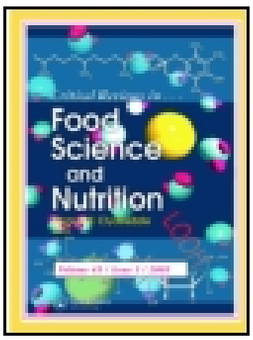

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

A review on furan: Formation, analysis, occurrence, carcinogenicity, genotoxicity and reduction methods

Zahra Batool, Dan Xu, Xia Zhang, Xiaoxi Li, Yuting Li, Zhiyi Chen, Bing Li & Lin Li

To cite this article: Zahra Batool, Dan Xu, Xia Zhang, Xiaoxi Li, Yuting Li, Zhiyi Chen, Bing Li & Lin Li (2020): A review on furan: Formation, analysis, occurrence, carcinogenicity, genotoxicity and reduction methods, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2020.1734532

To link to this article: https://doi.org/10.1080/10408398.2020.1734532

Published online: 09 Mar 2020.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2020.1734532

Taylor & Francis
Taylor & Francis Group

REVIEW

A review on furan: Formation, analysis, occurrence, carcinogenicity, genotoxicity and reduction methods

Zahra Batool[a], Dan Xu[a], Xia Zhang[a], Xiaoxi Li[a], Yuting Li[b], Zhiyi Chen[c], Bing Li[a], and Lin Li[a,b]

[a]Guangdong Province Key Laboratory for Green Processing of Natural Products and Product Safety, School of Food Science and Engineering, South China University of Technology, Guangzhou, China; [b]School of Chemical Engineering and Energy Technology, Dongguan University of Technology, Dongguan, China; [c]Sericultural & Agri-Food Research Institute, Guangdong Academy of Agricultural Sciences Key Laboratory of Functional Foods, Ministry of Agriculture and Rural Affairs, Guangdong Key Laboratory of Agricultural Products Processing, Guangzhou, China

ABSTRACT

Furan (C_4H_4O) is a volatile, heterocyclic and carcinogenic heterocyclic chemical compound occurring in a wide range of thermally processed foods. Several studies have been conducted to analyze the formation conditions, triggering furan formation via model systems. Furan can be encountered via various pathways including thermal degradation, oxidation of polyunsaturated fatty acids, thermal rearrangement of carbohydrates in the presence of amino acids, thermal degradation of certain amino acids. Furan has been proven to cause cancer in experimental animal models and classified as a possible human carcinogen by International agency for research on cancer based on sufficient evidences. Thus, different strategies should be developed to reduce furan contents in commercially available food stuffs while food processing. This review summarizes some current evidences of furan formation from different precursors, analytical methods for its detection, and its toxicity that might lead to carcinogenicity and genotoxicity with human risk assessment. In addition, furan occurrence in different thermally processed foods entailed by several recent studies as well as furan mitigation strategies during food processing have also been illustrated in this review.

KEYWORDS

Furan; formation mechanism; Maillard reaction; toxicity; reduction

Introduction

Furan (C_4H_4O) is a heterocyclic organic chemical compound (Fig. 1) with high volatility (furan b.p. 32 °C). The INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC), US Department of Health and Human Services and National Toxicology Program (NTP) had classified furan as a possible carcinogen (Class 2B) (IARC (International Agency for Research on Cancer) 1995; NTP (National Toxicology Program) 1993). Furan has shown to be carcinogenic in several experimental animal models entailing, rats and mice even at relatively lower doses in a year gavage study (Von Tungeln et al. 2017). Furan formation encountered during a variety of thermally driven processes, including baking, roasting, pasteurizing, cooking, and sterilizing (Crews and Castle 2007). Furan has attracted attention worldwide due to its carcinogenicity and frequent occurrence in a variety of thermally driven foods, such as different coffees, baby foods, cereals, meat products (EFSA (European Food Safety Authority) 2017, FSA (Food Standard Agency United Kingdom) 2018). Furan can also be absorbed by gastrointestinal tract and shown to be metabolized by a hepatic cytochrome P450 2E1 mediated ring opening, triggering toward *cis-2*-but-ene-1,4-diol formation (Fig. 1) (Chen, Hecht, and Peterson 1995), which is thought to be highly reactive metabolite and is able to react with amino and thiol groups in glutathione and other peptides (Lu and Peterson 2010). The bicyclic hemikel derivatives are the resultant products of a chemical reaction occurred among *cis-2*-but-ene-1,4-diol and exocyclic nitrogen of deoxyguanosine, deoxyadenosine and deoxycytidine Fig. 1 (Bohnert, Gingipalli, and Dedon 2004). The deoxyguanosine and deoxyadenosine adducts are relatively unstable and trigger ring opening and dehydration forming secondary etheno type DNA adducts. The deoxyadenosine and deoxycytidine adducts have been detected in the DNA by using a trapping agent termed as o-benzyl hydroxylamine, which reacted with *cis-2*-but-ene-1,4-diol (Byrns et al. 2006). Recently, the presence of deoxycytidine *cis-2*-but-ene-1,4-diol, has been thought to be more stable DNA adduct obtained from furan and detected in the liver analysis of F344 rats being treated with 4.4 mg furan/kg BW (Churchwell et al. 2015).

However, the main risks associated with furan consumption still remain unclear. Diminishing furan contents in foods using different strategies would be considered as challenging for prevention from human diseases. Hence, there is a great need to optimize the methods and finding some reasonable solution of problems related to furan

CONTACT Bing Li bli@scut.edu.cn; Lin Li lilin@dgut.edu.cn Guangdong Province Key Laboratory for Green Processing of Natural Products and Product Safety, School of Food Science and Engineering, South China University of Technology, Guangzhou, 510640, China.

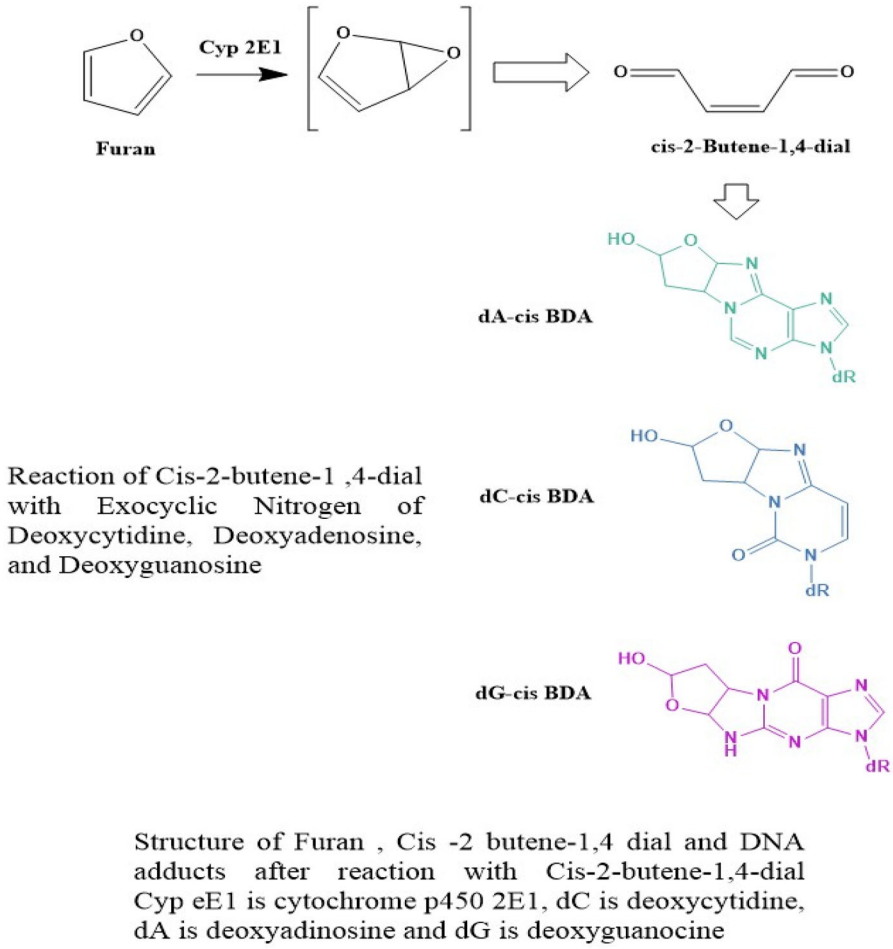

Figure 1. Structure of Furan, *Cis*-2 butene-1,4 dial and DNA adducts after reaction with *Cis*-2-butene-1-4-dial.

formation in food while food processing. The main objective of writing the present review was to discuss certain aspects entitled as furan formation, exposure, toxicology with human risk assessment and mitigation strategies.

