spelt, barley, and rice based products	149	50	73	230	150
Cereal-based baby foods	394	15	103	200	40
Chocolate powder	2	75	75	–	–
Fish and seafood products, crumbed, battered	4	35	35	–	–
Roasted Nuts and Fruits	145	25	98	–	–

[a] Mean, median, P95: mean, median and 95th percentile contamination level presented as the middle bound (MB) estimate. In case of too few observations (less than 60 for the 95th percentile), the estimation may be biased and is consequently not provided.
[b] The benchmark level is from EU Commission Regulation 2017/2158.

contain high concentrations of acrylamide following potato products (Table 1). In bakery products, type of flour and other ingredients had a strong effect on acrylamide formation. In cookies made by using refined bread wheat flour, lower amount of acrylamide is formed due to the lower content of acrylamide precursors compared to hull-less oat, durum wheat and rye flours (Žilić et al., 2020). On the other hand, acrylamide was not detectable in breadcrumbs, while higher levels were found in crust or toasted breads (Konings et al., 2003). Besides the precursor content, it was reported that increased baking temperature and time also caused in increased acrylamide levels in heated starch-based foods (Van Der Fels-Klerx et al., 2014).

Another significant food source of acrylamide intake is coffee. Coffee, one of the most consumed beverages in the world, is produced by roasting of coffee beans at temperatures exceeding 200 °C. The concentration of acrylamide increases in coffee with the increasing roasting time and temperature, however, then it decreases gradually from the maximum level due to the depletion of asparagine and the degradation of acrylamide (Guenther et al., 2007; Hamzalıoğlu and Gökmen, 2020). The type of bean species influences the acrylamide formation in coffee, and thus it was found that Robusta coffee beans contained slightly higher amount of acrylamide than Arabica due to the higher asparagine level in Robusta (Bagdonaite et al., 2008; Guenther et al., 2007). In addition, chicory has higher levels of acrylamide than the coffee substitutes and coffee (Loaëc et al., 2014).

Acrylamide tend to accumulate in low moisture systems such as extruded snacks ranging from 704 to 1560 μg/kg (Mulla et al., 2011). Breakfast cereals, another example for extruded products, contains high amounts of acrylamide ranging between 50 and 413 μg/kg as given in Table 1. Since they contain low moisture, roasted nuts and seeds are also suitable for acrylamide formation. It was indicated that acrylamide level in roasted nuts and seeds was variable between 33 and 251 μg/kg while the lowest mean value of acrylamide was found in roasted hazelnut with the concentration of 91 μg/kg (Nematollahi et al., 2020). Recently, Berk et al. (2019) reported high amounts of acrylamide (135–633 μg/kg) in roasted sesame seeds.

