Furan in processed food: formation, toxicology and monitoring: a Review

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ABSTRACT

Furan is an organic, and volatile compound that formed in some of the heat-treated foods during thermal processing. Thermal degradation of ascorbic acid, amino acids, carbohydrates, unsaturated fatty acids, and carotenoids can form this compound. In Europe, furan dietary exposure was estimated to range between 1.23 and 1.01 µg/kg bw/day for adults and 3 to 12 month-old infants, respectively. It is known that this compound has hepatotoxic and hepatocarcinogenic effects in rats and mice, also stimulate carcinogenicity is possible features in a genetic pathway. Since a genotoxic mode of action cannot be ejected for furan-induced tumor formation, there is a relatively small difference between possible human exposure and the doses in experimental animals required to produce carcinogenic effects. This review summarizes the present knowledge of furan toxicity, human dietary exposure to furan. As well as, the role of some important factors, for example, heating temperature for furan formation process in a vast range of heated foods, increases the need to establishing the risk resulting from the genotoxic and carcinogenic characteristics of this compound.


1. Introduction

Furan (C4H4O) is a colorless, and heterocyclic liquid composite with highly volatile that consisting of five-membered heterocycles containing four carbon atoms and one oxygen atom (1-5). It has been founded in a wide range of foods such as coffee, canned foods, seed oil, butter, fish and fish oil and beverage undergo thermal processing such as cooking, roasting, baking, pasteurization, and sterilization is contained in many foods preparing processes (1, 6, 7). The most important food constituents serving as precursors for furan production appear to be ascorbic acid, amino acids, carbohydrates, unsaturated fatty acids, and carotenoids. It is concluded that ascorbic acid has the highest potential to produce furan (8, 9). In Europe, the mean of human exposure to furan was estimated range from 0.34 to 1.23 µg/kg bw/day for adult and for the infant (3–12 months old) 0.3–1.0 µg/kg bw/day was calculated (10, 11). FDA reported coffee powders contain high amounts of furan up to 5,938 g/kg (7). The from 0.34 to 1.23 µg/kg bw/day for adult and for the infant (3–12 months old) 0.3–1.0 µg/kg bw/day was calculated (10, 11). FDA reported coffee powders contain high amounts of furan up to 5,938 g/kg (7). The heating process of food in closed systems, such as jars and cans lead to accumulation of furan in them. Therefore, heating of food products in open containers would be expected to reduce human exposure to furan content from the foods (12). In this review, we focus on the current status of furan and provide an overview including the origin, human dietary exposure, and risk assessment of this composite.

2. Formation

2.1. Oxidation of polyunsaturated fatty acids
Oxidative degradation of polyunsaturated fatty acids components such as a linoleic acid is initiated as a way to the generation of the lipid peroxidation products such as 2-alkenals, 4-oxo-alkenals, and 4-hydroxy-2-alkenals. Also, as a showing of figure 1, the mechanism of furan formation from 4-Hydroxy-2-butenal can be formed through cyclization and dehydration (13).

2.2. Thermal degradation of amino acids

Acetaldehyde and glycolaldehyde formation by degradation of amino acids are able to produce furan undergo aldol addition (13). The resulting 2-deoxyaldotetrose can then further react to furan. These reactions depend greatly on the type of amino acids involved in the process. For example, serine and cysteine amino acids can produce acetaldehyde and glycolaldehyde and do not require to form furan unlike aspartic acid, threonine, and α-alanine (14). Figure 1.

2.3. Oxidation of carbohydrates

One of the known reactions during thermal processing is the Maillard reaction. This is a type of non-enzymatic chemical reaction that also called the “browning reaction, accruing between reducing simple sugars and principally free amino acids and peptides when cooked at high temperature. Some studies were indicated that formation of a large amount of furan occurs during the Maillard reaction (13). Thermal degradation of carbohydrates is observed in the Maillard reaction or non-enzymatic browning reactions during food processing and cooking. Carbohydrates are organic molecules compound which consists of three atoms of hydrogen, carbon, and oxygen. Degradation of Carbohydrate can be divided into four stages which further That's more to aldotetrose derivatives. These molecules occur during degradation of hexoses and pentoses. Reaction conditions including temperature, time, and pH can significantly affect furan formation (15-17). For example, Fan et al. indicated heat treatment of food at 90 C for 10 min produced no measurable amount of furan, while result showed heating to 120 C in a time-dependent pattern can be increased furan production (17). Figure 1.