Formation of furan

Furan formation from different precursors

Various precursors including polyunsaturated fatty acids (PUFAs), amino acids, carbohydrates, ascorbic acid, under thermal or oxidative conditions can form furan via different classically thermally driven mechanisms (Fig. 2, Table 1). To date, four most important mechanisms featuring the major routes of furan formation have been revealed by different literature studies, entailing as (1) the oxidation of polyunsaturated fatty acids, (2) thermal degradation of amino acids under thermal conditions (3) thermal degradation or rearrangement of carbohydrates such as glucose, fructose and lactose (Mage 1979) or reaction with amino acids (Maillard reaction) (4) ascorbic acid decomposition including its derivatives as precursors (Locas and Yaylayan 2004; Crews and Castle 2007).

Lipids oxidation is most likely one of most studied pathway of furan formation by simulating different model systems. The (E)−4-hydroxybut-2-enal as the resulted intermediate degradation product, cyclised to 2,3-dihydro-2-furanol, triggering furan formation after water removal. Moreover, linolenic acid has been shown to be an efficient furan precursor among PUFA mixtures (Shen et al. 2015), particularly in the presence of transition metals, accelerating lipid oxidation with the subsequent formation of conjugated dienes. Conclusively, furan formation from fatty acids happens due to the formation of 4-hydroxyalk-2-enals, probably including (E)−4-hydroxybut-2-enal, produced by oxidation of but-2-enal (Owczarek et al. 2010) (Fig. 2 (1).

Thermal degradation of amino acids such as serine and cysteine also induce furan formation (Locas and Yaylayan 2004). The formation of acetaldehyde and glycolaldehyde during thermally driven degradation of serine gives rise to an intermediate 2-deoxyaldotetrose, whose cyclization and dehydration yield furan moiety (Fig. 2 (2). Certain other amino acids can also form furan, such as alanine, aspartic acid and threonine can furnish furan backbone by producing 2-deoxyaldotetrose, depending on amino acids condensation into acetaldehyde (Strecker aldehyde) only with involvement of glycoaldehyde. Thus, reducing sugar, serine or cysteine are required to form glycoaldehyde formed during strecker degradation, and further produces 2-deoxyaldotetrose, acting as an intermediate toward furan formation (Locas and Yaylayan 2004). Amino acids subjected toward oxidation reaction may also procure reactive carbon-2 units such as glycolaldehyde and acetaldehyde (Locas and Yaylayan 2004).

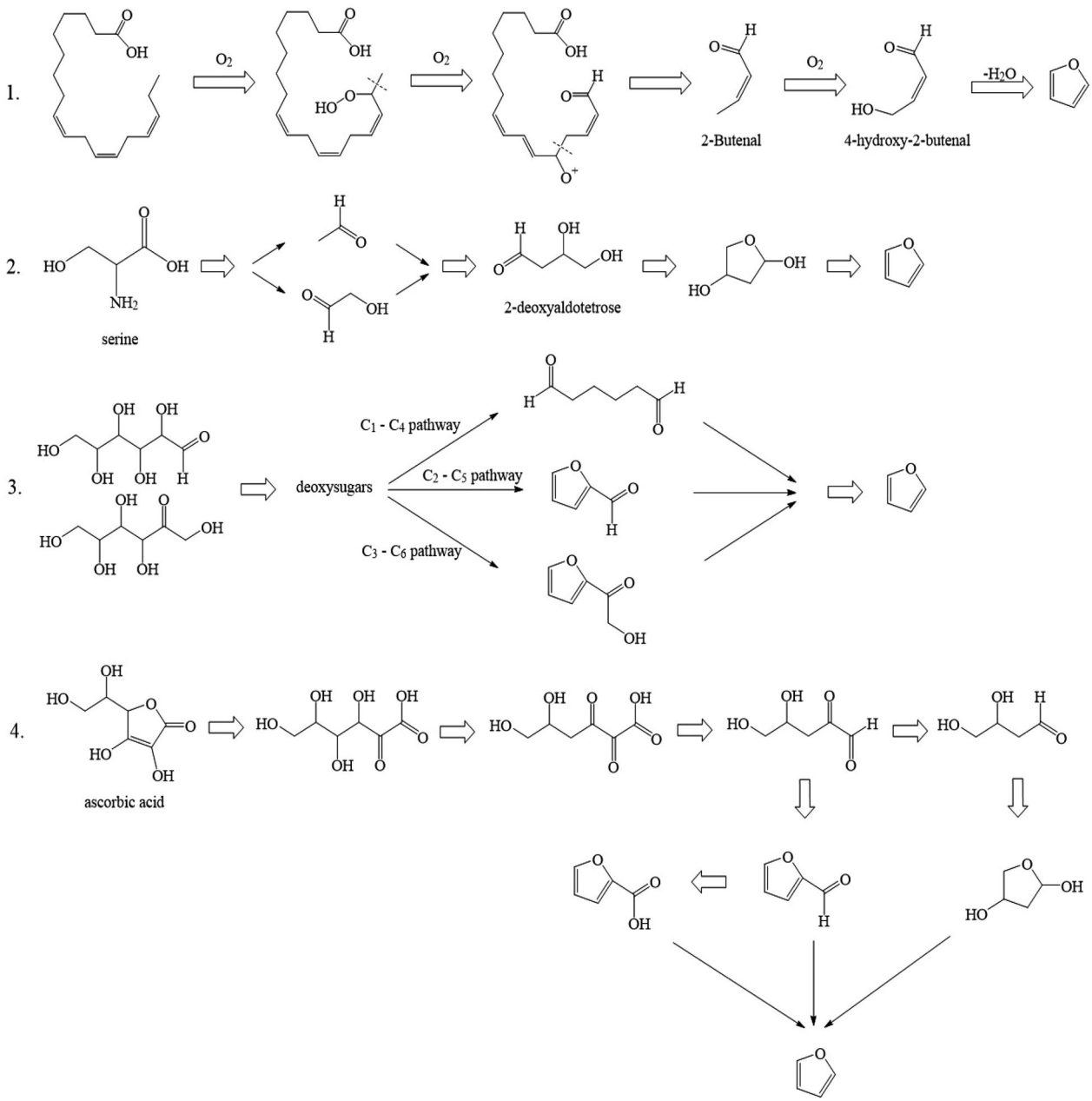

Figure 2. Suggested formation pathways of furan from different presusors (1) describes fromation pathway of furan from polyunsaturated lipids (2) describes formation of furan from serine amino acid (3) describes formation of furans from hexose sugar (4) describes furan formation from ascorbic acid precusors (Adapted from perez Locas and Yaylayan 2004; Limacher et al. 2007, 2008); Owczarek et al. 2010).

Furan formation from intact sugar skeleton has been implicated via various pathways including recombination of sugar fragmentation products from intact sugar skelton and its degradation (Van Lancker et al. 2011; Limacher et al. 2008). Condensation of glycolaldehyde and acetaldehyde mainly comprised of certain sugar fragmentation pathways (Limacher et al. 2008). Formation of deoxyosone intermediates by dehydration and further cyclization, and dehydration with loses of C1 and C2 of sugar have resulted in furan moiety (Fig. 2 (3). Additionally, it has been widely accepted that amino acid compounds favor furan formation from reducing sugars via classically thermally driven Maillard reaction. Carbohydrates reacting with amino acids during Maillard reaction process furnish 3,4-dihydroxybutanal that subsequently cyclizes to the furanoic backbone (Van Lancker et al. 2011). The reducing sugars, such as hexoses typically go through Maillard reaction by reacting amino acids and can produce reactive intermediates i.e 1-deoxyosone and 3-deoxyosones, aldotetrose and 2-deoxy-3-keto-aldotetrose. Furthermore, 1-deoxyosone undergoes α-dicarbonyl cleavage and forms aldotetrose. However, aldotetrose is derived from retro-aldol cleavage in the absence of amino acid, resulting furan in a limited quantity. After dehydration reaction, 2-keto-3-deoxy-aldotetrose formation can follow the retro-aldol cleavage. Furthermore, 3-deoxyosone undergoes α-dicarbonyl cleavage followed by oxidation and decarboxylation for forming 2-deoxyaldotetrose. Altogether, these aldotetrose derivatives can be furnished into furan. However, amino acids alone (for example, alanine, serine), or glucose alone, have been shown to represent only a minor route of furan.

Table 1. Mechanisms of furan formation from different precursors.

