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Abstract

Furan is an organic, volatile molecule used in some chemical manufacturing industries. Headspace gas chromatography, the analytical method of choice, produces reliable results on its occurrence. The presence of furan in some foods was known since the late 1970s, but the survey of the U.S. Food and Drug Administration (FDA) published in 2004 revealed the occurrence of furan in a broad variety of canned and jarred foods that undergo heat treatment, including baby food. Furan is clearly carcinogenic in rats and mice, showing a dose-dependent increase in hepatocellular adenomas and carcinomas. In rats, also a dose-dependent increase of mononuclear leukaemia was seen and a very high incidence of cholangiocarcinomas of the liver was present even at the lowest dose tested. There is evidence indicating that furan-induced carcinogenicity is probably attributable to a genotoxic mechanism. However, chronic toxicity with secondary cell proliferation may indirectly amplify the tumour response. From the available data it appears that there is a relative small difference between possible human exposure and the doses in experimental animals that produce carcinogenic effects. However, a reliable risk assessment would need further data on both toxicity and exposure. The European Food Safety Authority's (EFSA) Scientific Panel on Contaminants in the Food Chain (CONTAM) therefore recommended undertaking such studies as part of a reliable risk assessment on furan in food.

Keywords: Furan, data for risk assessment, carcinogenicity

Introduction

In May 2004, the U.S. Food and Drug Administration (FDA) published results on furan in food. The European Food Safety Authority's (EFSA) Scientific Panel on Contaminants in the Food Chain (CONTAM) recognised the importance of furan in food and published an initial report in December 2004.

Furan (C_4H_4O) (CAS-Nr. 110-00-9) is an organic, lipophilic, volatile compound which serves as an intermediate in some chemical manufacturing industries such as for the preparation of temperature-resistant structural laminates or in the preparation of copolymers used in machine dishwashing products (NTP 1993). The presence of furan in canned meat was already described by Maga (1979), however the report of the U.S. FDA outlined the occurrence of furan in a much broader variety of commonly used foods that undergo heat treatment such as canned or jarred foods including baby foods (U.S. FDA 2004).

Furan is classified by the International Agency for Research on Cancer (IARC) as group 2B, possibly carcinogenic to humans, and is carcinogenic in rodents (NTP 1993; IARC, 1995).

The purpose of this paper is to briefly summarize the conclusions of the CONTAM report and to highlight which data are essential to enable a comprehensive risk assessment of furan in food and providing scientific arguments to risk managers for possible regulatory measures and/or consumer advice. Unless otherwise stated, the primary source has been the CONTAM report (EFSA 2004). No new information since this time has been included

in this paper on analytical methodology as this will be dealt with in the subsequent papers from the Workshop in this journal. Also no new data on exposure was included as the CONTAM Panel awaits EFSA's collection of data from a European monitoring programme on furan in foods.

Analytical methodology

Furan is a small volatile molecule which can be determined by headspace gas chromatography (GC). This is a relatively simple and well-established methodology in which a food sample in liquid or slurry form is heated in a sealed vial to achieve partition equilibrium between the liquid phase and the gaseous headspace. The headspace gas is sampled and the vapour injected into a GC. Detection can be by non-selective means such as flame ionisation detector or by mass spectrometry (MS). The U.S. FDA developed a GC-MS method which involves heating the sample at 60°C for a minimum of 30 min, followed by sampling the headspace gas and GC/MS monitoring of m/z 39 and 68 (U.S. FDA 2006). Quantification is by internal standardisation using isotopically labelled furan (monitoring m/z 72 for d4-furan). The FDA method claims a limit of quantification (LOQ) of 2.0 - 5.0 ng/g depending on the food type. The advantage of this approach is, that there is no need for a sample clean-up and it can be automated for high sample throughput. The disadvantages are that the foodstuff is heated, meaning that furan might be formed during analysis, although this is unlikely at the low temperatures used; that sample sizes are small (typically 5 to 10 g), meaning good homogenisation is required; and that because furan has a low molecular weight and even with MS detection there may not be adequate specificity. For good quantification, the labelled internal standard is essential but there seem to be

problems of availability of the standard, meaning that laboratories may be undertaking this analysis with less ideal internal standards or using external standardisation.

