Furan in Food – a Review

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ABSTRACT

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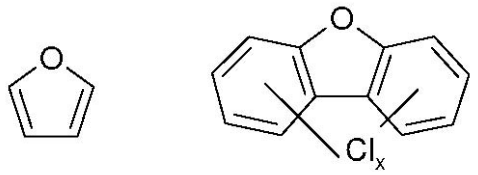
Furan and its derivatives were identified in a small number of heat-treated foods back in the 60's and 70's. In May 2004, US Food and Drug Administration published a report on the occurrence of parent furan in a number of thermally treated foods. Since furan has been classified as "possibly carcinogenic to human" by IARC, a great concern has been addressed to the analysis of this substance naturally-occurring in food. This paper gives a short overview on the mechanistic pathways of the parent furan formation in food by degradation of amino acids and/or reducing sugars, and oxidation of ascorbic acid and poly-unsaturated acids which can be induced by thermal or irradiation treatments; further, it deals with the metabolism and toxicology of furan as well as with the comparison of the methods of furan determination.

Keywords: furan; heat processing contaminants; headspace; solid-phase microextraction; mechanisms of furan formation

Furan is a colourless chemical (C_4H_4O) having a low molecular weight of 68 and a high volatility with the boiling point of 31°C (NTP 1993). Furan and its derivatives are naturally occurring compounds found at very low levels in many foods and drinks and they have been associated with the flavour of foods. These include commercially prepared foods as well as home made foods. Furans are a major class of compounds forming during the Maillard reactions and their presence in foods is well documented (Maga 1979).

However, the use of the general terminology may cause some confusion. It is important to note that the chemical compound, furan, is not the same as the dioxin-like family of furan compounds (polychlorinated dibenzofurans). The diagrams of the two compounds illustrate the difference (Figure 1). While furan unit is a part of the polychlorinated dibenzofuran structure, the latter are very different compounds with completely different effects.

The parent compound, furan, is widely used as a solvent for resins and lacquers as well as for the preparation of organic compounds (e.g. tetrahydrofuran) and pharmaceuticals (NTP 2001). After



furan polychlorinated dibenzofuran

Figure 1. Comparison of diagrams of furan and polychlorinated dibenzofuran

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classifying furan as "possibly carcinogenic to humans" (Group 2B) by the International Agency for Research on Cancer (IARC 1995), a great concern is given to the analysis of this substance naturally occurring in food. Furan induces tumours in animal assays; the most remarkable is the induction of hepatic cholangiocarcinomas in rats and mice. Just recently, the US Food and Drug Administration (US FDA) published a report on the occurrence of furan in a number of foods that undergo thermal treatment, especially canned and jarred foods (US FDA 2004a). Very similar results were published by the researchers from the Swiss Federal Office of Public Health (Reinhard *et al.* 2004). Parent furan was identified in a small number of heat-treated foods, such as coffee, canned meat, bread, cooked chicken, sodium caseinate, hazelnuts, soy protein isolate, hydrolysed soy protein, rapeseed protein, fish protein concentrate, and caramel back in 60's and 70's (Stoffelsma *et al.* 1968; Persson & Von Sydow 1973; Maga 1979). Recently, the database of information on the occurrence of furan in food has been widened as the analytical techniques capable of detecting extremely low levels of substances become increasingly more sensitive. Furan values for some foods on the Swiss Market are shown in Table 1 in accordance with the database mentioned being continuously completed.

ORIGIN AND MECHANISTIC PATHWAYS OF THE PARENT FURAN FORMATION

Literature data indicate multiple sources of furan formation originating from (*i*) thermal degradation/Maillard reaction reducing sugars, alone or in the presence of amino acids, (*ii*) thermal degradation of certain amino acids, and thermal oxidation of (*iii*) ascorbic acid, (*iv*) poly-unsaturated fatty acids and (*v*) carotenoids (Yaylayan 2006). The primary source of furan in food is the thermal degradation of carbohydrates such as glucose, lactose, and fructose (Maga 1979). According to the US FDA, a variety of carbohydrate/amino acid mixtures or protein model systems (e.g. alanine, cysteine, casein) and vitamins (ascorbic acid,

Table 1. Furan concentrations found in some foods commodities on the Swiss Market (according to Reinhard *et al.* 2004 and Swiss Federal Office of Public Health)