Different precursors	Mechanism of furan formation	References
Carbohydrates	Thermal degradation of sugars leads to aldotetrose derivative formation through cyclization reactions.	Limacher et al. (2008); Locas and Yaylayan (2004)
Carbohydrates and amino acids	A Maillard reaction between amino acids (Alanine, Threonine and Aspartate) and sugars that can generate acetaldehyde.	Limacher et al. (2008); Van Lancker et al. (2011)
	Furan formation through Maillard reaction by different combinations of sugars and amino acids such as Glucose and alanine	Bi et al. (2017)
Polyunsaturated fatty acids	Oxidation of precursors by ROS or by lipoxygenase, by a homolytic cleavage of resulting hydroperoxides and generation of alkenal derivatives that subsequently undergo cyclization and dehydration.	Mariotti et al. (2012); Cho and Lee (2014); Owczarek et al. (2010)
Ascorbic acid, sugars and polyunsaturated fatty acids	Described a reaction between different radicals and precursors, formed upon irradiation	Fan X (2007); Fan X (2015)
Ascorbic acid and ascorbates	Oxidative degradation of precursors by formation of intermediates such as derivatives of aldotetrose and 2-furoic acid	Limacher et al. (2007); Locas and Yaylayan (2004)
	Degradation of ascorbic acid produces the highest levels of furan in aqueous model systems heated at high temperatures	Mariotti et al. (2012)

Ascorbic acid is found in a wide variety of foods and implicated in furan formation (Becalski et al. 2010). Furan formation from ascorbic acid starts with hydrolytic ring opening of ascorbic acid, loses of water and triggering formation of 4-deoxyascorbic acid, which generates 2-deoxyaldotetrose. 4-deoxyascorbic acid could also be encountered during formation of 2-furfural, a furan precursor (Limacher et al. 2007; Limacher et al. 2008) (Fig. 2 (4). Moreover, when heated, ascorbic acid degraded and may follow the 3,4-dihydroxybutanal route as proposed by several literature studies (Crews and Castle 2007; Limacher et al. 2008; Mariotti et al. 2012). Alternatively, dehydroascorbic acid may reversibly rearrange to 2,3-diketo-L-gluconate, and after cyclization of the corresponding aldotetrose, cyclizes to 3-furanone and ultimately furnish furan.

Impact of different factors on furan formation during food processing

Different furan precursors, triggering furan generation while food processing via thermally driven pathways have been identified in previous section; however, several factors during food processing could have played significant roles in influencing furan formation from these precursor systems. The key factors included heating time, water, sugar to amino acid ratio, temperature, pressure, metals, oxidation conditions, pH, reactant types, and irradiations (Chakraborty, Rao, and Mishra 2015; Dhakal et al. 2017; Hu et al. 2016; Shen et al. 2015). Among these factors, oxidation conditions, pH, temperature and time, and irradiations might have played crucial roles in furan formation (Cho and Lee 2014; Nie et al. 2013).

Oxidation is a main factor influencing furan formation, particularly in ascorbic acid and lipid systems. Oxidative conditions trigger the oxidization of ascorbic acid into dehydroascorbic acid, which is further hydrolyzed into 2,3-diketogluconate after ring opening. Which is further converted to aldotetrose producing 2H-furan-5-one and 3H-furan-2-one after cyclization and dehydration reactions. Furan is converted from 3H-furan-2-one through reduction and dehydration process. However, under nonoxidative conditions, ascorbic acid is hydrolyzed and triggers β-elimination following by decarboxylation, resulting in 3-deoxypentosulose. Furan precursor 2-deoxyaldotetrose could further be produced after a-dicarbonyl cleavage (Owczarek et al. 2010; Locas and Yaylayan 2004). Oxidation conditions would also cause degradation of polyunsaturated fatty acids (PUFAs) and triggers lipid peroxides formation termed to be undesirable reaction products during food processing due to the rancid, off flavor of their decomposition products. Moreover, lipid hydroperoxides are produced from PUFAs after a combinatory reaction of oxygen species or an enzyme reaction by lipoxygenase (Owczarek et al. 2010; Locas and Yaylayan 2004). Hence, reduction in oxygen level in food products, featuring potato purees supplemented with ascorbic acid, fructose and polyunsaturated fatty acids (Palmers et al. 2016) has resulted in variable reduction in furan concentration.

pH has a great influence on furan formation in the presence of the same precursors having similar concentrations. For instance, in an acidic environment (pH = 4), furan formation from sugars degradation is less efficient in model systems compared to alkaline or neutral conditions (pH $\geq$ 7), in which furan formation is enhanced due to more carbohydrate fragmentation and enolisation. Actually, 1,2-enolisation happens at low pH, resulting in production of 3-deoxy-1-2 dicarbonyl compounds (3-deoxyosones). However, 2,3-enolisation is triggered at higher pH, leading to deoxy-2-3-dicarbonyl compounds (1-deoxyosones) production, however, the formation of 1-deoxysone has been indicated as most effective route of furan formation during Maillard reaction. Moreover, it has also been observed that pH has great influence on browning and carbohydrates degradation, hence, increasing rate of Maillard reaction (Owczarek et al. 2012).

Time and temperature as process variables also have been shown to have certain impacts on furan formation. Higher temperature can trigger thermal degradation of carbohydrates, producing furan precursors in further. Furan formation increase with an increase in heating time during sterilization, due to enhanced Maillard reaction or thermal degradation of food constituents and with formation of certain undesirable intermediate products. Sterilization conditions usually results in higher furan formation as compared

Table 2. Validated methods for furan analysis in different food samples.

Different techniques	Food items	References
Proton transfer reaction mass spectrometry	Different precursor systems	Mark et al. (2006)
Static Headspace approach with Solid Phase Microextraction	Baby Foods	Kubiak, Karasek, and Wenzl (2008)
Static Headspace approach without Solid Phase Microextraction	Canned and Jarred foods	Becalski et al. (2010)
Head Space Solid Phase Microextraction Gas Chromatography Mass Spectrometry	Baby foods, Chinese food	Condurso, Cincotta, and Verzera (2018); Sijia, Enting, and Yuan 2014

with pasteurization due to the higher applied temperature. However, roasting conditions seemed to be more intense to form furan up to higher levels by recombination of sugar fragments in sugar model systems other than sterilization or pasteurization. Coffee with high degree of roasting can encounter higher furan levels (Altaki, Santos, and Galceran 2011). It has also indicated that conventional sterilization techniques, autoclave sterilization or alternative heat treatment, have given lower furan levels due to lesser time and temperature impact (Palmers et al. 2015). Higher temperature (90–105°C) and pressure (600 MPa) treatment has also been reported to cause furan formation in fruit juices due to degradation of different juice constituents, such as ascorbic acids, certain sugars and amino acids under subsequent treatment conditions (Chakraborty, Rao, and Mishra 2015; Dhakal et al. 2017).

With the emergence of innovative food processing technology such as high static pressure technology, radiation technology, high electric field technology, etc., understanding of furan formation under these external fields is of great interest. Furthermore, the impacts of ionizing radiations and ultraviolet light (UV-C) treatments on furan formation have also been studied due to emergence of higher furan levels. The radiated sterilization of juices used for increasing their shelf life can trigger furan formation by influencing ascorbic acid or sugar degradation (Hu et al. 2016; Morehouse, Geraldo, and Timothy 2018).

Analytical methods for furan detection

Different reports describing methods for furan analysis have been originated and well described in literature. However, all sensitive analytical methods are based on the fundamental analytical techniques and chromatographic separation is applied in them such as porous layer open tubular columns for chromatographic separation are used except Proton Transfer Mass Spectrometery (PTR/MS) (Table 2). Although, detection techniques vary in them such as, mass spectrometric detection is applied in Gas Chromatography Mass Spectrometry (GC/MS) (Condurso, Cincotta, and Verzera 2018), while Gas Chromatography Flame Ionization Detection (GC-FID) uses a fundamental flame ionization detector for analytes detection purpose (Hu et al. 2016). Furan analysis starts with extraction and separation of analytes from sample matrix. Solid phase microextraction (SPME) and headspace approach have been widely applied for furan extraction from subsequent analyzed samples. SPME has been demonstrated to be getting more attention as an efficient technique for analytes extraction and fiber absorption, and further get desorbed in the GC column (Condurso, Cincotta, and Verzera 2018; Hu et al. 2016; Sijia, Enting, and Yuan 2014). SPME focuses on the application of a SPME needle, coated with different polymeric materials. Different parameters can influence volatiles extraction from subsequent samples such as extraction time, fiber types, sodium chloride concentration, stirring speed and most importantly the aqueous phase saturation in headspace vials. Selection of optimal fibers for an efficient furan analysis has been studied on the basis of their fiber extraction abilities. And carboxen/polydimethylsiloxane (CAR/PDMS) fiber (Goncalves et al. 2014; Hu et al. 2016; Lorenzo 2014; Sijia, Enting, and Yuan 2014), divinylbenzene/carboxen/polydimethylsiloxane (DVB/CAR/PDMS) fiber (Condurso, Cincotta, and Verzera 2018), divinylbenzene/polydimethylsiloxane (DVB/PDMS) and carbowax/divinylbenzene (CW/DVB) fiber have been tested for presenting higher sensitivity and an efficient analyte extraction from sample matrix.

