

OCCURRENCE AND PRODUCTION OF FURAN IN COMMERCIAL FOODS

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ABSTRACT

Furan (C₄H₄O) is a compound classified as "possibly carcinogenic to humans" by International Agency for Research on Cancer. As precursors, ascorbic acid, unsaturated fatty acids, amino acids and carbohydrates have been suggested to induce furan formation. Human exposure occurs mainly through consume of coffee, canned foods and Baby food. Average intake of furan is 1.5 µg/day for children aged 4-6 years and 27 µg/day for adults. Currently no limits for furan in food were fixed by European legislation. Since the carcinogenicity of furan, levels in food should be kept as low as reasonably achievable.

Keywords: baby food, food safety, furan

1. INTRODUCTION

Furan (C₄H₄O) is a small cyclic ether with aromatic character. It is a lipophilic compound with low molecular weight, high volatility, and 31°C as boiling point (NTP 1993) (Fig. 1). Furan and its derivatives (2-methylfuran, 2-ethylfuran, 2-pentylfuran, 2,5-dimethylfuran, 2-butylfuran, 2,3-benzofuran) have known to occur in heat-treated foods and drinks, and to contribute to the sensory property of foods (MAGA, 1979; MERRIT *et al.*, 1963; EFSA 2010).

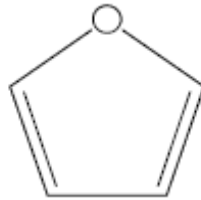


Figure 1: Chemical structure of furan.

Classified as *possibly carcinogen to humans* (group 2-B) by the International Agency for Research on Cancer (IARC, 1995), furan is carcinogenic for rats and mice. In the opinion of European Food Safety Authority (EFSA) the weight of evidence indicates that furan-induced carcinogenicity is probably attributable to a genotoxic mechanism (EFSA, 2004). Furan is formed during heating process used for the manufacture of foods, and has been detected in hot-air dried, baked, fried and roasted food items, such as cereal products and coffee, as well as canned or jarred prepared foods (US FDA, 2004a; EFSA, 2005; ZOLLER *et al.*, 2007). There appear to be multiple precursors (sugars, amino acids, ascorbic acid, poly-unsaturated fatty acids), and many pathways to the furan production (Fig. 2). The principal are:

- thermal degradation of certain amino acids;
- thermal degradation/Maillard reaction of reducing sugars;
- thermal oxidation of ascorbic acid, poly-unsaturated fatty acids and carotenoids (YAYLAYAN, 2006);
- thermal degradation of the common precursors in the process of roasting.

The primary source of furan in food is the thermal degradation of carbohydrates such as glucose, lactose, and fructose (MAGA, 1979).

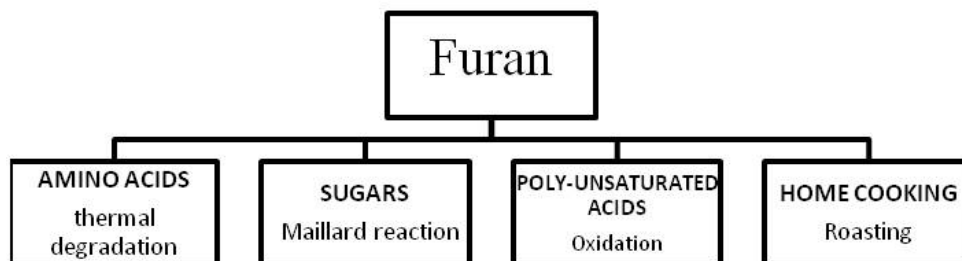


Figure 2: Precursors and sources of furan in food.

Amino acids serine and cysteine are able to metabolize acetaldehyde and glycolaldehyde, which react by aldol-condensation, then produce aldotetrose derivatives and furan. Alanine, threonine, and aspartic acid can generate only acetaldehyde; they require the presence of serine, or cysteine and reducing sugars, also, to produce glycolaldehyde and then furan (PEREZ and YAYLAYAN, 2004).

The reactions between several amino acids and carbohydrates on heating form aldotetrose derivatives, then after cyclisation can form furan (PEREZ and YAYLAYAN, 2004; LIMACHER *et al.*, 2008). When ascorbic acid was mixed in model systems with single amino acids (glycine or serine), sugar (erythrose) or unsaturated fatty acids (e.g. linoleic), the mixtures produced far less furan on heating than ascorbic acid alone did (MARK *et al.*, 2006).

Experimentally monounsaturated acid (oleic) did not form furan (BECALSKI and SEAMAN, 2005), and if furan is formed from unsaturated fatty acids the yield increases as the degree of unsaturation increases.

Furan production has been linked with free radicals autoxidation process (PEREZ and YAYLAYAN, 2004). So, Ferric ions increased furan formation in linoleic acid by 79%, and in trilinolein by 29% (MARK *et al.*, 2006), addition of commercially available antioxidants (such as tocopherol acetate) reduced the formation of furan (PEREZ and YAYLAYAN, 2004). Moreover the effects of lipid oxidation, catalysts such as Fe(II) or antioxidants are sometime contradictory. Given the complicated and competing reaction pathways available in autoxidation processes (some of which may lead to furan, and some not) limiting autoxidation may not always lead to a corresponding reduction in furan formation (Fig. 3).