In addition to high temperature processed foods (>120 °C), acrylamide formation was reported in prune juice, plum puree, and dried and smoked fruits (Becalski et al., 2011; Constantin et al., 2019; Surma et al., 2018). Becalski et al. (2011) indicated that substantial amounts of acrylamide were found in prune juice at higher moisture conditions even they are thermally processed at temperatures below 100 °C. Becalski et al. (2011) also pointed out that prolonged boiling and/or pasteurization were responsible for the increase in acrylamide level from 188 to 438 μg/kg in prune juices, despite it was reported in the literature that boiling had no significant effect on acrylamide formation (Hamzalıoğlu and Gökmen, 2019a). Surma et al. (2018) reported that smoked fruits (pear, apple and plum) and dried fruits (date, apricot, raisin, plum, cranberry) contain high levels of acrylamide reaching a maximum concentration of 730 μg/kg in smoked plums. On the other hand, low pH could restrain the acrylamide formation through the inhibition of imine formation compared to neutral and alkaline pH conditions (Becalski et al., 2011). In addition to prune juice and dried fruits, according to our unpublished findings, acrylamide was detected in different apple juice concentrates stored at 37 °C for 20 weeks. This was most probably due to the conversion of intermediates accumulated in apple juice concentrates under acidic juice conditions. In order to understand this, asparagine adducts of (3-deoxyglucosone and HMF) which are in high amounts in apple juice concentrates were confirmed using high-resolution mass spectrometry in full scan mode with very high mass accuracy ($\Delta < 2$ ppm). As an example, it is illustrated in Fig. 2 that the presence of $[M+H]^+$ ion having m/z of 295.11359 ($C_{10}H_{18}O_8N_2$) suggests the formation of 3-deoxyglucosone-asparagine adduct, whereas the adduct of HMF with asparagine has the $[M+H]^+$ ion with m/z of 259.09201 ($C_{10}H_{14}O_6N_2$, $\Delta = -1.75$ ppm) in 70 °Bx of apple juice concentrates stored. Considering these findings, dried fruits and fruit juices contain high amounts of sugars as well as Maillard reaction intermediates such
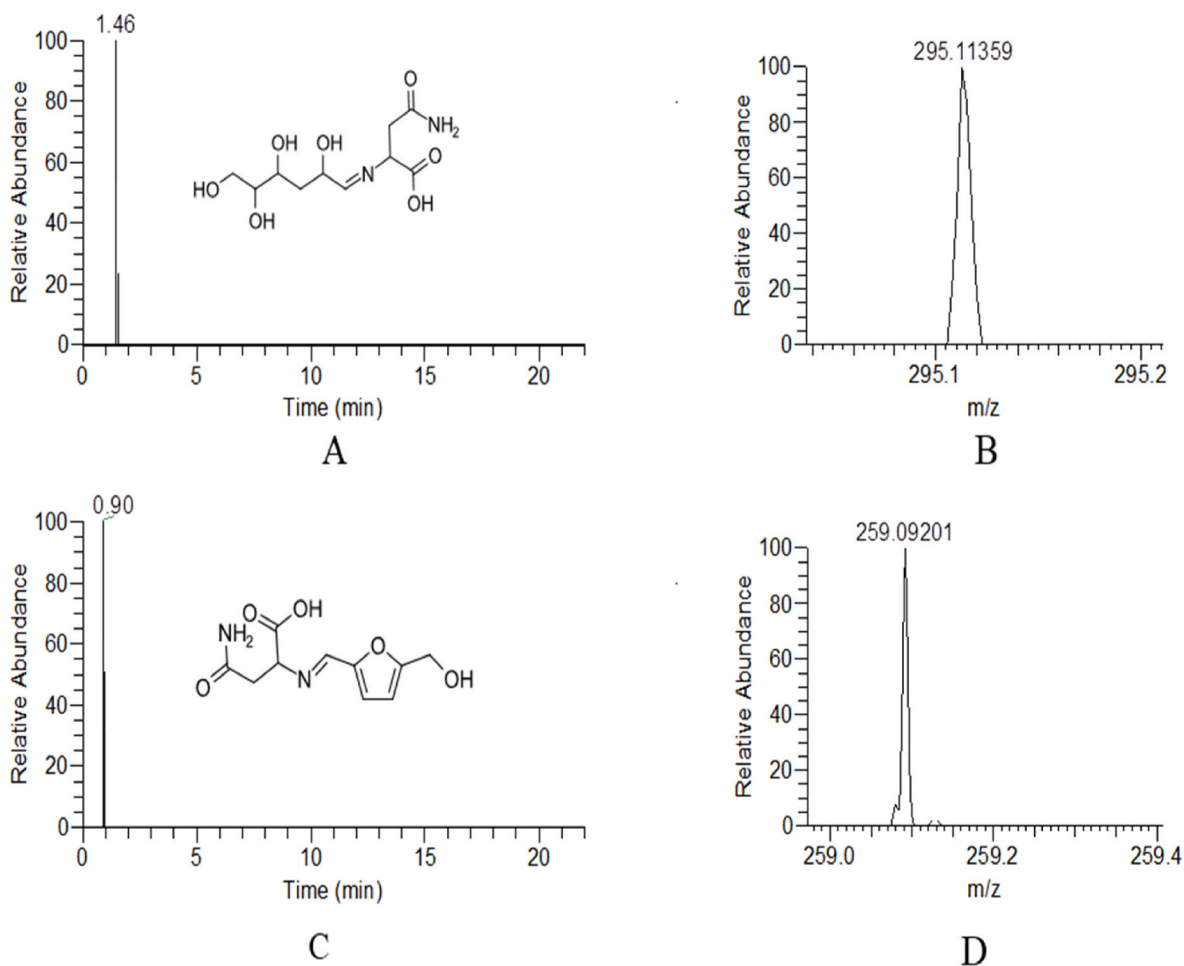
Fig. 2. Typical extracted ion chromatogram (A) and mass spectrum (B) of 3-deoxyglucosone - asparagine adduct; typical extracted ion chromatogram (C) and mass spectrum (D) of HMF-asparagine adduct formed in 70°Bx of apple juice concentrates at the end of 20 weeks storage at 37 °C.