Furthermore, headspace approach has also been reported to be used for analytes separation as well. It can be applied for furan extraction from analyzed samples before performing GC-MS, presenting an efficient analysis. The headspace approach can adapt by using different headspace vials which vary, depending on time, liquidity of samples and temperature. An effective separation could be performed in an appropriate equilibrium time and by magnet bar addition in the headspace vial for agitation purpose. Since, addition of water is also recommended to get insured that samples are entirely dissolved before being analyzed and the analytes are volatilized into headspace vials, while heating. However, excessive heating is not recommended for furan analysis due to high volatility (Condurso, Cincotta, and Verzera 2018). An increased headspace incubation temperature from 30°C to 50°C is reported to increase its 50% peak area. Moreover, an addition of salt may further increase the sensitivity of furan signal being generated (Mariotti et al. 2012; Sijia, Enting, and Yuan 2014).

Gas chromatography mass spectrometry (GC-MS) has been reported to be used as a golden method for furan detection as a consequence of its higher sensitivity and specificity (Condurso, Cincotta, and Verzera 2018). However, several factors still need to be evaluated for GC-MS detection such as GC retention time and ratio of quantification ion of furan at m/z 68 as compared with quantification ion at m/z 39 and another comparison with ratio of added standards for evaluating the exact quantity of analyte in the subsequent analyzed sample. Further analysis needs to be performed with generation of in-house standard calibration curve to identify the actual quantity of produced analyte in the sample (Cincotta et al. 2017; Condurso, Cincotta, and Verzera 2018). GC-FID method entailed the usage of GC column for

Table 3. Prevalence of furan in different brewed and non-brewed coffees.

Category 1 Coffee type	Average Furan [range] (mg/kg in coffee, non-brewed)	References
Roast & ground (cartridge delivery system) ($n = 117$)	3.14 [0.76–5.4]	Kettlitz et al. (2019)
Instant coffee ($n = 72$)	0.76 [0.05–3.2]	Kettlitz et al. (2019)
Instant coffee	0.74	Rahn and Yeretzian (2019)
Roast & ground (cartridge delivery system)	2.14	Rahn and Yeretzian (2019)
Roast & ground ($n = 8$)	3.16 [1.6–4.5]	Hamlet et al. (2018)
Instant coffee ($n = 6$)	0.44 [0.15–0.6]	Hamlet et al. (2018)
Roast & ground (cartridge delivery system) ($n = 3$)	2.3 [2.11–2.66]	Becalski et al. (2016)
Instant coffee ($n = 7$)	0.23 [0.047–0.74]	Becalski et al. (2016)
Roast & ground ($n = 7$) (decaffeinated)	2.45 [1.64–3.45]	Becalski et al. (2016)
Category 2 Coffee type	**Average Furan (mg/kg in coffee, brewed)**	**References**
Cartridge coffee	73–120	Kettlitz et al. (2019)
Instant coffee	6.7	Kettlitz et al. (2019)
Fully automated coffee machine	74–99	Rahn and Yeretzian (2019)
Filter coffee	47–53	Rahn and Yeretzian (2019)
Instant coffee	<5.8 (LoD)	Rahn and Yeretzian (2019)
Cartridge coffee	20–33	Rahn and Yeretzian (2019)
Espresso	28–199	EFSA (European Food Safety Authority) (2017)
Cartridge coffee	58–59	Becalski et al. (2016)
Instant coffee	0.7	Becalski et al. (2016)

sample separation; however the detection system is fundamentally based on flame ionization detector reported to be less sensitive than mass spectrometer. Alternatively, Proton Transfer Reaction Mass Spectrometry (PTR-MS) is an exceptional technique differing from other chromatographic techniques and based on an online quantity monitoring system without chromatographic separation of concerned analyte. However, a number of limitations hinder its sensitivity for furan analysis as it is just an online application, depending on in silico detection system. Moreover, it can only provide accurate standard calibration by treating every volatile separately as compared to GC-MS, which is really time consuming and Labor intensive. Furthermore, it is more specific for detection of atmospheric volatiles instead of real food matrix (Sekimoto et al. 2017). Hence, to date, GC-MS in combination with DVB/CAR/PDMS fiber has been denoted as the most sensitive and specific method for furan analysis.

Furan occurrence

Furan formation during thermally driven food processing has been considered as a public concern in several studies over the past decade. Some well recognized international agencies such as EFSA, FSA and FDA have contributed to monitor furan levels formed in food stuffs and uploaded their data on their respective databases. European Food Safety Authority (EFSA (European Food Safety Authority) 2017) has gathered some academia, research institutes and some well recognized business operators for collecting and submitting furan occurrence data encompassing different food samples. EFSA provided strong suggestions to the data collectors for furan analysis according to the guidance from EFSA description of standard samples for food and feed. The EFSA standard operational procedures have managed all data collection and in- house validation. The accurate indication of food products was also required for all data providers, explaining whether food products used for analysis, are purchased or consumed after preparation according to European Commission Recommendation 2007/196EC. The assessed data sets have included 10370 analytical results from some authenticated governmental organisations. All member states have sent their analytical results according to purchased or consumed commercial food items after being analyzed from their respective laboratories. Furthermore, data set have also included both analysed and consumed samples, with total numbers of reported results from 9663 samples. Moreover, the data provided by several countries was carefully evaluated by cleaning and further validated by EFSA. For instance, furan exposure studies have been reported, revealing that coffee contributes most significantly to an adult's dietary exposure. Coffee contains certain precursors entailed as carbohydrates and amino acids, which undergo degradation or can react with each other by thermally driven mechanisms under higher roasting temperature, leading to form furan up to higher extents (Rahn and Yeretzian 2019). Previous section under furan formation from different precursors has already demonstrated about different furan formation mechanisms by thermal degradation of carbohydrates or Maillard reaction. Several published reports have also provided evidence of furan occurrence in commercially available coffees (Becalski et al. 2016; Chaichi et al. 2015). These data reports have provided information on furan prevalence in coffees with different concentration ranges referenced by several recent studies (Table 3). Moreover, different studies until now have not presented significant differences in furan levels in caffeinated versus noncaffeinated beverages (Becalski et al. 2016). EFSA (European Food Safety Authority) (2017) has reported that one coffee cup would contain about 5.5 to 81.6 ng/mL of furan, causing the consumption of 0.8 to 13 µg of furan in a standardized serving, depending on processing and applied beverage method. The preparation methods, initial concentrations and storage time period can greatly influence furan levels in the final cup. Furthermore, the preparation methods and storage time period could also influence the furan losses from 27% to 92% in a ground coffee and similarly

Table 4. Occurrence of furan in Baby foods.

Baby food, main component (number of samples)	Furan Average [range]	References
Infant cereals ($n = 87$)	nd	Kettlitz et al. (2019)
Miscellaneous (dessert, milkies, snacks) ($n = 11$)	9.1 [5–19]	Kettlitz et al. (2019)
Fruit ($n = 13$)	7.2 [4.3–17]	Kettlitz et al. (2019)
Vegetables ($n = 37$)	5.5 [1–14]	Kettlitz et al. (2019)
Savory (meat or fish or pasta) ($n = 114$)	33.3 [2.5–98]	Kettlitz et al. (2019)
Meat ($n = 9$)	28.9 [<2–98]	Hamlet et al. (2018)
Fruit ($n = 8$) 4 [3.8–4.2]	4 [3.8–4.2]	Condurso, Cincotta, and Verzera (2018)
Vegetables ($n = 13$)	2 [<2–6]	Hamlet et al. (2018)
Vegetables ($n = 6$)	6.3 [2.6–16.2]	Shen et al. (2016)
Fruit ($n = 3$)	1.03 [<1–1.6]b	Shen et al. (2016)

these losses can be from 0% to 55% for instant coffee (EFSA (European Food Safety Authority), 2017). Losses of furan were also presented as ranged from 40% to 78% for cartridge coffee and another range was 0% to 50%, to be presented for an instant coffee by a recent report inconsistency with EFSA (Kettlitz et al. 2019).