3. Toxicology of furan

Furan is a strong hepatotoxin and hepatocarcinogen chemical compound in rodents which is classified as a group 2B, i.e. probably carcinogenic to humans according to the assessments conducted by International Agency for Research on Cancer (18). In rats, liver than other organs are the main target of furan toxicity due to the high activity of CYP2E1 metabolizer to bioactivate furan to its reactive intermediate that is the initiating phase in furan toxicity (19). Sprague-Dawley rats given a single dose of 40 mg/kg bw by oral gavage for 14 days showed decreased body weights, increased relative liver

Figure 1. Summary of potential routes of furan formation from different components present in food. PUFAs = polyunsaturated fatty acids (8, 14).
weights, and significant increases in serum transaminases, alkaline phosphatase, cholesterol, triglycerides, and total bilirubin (20). Treatment of female B6C3F1 mice with 0.5, 2, and 4 mg furan/kg bw by gavage over 3 weeks, 5 days per week induced significant hepatotoxicity at and above 0.5 mg/kg bw and a mild subcapsular inflammation of the liver at the lowest dose (21).

In the other study evaluation of rat livers showed that furan exposures lead to genotoxicity only at relatively high doses levels through an indirect mechanism (22, 23). In a toxicity study, oral treatment of male B6C3F1 mice over 28 days, at dose levels of 2, 4, 8 and 15 mg/kg bw per day caused necrosis and regenerative hyperplasia (at 8 and 15 mg/kg bw) and an increase in apoptotic (at 15 mg/kg bw). Low doses of Furan induce hepatotoxicity and cause proliferation changes in liver cells (0.1 mg/kg bw) (21, 24).

Chronic toxicity and carcinogenicity of furan were checked in juvenile male Wistar rats administered furan at doses of 2, 4 or 8 mg/kg bw per day over 90 days by oral gavage. Rats of 4 mg/kg bw and above showed reduced liver weights and notable changes in serum Alanine Aminotransferase (ALT), alkaline phosphatase (ALP) and low-density lipoprotein (LDL). Furthermore, hepatic tumor necrosis factor (TNF)-a was significantly increased and numerous histopathological alterations of the liver as well as morphological changes of the kidney were found at the lowest dose range (2 mg/kg bw) (25). In a 90-day oral toxicity study male and female Fischer 344 rats exposed to furan by oral gavage over a 90-day period with 0.03, 0.12, 0.5, 2.0 and 8.0 mg/kg bw per day. The liver was found to be the major target organ with changes in serum enzymes, increased liver weight, and various histological lesions. There was a significant increase in serum thyroxine (T4) and triiodothyronine (T3) in males. At a dose range above 0.5 mg/kg body weight, a change was revealed in clinical biochemistry and hematological parameters, whereas both male and female rats exposed to much lower doses of furan indicated mild hepatic histological lesions that were observed at doses ≥0.12 mg/kg. At this dose level, serum T4 was increased significantly in male rats, and further increased with increasing furan doses. Clear gender differences were also observed in reaction to furan (26). Effects of orally administered furan (by gavage) in acute, sub-acute and sub-chronic (≤90 days) studies in experimental animals are shown in table2.

The results of evaluate the toxicity of furan on the thyroid gland, adrenal gland, and pancreas of prepubertal male rats with 2, 4 and 8 mg/kg bw by gavage over 90 days, indicated histopathological changes such as congestion in the pancreas and mononuclear cell infiltration, hyperplasia, and fibrosis in the adrenal gland (27). In a separate study female mice were exposed to 0, 0.5, 1, 2, 4 and 8 mg/kg bw per day furan in corn oil 5 days per week for 2 years. Hepatocellular adenosomas were observed at the two highest doses and hepatocellular carcinomas only at 8 mg/kg bw. Furan promote hepatotoxicity, compensatory cell replication and tumorigenesis at high doses ≥4.0 mg/kg (21). Also, the summary of furan genotoxicity studies shown in table1.