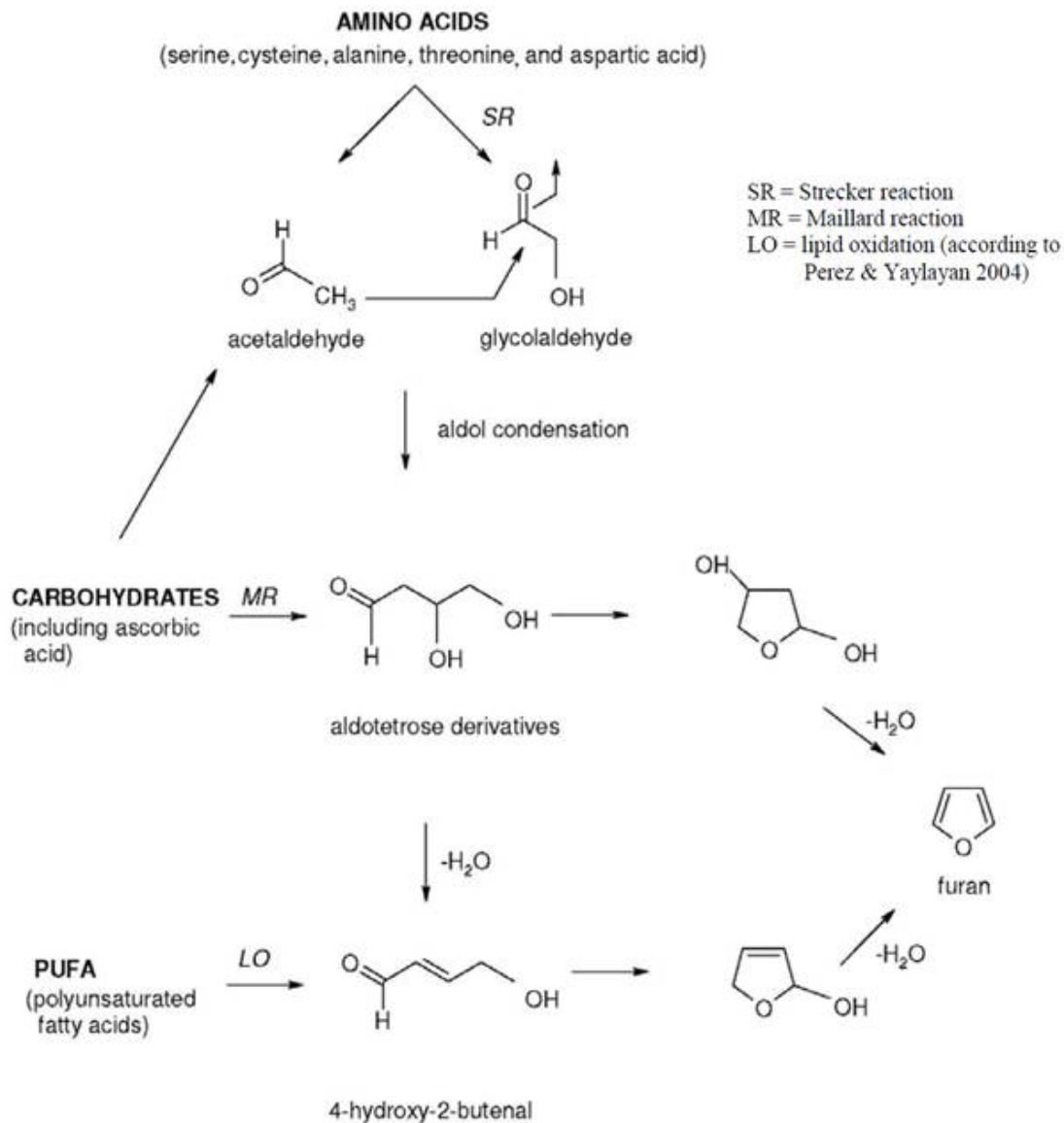


Figure 3: Proposed pathways of formation of parent furan from three main groups of sources: amino acids, carbohydrates, and polyunsaturated fatty acid (VRANOVA and CIESAROVA, 2009).

Due to its low polarity, furan can pass through biological membranes and enter various organs, it is rapidly and extensively absorbed from the intestine, and the lung. Repeated doses accumulate in the liver (EFSA, 2004a) and kidney, and in fewer quantities in intestine, stomach, blood and lung (BURKA *et al.*, 1991).

Absorbed furan is metabolized rapidly by cytochrome P-450 (CYP) enzymes via ring opening to form (Z)-2-butene-1,4-dialdehyde. The rapid hepatic metabolism seems to limit, however, its systemic delivery. The capacity to furan's bioactivity is also of relevance for the distribution, since it can result in an irreversible binding to the respective tissue. Within the first 24 hours after a single oral application of furan (8 mg/kg bw), 80% of the total radioactivity was eliminated via the lung, urine and feces (BURKA *et al.*, 1991).

In the 2-year rat study, animals of each sex (n=70) were administered furan at 2, 4, or 8 mg/kg bw 5 days per week. Mean body weights of male rats that received 8 mg/kg furan were lower than controls. Increased incidences of numerous non-neoplastic liver lesions (biliary tract fibrosis, hyperplasia, chronic inflammation, and proliferation and hepatocyte cytomegaly, cytoplasmic vacuolization, degeneration, nodular hyperplasia, and necrosis) were present in treated rats. Cholangiocarcinoma of the liver occurred in all groups of dosed rats. A separate 2-year study was conducted in which 50 male rats were administered 30 mg/kg furan 5 days per week. Cholangiocarcinoma of the liver occurred with an overall incidence of 100% (40/40) and hepatocellular carcinoma occurred with an overall incidence of 15 % (6/40) (BURKA *et al.*, 1991; NTP, 1993).

Both in vitro and in vivo studies show that metabolic activation by cytochrome P-450 (CYP) enzymes is involved in furan-induced toxicity (KEDDERIS *et al.*, 1993). It is likely that furan or (Z)-2-butene-1,4-dial reacts with DNA in target cells and can play a role in furan induced tumors.

Furan causes loss of ATP after bioactivation to metabolites which cause an irreversible uncoupling of hepatic mitochondrial oxidative phosphorylation, this activates cytotoxic enzymes, including endonucleases, that produce DNA double-strand breaks prior to cell death (MUGFORD *et al.*, 1997; KEDDERIS and PLOCH, 1999).

Furan was able to induce:

- a) gene mutations, chromosome aberrations and sister chromatid exchanges (SCE) in cultured mammalian cells, and chromosomal aberrations in mice bone marrow cells;
- b) hepatocellular tumours after *ras* oncogene activation, suggesting that furan, or a reactive metabolite, can directly activate protooncogenes (REYNOLDS *et al.*, 1987);
- c) chronic hepatic cytotoxicity in the genesis of liver tumours in infant male mice (JOHANSSON *et al.*, 1997);
- d) monocytic cell leukemias with minimal hyperplasia of bone marrow.

Hepatocytes from human livers donors oxidized furan at rates equal to, or greater than, those of rat hepatocytes in vitro (KEDDERIS *et al.*, 1993) (Fig. 4).

Species	Blood furan (μM)	Liver perfusion ^b ($\mu\text{mol}/\text{min}$)	Furan oxidation ^c ($\mu\text{mol}/\text{min}$)
Rat	0.80	0.017	0.213
Mouse	0.80	0.005	0.122
Human	0.68	1.02	25.6–37.7

^a Simulations of exposure to 10 ppm furan for 4 hr using the physiologically based dosimetry models for humans, mice (Table 1 and Fig. 1), and rats (Kedderis *et al.*, 1993).

^b The rate of liver perfusion with furan equals the blood furan concentration times the liver blood flow rate.

^c The rate of furan oxidation in the liver under these conditions equals the initial rate of metabolism (V_{max}/K_M) times the blood furan concentration.

Figure 4: Blood flow limitation of furan biotransformation (KEDDERIS *et al.*, 1993).

In alcohol consumption the furan metabolism is higher due induction of cytochrome P450 2E1 in humans by ethanol (PERROT *et al.*, 1989). However there is small difference

between the levels of human exposure and doses that induce carcinogenic effects in experimental animals.

1.1. Hydroxymethyl-2-furfural heat-induced formation and occurrence in food

Furan and 5-hydroxymethylfurfural (HMF) are compounds that are formed in a variety of heat-treated commercial foods. Such a widespread occurrence of furan and HMF in many types of food is due to the fact that they are products of different reactions following multiple routes and involving different precursors and intermediate (ANESE and SUMAN, 2013). In particular, HMF can be formed as an intermediate in the Maillard reaction, which occurs when carbohydrates are heated in the presence of amino acids or proteins (MAURON, 1981), or, alternatively, by thermal dehydration of a sugar under acidic conditions (KROH, 1994). At low pH, glucose or fructose may undergo 1,2 enolization and dehydration to form 3-deoxyosone, which is the key intermediate in HMF formation. Fructose is more reactive than glucose in the formation of HMF (LEE and NAGY, 1990). According to PEREZ LOCAS and YAYLAYAN (2008), HMF can form from fructose or sucrose via the generation of a highly reactive fructofuranosyl cation. At high temperatures and in dry systems this cation can quickly be converted into HMF.

HMF formation in foods has been found to be affected by sugar type, pH, water activity and the presence of divalent cations (GOKMEN *et al.*, 2008). As furan and HMF formation is concomitant to that of color and flavor of heated foods, it is very difficult to mitigate their formation without compromising the food sensory acceptability. Changes in process parameters, i.e. heating regime modification, and formulation can be regarded as strategies that can be applied to prevent furan and HMF formation (ANESE and SUMAN, 2013).