Several studies entailed furan occurrence in canned/jarred baby foods over the past decade and are well documented by EFSA reports (EFSA (European Food Safety Authority Journal) 2011; EFSA (European Food Safety Authority) 2017). The classification of analyzed samples was performed according to their constituents, such as segregating meat with vegetables, only vegetables, fruits, fish and fruits in combination with vegetables. The precursors representing baby food made with different food constituents may vary due to different concentrations of carbohydrates and proteins and lipids, hence, their potential to trigger furan formation was also varied. Moreover, different processing conditions may contribute differently on furan formation. Relatively, higher furan levels in vegetables/meat were also mirrored by EFSA reports, describing lesser furan levels in cereal-based baby foods containing fruits and vegetables (EFSA (European Food Safety Authority Journal) 2011; EFSA (European Food Safety Authority) 2017). Hence, it can be reasoned that processing techniques, raw material and ingredients composition would present greater influence on formation of food processing contaminates. Furan occurrence data in baby food have also been shown in (Table 4). Interestingly, a recent study entailed baby foods sold in Italy has provided confirmation of previous studied data for prevalence of lower furan concentrations (4 ng/g) in fruit based baby food than meat segregated baby food (26 ng/g) (Condurso, Cincotta, and Verzera 2018). Another survey on commercial products in Technical University of Denmark (DTU) has demonstrated lower furan levels in ready to eat breakfast cereals as compared to honey coated cereals (Fromberg et al. 2014) due to presence of different ingredients, changed food formulations and respective food processing methods, triggering several changes in furan concentrations. The FSA (Food Standard Agency United Kingdom) (2018) from UK has also published data on furan occurrence in breakfast cereals with comparably same results as provided by DTU (Hamlet et al. 2018) (Table 5). Hence, prevalence of furan in different food stuffs entailed as coffee, baby foods and cereals might have a serious impact on overall human exposure to furanoic compounds, posing a great need to being acknowledged by health risks associated with their consumption.

In vivo study on furan carcinogenicity and genotoxicity

Toxicology of furan is well documented and demonstrated by several experimental animal model studies and organizations, ensuring furan toxicity (Table 6). Furan has been demonstrated as a liver toxicant in rodents after acute or chronic oral exposure. It can efficiently get absorbed and metabolized to reactive intermediate by cytochrome P450 CYP2E1, mediating ring opening and produces *cis*-2-butene-1,4-diol (BDA). This metabolite is thought to be responsible for health hazardous effects in vivo analysis due to generation of covalent interactions with tissue molecules, mainly DNA and proteins (Moro et al. 2012; Von Tungeln et al. 2017). Moreover, furan incorporation into liver and kidney DNA has also been documented by orally administering 14 C-labelled furan in rats for up to 28 days. It was examined that no any DNA adducts were formed through in situ biochemical reaction of BDA with 2-deoxyribonucleotides and lower carcinogenic effects were identified after single oral dose for approximately 360 days and have shown non-genotoxicity of furan in vivo (Neuwirth et al. 2012; Churchwell et al. 2015). In an experimental animal model experiment, the female Big Blue cII transgenic B6CF1 mice was fed with furan for 6 week time period with 15 mg/kg bw dose and noticed no certain elevation in mutation frequency. In vitro treatment was also performed to investigate BDA for carrying out mutational potential in the same target gene for mouse embryo fibroblasts, derived from transgenic mouse. Resultantly, the mutational spectrum was shifted with an increased AT < CG transversion after being treated with BDA and encountered major effects on genetic code changes due to BDA treatment (Terrell et al. 2014).

Furthermore, experiments on gpt delta rats have determined Gpt and Spi mutations. Furan specific gpt mutation and increased mutational frequencies were not identified. However, a certain rise in the numbers of PCNA positive hepatocytes, mRNA levels of cyclin d1 and cyclin e1, glutathione S-transferase placental form (GST-P) positive loci was detected in high dosage groups. Hence, it can be reasoned that cell proliferation took part in the initial stages of furan induced hepatocarcinogenesis rather than genotoxicity mechanisms (Hibi et al. 2017). The induction of epigenetic

Table 5. Occurrence of furan in breakfast cereals.

Category	Furan Average [range]	References
Breakfast cereal ($n = 24$)	27.5 [<10–116]	Hamlet et al. (2018)
Honey coated breakfast cereal ($n = 11$)	57.4 [<2.4–387]	Fromberg et al. (2014)
Breakfast cereal ($n = 95$)	27 [1–140]	Kettlitz et al. (2019)
Biscuits, crackers, crispbread, and similar ($n = 30$)	32.4 [<10–108]	Hamlet et al. (2018)

Table 6. Description of furan risks by different organizations.

Organization	Class	Description
IARC	2B	Possibly carcinogenic to human
NTP	R	Anticipated to be carcinogenic to human
EU	C2	Substances which should be regarded as human carcinogens

changes by encountering furan has shown chromatin instead of DNA damage, which resulted in mutations and further carcinogenic transformation (de Conti et al. 2016), leading toward gene expression and changes in gene activity. Hence, these furans induced changes have affected DNA methylation of its acetylation at a wider level, and has also influenced the chromatin modifying genes. Such furan induced changes have been shown to be affecting DNA acetylation or methylation at a broader level and influencing chromatin modifying genes and histones (Tryndyak et al. 2017; de Conti et al. 2015) or causing changes in microRNAs in rat liver (de Conti et al. 2016; Dong et al. 2016). Furthermore, the histone modifications with GSH-BDA conjugate have also been shown after a lower oral dose of furan being presented at the precarcinogenic stage (Nunes et al. 2016). Moreover, some epigenetic changes lacking direct and non thresholded genotoxic mechanism of action could have an agreement with nongenotoxic mechanism of action (de Conti et al. 2016).

Human risk assessment

Furan has been documented to be carcinogenic and hepatocarcinogenic in experimental animal models entailed as rats and mice. However, its adverse effects with relevancy to humans still remain unclear. Current aspects related to the main pathways for furan carcinogenicity with nongenotoxic mechanisms of action have involved liver injury induced by oxidative stress, cytotoxictiy, regenerative inflammation and proliferation. The consideration with a number of critical parameters entailing, detoxification, inter-species toxicokinetic differences in activation and some other potential differences in probability of interaction with DNA as a genetic material is lacking in relation to humans. A clear understanding of adverse effects caused by furan exposure can be supported by examining the health hazardous effects due to exposure (consumption) of some components such as coffee, containing furans levels in it (EFSA (European Food Safety Authority) 2017). EFSA (European Food Safety Authority) (2017) assumptions have shown the study limitations, including animal model relevancy and limited consideration of adverse outcomes from furan exposure. Hence, margin of exposure (MoE) approach was applied to assess the nonneoplastic effects and assumed to be driven by genotoxic mechanism. EFSA has evaluated the non-neoplastic effects against MoE of 100, and a tolerable dose (0.64 µg/kg bw/day) was applied. It has been considered that rodents are not sensitive species and provided a conservative estimate for human exposure at the maximum exposure scenario. Another main point is the research for uninary markers being representative of furan exposure and more specifically on dietary furan exposure, which would considerably improve furan exposure assessments, which is still not found (Rietjens et al. 2018).

Mitigation strategies of furan in food

Different mitigation strategies have been implicated by food industries, which might affect the nutrition and safety of final product. Furthermore, any reduction strategy should be mindful of its impacts, such as the extent of its acceptability and desirable sensory properties (Kettlitz et al. 2019). Different furan mitigation strategies have been applied in food systems such as traditionally leaving hot beverage in an open atmosphere, recipe modification, changing thermal processing conditions, changing precursor level, high pressure and temperature approach and most importantly addition of certain antioxidants in food system to trigger significant reduction. This section will describe these approaches with subsequent pros and cons.

The first and most simple strategy to be applied by considering the volatile nature of furan leaving hot beverage/food in an open atmosphere before being ready to eat, can significantly decrease furan concentration. Stirring and agitation can be an additional factor causing reduction effects, after food has become ready to eat (Mesias and Morales 2014). However, this approach can cause an increased exposure of food constituents toward environmental pathogens, posing some hygienic concerns.

Different food ingredients are pretreated by steaming or drying before being used in a food recipe, contributing toward furan formation. Hence, different steps regarding recipe pretreatment may cause significant impacts on its formation. Several studies entailing model systems particularly vegetable model systems have indicated that more complex the food matrix, the less clear information can be obtained about factors contributing toward furan formation due to their multiple interactions, which would, made furan mitigation approach highly challenging. Moreover, recipe modification will need to be carried out on case by case bases for every recipe and further simulation of thermal process conditions can be optimized at factory level. However, recipe modification did not seem to be an easily applied approach even for a simple vegetable puree due to limitation of current knowledge about the proper ingredients and their final fate into finished product hence, achieving a meaningful reduction without affecting the nutritional loss is termed as a challenging factor.