Sample description	Furan value (PPB)		Median (PPB)	Number of samples
	minimum	maximum		
Baby food in small glass jars	1	153	12	102
Fruit and vegetable juices for babies and young children	1	40	3	4
Coffee (drink)	13	146	74	9
Hot chocolate and malt beverage	< 2	< 2		2
Canned or jarred vegetables	< 2	12	3	15
Canned soups	19	43		2
Canned fruits	< 1	6		2
Tin containing meat	4	4		1
Tin containing meat and pasta	14	14		1
Sugo, tomato and Chilli sauces	< 4	39	6	13
Soy sauce, hydrolysed vegetable protein	18	91	50	7
Vegetables, fresh	< 1	< 2	< 1	7
Bread and toast	< 2	30	< 2	7
Whole milk UHT	< 0.5	< 0.5		1
Plum beverage	6	6		1
Beetroot juice with fruit juices (organic)	1	1		1
Potato flakes for mashed potatoes (flakes, not prepared)	< 5	< 5		1

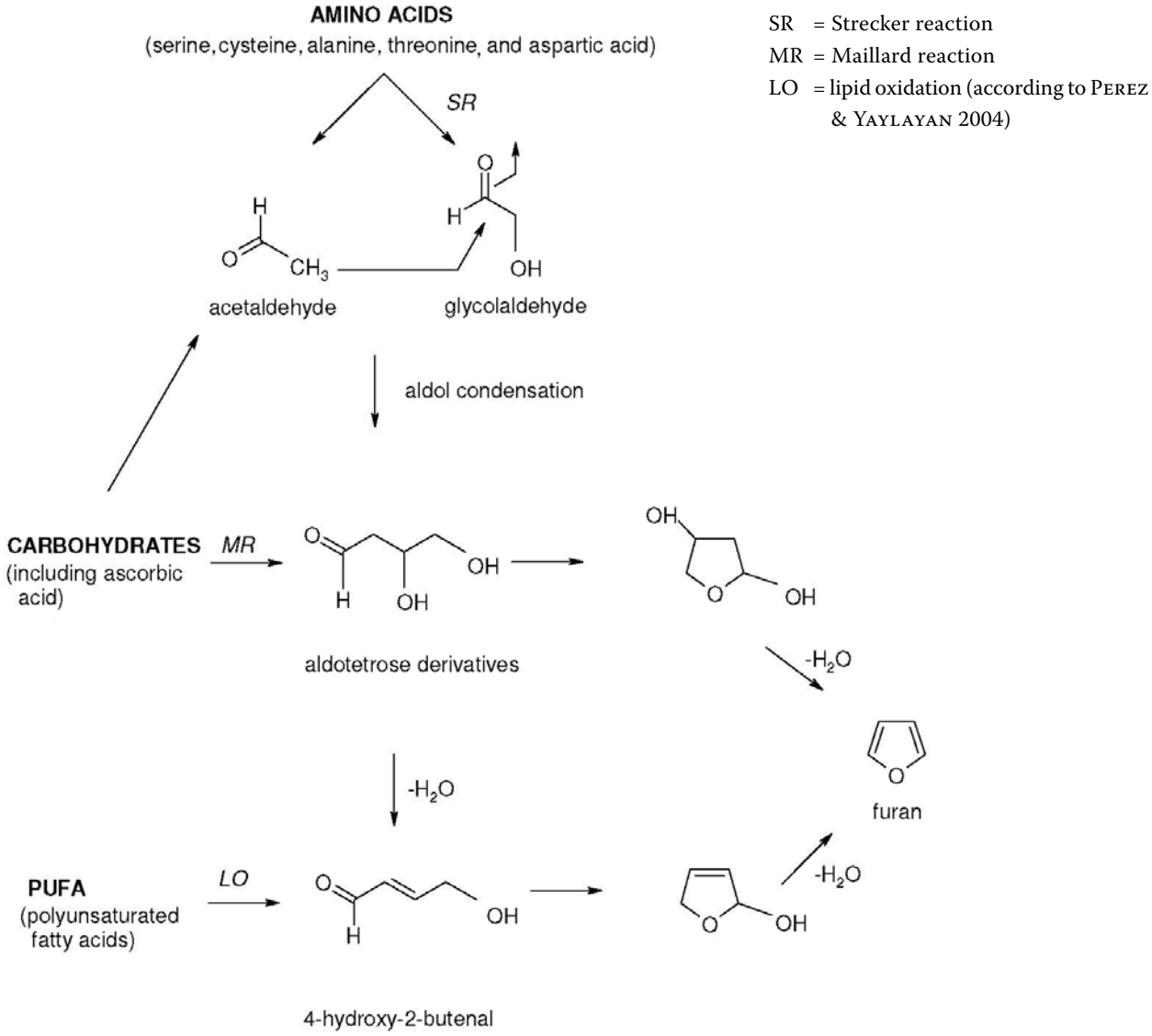

Figure 2. Proposed pathways of formation of parent furan from three main groups of sources, i.e. amino acids, carbohydrates, and polyunsaturated fatty acids

dehydroascorbic acid, thiamin) have been used to generate furan in food. Becalski and Seaman (2005) reported that furan can be formed through the oxidation of poly-unsaturated fatty acids (PUFA) at elevated temperatures while the addition of commercially available antioxidants (such as tocopherol acetate) reduced the formation of furan up to 70%. Perez and Yaylayan (2004) described the proposed pathways of the parent furan formation from amino acids, sugars, amino acid/sugar mixtures, and ascorbic acid. Figure 2 summarises the general pathways leading to the furan formation from these sources.

Furan formation through amino acid degradation

Amino acids such as serine or cysteine undergo the thermal degradation producing furan without the need of any other source. Both of them are able to metabolise to acetaldehyde and glycolaldehyde which react by aldol condensation producing aldotetrose derivatives and, eventually, furan. On the other hand, alanine, threonine, and aspartic acid alone do not produce furan. These amino acids can generate only acetaldehyde and they require the

presence of reducing sugars, serine, or cysteine to produce glycolaldehyde (Figure 2) (Perez & Yaylayan 2004).