as α-dicarbonyl compounds and HMF (Aktağ and Gökmen, 2020) which might probably react with asparagine to form acrylamide even in high moisture, low pH conditions and temperatures below 120 °C. The recent findings in apple juice concentrates highlighted the possibility and importance of conversion of asparagine adducts to acrylamide even in mild conditions.

4. The fate of acrylamide during digestion

Up to now, the main formation pathway, the effect of reaction intermediates on the formation of acrylamide, and occurrence in different foods were discussed in the review. However, in order to have a real understanding of acrylamide exposure, behavior of acrylamide and its precursors in the gastrointestinal tract should be discussed. Studies on this subject has gained momentum in recent years, however the data on the changes in acrylamide during digestion in different food matrices is still controversial.

Starting in the mouth, then stomach and intestine, each step of digestion cause changes in the structure and chemical composition of ingested food due to different pH values and enzyme activities. Under these conditions, new nucleophilic compounds are formed by hydrolysis, and then these might also act as a reactant. Considering this, several researchers conducted *in vitro* studies to monitor the fate of acrylamide in foods during digestive process. Hamzalıoğlu and Gökmen (2015) evaluated the fate of acrylamide in fried potato and bakery during *in vitro* multistep enzymatic digestion process simulating gastric, duodenal, and colon phases. According to the results, the acrylamide

concentration in potato fries and chips increased dramatically at the end of the gastric phase (Hamzalıoğlu and Gökmen, 2015). It was indicated that the gastric pH may facilitate the conversion of Maillard reaction intermediates into acrylamide (Fig. 3). Following this finding, in order to get a better understanding about the contribution of intermediates to acrylamide formation during the gastric phase, asparagine-glucose model systems were heated at 180 °C for 10 min. The intermediates were monitored during different stages of *in vitro* digestion. Results showed a rapid disappearance of Schiff base during the gastric phase while acrylamide level increased, indicating the possible conversion of Schiff base and other intermediates which might act as potential precursors of acrylamide under gastric conditions (Fig. 3). Sansano et al. (2017) also observed a similar increase in acrylamide content in different food matrices such as potato fries and chips, chicken nuggets, onion rings, biscuits, crackers, instant coffee and coffee substitutes during *in vitro* gastric phase. In the same study, acrylamide showed different kinetic patterns during gastric digestion depending on the food matrix. The rapid increase in acrylamide was observed at the beginning of gastric phase in some products such as coffee substitute, crackers, breakfast cereals whereas a longer gastric digestion was needed to the acrylamide increase for other products, instant coffee, potato chips, french fries (Sansano et al., 2017). This could be explained by the matrix degradation rate.