Particularly breakfast cereals, coffee, honey as well as pasteurized juices or pulps etc. are subjected to intensive HMF formation.

- Cereal products: RUFÍAN-HENARES *et al.* (2006) revealed that the HMF concentration varied between 6.59 and 240.51 mg/kg (w/w). The highest average concentration of HMF was found in maize-based breakfast cereal (42.81±7.92 mg/kg), followed by wheat (40.79±8.57 mg/kg) and rice (32.14±10.79 mg/kg) products. Authors have also compared products with and without the addition of honey and stated that HMF concentration was higher in the former group, 43.44±10.35 versus 34.24±6.17 mg/kg, respectively. HMF formation was also studied as one of the factors influencing browning of infant cereals. Increases in HMF concentration were investigated at different stages of cereals processing (toasting, hydrolysis, drying) in model systems (FERNANDEZ-ARTIGAS *et al.*, 1999). The hydrolysis process was connected with increases in HMF concentration. The drying stage, however, did not contribute to overall HMF synthesis probably due to short processing times.
- Coffee: On the basis of analysis of 22 coffee samples MURKOVIC and PICHLER (2006) stated that HMF concentration in the investigated products ranged from 300 to 1900 mg/kg. They found that roasting coffee at 240°C caused a rapid increases in HMF (up to 900 mg/kg) in the first 3 min. Further roasting was connected with decreases in HMF contents probably because of the occurrence of consequent degradation reactions. ARRIBAS-LORENZO and MORALES (2010) analysed 35 commercial roasted coffee brands as well as 19 soluble coffee brands. They estimated four levels of HMF: 110, 625, 1734, and 2480 mg/kg for natural, blend (mixture of torrefacto and natural coffee), torrefacto (coffee roasted with sugar addition) and soluble coffee, respectively. The largest differentiation in HMF level was found in soluble coffee clusters (min. 691, max. 4023 mg/kg). The authors

established that the different modes of coffee brewing (espresso, filtered, Italian, soluble) influence potential content of HMF. A possible mitigation strategy is represented by the physical removal of furan and HMF by means of vacuum treatments. The vacuum technology has already been studied as a tool to remove HMF from roasted coffee, by exploiting the chemical and physical properties of these molecules (QUARTA and ANESE, 2012). In this case, thinking of a possible industrial exploitation of this technology for coffee, the product coming from the tunnel oven could be moved to a hydration step (e.g. carried out by means of a spray of pressurized water) followed by a vacuum step. The vacuum-treated food with reduced furan and/or HMF and water contents can be then subjected to eventual flavor enrichment and finally packaged (ANESE and SUMAN, 2013).

- Fruit and vegetable products: These products are usually rich sources of sugars and organic acids as well as amino acids. Processing of this group of foodstuffs thus leads to the formation of significant amounts of HMF. BURDURLU and KARADENIZ (2003) investigated the influence of extract, storage time and temperature on non-enzymatic browning of apple juice concentrates. Browning index was correlated with HMF concentration. Juice samples were stored at different temperatures (5, 20, 37°C) for four months. For juices stored at 5°C as well as 20°C, increases in HMF level were minor (increase from 0.62 up to 4.37 mg/kg). HMF formation was much more significant at 37°C reaching 190 and 963 mg/kg. On the basis of the results, the authors confirmed the usefulness of HMF both as a heat processing index and an indicator of storage conditions. Recently, SALDO *et al.* (2009) demonstrated that processing apple juice by means of ultrahigh-pressure homogenization could represent an alternative to conventional pasteurization. Ultrahigh-pressure homogenization, while causing a significant decrease in microbial counts, allowed HMF formation to be reduced. HMF concentration in pasteurized juice was indeed 100-fold higher than in ultra-high-pressure homogenized and raw counterparts.
- Honey: in case of honey, the level of HMF is strictly normalized (COUNCIL DIRECTIVE, 2001). According to normalization, HMF concentration should not exceed 40 mg/kg with exception of honeys from tropical climate (not more than 80 mg/kg). Increased amounts of HMF can result from improper processing or prolonged storage (TOSI *et al.*, 2002; 2004; 2008; FALLICO *et al.*, 2004). An increased of HMF level in honey was also found to be connected with initial pH (acidity) (FALLICO *et al.*, 2004). TOSI *et al.* (2002; 2004; 2008) investigated the kinetics of HMF formation and changes in enzymatic activity during honey heating. It was shown that the initial HMF concentration did not influence the kinetics of its formation. Even after intensive heating (90°C for 20 min) HMF concentration did not reach 40 mg/kg. FALLICO *et al.* (2008) however, pointed out that under different storage conditions degradation HMF can occur in honey samples. Rate constants of degradation process at temperatures between 25 and 50°C (for citric as well as chestnut honey) were higher than the corresponding rate constant of formation. These findings should be taken under consideration in proper legislation process (FALLICO *et al.*, 2008).
- Dairy products: Sterilization processes are the origin of HMF in dairy products and may be connected with their colour change (browning). The total HMF-value has generally been applied to distinguish heat-treated milk (pasteurized, UHT, concentrated and powdered). ALBALA-HURTADO *et al.* (1998) studied changes of HMF concentration during storage of infant milk. Powdered infant milk had more HMF than corresponding liquid milks (34.7 and 12.2 µg/kg (w/v), respectively, after 9 month, 37°C). The influence of different temperatures on HMF formation

during the storage of UHT milk was studied by CAIS-SOKOLINSKA *et al.* (2004). There were no significant differences in HMF concentration in milk stored at 4 and 8°C, but storage at room temperature caused a two fold increase in its amount when compared with freshly sterilized product (CAIS-SOKOLINSKA *et al.*, 2004). ORAL *et al.* (2011) compared changes in total HMF fraction in sweet whey powder (SWP) and skim milk powder (SMP) at 3 different temperatures (25, 35 and 45°C) and moisture (2.5, 5, 7.5% for SWP and 5.5, 7.7, 10% for SMP) during eight month storage period. Small formation of HMF was observed during storage at 25°C in all studied samples but a great increase in HMF during storage at 45°C was observed, which indicates a large dependence of the formation of HMF on time and temperature of storage and moisture content. Since milk powder is used in the formulation of infant formula, instant beverage, bakery products, chocolate, its HMF content should be under consideration for end product quality and nutritional value.