Furan formation through carbohydrate degradation

Under the roasting conditions in the absence of amino acids, furan was mainly formed from the intact sugar skeleton. Formic and acetic acids were identified as byproducts of the sugar degradation, indicating the split of C_1 and/or C_2 units from hexoses. The presence of alanine, threonine, or serine promoted the furan formation by recombination of C_2 fragments, such as acetaldehyde and glycolaldehyde, which might originate from both sugars and amino acids. In the aqueous solution, about a half of furan was generated by the recombination of the sugar fragments (Limacher *et al.* 2008).

There are four pathways (A, B, C, and D; Figure 3) of carbohydrate degradation that can lead to the formation of aldotetrose derivatives and after eventual cyclisation can form furan (according to Perez & Yaylayan 2004).

Reducing hexoses undergo Maillard reactions in the presence of amino acids and generate reactive intermediates such as 1-deoxy- and 3-deoxyosones (pathways A and D). The 1-deoxyosone has to undergo alpha-dicarbonyl cleavage to produce aldotetrose (Weenen 1998). Aldotetrose is formed also by retro-aldol cleavage in the absence of amino acids (e.g. pathway B), however, to a lesser extent. The pathway C of Figure 3 shows the formation of 2-deoxy-3-keto-aldotetrose after a dehydratation reaction, followed by retro-aldol cleavage. Finally, 3-deoxyosone undergoes alpha-dicarbonyl cleavage, followed by oxidation and decarboxylation to generate 2-deoxyaldotetrose (pathway D). All the aldotetrose derivatives can be easily converted into furan as shown in Figure 3 (Perez & Yaylayan 2004).

Pentose sugars such as ribose can also generate the parent furan but more so in the presence of amino acids. Similar to hexoses, pentoses can be converted into their 3-deoxyosone derivatives either through a reaction with amino acids or through dehydration at the C-3 hydroxyl group (Weenen 1998). The resulting intermediate can undergo alpha-dicarbonyl cleavage to produce 2-deoxyaldotetrose, a direct precursor of furan (Figure 3).