Despite the significant increases in the acrylamide content at the gastric digestion, a dramatic decrease in acrylamide content was observed at the end of duodenal phase in both two studies mentioned above (Hamzalıoğlu and Gökmen, 2015; Sansano et al., 2017). The
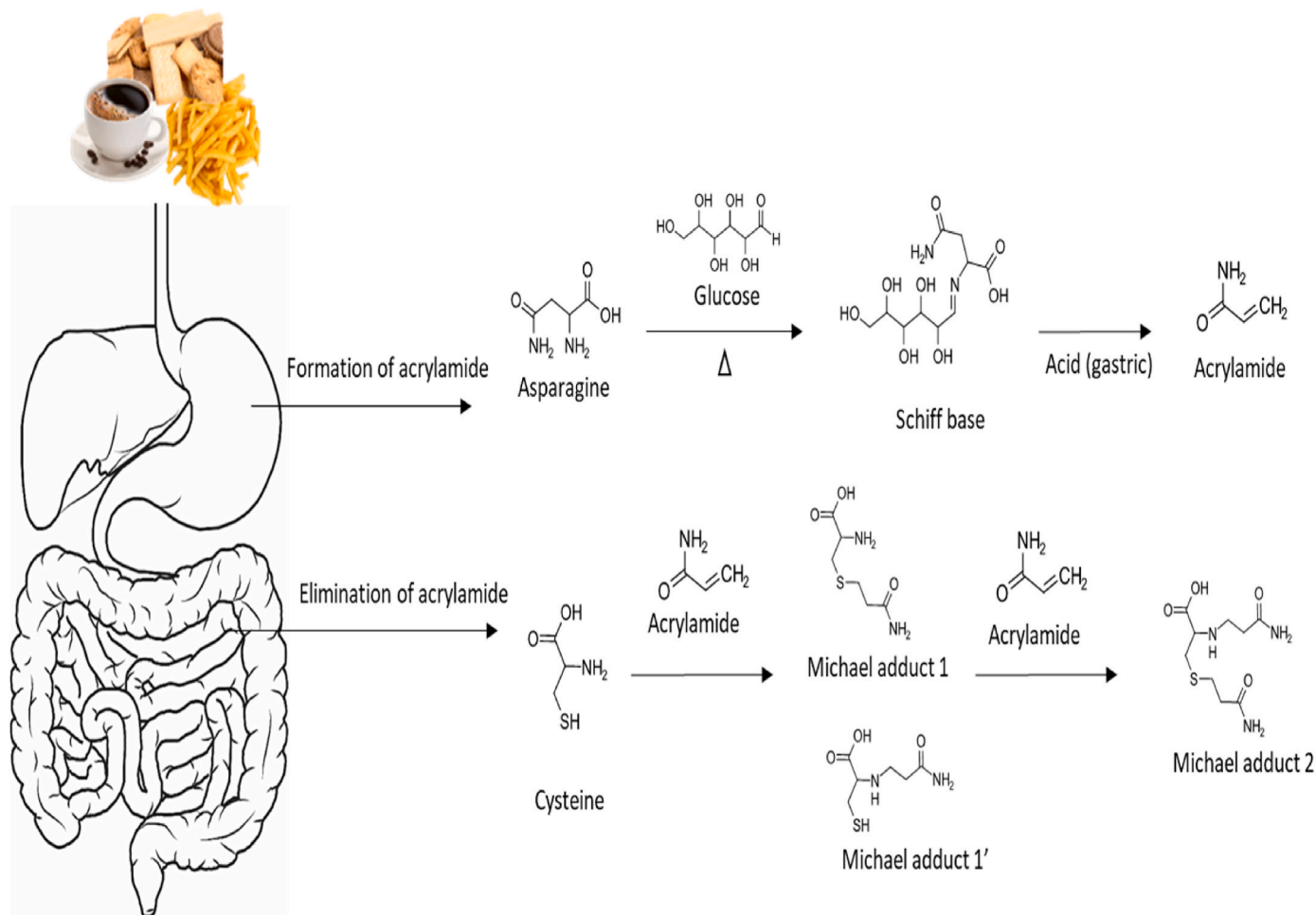
Fig. 3. Proposed mechanism for the formation and elimination of acrylamide at gastric and intestine phase of digestion (Hamzalıoğlu and Gökmen, 2015).