Several techniques have been used for HMF detection in foods. Liquid chromatography is the most widely method used. These techniques utilize ultraviolet (UV) detection because of the strong absorption of HMF at 280-285 nm. However, many compounds naturally present or formed in foods during processing may also absorb at this wavelength. Poor chromatographic resolution of these compounds may adversely affect the quantification of HMF during UV detection (GOKMEN *et al.*, 2006). For this reason several techniques involve the protein hydrolysis step process. ORAL *et al.* (2014) studied the HMF binding capacity of the most common proteins (e.g. casein) in infant formulas and determined separability from them by acid digestion. Consequently, the HMF levels of the samples were evaluated separately either by no treatment or by the acid-heat treated method. The HMF values of the 10%, 5% and 2.5% casein solutions prepared with HMF stock solution (131.89 mg/L) were found as 116.31, 122.31 and 127.48 mg/L respectively, without acid hydrolysis. After acid hydrolysis, the HMF levels of the casein solutions were determined as 115.52, 121.10 and 124.51 mg/L in 10%, 5% and 2.5% respectively. Acid application have not got any statistical importance at all concentration for making free of bounded HMF ($p < 0.05$). Also, HMF was produced by the chemical reaction between acid and carbohydrates (certain food ingredients) during the acid hydrolysis stage. To avoid this situation, the acid hydrolysis phase of the analysis should be omitted. In the samples prepared without acid hydrolysis stage, the level of HMF did not change with varying of sample concentration. Also, during the acid hydrolysis stage the HMF levels in samples are thought to be dependent on the amount of sample. This is because, during the degradation of proteins with acid, acid is consumed more due to the solution having a high concentration. Therefore, in this study, HMF level was lower in 10% than in 2.5% concentrations due to the decrease in the amount of acid per food compound (carrageenan, sucrose, inulin and fructose). As a result, it was concluded that HMF cannot be evaluated by the traditional method which is based on the principle of separating it from proteins for measurement (ORAL *et al.*, 2014).

Although HMF has been used for years as a quality indicator of thermally processed foods, recently some toxicological concerns are raised. HMF has a number of structural alerts (furan ring, α,β -unsaturated carbonyl group, and allylic hydroxyl group) that pose possible genotoxic and carcinogenic risks (ANESE and SUMAN, 2013).

However, further studies suggest that HMF does not pose a serious health risk, but the subject is still a matter of debate (GOKMEN *et al.*, 2006).

HMF can initiate and promote the growth of aberrant crypt foci (ACF) in rat colons in a dose-dependent manner (ZHANG *et al.*, 1993). HMF induced a significant number of chromosome aberrations and a significant lowering of mitotic activity in cultured Chinese hamster V79 cells (NISHI *et al.*, 1989). In a two years study conducted by the National

Toxicology Program, HMF was found to increase the incidence of hepatocellular adenomas in female B6C3F1 mice, whereas no carcinogenic activity was observed in male or female F344/N rats as well as in male B6C3F1 mice (NTP, 2010). In addition, HMF was associated with increased lesions of the olfactory and respiratory epithelium of the nose in male and female rats and mice (NTP Technical Report, 2010). Its derivative 5-sulfidemethylfurfural (SMF), exhibited direct mutagenicity in human lymphoblasts and induced 8-azaguanine-resistant mutants in *Salmonella typhimurium* TM677 in a dose-dependent manner (SURH *et al.*, 1994). Histopathological analyses revealed that SMF induced moderate damage to liver tissue and notable damage to the kidneys (nearly all proximal tubules in SMF exposed animals were destroyed). The molecular mechanism underlying this selective toxicity of SMF for proximal tubules is unknown (BAKHIYA *et al.*, 2009). On the basis of kinetic data (MONIEN *et al.*, 2009), it was estimated that between 452 and 551 mg/kg of the initial HMF dose (500 mg/kg) was converted in mice into SMF which was subsequently circulated. The sulfotransferases (SULT) are the enzymes that converted HMF to SMF. Human SULT isoforms have a widespread tissue distribution and are expressed in many tissues including liver, lung, brain, skin, platelets, breast, kidney, and gastrointestinal tract (SALMAN *et al.*, 2009). Moreover, humans express SULT in extrahepatic tissues more extensively than rodents do and may therefore be more sensitive to HMF (TEUBNER *et al.*, 2007). Some studies on mutagenicity or carcinogenicity of other HMF derivatives showed that furfuryl alcohol and furfural were not observed to be mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535, or TA1537 (NTP, 1999).

It should be noted that studies which demonstrate the positive and protective role of HMF are also available. WANG *et al.* (2010) revealed that HMF protects LO2 hepatocytes cell from oxidative damage. YAMADA *et al.* (2011) have been suggested that HMF could be useful for the treatment or prevention of type I allergic diseases. Due to the fact that there is inconclusive evidence regarding HMF's potential toxicity to human health, it cannot be determined whether HMF should be considered unsafe or whether the benefits of its use in industry outweighs the risks it may pose. Additional studies are needed to elucidate the potential effects that long-term exposure to HMF could have on human health.

1.2. Formation of furan in food

Different factors, such as temperature, pH, water activity, storage and time conditions, presence/absence of inhibitors and activators may influence the furan levels in food.

In industrial field, at temperature around 200°C, the furan levels increase with the temperature increasing. However when it exceeds the value of 200°C the concentration of furan is independent from the temperature values. In domestic cooking furan formation depends on the type of cooking. Frying (150°-200°C) produces higher levels, if compared with the baking. Furan has been associated with the flavor of foods. Since it is a highly volatile compound, an important part of the furan formed during thermal treatment will be lost during food handling and food preparation by evaporation, depending on the food matrix.

The combination of higher temperatures and lower water content leads to a higher furan content. Furan seems likely to form in browned products, especially if the water activity is low. In particular high levels of furan were founded in bread toasted from a brown to very dark colour.

Furan levels may formed at various pH and temperatures in experimental model systems (NIE *et al.*, 2013), and pH has a significant effect on thermally induced furan formation, if temperature is greater than 110°C. At pH 7.00 higher levels of furan were observed than at pH 9.40 and 4.18, suggesting that pH is an important factor influencing furan formation as

a function of thermal treatment and temperature. For instance, after heating for 30 minutes at 150°C in experimental model at pH 7.00, 9.40, and 4.18 the furan concentration was founded at 304, 238, and 40 ng/mL, respectively. Also it is reported (FAN, 2005a) that less furan is formed at pH 3.00 than at pH 7.00 for glucose solution. At pH 7.00 furan content increase rapidly from 34 to 304 ng/mL with temperature increasing from 120° to 150°C. These data suggest that temperature is also a major factor affecting furan formation in model system (NIE *et al.*, 2013).

Under sterilization conditions, fructose-glycine system produces high level of furan, while less furan significantly is formed in glucose-glycine system (NIE *et al.*, 2013) (Fig. 5). It seems that formation of furan by Maillard reactions is dependent, as activators, on the amino acids and sugars used. The addition of phenylalanine to glucose results in an increase of about 50% of furan. Moreover the presence of the amino acids alanine, threonine, and serine results in higher furan amounts. In contrast, the furan amount decreases by 20% in a binary mixture of fructose and phenylalanine (LIMACHER *et al.*, 2008).

Carbohydrates and amino acids are also commonly used as additives in food products, thus if carbohydrates and amino acids are required together in formulation, sucrose would be a better choice than glucose and fructose to reduce the accumulation of furan by Maillard reactions during the heating (LIMACHER *et al.*, 2008).