There are no precision data given in terms of repeatability, and neither of the methods have been validated, so there is no available insight into the robustness of the method. There has been no proficiency testing undertaken to date, but it is foreseen to perform a European proficiency testing on furan in diverse foods in the future, which will establish the comparability of data obtained by different laboratories.

Occurrence

Furan occurs widely in different foods such as roasted coffee, canned and jarred foods including baby food containing meat and various vegetables. This suggest that there are multiple routes of formation rather than a single mechanism such as carbohydrate thermal decomposition.

In 2004, there was only a limited set of data available for occurrence of furan in food. Therefore, the CONTAM Panel decided not to calculate mean, median or standard deviations for intake, but to present the range of estimated exposure using consumption data from the GEMS/Food Regional Diets (WHO 2003) as at that time no European food consumption database was available. Such data can allow ranking of food categories as a function of their contribution to the overall exposure via food. Table 1 gives an overview of the occurrence of furan and intake estimates in twelve different food categories.

[Insert table 1 about here]

Most data were available for baby food (n=273). The range of the concentration of furan in baby food was from non-detectable to 112 µg/kg. Considering a consumption of 234 g per day of canned baby food (Kersting *et al.* 1998), this would result in an exposure of < 0.03 to 3.5 µg/kg body weight (b.w.) per day assuming a body weight of 7.5 kg for a 6 month old baby (EC 1993).

For a sound exposure assessment, the CONTAM Panel concluded that the following information is needed: (i) Occurrence data from a broad variety of food categories including beverages. (ii) Data on variability between and within brands. (iii) Information on freshly prepared foods from home cooking and catering (iv) Release of furan from food due to volatilisation in foods. (v) Other routes of furan exposure such as via inhalation during cooking. (vi) Identification of suitable biomarkers to clarify internal exposure. (vii). Mechanism of formation and stability in foods.

As it is within EFSA's remit to collect data (Article 33, EC 2002) a monitoring database on furan in foodstuffs with inputs from the European Member States was developed. The online submission of data via the Authority's website is possible since 1 November 2006. The European Commission supports this activity by preparing a recommendation on the monitoring of furan levels in foodstuffs which is expected to be published early 2007.

Toxicokinetics and Metabolism

Furan has a low polarity and can pass biological membranes and is readily absorbed from the lung or intestine, probably also from the skin. In a two compartment physiologically based pharmacokinetic (PBPK) model, Kedderis *et al.* (1993) predicted 84 % metabolism

and 16 % exhalation of a single oral dose of 8 mg furan/kg b.w. in rats within 24 hours. In agreement with other studies (Burka *et al.* 1991; Kedderis and Held 1996) it can be concluded that the amounts of furan reaching body tissues are limited by the high capacity of the liver to eliminate furan from the blood stream by first-pass metabolism catalysed by cytochrome P450 (CYP2E1). The major primary metabolite of furan is a reactive dialdehyde, cis-2-butene-1,4-dial, which has been found to bind irreversibly to nucleophiles such as proteins and nucleotides (Burka *et al.* 1991; Byrns *et al.* 2002).

Toxicology

The toxicity database of furan is incomplete. Only qualitative data are available on the acute toxicity (vapours are narcotic, anaesthetic and convulsant; U.S. National Research Council NRC 2000), no data are available on reproductive and developmental toxicity of furan and there are no data from human studies.

Toxicology and carcinogenicity studies were conducted by the National Toxicology Program (NTP) by administering furan (purity > 99 %) in corn oil by gavage to groups of F344/N rats and B6C3F1 mice of each sex for 16 days, 13 weeks, and 2 years (NTP 1993). These studies are summarized in detail in the CONTAM report (EFSA 2004) and are briefly reviewed here.

In the 16-day studies, furan resulted in increased mortality in both species and both sexes at 80 mg/kg b.w. per day and higher, in male mice already at 40 mg/kg b.w. per day. Final mean body weights of male rats that received 20 mg/kg b.w. per day and of male and

female rats that received 40 mg/kg b.w. per day were significantly lower than controls (National Research Council, 2000).