Proposed pathway from ascorbic acid

Studies with ^{13}C-labelled ascorbic acid indicated that furan comprises an intact C_4 unit, mainly C-3 to C-6, generated by splitting off two C_1 units, i.e. CO_2 and formic acid. Possible intermediates are 2-deoxyaldoteroses, 2-furoic acid and 2-furaldehyde, which are known as ascorbic acid degradation products. The mechanism of furan formation from ascorbic acid was validated based on the labelling pattern of furan and the identification of $^{13}CO_2$ and $H^{13}COOH$ (Limacher *et al.* 2007).

Ascorbic acid can oxidise quickly to dehydroascorbic acid and hydrolyse in food systems into 2, 3-diketogulonic acid (DKG) (Liao 1987). DKG is converted to aldotetrose and later to furan (Figure 3). Nevertheless, under mainly nonoxidative pyrolytic conditions, ascorbic acid cannot undergo oxidation to produce DKG. Instead of this, it can hydrolyse and undergo beta-elimination (Niemelä 1987) followed by decarboxylation to produce 3-deoxypentosulose (DP), and then follow the ribose pathway to generate furan (Figure 3). However, under dry-heating conditions, dehydroascorbic acid can cyclise and it exists the mainly in its hemiketal form, thus preventing the formation of furan (Perez & Yaylayan 2004).

Formation of furan following exposure to ionising radiation

All these proposed pathways of furan formation were studied in model systems using pyrolysis-GC-MS, which means that in these cases the effect of high temperature was observed. Only recently, Fan (2005a) reported that ionising radiation induced the formation of furan in apple and orange juices. Furan levels increased linearly as the radiation dose increased from 0 to 5 kGy. Furthermore, in the first 3 days of storage after the irradiation treatment, the furan levels continued to increase in both apple and orange juices. According to Fan (2005ab), the increase in furan during the earlier storage period may be due to the residual effect of irradiation. Irradiation exerts its effect through generation of primary radicals from radiolysis of water (Simic 1983). The primary radicals include hydrated electrons, hydrogen atoms, and hydroxyl radicals. The primary radicals then react with the food components to form secondary radicals. Most of the free radicals are very short-lived (sub-