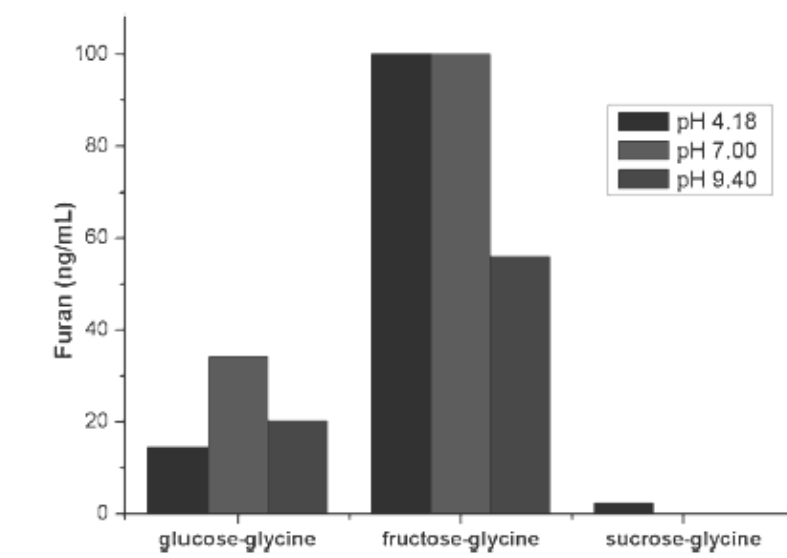


Figure 5: Furan formation in a glucose-glycine, fructose-glycine and sucrose-glycine heating model system at 120° C for 30 minutes, simulating sterilization conditions (NIE *et al.*, 2013).

Furan may be produced from polyunsaturated fatty acids during thermal and UV-C treatment. (FAN, 2015). Furan is also produced from linolenic acid emulsion during storage at 25 °C. At pH 9 more furan was formed than at pHs 3 or 6 during longer storage (FAN, 2015).

Part of the furan concentrations founded in commercially available food products might originate from chemical deterioration reactions during storage (PALMERS *et al.*, 2015). A range of individual vegetable purées was stored at two different temperatures to investigate the effects of storage on the furan concentrations of shelf-stable, vegetable-based foods. After 5 months of storage at 35°C (temperature-abuse conditions), a general

increase in furan concentrations was observed. The furan formation during storage could be reduced by storing the vegetable purées at a refrigerated temperature of 4°C, at which the furan concentrations remained approximately constant for at least 5 months. Following storage, the vegetable purées were briefly reheated to 90°C to simulate the effect of the final preparation step before consumption. Contrary to storage, furan concentrations decreased as a result of evaporative losses. Consequently, both refrigerated storage and the reheating step prior to consumption showed the potential of mitigation measures for furan formation in vegetable-based foods (e.g. canned vegetables, ready-to-eat soups, sauces or baby foods). On the contrary methylfuran concentrations rapidly decreased during storage (PALMERS *et al.*, 2015).

Therefore, the retention or release of furan by different food constituents was systematically evaluated. The presence of oils in foods decreases the volatilization of furan and may as such increase the actual intake of furan to a large extent (BECALSKI and SEAMAN, 2005).

For oils, furan concentrations are similar in olive oil and in corn oil. Palm oil contains significantly more furan. It is believed that the high amounts of carotenoids in crude palm oil are responsible for this difference (SHAHIDI, 2005), since carotenoids were identified as important precursors of furan by BECALSKI and SEAMAN (2005). It is possible that furan have been formed by lipid oxidation and has accumulated over time during oils storage.

FROMBERG *et al.* (2009) evaluated the influence of the browning process in fried meat and fish meat balls using either vegetable oil or butter. Furan was found at low level in the heavily fried fish meat balls using butter (3.1 ng/g) as frying agent and in medium fried fish meat balls using vegetable oil (2.5 ng/g) as frying agent. However furan was not found above the limit of quantification of 2.4 ng/g in the crust of the medium fried meat balls using vegetable oil as frying oil. On the other hand furan was found in the crust (2.4 ng/g) of the heavily fried meat balls using butter, but not in the heavily fried meat balls when the whole meat balls were analysed. Surprisingly, FROMBERG *et al.* (2009) founded furan in the minced ingredients before frying, even if they were not able to find the explanation for the context (Fig. 6).

	Lightly fried	Medium fried	Heavily fried	Medium fried	Crust from heavily fried	Crust from medium fried	Minced ingredients before frying
Frying agent	Butter	Butter	Butter	Oil	Butter	Oil	
Meat balls	<2.4	<2.4	<2.4	<2.4	2.4	-	6.6
Fish meat balls	<2.4	<2.4	3.1	2.5	2.4	<2.4	<2.4

Figure 6: Levels of furan [ng/g] in home fried meat balls and fish balls (FROMBERG *et al.*, 2009).

Some conservation treatments such as irradiation may facilitate the production of high concentrations of the contaminant. 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.

To monitor the presence of furan in food, the Commission Recommendation 2007/196/EC requests the Member States to collect data on heat-treated commercial food products. In response to the Commission request, a total of eighteen Member States have so far submitted analytical results for furan content in food to the European Food Safety Authority (EFSA). A total of 4186 complete results were reported for foods sampled between 2004 and 2009 (Table 1). Data were sorted into 21 different food categories (5 coffee and 16 non coffee categories). The 'baby food' category was subcategorised into 6 groups according to the ingredient combination and the category 'others' was subcategorised into more homogenous subgroups in order to extract further information (EFSA, 2010).

Table 1: Number of samples collected by Member States (indicated by ISO country code) between 2004 and 2009 for the analysis of furan content in food (EFSA, 2010)

Food group	AT	BE	CY	DE	DK	ES	FI	GB	GR	HU	IE	IT	LT	NL	NO	PL	SK	SI	Total
Coffee instant ¹	0	25	0	20	7	0	0	2	0	0	1	2	1	0	0	0	0	0	57
Coffee roasted bean ¹	0	1	0	0	0	0	0	5	0	1	5	0	0	0	0	0	2	1	15
Coffee roasted ground ¹	8	12	5	0	1	4	0	15	12	0	3	17	0	0	0	0	8	3	88
Coffee not specified ¹	0	25	11	420	3	0	1	0	0	0	12	5	1	0	0	0	0	0	478
Coffee ready-to-drink	8	0	0	0	0	0	0	0	12	0	31	0	0	0	0	0	10	7	68
Baby food	12	78	15	619	4	8	20	20	14	0	214	22	0	10	24	252	0	10	1322
Infant formula	0	0	0	0	0	0	0	0	0	0	1	9	0	1	0	0	0	0	11
Vegetables	0	59	0	13	11	6	2	11	1	0	7	9	3	9	4	0	16	5	156
Fruits	2	35	0	30	2	0	3	0	1	0	5	13	2	10	0	0	5	0	108
Vegetable juices	0	17	0	25	0	0	0	0	0	0	0	0	0	0	0	0	3	0	45
Fruit juices	0	14	0	129	6	0	34	0	7	15	8	16	1	13	0	0	3	0	246
Fish	2	29	0	0	0	0	0	4	0	6	0	0	0	2	0	0	0	0	43
Cereal products	40	68	0	38	0	0	1	0	0	0	32	1	1	0	0	0	0	0	181
Meat products	26	61	0	15	1	0	0	4	2	1	11	0	0	0	0	0	0	12	133
Milk products	0	44	0	9	0	0	0	0	0	0	0	0	0	11	0	0	0	0	64
Beer	3	15	0	67	0	0	0	0	6	0	0	0	0	7	0	0	4	0	102
Soy sauces	0	46	0	2	0	0	0	3	0	0	0	0	0	0	0	0	0	0	51
Soups	4	16	10	136	10	0	0	1	0	0	32	0	0	16	0	0	12	8	245
Sauces	4	59	4	105	0	0	3	8	5	0	30	2	1	2	8	0	3	11	245
Baked beans	2	3	0	0	1	2	1	6	2	0	36	0	0	0	2	0	1	0	56
Other products	2	118	0	272	3	0	0	53	0	0	0	13	0	7	0	0	3	0	471
Total	113	725	45	1900	49	20	65	128	66	17	434	109	10	88	38	252	70	57	4186

The report data have identified as types of foods most responsible of dietary exposure (content > 100 mg / kg) (Table 2):

- coffee,
- baby foods,
- sauces and soups.