Table 7. Furan reduction strategies in food.

Area	Food Category	Furan Reduction Strategies	References
Ingredients and processing	Vegetable/purée	Up to 50% lower furan levels in nitrogen-flushed compared with oxygenated potato purée after sterilization. Strongest effects at pH 7. Impact of O2 removal and possible microbial consequences in the cooked/stored product need careful study.	Palmers et al. (2016)
		Lower furan levels (2- to 3-fold) in potato purée at pH 3 compared to pH 7 after sterilization	Palmers et al. (2016)
		Faster heating rate versus retort sterilization, lower furan formation at same F0 than retort (2- to 3-fold less); recipe mainly based on carrots and peas.	Hradecky et al. (2017)
		Lower furan formation (>80%), but small batch size <100 g and Quality/Safety parameters (micro) need more study.	Sevenich et al. (2015)
Food additives	Food Model system (glucose, alanine, serine) and soy sauce model system	Addition of metal ions (Magnesium sulfate, iron sulfate, calcium sulfate and zinc sulfate) and antioxidants (Butyl hydroxyanisole (BHA), butyl hydroxytoluene (BHT) and sodium sulfite).	Kim, Her, and Lee (2015); Kim, Her, and Lee (2015)
Antioxidants	Precursor system, glucose–glycine and asparagine–fructose system	Ellagic acid, vitamin E, oleuropein, caffeic acid, tyrosil epicatechin, chlorogenic acid, oleuropein, tyrosol, and punicalagin.	Oral, Dogan, and Sarioglu (2014)
	Canned coffee model	Plant Tea Polyphenols	Bi et al. (2017)

Additionally, changing precursor levels entailed as carbohydrates, PUFAs and proteins which can produce furan rapidly under thermal oxidative conditions can also cause changes in the taste of food developed by Maillard reaction or caramelization of these precursors present in food system. However, certain information on some principle precursors, such as carbohydrates, ascorbic acid, PUFAs, proteins and different antioxidants is still available via model system studies (Table 1), and very carefull mitigation has been applied by some strategies in model systems and real food matrix (Table 7), although its important and final fate in the finished product still need to be get acknowledged in further studies.

The modification of thermal treatment conditions is another simple and easily acceptable approach according to the optimized time and temperature (low temperature) conditions. A thermal pressure (temperature/time) and its distribution in the system would be a major parameter impacting furan formation. This profile can be optimized in certain conditions, for instance, as the emerging technology, High Pressure and High Temperature (HPHT) has generated lower furan levels in vegetable purees by reducing the thermal kill step albeit being careful about quality and safety of product. This lower furan formation might be due to preheating time to reach toward holding temperature, and finally fast temperature drops down upon pressure release. This rapid pressure release may drive off furan formed during processing (Palmers et al. 2014). Moreover, an application of 600 MPa pressure in vegetable purees to achieve sterilization (F0 = 7), have proven furan reduction from 81% to 96% as compared with conventional restort system (Sevenich et al. 2014). However, these pressure treatments can cause degradation of food matrix constituents and are still under consideration to apply on the factory scale.

Certain antioxidants have been demonstrated by several studies to be promising factors for furan reduction, due to the delays in lipid oxidation. A number of polyphenolics (caffeic acid, epicatechin, chlorogenic acid, oleuropein, tyrosol, punicalagin and ellagic acid) can effectively reduce furan formation due to their radical scavenging activity (Oral, Dogan, and Sarioglu 2014; Bi et al. 2017). The most significant effect of furan mitigation was observed during UV-C light treatment of simulated fruit juice after addition of malic acid and galic acid as an antioxidant and has been proven to mitigate furan formation by terminating free radical chain reactions (Hu et al. 2018). Similarly, Kim, Her, and Lee (2015) have attempted to reduce furan levels by metal ions (magnesium sulfate, iron sulfate, calcium sulfate and zinc sulfate) and antioxidants (butyl hydroxyanisole (BHA), butyl hydroxytoluene (BHT) and sodium sulfite) in food model systems. Furan reduction was occurred in the following order: sodium sulfite > BHA > iron sulfite > BHT > calcium sulfite. However, significant reductions in furan levels and efficiency of different additives depend on food matrix system environment. Furthermore, most of these studies are based on model systems (Table 1) actual food matrix systems consist of more complex group of different precursors. Hence, the effect of different antioxidants on the food systems varies. These facts can be evidenced by coffee which contains several radical scavenging agents and antioxidants, however, still contains relatively high furan level.

To conclude, the most promising strategy can be the combination of an optimized time and temperature condition, selection of ingredients and precursors, and the addition of some trapping agents by careful selection of all these factors, however further studies still need to be conducted to get very careful mitigation strategies with less disadvantages.

Conclusion

Furan is a naturally occurring possibly carcinogenic compound which is being found in several thermally driven processed foods particularly different types of coffee, baby foods containing meat constituents and breakfast cereals. Several pathways are involved in furan formation such as thermal degradation of carbohydrates, rearrangement of carbohydrates alone or in the presence of some amino acids, sometimes oxidation of ascorbic acids and lipids at a

relatively higher temperature. In this review, different studies involving formation, occurrence, and precursors involving furan formation, in vivo carcinogenicity and genotoxicity as well as its reduction strategies have been discussed critically for readers understanding about the subject. These studies have provided recent insights into different analytical methods and reduction strategies; however, still there is a need for getting better approaches in future to get new insights into the formation, analysis and reduction of this possible carcinogen from our diet. More sensitive techniques are needed to detect even lower furan levels in food and even more focus should be given to reduction approaches during food processing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The authors thank the National Key R & D Program of China (No. 2017YFC1600401), National Natural Science Foundation of China (Nos. 31671961 & 31701727), Key Projects of Guangdong Natural Science Foundation (No. 2017A030311021), Key Project of Guangzhou S&T Program (No. 201904020005), YangFan Innovative and Enterpreneurial Research Team Project (2014YT02S029), and the 973 program (No. 2012CB720801).

References

Altaki, M. S., F. J. Santos, and M. T. Galceran. 2011. Occurrence of furan in coffee from Spanish market: Contribution of brewing and roasting. *Food Chemistry* 126 (4):1527–32. doi: 10.1016/j.foodchem.2010.11.134.

Becalski, A., S. Hayward, T. Krakalovich, L. Pelletier, V. Roscoe, and E. Vavasour. 2010. Development of an analytical method and survey of foods for furan, 2-methylfuran and 3-methylfuran with estimated exposure. *Food Additives & Contaminants: Part A* 27 (6):764–75. doi: 10.1080/19440040903473332.

Becalski, A., T. Halldorson, S. Hayward, and V. Roscoe. 2016. Furan, 2-methylfuran and 3-methylfuran in coffee on the Canadian market. *Journal of Food Composition and Analysis* 47:113–9. doi: 10.1016/j.jfca.2016.01.006.

Bi, K. H., L. Zhang, X. G. Qiao, and Z. X. Xu. 2017. Tea polyphenols as inhibitors of furan formed in the maillard model system and canned coffee model. *Journal of Food Science* 82 (5):1271–7. doi: 10.1111/1750-3841.13691.

Bohnert, T., L. Gingipalli, and P. C. Dedon. 2004. Reaction of 20-deoxyribonucleosides with cis- and trans-1,4-dioxo-2-butene. *Biochemical and Biophysical Research Communications* 323 (3):838–44. doi: 10.1016/j.bbrc.2004.08.164.

Byrns, M. C., C. C. Vu, J. W. Neidigh, J. L. Abad, R. A. Jones, and L. A. Peterson. 2006. Detection of DNA adducts derived from the reactive metabolite of furan, cis-2-butene-1,4-dial. *Chemical Research in Toxicology* 19 (3):414–20. doi: 10.1021/tx050302k.

Chaichi, M., V. Ghasemzadeh-Mohammadi, M. Hashemi, and A. Mohammadi. 2015. Furanic compounds and furfural in different coffee products by headspace liquid-phase micro-extraction followed by gas chromatography-mass spectrometry: Survey and effect of brewing procedures. *Food Additives & Contaminants. Part B, Surveillance* 8 (1):73–80. doi: 10.1080/19393210.2014.981601.

Chakraborty, S., P. S. Rao, and H. N. Mishra. 2015. Effect of combined high pressure–temperature treatments on color and nutritional quality attributes of pineapple (Ananas comosus L.) puree. *Innovative Food Science & Emerging Technologies* 28:10–21.

Chen, L. J., S. S. Hecht, and L. A. Peterson. 1995. Identification of cis-2-butene-1,4-dial as a microsomal metabolite of furan. *Chemical Research in Toxicology* 8 (7):903–6. doi: 10.1021/tx00049a001.