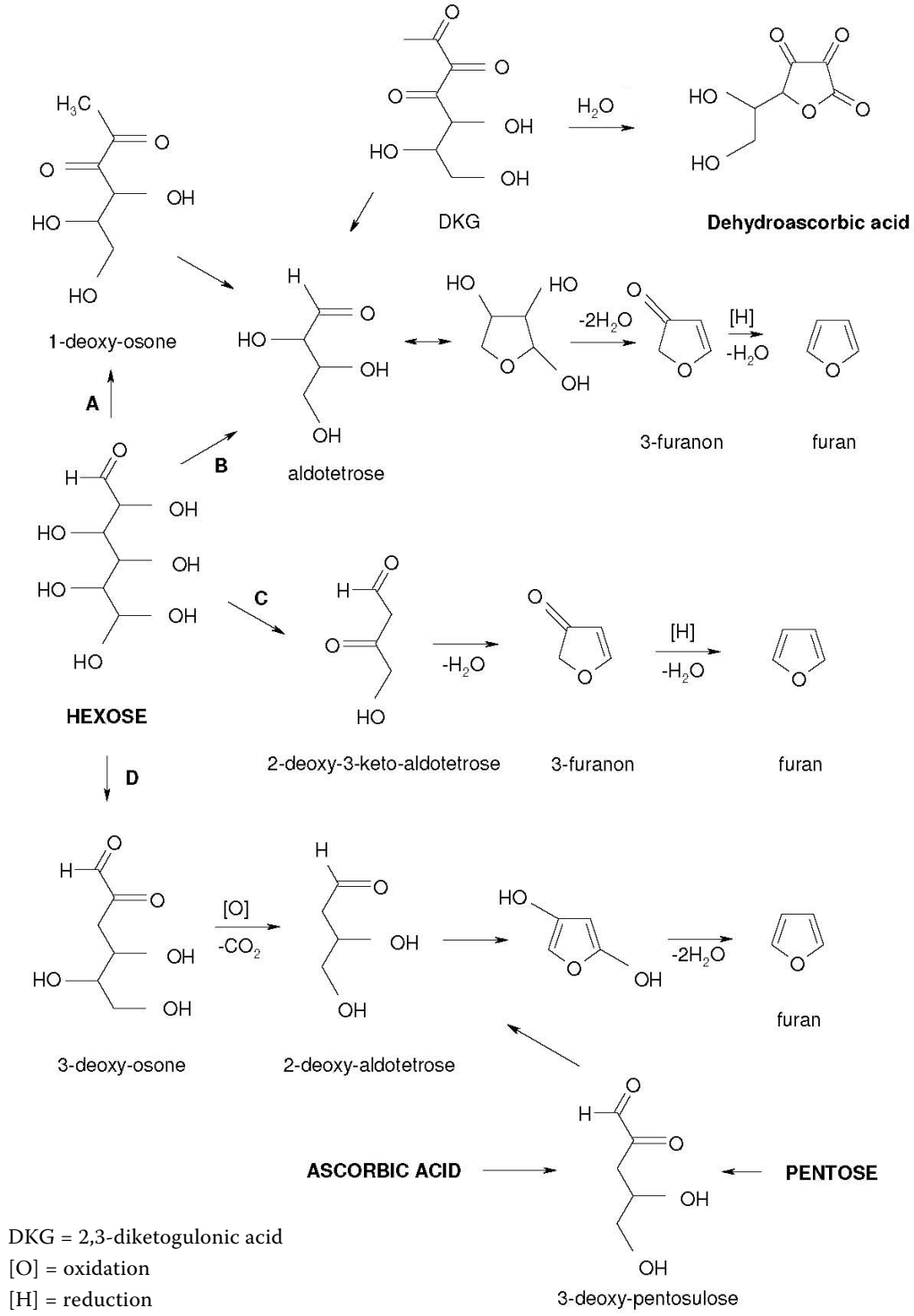

Figure 3. Schematic formation of furan from hexoses (A, B, C, and D pathway), pentoses and ascorbic and dehydroascorbic acid (according to Perez & Yaylayan 2004 with some modification)

seconds). However, some radicals and reactive compounds may be present for a much longer time (days). These stable radicals and reactive compounds may continue to induce the formation of furan (Fan 2005a).

The effect of irradiation on furan formation in model systems was studied by the same author later (Fan 2005b). His results showed that irradiation induced the formation of furan from ascorbic acid, fructose, sucrose, and glucose. Compared

to the thermal treatment (sterilisation), irradiation (5 kGy) of sugars and ascorbic acid produced similar amounts of furan.

METABOLISM AND TOXICOLOGY OF FURAN

Experiments in animals showed that furan is rapidly and extensively absorbed from the intestine and the lung (Egle & Gochberg 1979; Burka *et al.* 1991). Due to its low polarity, furan can pass through biological membranes and enter various organs. 24 hours after oral gavage of [^{14}C]-labelled furan to rats at a dose level of 8 mg/kg b.w., the recovery of radioactivity (expressed as furan equivalent) in nmol per g of tissue was: liver 307, kidney 60, large intestine 25, small intestine 13, stomach 6, blood 6, and lung 4, respectively. In total, 15% of the dose was recovered in these tissues (Burka *et al.* 1991). Seven days after the treatment, the radioactivity had almost returned to the limit of detection. After repeated dosing, the accumulation of radioactivity was found particularly in liver and kidney.

Cis-2-butene-1,4-dial has been identified as a key reactive and cytotoxic metabolite of furan, and has been found to bind to proteins (Burka *et al.* 1991) and nucleosides (Byrns *et al.* 2002). This metabolite will be formed by oxidation of one of the double bonds of furan, possibly with the formation of an epoxide intermediate, followed by spontaneous rearrangement and ring opening. Both *in vitro* and *in vivo* studies show that metabolic activation by cytochrome P450 (CYP) enzymes is involved in furan-induced toxicity. Inhibition and induction experiments revealed that CYP2E1 is the major enzyme involved in furan biotransformation indicating that furan metabolism can be enhanced by pre-treatment of rats with acetone (induction of CYP2E1) but not with phenobarbital (induction of CYP2B2 isozymes) (Kedderis *et al.* 1993). However, Kedderis and Held (1996) concluded that even the induction of hepatic CYP2E1 would not affect the rate of hepatic metabolism because the metabolic capacity of CYP2E1 for furan is so high that hepatic blood flow is the rate-limiting step in the elimination of the parent compound.