Table 2: Furan content in food per main food category (EFSA, 2010).

Product category	N	Furan content $\mu\text{g}/\text{kg}$						
		P05	P25	Median	Mean	P75	P95	Max
Coffee instant ¹	57	2.8-3	72	271	569	850	2118	2200
Coffee, roasted bean ¹	15	38	905	3998	3611	5303	6407	6407
Coffee, roasted ground ¹	88	19	296	1695	1786	2610	5749	6900
Coffee, not specified ¹	478	13	933	1819	1850	2481	4783	6500
Coffee ready-to-drink	68	0-5	0-5	11	37-40	53	154	360
Baby food	1322	0-2	4-6.6	22	28-29	42	79	224
Infant formula	11	0-2.2	0-2.5	0-2.5	0.2-3.2	0-2.5	2.2-10	2.2-10
Baked beans	56	0-4	5-10	21	23-24	32	57	80
Beer	102	0-1.6	0-2	0.14-3	3.3-5.2	4-8	13	28
Cereal product	181	0-0.3	0-4	5-10	15-18	20-20.5	60	168
Fish	43	0-0.3	0-1.2	2.4-4.3	17-18	16	86	172
Fruit juice	246	0-0.7	0-1.42	0-2	2-5	1.4-5	8-10	90
Fruits	108	0-1	0-2.4	0-5	2-5	2-6	13	36
Meat products	133	0-0.32	0-2	3-10	17-19	22	85	160
Milk products	64	0-0.18	0-0.32	0.4-0.9	5-6	7	20	80
Sauces	245	0-2.3	0-3.2	2.4-8	8.5-11	11	30	175
Soups	245	0-1.4	2.5-5	17	23-24	34	72	225
Soy sauce	51	0-3	13	19	23-24	33	55	78
Vegetable juice	45	0-1	0-3	0-5	2-6	0-9	14	20
Vegetables	156	0-0.32	0-3	0-5	7-9	6-8	39	74
Others	471	0-0.32	0-2.4	7-8	15-16	22	61	164

Among all products tested, the highest furan content was reported in roasted coffee beans with an average of 3.611 $\mu\text{g}/\text{kg}$. Furan and furan derivatives have long been known as intrinsic components of coffee flavours. Green coffee beans contain only traces of furan. The furan levels in the roasted coffee are correlated with the roast colour (GUENTHER *et al.*, 2010). Furan retention studies were also conducted with coffee, since it is believed to be the major source of furan in adults diet. In coffee, furan retention was mainly caused by the lipophilic fraction. Defatted coffee brew showed a significantly lower retention of furan than coffee brew: the furan response increased significantly from 78 to 89% after defatting. On the one hand, oils are precursors of furan. Palm oil contains significantly more furan and it is responsible for the high content of furan in roasted coffee (LACHENMIER *et al.*, 2009).

Automatic coffee machines produced brews with the highest levels of furan, because a higher ratio of coffee powder to water is used giving a lower dilution factor, and because the closed system favors retention of furan. Much lower levels were produced by standard home coffee-making machines and by manual brewing (GOLDMAN *et al.*, 2005; ZOLLER *et al.*, 2007).

Furan is found in a wide assortment of foods including potato chips, tortilla chips (FDA, 2004a), dried fruits, popcorn, corn crisp, cereal product (puffed rice) might be consumed by children and findings of furan in these products may cause food safety concern (FROMBERG *et al.*, 2009).

Milk based processed food showed low mean furan content (6 $\mu\text{g}/\text{kg}$), but interestingly a maximum furan content of 80 $\mu\text{g}/\text{kg}$ was found in sweetened condensed milk (EFSA, 2006). Maximum values exceeding a level of 100 $\mu\text{g}/\text{kg}$ were found in fish products such as mackerels and sardines in tomato sauce, in meat products like canned duck with lentils or rabbit with prunes, in soups such as tomato soup and in gravy (FROMBERG *et al.*, 2009).

Department of Nutrition, National Food Institute has developed a recipe database with potential furan containing dishes which was used as a platform for analyzing furan in

commonly eaten freshly prepared home cooked dishes. The recipes have been chosen on basis of knowledge upon potential furan containing ingredients after heating (ZOLLER *et al.*, 2007) as well as knowledge on dietary habits in the European region (MÄNNISTÖ *et al.*, 2003; ELMADFA and WEICHSELBAUM, 2005; DEBACKER *et al.*, 2007; FAGT *et al.*, 2008). As worst-case scenarios, foods were home cooked using canned ingredients which contained furan. However, this did not lead to elevated levels of furan in the prepared home cooked foods. For ready-to-eat foods with an initial level of furan, cooking reduced the level of furan in the food to about half the original content probably due to evaporation of furan during heating. Nevertheless furan is relatively stable in heated foods left for cooling where the losses of furan were insignificant (ZOLLER *et al.*, 2007; FROMBERG *et al.*, 2009) (Figg. 7, 8).

Recipe	Canned	Vegetables	Meat/poultry	Fish	Milk/dairy	Egg	Cereals	Comments on ingredients and preparation
Oatmeal porridge ¹							•	Oats heated by cooking (oats are steamed, dried and toasted)
Oatmeal porridge in microwave oven ¹							•	Oats heated by microwave cooking (oats are steamed, dried and toasted)
Tomato soup ¹	•	•						Canned tomatoes and onion
Minestrone ¹	•	•	•					Canned tomatoes and several vegetables
Fish meatballs ¹				•		•		Minced fish
Ragu/Sauce Bolognese ¹	•	•	•					Minced meat, canned tomatoes and tomato puree, vegetables
Gulasch ¹	•	•	•		•			Beef, canned tomatoes
Meat balls ¹			•			•		Minced meat
Wok fried pork with vegetables ¹	•	•	•					Pork fried in wok with canned vegetables and soy sauce
Omelette ¹						•		Very traditional dish eaten all over Europe

1. Fogt *et al.* 2007.

Figure 7: Main ingredients and preparation procedure in selected recipes (FOGT *et al.*, 2007).

Meat sauce (finished)	< 2.4
Vegetable oil	5.1
Beef bouillon	< 2.4
Tomato puree	< 2.4
Tinned tomato	6.0

Figure 8: Levels of furan in homemade meat sauce including ingredients [ng/g] (FROMBERG *et al.*, 2009).

High levels of furan were found in toasted bread slices (e.g. 83 µg/kg furan for dark toasted bread) and this was correlated to the browning level (FROMBERG *et al.*, 2009). The dark and black toasted bread had high to very high levels of furan and the degree of browning of the toasted bread has very high influence on the amount of furan in the food item and therefore influence on the amount of furan consumed. The furan level might be

associated with the use of ascorbic acid in the flour used for the bread combined with a baking process leaving low levels of water in the final products. The untoasted bread analysed did not contain furan above 2.4 ng/g (FROMBERG *et al.*, 2009). The crust always contained more furan than the entire bread, with a 3- to 20-fold difference depending on the surface-to-volume ratio (ZOLLER *et al.*, 2007).

When an initial level of furan is present in the food item heated, changes in furan levels appear when the food item is heated. Heating the food item almost reduced the furan level in the food by 50%, however the furan level in the foods do not change when left for cool for one hour, and furan therefore seems to be stable in the food when it is not heated (FROMBERG *et al.*, 2009) (Fig. 9).