elimination ratio of acrylamide in fried potatoes reached to 97% at the end of intestinal phase, whereas in biscuits, this ratio was between 49% and 73% through gastric, duodenal, and colon phases of *in vitro* digestion (Hamzalıoğlu and Gökmen, 2015). In order to understand this decrease, researchers investigated the interaction of acrylamide with nucleophiles (cysteine and lysine) in model systems during digestion (Hamzalıoğlu and Gökmen, 2015) and it was evidenced that *in vitro* multistep enzymatic digestion resulted in the formation of Michael adducts between acrylamide and amino acids in the intestinal phase (Fig. 3). Additionally, cysteine was more effective on the elimination of acrylamide owing to its highly nucleophilic sulfhydryl group than other amino acids. Likewise in another study, a similar decrease in the acrylamide content of potato fries was reported in the intestinal phase (Sansano et al., 2017). During the intestinal stage, a rapid reduction in the amount of acrylamide was observed at the beginning, and while acrylamide concentration was found to be constant after 15 min of intestinal digestion (Sansano et al., 2017). The results obtained by these studies demonstrated that the interactions of amino acids with acrylamide possibly occur under intestinal conditions (Hamzalıoğlu and Gökmen, 2015; Sansano et al., 2017). Hydrolysis of food proteins form smaller peptides, and amino acids which might possibly interact with acrylamide (Hamzalıoğlu and Gökmen, 2019a). In line with that, it is well known that the glutathione, a tripeptide containing a cysteine residue, reacts with acrylamide resulting in a significant decrease (81%) of acrylamide after incubation at pH 8.0, simulating alkaline intestinal conditions (Schabacker et al., 2004). However, in the same study, acrylamide concentration showed no significant change at acidic or neutral pH conditions indicating that the alkaline digestion conditions

make possible the Michael addition of cysteine to acrylamide. In addition to the *in vitro* digestive behavior of potato products and biscuits, another high amounts of acrylamide containing food, coffee was also studied by Badoud et al. (2020). Contrarily, in this study, no significant change was observed in acrylamide levels of coffee samples during *in vitro* gastric, duodenal and colonic digestion. This should be related to the thermal conditions of food process applied and the concentrations of precursors. As in the potato case, both the heating conditions and the high amounts of asparagine leading to the accumulation of intermediates is possible so that they may convert into acrylamide during gastric phase. However, coffee is an extensively heated food product in which the amino acids and sugars deplete at the initial stages of roasting and in the later stages the intermediates may pyrolyze and deplete. Considering the results of these studies, formation of the adducts of acrylamide in the gastrointestinal tract might alter the toxicity of acrylamide. Recently, Michael adduct of acrylamide with GABA was shown to exert less cytotoxicity in Caco-2 cells and GES-1 cells than acrylamide (Li et al., 2022). These results might highlight the importance of the formation of these adducts as a mitigation strategy either in the body or in the foods, however the toxicity of the adducts are largely unknown.

5. Acrylamide exposure

The changes in acrylamide during *in vitro* digestion process encourages to reconsideration of the dietary exposure calculation. The net amount of acrylamide formed in processed foods were considered in risk calculations, however, the aforementioned *in vitro* studies highlights

that acrylamide itself might not reflect the real dietary exposure levels (Badoud et al., 2020; Hamzalıoğlu & Gökmen, 2015, 2016; Jiang et al., 2019; Sansano et al., 2017). Although *in vitro* protocols used in these studies have some limitations, the results provide an insight and should be considered in the calculation of acrylamide exposure.