In the 13-week studies, nine male and four female rats that received furan doses of 60 mg/kg b.w. per day died before the end of the studies (National Research Council, 2000). There were no chemical-related deaths in mice. Final mean body weights of male rats that received 15 mg/kg b.w. per day or more, female rats that received 60 mg/kg b.w. per day and male mice that received 30 mg/kg were significantly lower than controls. A dose-dependent increase in relative liver- and kidney weights was found in both sexes of rats that received 15 mg/kg b.w. per day or more. Toxic lesions of the liver (bile duct hyperplasia, cholangiofibrosis, cytomegaly and degeneration of hepatocytes, and nodular hyperplasia of hepatocytes) were associated with furan administration in all dose groups of rats; the severity of the lesions increased with dose. Other effects such as decreased thymus weights and kidney lesions were also seen in rats that received 30 or 60 mg/kg b.w. per day. Relative and absolute liver weights in mice of both sexes were dose-dependently increased in male mice that received 15 or 30 mg/kg b.w. per day and in females that received 30 or 60 mg/kg b.w. per day. Toxic liver lesions (cytomegaly, degenerationnecrosis) were present in all groups of furan-exposed mice. Bile duct hyperplasia and cholangiofibrosis were observed in groups of mice receiving 30 or 60 mg/kg b.w. per day.

In the 2-year rat study, animals of each sex were administered furan at 2, 4, or 8 mg/kg b.w. per day five days per week. Mean body weights of male rats that received 8 mg/kg b.w. per day were lower than controls from approximately week 73 to the end of the study.

Survival of male and female rats that received 8 mg/kg b.w. per day was lower than controls from approximately week 85 to the end of the studies as a result of moribund condition associated with liver and biliary tract neoplasms and mononuclear cell leukaemia (see below). Increased incidences of numerous non-neoplastic liver and kidney lesions were present in treated rats. The incidence of forestomach hyperplasia was increased in male and female rats and the incidence of sub-acute inflammation of the forestomach was increased in female rats. Cholangiocarcinoma of the liver occurred in all groups of dosed rats (males: 0/50; 43/50; 48/50; 49/50; females: 0/50; 49/50; 50/50; 48/50) and was present in many rats of each sex at the 9- and 15-month interim evaluations. Hepatocellular adenomas or carcinomas (combined) were significantly increased in male rats after 2 years of administration (1/50, 5/50, 22/50, 35/50) and hepatocellular adenomas were significantly increased in female rats (0/50, 2/50, 4/50, 7/50); hepatocellular neoplasms were not observed at the 9- or 15-month interim evaluations. The incidence of mononuclear cell leukaemia was increased in male and female rats that received 4 or 8 mg/kg furan (males: 8/50, 11/50, 17/50, 25/50; females: 8/50, 9/50, 17/50, 21/50); the incidence in the 8 mg/kg groups of each sex exceeded the historical control ranges for corn oil gavage studies.

In the 2-year mice study, animals of each sex received doses of furan of 8 or 15 mg/kg b.w. per day five days per week. Mean body weights of male and female mice that received 15 mg/kg b.w. per day were lower than controls during the studies. Survival of low- and high-dose male and high-dose female mice was lower than controls from approximately week 80 to the end of the study as a result of moribund condition associated with liver neoplasms (see below). The incidences of squamous papilloma, focal

inflammation, and papillary hyperplasia of the forestomach were increased in male mice. The incidences of benign pheochromocytoma and focal hyperplasia of the adrenal medulla were increased in low- and high-dose male and in high-dose female mice. The incidence of hepatocellular lesions was increased in dosed mice, including hepatocyte cytomegaly, degeneration, necrosis, multifocal hyperplasia, and cytoplasmic vacuolization and biliary tract dilatation, fibrosis, hyperplasia, and inflammation. The incidences of hepatocellular adenomas and carcinomas were significantly increased (males: adenoma 20/50, 33/50, 42/50; carcinoma 7/50, 32/50, 34/50; females: adenoma 5/50, 31/50, 48/50; carcinoma 2/50, 7/50, 27/50).