	Finished soup	10 min.	20 min.	30 min.	40 min.	50 min.	60 min.
Tomato soup	<2.4	<2.4	<2.4	2.4	<2.4	2.8	2.4
Minestrone	<2.4	<2.4	3.8	<2.4	<2.4	<2.4	3.0

Figure 9: Development in the furan concentrations over time in homemade soups [ng/g] (FROMBERG *et al.*, 2009).

The exceptions are vigorous boiling or cooking where furan can be lost, presumably by evaporation and by entrainment in the large volumes of steam that are released. On the other hand, warming the food even in lightly lidded containers can increase furan levels, so any additional formation appears to be balanced by evaporative losses (HANSIP *et al.*, 2006).

1.3. Presence of furan in baby food

Children are sensible consumers, for this reason food safety and quality are essential. In EFSA report (EFSA, 2010), the highest maximum concentrations of furan for the non-coffee categories were found in baby food with 224 µg/kg.

Children have high capacity of absorption nutrients and non-nutrients (FIMP, 2011) but they have a reduced capacity of detoxification compared to an adult organism (GINSBERG, 2004). The metabolic differences baby\adult decrease with increasing age, but still have an influence through adolescence, for which there is still a high degree of risk of exposure to toxic agents (MADHAVAN and NAIDU, 1995; GINSBERG, 2004).

With the exception of coffee products, commercial complementary foods (6-24 months) were the food group with the highest furan concentrations. The problem is restricted only to commercially sterilized baby foods, while freshly cooked home-made complementary food was found to be furan-free (LACHENMEIER *et al.*, 2009). The exposure assessment for babies is therefore challenging as it is not the total consumption that has to be evaluated, but more specifically, only the consumption of commercial products.

In EFSA report (2010) were analyzed, between 2004 and 2009, 11 samples of Infant Food (infant formula) and 1322 samples of Baby Food, divided in 6 sub-categories. Jarred baby food and infant formulae are of particular interest as they may form the sole diet for many infants and furan has been reported in those products (EFSA, 2010) (Fig. 10).

Food group	AT	BE	CY	DE	DK	ES	FI	GB	GR	HU	IE	IT	LT	NL	NO	PL	SK	SI	Total
Baby food	12	78	15	619	4	8	20	20	14	0	214	22	0	10	24	252	0	10	1322
Infant formula	0	0	0	0	0	0	0	0	0	0	1	9	0	1	0	0	0	0	11

Figure 10: Number of samples collected by Member States between 2004 and 2009 for the analysis of furan content in food (EFSA, 2010).

The mean furan content in infant formulae was 3 µg/kg, the furan content of jarred commercial baby food with an overall mean content of 29 µg/kg and a maximum value of 224 µg/kg was similar to previously reported data (CREWS and CASTLE, 2007).

Mean furan content in baby food containing only fruits is 5 µg/kg and 40 µg/kg in baby food containing only vegetables. BIANCHI *et al.* (2006) assumed that this difference in furan content could be due to different heating treatment as fruit samples are generally pasteurised whereas the vegetables are generally sterilized (EFSA, 2010) (Fig. 11).

Baby food subcategory	N	Furan content µg/kg						
		P05	P25	Median	Mean	P75	P95	Max
Cereal based	132	0-2.4	0-10	19	19	38	59	96
Meat and vegetables	447	7-8.1	24	38	39-40	51	78	129
Vegetables only	201	9.3-9.5	21	31	39-40	50	82	224
Fruits and vegetables	69	0-2	0-3	4-5	10-12	16	42	66
Fruits only	239	0-1.3	0-2.1	0-4.4	2.5-5	3.6-6	8.8-10	58
Non classified	234	0-2	6.2-7.3	17	31-32	40	130	215

Figure 11: Furan content in baby food sub categories (EFSA, 2010).

Baby food containing mainly vegetables and meat show mean furan concentrations of 40 µg/kg whereas cereal based baby food show lower mean values (19 µg/kg).

Furan was analysed in 21 different baby-food samples purchased from the Finnish markets. The mean levels of furan varied between 4.7 and 90.3 µg/kg (JESTOI *et al.*, 2009). US FDA (2004a) internet database is rather extensive, and data from years 2004-2005 show furan concentrations in fruit-based baby-foods below 8 µg/kg, vegetables and mixed vegetables up to 112 µg/kg and meat containing mixed baby and toddler foods up to 90 µg/kg.

In another study the retention of furan was significantly higher in baby food “beef and vegetables” and even more in baby food “spinach”. Baby food “spinach” and baby food “beef and vegetables” contained 2 and 1% corn oil, respectively. Although the total fat content of baby food “beef and vegetables” (3.4%) was higher than the total fat content of baby food “spinach” (1.9%), the retention of furan by baby food “spinach” was significantly higher than the retention by baby food “beef and vegetables”. These results lead to the assumption that the addition of a low amount of oil significantly increased the retention of furan, and this to a much higher extent than the total fat content. This implies that the presence of oils influences the actual intake of furan. As, from a nutritional point of view, elimination of oils from baby food is not an option, it would be better to add the oils after heat-processing, right before consumption of the baby food (LACHENMEIER *et al.*, 2009; JESTOI *et al.*, 2009). The problem is restricted only to commercially sterilized

baby foods, while freshly cooked home-made baby food was found to be furan-free (LACHENMEIER *et al.*, 2009).

Therefore, the differences in furan retention caused by various food constituents are an important problem to be systematically studied.

1.4. Dietary furan intake

The Danish National Survey of Dietary Habits and Physical Activity 2000-2004, calculated the exposure of furan. The dietary survey comprised a random sample of 4120 individuals aged 4-75 years. Dietary intake was obtained using a 7 d pre-coded food diary. The amounts of food consumed were given in household measures (cups, spoons, slices, etc.) or estimated from photos of different portion sizes showing four to six different portions. The mean food intakes were calculated for each individual using the General Intake Estimation System (GIES) version 0.995a (Danish Institute for Food and Veterinary Research, Søborg, Denmark). In this analysis were used data from children 4-6 years (n=335) and adults 15-75 years (n=4692). Calculations of the furan exposures showed a median intake of 1.1 $\mu\text{g}/\text{day}$ for children (mean 1.5 $\mu\text{g}/\text{day}$) and a median intake of 33.5 $\mu\text{g}/\text{day}$ for adults (mean 27 $\mu\text{g}/\text{day}$) (FROMBERG *et al.*, 2009).

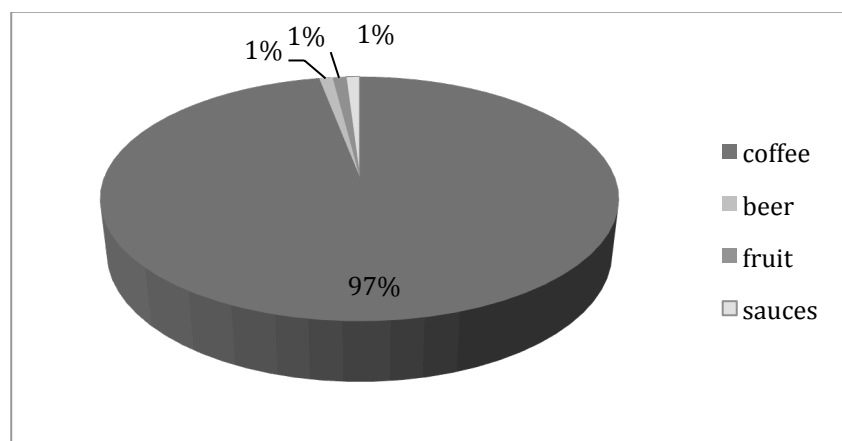


Figure 12: Foods contributing to the median intake of furan for adults of 34 $\mu\text{g}/\text{day}$ (FROMBERG *et al.*, 2009).