In general, the dietary exposure of acrylamide is calculated by multiplying the mean daily consumption for each food with the corresponding mean occurrence level, summing up the respective intakes throughout the diet, and dividing the results by the individual's body weight. In another words, the estimation of daily intake of acrylamide is mainly based on its concentration found in foods. The scenario about the estimation of average intake of acrylamide differs depending on the dietary habits of consumers in different countries, but it can be considered that the average intake is about 0.4 μg/kg bw/d while it is about 1.0 μg/kg bw/d for a high-level consumer (Mills et al., 2008). Tardiff, Gargas, Kirman, Leigh Carson, and Sweeney (2010) indicated that tolerable daily intake of acrylamide was estimated to be 40 mg/kg bw/d for neurotoxicity while it was 2.6 mg/kg bw/d for cancer. However, EFSA and WHO announced that a tolerable daily intake of acrylamide in food cannot be set, since any level of exposure might damage DNA and lead to genotoxicity and cancer (EFSA, 2015a; WHO/, 2002). It should also be considered that this is a life-time exposure unlike many other regulated environmental toxins. Nevertheless, toxicological studies on acrylamide have been demonstrated that oral lethal dose 50% (LD_{50}) values for acrylamide were reported as > 150 mg/kg bw for rats, 107 mg/kg bw for mice, and 150–180 mg/kg bw for rabbits and guinea pigs (EFSA, 2015b). The no observed adverse effect level (NOAEL) value of acrylamide for morphological changes in nerves of rats were reported as 0.2 mg/kg bw whereas the margin of exposure (MOE) value of 0.43 mg/kg bw/d indicate a concern for neoplastic effects based on animal evidence (EFSA, 2015b). In addition, the EFSA suggested a limit called the Benchmark Dose Lower Confidence Limit ($BMDL_{10}$) which is used for estimation the dose range within which acrylamide may cause a small but measurable tumor incidence or other potential adverse effects such as neurological. A $BDML_{10}$ of 0.17 mg/kg bw/d was selected for tumors and a $BDML_{10}$ of 0.43 mg/kg bw/d can cause neurological changes in the body. Considering this, a study indicated that the daily consumption of potato and corn chips may lead to the exposure of acrylamide 7- to 40-fold higher risky than the risk intake set as $BMDL_{10}$ by EFSA for neurological changes (Rifai and Saleh, 2020). Based on the comprehensive data in the scientific and market reports all over the world (EFSA, 2015b), it is possible to say that the main contributors to the total acrylamide intake for consumers at all ages in most countries are potato products (6%–46%), coffee (13%–39%), sweet biscuits (10%–20%) and cereal based products (10%–30%) (EFSA, 2015b). This brings us back to the main discussion about the reliability of dietary exposure of acrylamide since the significant formation of acrylamide in potato products during digestion was reported in different studies mentioned above (Hamzalıoğlu and Gökmen, 2015; Sansano et al., 2017).

In addition to dietary exposure, the elimination of acrylamide in the human body is of importance in terms of risk assessment of acrylamide. Its elimination occurs by the reactions with nucleophiles such as sulfhydryl groups, α-NH_2 groups of free amino acids and N-terminal amino acid residues of proteins (Kocadağlı and Gökmen, 2016). After being ingested and absorbed from the gastrointestinal track, acrylamide is rapidly converted to metabolites including mercapturic acid derivatives (*N*-acetyl-*S*-(2-carbamoylethyl)-L-cysteine (AAMA) and *N*-acetyl-*S*-(2-carbamoy-2-hydroxylethyl)-L-cysteine (GAMA)), hemoglobin adducts (*N*-(2-carbamoylethyl)-L-valine (AA-Hb) and *N*-(2-carbamoy-2-hydroxylethyl)-L-valine (GA-Hb)) and DNA adducts (Kocadağlı and Gökmen, 2016). Nevertheless, epidemiological studies revealed that the acrylamide metabolites may not be sufficient enough to estimate the acrylamide exposure since the dietary intake of acrylamide estimated from hemoglobin adduct of acrylamide was found higher than intake levels estimated from dietary questionnaires (Dybing et al., 2005; Hagmar et al., 2005). In order to understand whether acrylamide is