### 4. Analytical methods for furan detection

For the first time, the original testing of furan levels in some of the food product that has undergone heat treatment was performed by the US-FDA. The determination of furan in food is not simply because of the extremely high volatility of furan The FDA reported the first quantitative technique for furan detection in food using head-space extraction coupled with gas chromatography-mass spectrometric (HS-GC/MS) determination (28). Temperature and the mobility of the sample are the factors affected the detection of furan from the food fragments. To ensure an effective extraction of furan, glass beads should be added to the

### Table1. Summary of furan Genotoxicity studies

<table>
<thead>
<tr>
<th>cell/animals</th>
<th>Dose(mg/kg bw per day)</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>B6C3F1 mice</td>
<td>orally for 4 weeks with 2, 4, 8 and 15</td>
<td>micronuclei in mitogen-stimulated splenocytes (4-15 mg/kg)</td>
<td>(29)</td>
</tr>
<tr>
<td>F344 rats</td>
<td>Oral administration of 0.1, 0.5 and 2 for 5 and 28 days</td>
<td>some evidence of DNA adducts in the liver and kidney</td>
<td>(30)</td>
</tr>
<tr>
<td>Transgenic gpt F344 male and female rats</td>
<td>Gavage for 13 weeks (0, 2, 8)</td>
<td>no increase in mutation</td>
<td>(31)</td>
</tr>
<tr>
<td>Serum of furan-treated Sprague–Dawley rats</td>
<td>Gavage. 16 over 30 days</td>
<td>large increases in 8-oxodeoxyguanosine levels</td>
<td>(32)</td>
</tr>
<tr>
<td>Serum of furan-treated BALB/c mice</td>
<td>i.p. 8 over 7 days</td>
<td>increased ROS levels; threefold increase in 8-Oxodeoxyguanosine</td>
<td>(33)</td>
</tr>
</tbody>
</table>

http://jfsh.tums.ac.ir
Strategies for furan reduction in food

5. Strategies for furan reduction in food

   5.1. Determining the thermal conditions, time, pH and incorporating the precursor levels (39). On the other hand, changing some of the parameters as temperature and time is challenging because of microbial growth followed by food safety problems. Also, polyunsaturated fatty acids, carbohydrates and amino acids are the most precursors to furan formation which Control of these pathways in a product is more challenging. Addition of food additives is the other way of controlling this toxin (40). In a previous study, the effect of pH on furan reduction in baby foods has been reported. The result showed that higher pH and temperature significantly increased the furan formation and reduce the level of this parameter has a positive effect in the decrease of furan (41). In the other study, the effect of antioxidants such as BHA in the decrease of furan formation was evaluated. They found that formation of this compound from PUFA when using of antioxidant significantly reduced (up to 70%) (42). Similarity, the research of EFSA indicated that it is possible to mitigate the furan level by heating of container closed in an open condition (16). Although, all of these actions should not cause a new hazard in the products.

6. Conclusion

   It is shown the effect of temperature, pH and some another factor must be considered during the food processing since they clearly influence the furan formation. Some studies have indicated that oral gavage administration of furan duration of up to 90 days, clearly hepatotoxic and moderately nephrotoxic in rats and mice. Rats appear to be more sensitive to the effect of this compound. Furan associated with changes in serum biochemical markers due to hepatotoxicity as well as adverse histopathological damage in the liver. A 90-day toxicity study in rats, at a dose of 0.12 mg/kg bw showed significant increases in serum thyroid hormones, also severe histopathological changes in the liver of male rats were observed. In long-term studies, furan was related to liver toxicity. Cholangiofibrosis was indicated in rats as an early and sensitive response after 36 weeks at ranges of ≥0.44 mg/kg bw. In rodents, exposure to the furan induced formation of low levels of DNA adducts in liver and kidney. Considering that humans can be exposed to especially high doses of furan in the source of dietary intake and that the knowledge about the mechanism of tumor induction risk by furan residues uncertain, it is crucial to develop some strategies for reducing furan formation in food products in order to prevent some human diseases as a number of cancers.

Conflict of interest

   The authors declare that they have no conflict of interest.

Acknowledgement

   None

References


11. EFSA. Results on themonitoring of furan levels in food. EFSA Scientific Report 2009, 304, 1–23.