A separate 2-year study was conducted in which 50 male rats were administered 30 mg/kg furan in corn oil by gavage five days per week for 13 weeks and then maintained for the remainder of the 2 years without additional furan administration (NTP 1993). Groups of 10 animals were evaluated for the presence of treatment-related lesions at the end of the 13-week period of furan administration and at 9 and 15 months. 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) in stop-exposure male rats that survived at least 9 months. Cholangiocarcinoma was observed in all 10 males at both the 9-month and 15-month interim evaluations. Hepatocellular carcinoma was first observed in 2 males at the 15-month interim evaluation.

According to FDA (2004), a preliminary report from a second 2-year bioassay in female mice found an increased incidence and multiplicity of hepatic tumours and a decreased

tumour latency in mice dosed with 4 or 8 mg furan/kg b.w. per day, but not in mice dosed with 0.5, 1.0, or 2.0 mg furan/kg b.w. per day (Goldsworthy *et al.* 2001).

Several other non-standard carcinogenicity studies were performed, all confirming the carcinogenic potential of furan: Prewaning male B6C3F1 mice were treated by intraperitoneal administration of furan in tricaprylin either as a single dose of 400 mg/kg b.w. per day (LD₁₀) or six doses of 200 mg/kg b.w. per day. The mice were sacrificed between 28 and 95 weeks after dosing (Johansson *et al.* 1997). In the single-dose group the furan-treated mice showed a statistically non-significant increase of the overall frequency of hepatocytic neoplasia and of the overall liver tumour multiplicity, compared with the vehicle control group. No treatment-related histopathological lesions other than development of liver tumours were found. In mice given six doses of 200 mg/kg b.w. per day, there was a statistically significant increased incidence of hepatocellular neoplasms (adenomas and carcinomas) and tumour multiplicity compared with the vehicle control group (Vesselinovitch and Mihailovich 1983; Wiseman *et al.* 1986).

In male F344 rats, furan (30 mg/kg b.w. per day by gavage, five days/week) for 9, 12, and 13 weeks induced primary hepatic adenocarcinomas exhibiting small intestine mucosal cell differentiation at 70 to 90 % incidences by 16 months (Elmore and Sirica 1993). The incidences of primary hepatocellular carcinomas ranged from 0 to 20 % (two hepatocellular carcinomas).

Metaplastic small intestinal-like glands were selectively derived from putative hyperplastic bile ductule-like progenitor structures of young adult F344 male rats given

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4 furan by gavage at a daily dose of 30-45 mg/kg b.w. per day five times/week for 2 to 6
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6 weeks (Sirica 1996). Administration of furan at 30 mg/kg b.w. per day for 9 to 19 weeks
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8 resulted in the preferential development of primary hepatic adenocarcinomas, which were
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10 characterized by small intestine mucosal cell differentiation.
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16 **Genotoxicity**

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18 *In vitro*

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20 Furan was not mutagenic in the *Salmonella typhimurium* strains TA100, TA1535, TA1537
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22 and TA98 with and without S9 metabolic activation (NTP 1993). In another study (Lee *et*
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24 *al.* 1994) furan was weakly mutagenic in strain TA100 with and without S9 activation.
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26 Furan was negative in the sex-linked recessive lethal mutation test in *Drosophila*
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28 *melanogaster* (Foureman *et al.* 1994) but was mutagenic in the thymidine kinase locus of
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30 L5178Y mouse lymphoma cells in the absence of S9 activation (McGregor *et al.* 1988)
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32 and, in another study, with and without S9 activation (NTP 1993). Furan induced
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34 chromosomal aberrations and sister chromatid exchanges (SCE) in Chinese hamster ovary
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36 cells (CHO) both with and without S9 activation (NTP 1993). In another study on CHO
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38 cells (Stich *et al.* 1981) furan caused chromosome aberrations only in the presence of S9
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40 metabolic activation. Furan produced DNA double-strand breaks in isolated rat
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42 hepatocytes (Mugford and Kedderis 1996).
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52 The furan metabolite cis-2-butene-1,4-dial was directly mutagenic at non-toxic
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54 concentrations in the *S. typhimurium* strain TA104, a strain sensitive to aldehydes
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56 (Peterson *et al.* 2000). The mutagenic activity of furan in TA104 is similar to that of
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58 crotonaldehyde, acrolein and glyoxal. Cis-2-butene-1,4-dial was negative in strains TA97,
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TA98, TA100 and TA102; its mutagenic activity was inhibited by glutathione. Cis-2-butene-1,4-dial caused DNA single-strand breaks and DNA cross-links in CHO cells (Marinari *et al.* 1984) and produced DNA adducts *in vitro* (Byrns *et al.* 2002).