Cho, H., and K. G. Lee. 2014. Formation and reduction of furan in Maillard reaction model systems consisting of various sugars/amino acids/furan precursors. *Journal of Agricultural and Food Chemistry* 62 (25):5978–82. doi: 10.1021/jf501619e.

Churchwell, M. I., R. C. Scheri, L. S. Von Tungeln, G. G. da Costa, F. A. Beland, and D.R. Doerge. 2015. Evaluation of serum and liver toxicokinetics for furan and liver DNA adduct formation in male Fischer 344 rats. *Food and Chemical Toxicology* 86:1–8. doi: 10.1016/j.fct.2015.08.029.

Cincotta, F., A. Verzera, G. Tripodi, and C. Condurso. 2017. Non-intentionally added substances in PET bottled mineral water during the shelf-life. *European Food Research and Technology* 2:1–7. http://dx.doi.org/10.1007/s00217-017-2971-6.

Condurso, C., F. Cincotta, and A. Verzera. 2018. Determination of furan and furan derivatives in baby food. *Food Chemistry* 250: 155–61. doi: 10.1016/j.foodchem.2017.12.091.

Crews, C., and L. Castle. 2007. A review of the occurrence, formation and analysis of furan in heat-processed foods. *Trends in Food Science & Technology* 18 (7):365–72. doi: 10.1016/j.tifs.2007.03.006.

de Conti, A., T. Kobets, V. Tryndyak, S. D. Burnett, T. Han, J. C. Fuscoe, F. A. Beland, D. R. Doerge, and I. P. Pogribny. 2015. Persistence of furan-induced epigenetic aberrations in the livers of F344 rats. *Toxicological Sciences* 144 (2):217–26. doi: 10.1093/toxsci/kfu044.

de Conti, A., V. Tryndyak, D. R. Doerge, F. A. Beland, and I. P. Pogribny. 2016. Irreversible down-regulation of miR-375 in the livers of Fischer 344 rats after chronic furan exposure. *Food and Chemical Toxicology* 98:2–10. doi: 10.1016/j.fct.2016.06.027.

Dong, H. Y., S. Gill, I. H. Curran, A. Williams, B. Kuo, M. G. Wade, and C. L. Yauk. 2016. Toxicogenomic assessment of liver responses following subchronic exposure to furan in Fischer F344 rats. *Archives of Toxicology* 90 (6):1351–67. doi: 10.1007/s00204-015-1561-2.

Dhakal, S., V. M. Balasubramaniam, J. C. Cocuron, A. P. Alonso, E. Agcam, and S. Kamat. 2017. Pressure-thermal kinetics of furan formation in selected fruit and vegetable juices. *Food and Bioprocess Technology* 10 (11):1959–69. doi: 10.1007/s00204-015-1561-2.

EFSA (European Food Safety Authority Journal). 2011. Consideration of 40 furan substituted aliphatic hydrocarbons, alcohols, aldehydes, ketones, carboxylic acids and related esters, sulfides, disulfides and ethers evaluated by JECFA at the 65th meeting and reevaluated at the 69th meeting. *European Food Safety Authority Journal* 9 (10):2315.

EFSA (European Food Safety Authority). 2017. Risks for public health related to the presence of furan and methylfurans in food. *EFSA Journal* 15 (10):5005.

Fromberg, A., M. S. Mariotti, F. Pedreschi, S. Fagt, and K. Granby. 2014. Furan and alkylated furans in heat processed food, including home cooked products. *Czech Journal of Food Sciences* 32 (5):443–8.

FSA (Food Standard Agency United Kingdom). 2018. European Commission Recommendation on the monitoring of the presence of furan in foodstuffs (2007). OJ L88/56.

Goncalves, J. L., J. A. Figueira, F. P. Rodrigues, L. P. Ornelas, R. N. Branco, and C. L. Silva. 2014. A powerful methodological approach combining headspace solid phase microextraction, mass spectrometry and multivariate analysis for profiling the volatile metabolomic pattern of beer starting raw materials. *Food Chemistry* 160 (1):266–80.

Hu, G., Z. A. Yan, H. A. Marta, K. A. Tatiana, and S. Suqin. 2016. An efficient method for the simultaneous determination of furan, 2-methylfuran and 2-pentylfuran in fruit juices by headspace solid phase microextraction and gas chromatography–flame ionisation detector. *Food Chemistry* 192:9–14.

Hu, G., H. Liu, Y. Zhu, M. Hernandez, T. Koutchma, and S. Shao. 2018. Suppression of the formation of furan by antioxidants during UV-C light treatment of sugar solutions and apple cider. *Food Chemistry* 269:342–6. 10.1016/j.foodchem.2018.07.009.

Hamlet, C. G., L. Liang, B. Baxter, and D. Apostilova. 2018. Survey of acrylamide and furans in UK retail products: Results for samples purchased between January 2017 and November 201. A Report

Prepared for the Food Standards Agency. https://www.food.gov.uk/sites/default/files/media/document/Acrylamide%20Furans_Summary%20report%20%28Jan%2017_Nov%2017%29.pdf.

Hradecky, J., E. Kludska, B. Belkova, M. Wagner, and J. Hajslova. 2017. Ohmic heating: A promising technology to reduce furan formation in sterilized vegetable and vegetable/meat baby foods. *Innovative Food Science & Emerging Technologies* 43:1–6. doi: 10.1016/j.ifset.2017.07.018.

Hibi, D., Y. Yokoo, Y. Suzuki, Y. Ishii, M. Jin, A. Kijima, T. Nohmi, A. Nishikawa, and T. Umemura. 2017. Lack of genotoxic mechanisms in early-stage furan-induced hepatocellular tumorigenesis in GPT delta rats. *Journal of Applied Toxicology* 37 (2):142–9. doi: 10.1002/jat.3331.

IARC (International Agency for Research on Cancer). 1995. Furan. *IARC Monographs* 63:393–407. http://monographs.iarc.fr/ENG/Monographs/vol63/mono63-16.pdf.

Kettlitz, B., G. Scholz, V. Theurillat, J. Cselovszky, N. R. Buck, S. O. Hagan, E. Mavromichali, K. Ahrens, K. Kraehenbuehl, G. Scozzi, et al. 2019. Furan and methylfurans in foods: An update on occurrence, mitigation, and risk assessment. *Comprehensive Reviews in Food Science and Food Safety* 18 (3):738–52. doi: 10.1111/1541-4337.12433,.

Kim, J. S., J. Y. Her, and K. G. Lee. 2015. Formation and reduction of carcinogenic furan in various model systems containing food additives. *Food Chemistry* 189:108–13. doi: 10.1111/1541-4337.12433.

Kim, M. Y., J. Y. Her, M. K. Kim, and K. G. Lee. 2015. Formation and reduction of furan in a soy sauce model system. *Food Chemistry* 189:114–9. doi: 10.1016/j.foodchem.2015.02.015.

Kubiak, A., L. Karasek, and T. Wenzl. 2008. Proficiency test on the determination of furan in baby food. *JRC Scientific and Technical Reports*. http://publications.jrc.ec.europa.eu/repository/bitstream/JRC48419/jrc48419%20%20eur%2023544.pdf.

Limacher, A., J. Kerler, B. Conde-Petit, and I. Blank. 2007. Formation of furan and methylfuran from ascorbic acid in model systems and food. *Food Additives and Contaminants* 2:122–35. doi: 10.1080/02652030701393112.

Limacher, A., J. Kerler, T. Davidek, F. Schmalzried, and I. Blank. 2008. Formation of furan and methylfuran by Maillardtype reactions in model systems and food. *Journal of Agricultural and Food Chemistry* 56 (10):3639–47. doi: 10.1021/jf800268t.

Locas, P. C., and A. V. Yaylayan. 2004. Origin and mechanistic pathways of formation of the parent furan: A food toxicant. *Journal of Agricultural and Food Chemistry* 52 (22):6830–6. doi: 10.1021/jf0490403.

Lorenzo, J. M. 2014. Influence of the type of fiber coating and extraction time on foal dry-cured loin volatile compounds extracted by solid-phase microextraction (SPME). *Meat Science* 96 (1):179–86. doi: 10.1016/j.meatsci.2013.06.017.

Lu, D., and Peterson. L. A. 2010. Identification of furan metabolites derived from cysteine-cis-2-butene-1,4-dial-lysine cross-links. *Chemical* Research in Toxicology 23 (1):142–51.

Mariotti, M., K. Granby, A. Fromberg, J. Risum, E. Agosin, and F. Pedreschi. 2012. Furan occurrence in starchy food model systems processed at high temperatures: Effect of ascorbic acid and heating conditions. *Journal of Agricultural and Food Chemistry* 60(40): 10162–9.