formed *in vivo* or not Tareke et al. (2008) performed a study that mice were exposed to iron which is known to generate hydroxyl radicals. To the results from this study, a slight but significant increase in the levels of hemoglobin adduct of acrylamide was observed with the treatment of $FeSO_4$, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-hydrochloric acid (MPTP) and methamphetamine (METH). Therefore, the authors hypothesized that acrylamide was formed *in vivo* as a result of oxidative stress and acrolein may be a precursor (Tareke et al., 2008). On the other hand, Boettcher et al. (2006) investigated the effect of fasting on AAMA and GAMA levels in the human urine after a few days. The results showed that the concentrations of mercapturic acid metabolites have decreased by about 95% (Boettcher et al., 2006). This confirmed that the diet is the main contributor to acrylamide exposure in humans except smoking (Kocadağlı and Gökmen, 2016). The fate of acrylamide during digestion process and the intermediates of acrylamide formation which may release acrylamide during digestion should also be taken into account for the better estimation of exposure to acrylamide. Therefore, for example, it is possible to speculate that this discussion may help partly explaining the baseline urinary metabolites after fasting. On the other hand, these results should be evaluated and proven by the untargeted metabolomic analysis in the samples collected from the controlled *in vivo* studies. Recently, different new metabolites, particularly the adducts of heat treatment markers such as furan, HMF, pyrazines, were identified in the human urine samples collected after ingestion of potato products indicating the influence of heat treatment on human health (Zhou et al., 2020). Accordingly, more *in vivo* studies on acrylamide metabolites and markers should be conducted in order to better understand the effects of thermally processed foods on health. In sum, it is clear that the difficulties in estimation of dietary exposure of acrylamide and more important the lack of digestion studies about the fate of acrylamide pose an obstacle for making a realistic risk assessment in the case of acrylamide intake.

6. Conclusion

Since April 2002, acrylamide is of concern due to its classification as probable human carcinogen in class 2A especially in carbohydrate-rich foods processed at temperatures above 120 °C. Thus, the present study has addressed: (i) the roles of neglected intermediates and interactions on the formation and elimination of acrylamide in the gastrointestinal system, (ii) the actual risk for acrylamide intake from underestimated foods, and (iii) the importance of the studies on the fate of acrylamide during digestion in order to estimate reliable dietary exposure calculations of acrylamide. It is apparent in the literature that the intermediates, such as HMF or α-dicarbonyl compounds contribute to the acrylamide formation at least as much as reducing sugars under acidic conditions. Besides, nucleophilic compounds such as amine and thiol groups of amino acids cause the elimination of acrylamide. Similar to the formation and elimination mechanism of acrylamide in foods, the acrylamide level increases through the conversion of intermediates in the gastric phase (pH around 2.0) of digestion. This might be important even very limited amount of absorption takes place from stomach. On the other hand, decrease in the concentration of acrylamide is observed by the interactions between acrylamide and nucleophiles during intestinal phase under alkaline pH. This might affect the amount of acrylamide absorbed as the intestines are the main part of the body that all nutrients are absorbed from. Overall, it is recommended that further research on the importance of disregarded intermediates and nucleophiles for the dietary exposure assessment of acrylamide should be undertaken.

Compliance with ethics requirements

This study does not contain any studies with human participants or animals performed by any of the authors.

CRediT authorship contribution statement

Işıl Gürsul Aktağ: Methodology, Formal analysis, Investigation, Data curation, Visualization, Writing – original draft. **Aytül Hamzalıoğlu:** Methodology, Formal analysis, Investigation, Data curation, Visualization, Writing – review & editing. **Tolgahan Kocadağlı:** Methodology, Formal analysis, Investigation, Data curation, Visualization, Writing – review & editing. **Vural Gökmen:** Conceptualization, Methodology, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

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

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