According to the toxicology and carcinogenesis studies of furan made by U.S. National Institutes of Health, furan is clearly carcinogenic to rats and mice, showing a dose-dependent increase in hepatocellular adenomas and carcinomas in both sexes (NTP 1993). In rats, also a dose-dependent increase in mononuclear leukaemia was seen in both sexes and a very high incidence of cholangiocarcinomas of the liver was present in both sexes, even at the lowest dose tested (2 mg/kg b.w.). The International Agency for Research on Cancer (IARC) of the WHO classified furan in 1995 as possibly carcinogenic for humans (IARC 1995).

ANALYSIS OF FURAN IN FOOD

Headspace sampling is the most suitable method for the analysis of very volatile compounds (Tassan & Russell 1974; Yang & Peppard 1994). This is a relatively simple and well-proven methodology in which a food sample in liquid or slurry form is heated in a sealed vial to achieve equilibrium partition between the liquid phase and the gaseous headspace. The headspace gas is sampled and the vapour injected into a GC. The detection can be carried out by non-selective means such as FID or by mass spectrometry.

Due to its high volatility, furan may also be analysed using a headspace gas chromatography-mass spectrometry (HS-GC-MS). A simple headspace method for the furan determination in food was developed by US FDA. Five gram test portions of semi-solid or solid foods are diluted with water, fortified with internal standard (*d4*-furan), and sealed in headspace vials. Similarly, ten gram test portions of liquid foods are fortified with *d4*-furan and sealed in headspace vials. Automated headspace sampling followed by gas chromatography/mass spectrometry (GC/MS) analysis is used to detect furan and *d4*-furan in selected-ion monitoring mode (SIM). Furan is quantified by using a standard additions curve, where the concentration of furan in the fortified test portions is plotted versus the furan/*d4*-furan response factors using the following ions: *m/z* 68 and 39 for furan and *m/z* 72 and 42 for *d4*-furan (US FDA 2004b). The experts from the Swiss Federal Office of Public Health used a similar method, except that quantification of furan was achieved by using only the furan/*d4*-furan ratio, rather than the standard additions curve (Reinhard *et al.* 2004). Becalski and Seaman (2005) simplified the headspace method by using autosampler vials to minimise possible losses of the analyte by reducing the number of transfer steps. In this approach, a 2 ml autosampler vial was used containing 1 g

of the sample instead of 10 ml vial with 5 g of the test portion (Becalski *et al.* 2005).

The headspace method has the advantage in that no sample purification is required and it can be automated for high sample throughput. The disadvantage is that the foodstuff is heated (according to FDA method at 80°C for a minimum of 30 min), meaning that furan might be formed during analysis. Senyuva and Goekmen (2005) recently described the formation of furan in unprocessed foods including green coffee, tomato juice, and orange juice during HS-GC-MS analysis even under mild (40°C) thermal conditions. On the other hand, Castle and Crews (2005) reported that the temperature range of 40–60°C had no significant effect on the furan formation during headspace incubation.

The researchers from the National Food Processors Association and Nestlé Research Centre developed and validated an analytical method using solid-phase micro-extraction (SPME) in combination with GC-MS (Goldmann *et al.* 2005; Ho *et al.* 2005; Bianchi *et al.* 2006). SPME is a fibre coated with a liquid (polymer), a solid (sorbent), or a combination of both. The fibre coating removes the compounds from the sample by absorption in the case of liquid coatings or adsorption in the case of solid coatings. The SPME fibre is then inserted directly into the gas chromatograph for desorption and analysis.

Only recently, Märk *et al.* (2006) studied furan formation using three main furan precursors, i.e. ascorbic acid, Maillard precursors, and polyunsaturated lipids. For the identification and quantification of furan in the headspace, they used the coupling of proton transfer reaction mass spectrometry and gas chromatography-mass spectrometry (PTR-MS/GC-MS). Ascorbic acid showed the highest potential to generate furan, followed by glyceryl trilinoleate. The furan yields from ascorbic acid were lowered in an oxygen-free atmosphere (30%) or in the presence of reducing agents, indicating the important role of oxidation steps in the furan formation pathway.

Kuballa and Ruge (2005) published a comparison of FDA-method (HS-GC-MS) and microdistillation-GC-MS. By this method, six headspace vials were distilled using an automated microdistiller into prepared vials with a cooled solution. An aliquot from each solution was sampled and injected into GC/MS system. The authors declared that this method can shorten the total time of analysis (in comparison with FDA method) by parallel distillation of six samples. Furthermore, the analysis of complex matrices, i.e. coffee, is easier.