Märk, J., P. Pollien, C. Lindinger, I. Blank, and T. Märk. 2006. Quantitation of furan and methylfuran formed in different precursor systems by proton transfer reaction mass spectrometry. *Journal of Agricultural and Food Chemistry* 54 (7):2786–93. https://doi.org/10.1021/jf052937v.

Mesias, M., and F.J. Morales. 2014. Reliable estimation of dietary exposure to furan from coffee: An automatic vending machine as a case study. *Food Research International* 61:257–63. doi: 10.1016/j.foodres.2013.07.054.

Morehouse, K. M., P. Geraldo, and P. M. Timothy. 2018. Identification and quantitation of furan in irradiated fruit and vegetable Juice. *Radiation Physics and Chemistry* 152:81–8. doi: 10.1016/j.radphyschem.2018.06.044.

Moro, S., J. K. Chipman, J. W. Wegener, C. Hamberger, W. Dekant, and A. Mally. 2012. Furan in heat-treated foods: Formation, exposure, toxicity, and aspects of risk assessment. *Molecular Nutrition & Food Research* 56 (8):1197–211. doi: 10.1002/mnfr.201200093.

Neuwirth, C., P. Mosesso, G. Pepe, M. Fiore, M. Malfatti, K. Turteltaub, W. Dekant, and A. Mally. 2012. Furan carcinogenicity: DNA binding and genotoxicity of furan in rats in vivo. *Molecular Nutrition & Food Research* 56 (9):1363–74. doi: 10.1002/mnfr.201200226.

NTP (National Toxicology Program). 1993. Toxicology and carcinogenesis studies of furan (CAS No. 110-00-9) in F344 Rats and B6C3F1 Mice (Gavage Studies). National Toxicology Program Technical Reports Series. 402 286.

Nie, S., J. Huang, J. Hu, Y. Zhang, S. Wang, C. Li, M. Marcone, and M. Xie. 2013. Effect of pH, temperature and heating time on the formation of furan in sugar – glycine model systems. *Food Science and Human Wellness* 2 (2):87–92.

Nunes, J., I. L. Martins, C. Charneira, I. P. Pogribny, A. de Conti, F. A. Beland, and A. M. Antunes. 2016. New insights into the molecular mechanisms of chemical carcinogenesis: In vivo adduction of histone H2B by a reactive metabolite of the chemical carcinogen furan. *Toxicology Letters* 264:106–113. https://doi.org/10.1016/j.toxlet.2016.10.018

Oral, R., M. Dogan, and K. Sarioglu. 2014. Effects of certain polyphenols and extracts on furans and acrylamide formation in model system, and total furans during storage. *Food Chemistry* 142:423–9.

Owczarek, F. A., B. D. Meulenaer, G. Scholl, A. Adams, F. V. Lancker, P. Yogendrarajah, G. Eppe, E. D. Pauw, M. L. Scippo, and N. D. Kimpe. 2010. Furan formation from vitamin C in a starch-based model system: Influence of the reaction conditions. *Food Chemistry* 121:1163–70. doi: 10.1016/j.foodchem.2010.01.065.

Owczarek, F. A., B. D. Meulenaer, G. Scholl, A. Adams, F. V. Lancker, P. Yogendrarajah, G. Eppe, E. D. Pauw, M. L. Scippo, and N. D. Kimpe. 2012. Furan formation in starch-based model systems containing carbohydrates in combination with proteins, ascorbic acid and lipids. *Food Chemistry* 133:816–21. doi: 10.1016/j.foodchem.2012.01.098.

Palmers, S., T. Grauwet, L. V. Avenne, T. Verhaeghe, B.T. Kebede, M.E. Hendrickx, and A. Van Loey. 2016. Effect of oxygen availability and pH on the furan concentration formed during thermal preservation of plant-based foods. *Food Additives & Contaminants: Part A* 33:612–22. doi: 10.1080/19440049.2016.1154613.

Palmers, S., T. Grauwet, C. Buve, L.V.D. Vondel, B.T. Kebede, M.E. Hendrickx, and A. Van Loey. 2015. Furan formation during storage and reheating of sterilised vegetable purees. *Food Additives & Contaminants: Part A* 32 (2):161–9. doi: 10.1080/19440049.2014.999720.

Palmers, S., T. Grauwet, B.T. Kebede, M.E. Hendrickx, and A. Van Loey. 2014. Reduction of furan formation by high-pressure high-temperature treatment of individual vegetable purées. *Food and Bioprocess Technology* 7 (9):2679–93. doi: 10.1007/s11947-014-1300-3.

Rahn, A., and C. Yeretzian. 2019. Impact of consumer behavior on furan and furan-derivative exposure during coffee consumption. A comparison between brewing methods and drinking preferences. *Food Chemistry* 272:514–22. doi: 10.1016/j.foodchem.2018.08.078.

Rietjens, I. M. C. M., P. Dussort, H. Günther, P. Hanlon, H. Honda, A. Mally, S. O'Hagan, G. Scholz, A. Seidel, J. Swenberg, et al. 2018. Exposure assessment of process-related contaminants in food by biomarker monitoring. *Archives of Toxicology* 92 (1):15–40. doi: 10.1007/s00204-017-2143-2.

Sijia, W., W. Enting, and Y. Yuan. 2014. Detection of furan levels in select Chinese foods by solid phase microextraction–gas chromatography/mass spectrometry method and dietary exposure estimation of furan in the Chinese population. *Food and Chemical Toxicology* 64: 34–40. doi: 10.1016/j.fct.2013.11.012.

Sekimoto, K., S.-M. Li, B. Yuan, A. Koss, M. Coggon, C. Warneke, and J. de Gouw. 2017. Calculation of the sensitivity of proton-transfer-reaction mass spectrometry (PTR-MS) for organic trace gases using molecular properties. *International Journal of Mass Spectrometry* 421:71–94. http://dx.doi.org/10.1016/j.ijms.2017.04.006.

Sevenich, R., E. Kleinstueck, C. Crews, W. Anderson, C. Pye, K. Riddellova, J. Hradecky, E. Moravcova, K. Reineke, and D. Knorr. 2014. High-pressure thermal sterilization: Food safety and food quality of baby food puree. *Journal of Food Science* 79 (2): M230–237. doi: 10.1111/1750-3841.12345.

Shen, M., Q. Liu, H. Jia, Y. Jiang, S. Nie, J. Xie, C. Li, and M. Xie. 2016. Simultaneous determination of furan and 2-alkylfurans in heat-processed foods by automated static headspace gas chromatography-mass spectrometry. *Lwt - Food Science and Technology* 72: 44–54. doi: 10.1016/j.lwt.2016.04.030.

Shen, M., Q. Liu, Y. Jiang, S. Nie, Y. Zhang, J. Xie, S. Wang, F. Zhu, and M. Xie. 2015. Influences of operating parameters on the formation of furan during heating based on models of polyunsaturated fatty acids. *Journal of Food Science* 80 (6):T1432–T1437. doi: 10.1177/0192623310386499.

Terrell, A. N., M. Huynh, A. E. Grill, R. C. Kovi, M. G. O'Sullivan, J. B. Guttenplan, Y.-Y. Ho, and L. A. Peterson. 2014. Mutagenicity of furan in female Big Blue B6C3F1 mice. Mutation Research. *Mutation* Research/Genetic Toxicology and Environmental Mutagenesis 770:46–54. doi: 10.1016/j.mrgentox.2014.04.024.

Tryndyak, V., A. de Conti, D.R. Doerge, G.R. Olson, F.A. Beland, and I.P. Pogribny. 2017. Furan-induced transcriptomic and gene-specific DNA methylation changes in the livers of Fischer 344 rats in a 2-year carcinogenicity study. *Archives of Toxicology* 91 (3):1233–43. doi: 10.1007/s00204-016-1786-8.

Van Lancker, F., A. Adams, A. Owczarek, B. D. Meulenaer, and N. De Kimpe. 2011. Mechanistic insights into furan formation in Maillard model systems. *Journal of Agricultural and Food Chemistry* 59 (1): 229–35. doi: 10.1021/jf102929u.

Von Tungeln, L. S., N. J. Walker, G. R. Olson, M. C. Mendoza, R. P. Felton, B. T. Thorn, M. M. Marques, I. P. Pogribny, D. R. Doerge, and F. A. Beland. 2017. Low dose assessment of the carcinogenicity of furan in male F344/N Nctr rats in a 2-year gavage study. *Food and Chemical Toxicology* 99:170–81. doi: 10.1016/j.fct.2016.11.015.