For adults the main contributor (95%) to the exposure of furan is coffee with an average daily intake of more than 0.6 L of coffee (the coffee is mostly made of 40 g medium roasted ground coffee per litre water) (JOHANSSON *et al.*, 1998; FAGT *et al.*, 2008) (Fig. 12).

As children do not have a high intake of coffee, the foods contributing to the intake are from other sources. The main food group contributing to furan is the breakfast cereal as high levels of furan was found in the breakfast cereals combined with children's high consumption (FROMBERG *et al.*, 2009) (Fig. 13).

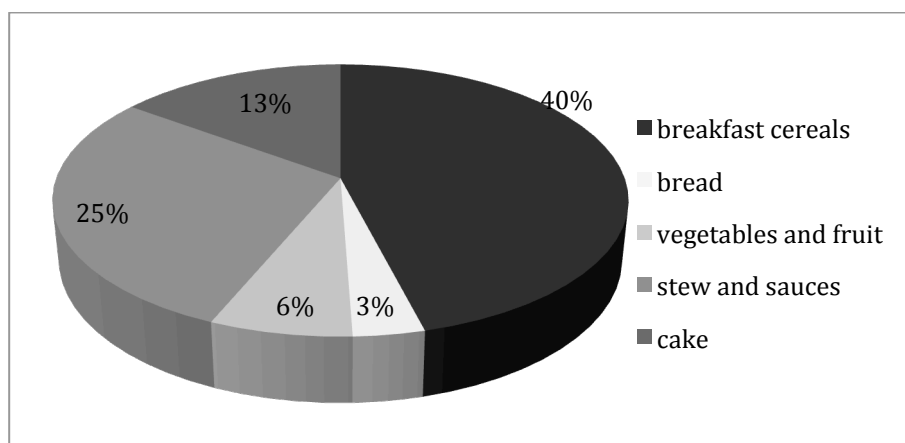


Figure 13: Foods contributing to the median intake of furan for children of total 1.1 $\mu\text{g}/\text{day}$ (FROMBERG *et al.*, 2009)

The DONALD data show that the consumption of jarred baby foods in children 3 months aged is rather low. The highest exposure occurs in the children 9 months aged, and may reach a daily intake over 1 $\mu\text{g}/\text{kg}$ bw. Afterwards, the exposure again decreases, due to the fact that both bodyweight and the use of non-jarred foods increase. The EFSA assumed a daily mean exposure of 1.01 $\mu\text{g}/\text{kg}$ bw for children 9 months aged (BFR, 2009; KIM *et al.*, 2009; BAKHIJA and APPEL, 2010; LACHENMEIER *et al.*, 2012). The only exception is the study of Kim *et al.* (2009a) from Korea, which reported a considerably lower exposure (0.017-0.084 $\mu\text{g}/\text{kg}$). The difference between Korea and the high exposures in Europe might be explained by cultural differences (e.g. less consumption of commercially jarred foods) or that major sources were overlooked in the study. The data show a potential public health concern for this contaminant mostly for consumers 9 months aged (EFSA, 2005).

The exposure data were then used to characterize risk using the margin of exposure method based on a benchmark dose lower confidence limit for a 10% response (BMDL10) of 1.28 mg/ kg bw/ day for hepatocellular tumours in rats (CARTHEW *et al.*, 2010). The margin of exposures (MOEs) was below the threshold of 10000, which is often used to define public health risks (LACHENMEIER *et al.*, 2012).

The foremost question that should be considered in the exposure estimation of furan in complementary foods is the treatment of the different subgroups of complementary foods, as beverages in particular contain lower concentrations than other groups. In the past, this differentiation was not made. Therefore, depending on the proportion of analysed beverages, the average furan content might be underestimated mostly in children 9 months aged.

2. CONCLUSIONS

We can conclude that furan is present in a variety of heat-treated commercial foods for adults (coffee, sauce and soup) and infants (jarred and canned baby food, breakfast cereal). Preliminary studies indicate that home-prepared food, with the exception of coffee, hardly contain any furan above the limit of detection (EFSA, 2010).

For the home cooked foods, foods rich in carbohydrates are most likely to form furan, probably due to a Maillard browning reaction of the food. High levels were found in

toasted bread and the content was correlated to the browning level, therefore not to toast the bread to a dark brown color might reduce the intake of furan. Even the worst case scenarios using ingredients containing furan for the home cooked foods did not lead to evaluated levels of furan during cooking. For ready-to-eat foods with initial occurrences of furan, cooking reduces the level of furan in the food to about half the initial concentration. Nevertheless, furan is stable in hot food items and the loss of furan present in the food before heating compared to the content after boiling the food is negligible. The furan level remained stable for one hour after heating and it can therefore be concluded that furan is stable in the food items. It was not until the food was reheated that the level of furan decreased (FROMBERG *et al.*, 2009).

It appears to be possible to reduce the furan content in some food by volatilisation through heating and stirring of canned or jarred foods in an open saucepan. Recent studies have suggested that a simple approach to avoiding furan would be to heat infant foods in an open can while applying stirring (JESTOI *et al.*, 2009; LIU and TSAI, 2010). This would really result in a considerable evaporation of furan, if parents would adhere to this practice. The first studies regarding this phenomenon reported losses of 29-55% in vegetable purees during different warming procedures in microwave ovens (ZOLLER *et al.*, 2007), or even losses of up to 85% reported during heating opened jars over a period of 5.5 h in boiling water, and a reduction of ca.50% if the baby food jar was opened but not heated (GOLDMANN *et al.*, 2005).

Reduction of furan in foods is likely to be more challenging compared to other process contaminants, for two reasons. First, there may be little room for maneuver to lower heating times and temperatures because the processes of pasteurisation and sterilisation are indispensable for the microbiological safety of foods. Second, furan has a wide range of precursors. Ascorbic acid shows the highest potential to form furan, followed by polyunsaturated fatty acids and then sugars (STADLER, 2006). Ascorbic acid and polyunsaturated fatty acids are regarded as desirable food components because of their health benefits.

The best approaches appear so far to involve intervention in the reaction mechanisms. For example, formation of furfural from ascorbic acid in model orange juice was repressed by the presence of ethanol and mannitol acting as free radical scavengers (SHINODA *et al.*, 2005). Reduction of atmospheric oxygen reduces the autoxidation of unsaturated fatty acids and also reduces furan formation from several precursors, notably ascorbic acid, as the addition of sulphite does (MARK *et al.*, 2006). Therefore, modification of the atmospheres within heating systems might be effective in reducing furan in foods.

Since the carcinogenicity of furan is probably attributable to a genotoxic mechanism (EFSA, 2004) levels in food should be kept ALARA as low as reasonably achievable. Currently, the limits for furan in food have not been established yet by European legislation.

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 (FDA 2004c). Under the circumstances described previously, the continuation of the research is desirable for achieving safer and healthier foods.

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