Considering pros and cons of all the approaches mentioned, a reliable simplified method for furan determination in foods based on headspace GC-MS technique was recently tried and validated for routine application in the food control. The validation was performed by evaluating the following characteristics: accuracy, trueness, recovery, limit of detection, limit of quantification, operating range, and calibration. Uncertainty statements obtained in the validation process in the complex matrix represented by tomato ketchup (LOD = 0.9 ng/g; LOQ = 2.9 ng/g; recovery = 103, 107 and 115%, respectively; RSD = 4, 5 and 8%, respectively) confirm that the method mentioned is suitable for the determination of furan in this food matrix. The method was extended for the determination of furan in foods such as baby food, canned meat and vegetables, liquid seasoning, sauces, and coffee (Vranová *et al.* 2007).

EXPOSURE ASSESSMENT FOR FURAN

In May 2004, the US Food and Drug Administration (US FDA) published a report on the occurrence of furan in thermally treated food commodities (US FDA 2004a). According to this report and other ones discussing the acute and chronic toxicity of furan, European Food Safety Authority (EFSA) requested its Scientific Expert Panel on Contaminants in the Food Chain (CONTAM) to establish an ad hoc Working Group to investigate further the issue. The Working Group was charged with the collection of information on the chemical furan, its formation, and measured concentrations of furan in various foods and food products. EFSA initiated also a meeting of the European Commission's Committee of Experts on Environmental and Industrial Contaminants in Food. The first meeting took place in Brussels in October 2004, the second in May 2006. At both meetings the problems of the occurrence of furan in foods as well as analytical methodology for the determination of furan levels found in foods and food products were discussed.

Only a limited set of data on the occurrence of furan in various food categories as well as consumption data are available to date. According to this, the Scientific Panel on Contaminants in the Food

Chain EFSA decided to present in its reports the range of the estimated exposure rather than the average exposure (EFSA 2004). US FDA presented the range of furan concentrations in 273 baby food samples from not detectable to 112 ng/g (US FDA 2004a). Considering a consumption of 234 g/day of canned baby food (Kersting *et al.* 1998), this would result in an exposure of < 0.03 to 3.5 µg/kg b.w./day (assuming a body weight of 7.5 kg of a 6 month old baby, EC 1993). However, for a reliable exposure assessment definition, the occurrence data on furan in a wide spectrum of food commodities as well as toxicological studies are needed (Heppner 2006).

CONCLUSION

Furan and its derivatives are naturally occurring compounds found at very low levels in many foods and drinks; they have been associated with the flavour of foods. They are a major class of compounds forming during the Maillard reactions (Maga 1979). The formation of furan under pyrolytic conditions has been studied in simple model systems revealing more precursor classes, i.e., (*i*) ascorbic acid and related compounds; (*ii*) Maillard type systems containing amino acids and reducing sugars; (*iii*) lipid oxidation of unsaturated fatty acids or triglycerides; and (*iv*) carotenoids (Perez & Yaylayan 2004; Becalski & Seaman 2005; Yaylayan 2006). Furthermore, the effect of ionising radiation on the furan formation in real (apple and orange juice) and model systems has been studied (Fan 2005a, b). Due to its high volatility, furan can be analysed using a headspace or SPME coupled with gas chromatography-mass spectrometry. Furan is rapidly and extensively absorbed from the intestine and the lung. It can pass through biological membranes and enter various organs (Burka *et al.*1991). Experiments have shown that furan is carcinogenic to rats and mice, showing a dose-dependent increase in hepatocellular adenomas and carcinomas in both sexes (NTP 1993). Furan has been classified as possibly carcinogenic for humans (IARC 1995). However, preliminary exposure data suggest that the levels of furan found in foods are well below the levels that would cause harmful effects. Until more is known, FDA recommends that consumers eat a balanced diet, choosing a variety of foods that are low in trans-fat and saturated fat, and rich in high-fibre grains, fruits, and vegetables (US FDA 2004c). Under the circumstances described previously, the continuation of the research is desirable for achieving safer and healthier foods.

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