In vivo

Furan (250 mg/kg b.w. by i.p. injection) induced structural chromosome aberrations in mice bone marrow cells, but not sister chromatid exchange (SCE) up to the dose of 350 mg/kg b.w. i.p. (NTP 1993). Furan did not induce unscheduled DNA synthesis (UDS) in mouse or rat hepatocytes *in vivo* after a single oral dose of 200 or 100 mg/kg b.w., respectively (NTP 1993).

In the study with [2,5-¹⁴C]-furan by Burka *et al.* (1991) which was discussed earlier, the liver contained more radioactivity than other tissues and 80 % was associated with proteins, while no radioactivity was associated with DNA. Repeated daily administration of the radiolabelled furan at four dose levels resulted in an approximately linear increase in covalent protein binding. There was either no binding to DNA or the furan-DNA adduct was not stable to the isolation procedure. The results of this study were considered inconclusive by the CONTAM Panel as the specific activity of [2,5-¹⁴C] furan was probably too low to detect DNA adducts and because the labelled carbon atoms at position two and five are the labile carbons giving rise to CO₂, further reducing the sensitivity of the radioactivity determinations on DNA in addition to the potential instability to the isolation method used. A study performed with ¹⁴C-furan labelled on carbons three and/or four, using a DNA extraction method different from that based on phenol and possibly the

Accelerator Mass Spectrometry as analytical technique would allow for a more conclusive evaluation on the potential DNA binding of furan metabolites.

Mutation of proto-oncogenes in liver tumours induced in mice by furan

Ras proto-oncogene activation was studied in hepatocellular tumours (both adenomas and carcinomas) induced in mice by furan (Reynolds *et al.* 1987). The frequencies of activated *H-ras* and *K-ras* oncogenes were similar in liver tumours from 12/29 treated mice and 15/27 vehicle controls, but the spectrum of mutations in the *H-ras* gene differed significantly. In addition to finding five tumours with commonly occurring point mutations in codon 61 of *Hras1*, Reynolds *et al.* found novel mutations in eight liver tumours, including G-T and G-C transversions in codon 117 of *Hras1* in four tumours and activation of *Ki-ras*. The unique *ras* oncogene mutational profile was interpreted by the authors as a suggestion that the novel mutations could have been due to a genotoxic effect of furan.

Mode of Action

The mechanism of carcinogenic activity of furan in rodents has not yet been fully elucidated. Hypotheses of both direct (genotoxic) and indirect mechanisms have been formulated.

While several pieces of evidence available suggest that furan or its proximate metabolite cis-2-butene-1,4-dial can react directly with DNA in target cells and can play a role in furan-induced tumours Wilson *et al.* (1992) found no evidence of unscheduled DNA synthesis (UDS) after short-term exposure of male mice to furan by gavage (up to 200

mg/kg), but did find evidence of cytotoxicity and secondary enhanced cell proliferation after exposure to 15 mg/kg b.w. furan for up to 6 weeks. These authors postulated that furan-induced hepatocellular proliferation secondary to cytotoxicity (necrosis/apoptosis), rather than *in vivo* genotoxicity, was primarily responsible for the production of liver tumours. Supporting evidence available at that time for an indirect mechanism was the observation that radiolabelled furan given orally to rats produced metabolites that covalently bound to proteins but not to DNA (Burka *et al.* 1991). However, the results of Burka *et al.* were considered to be inconclusive by the CONTAM Panel because of limitations in the experimental protocol. Furthermore, the CONTAM Panel noted that negative results of the liver UDS cannot be taken as a proof of absence of genotoxicity of furan, because this assay detects only bulky DNA adducts in hepatocytes and is unable to detect mutagenicity resulting from misrepair and non-repair.

Kedderis and Ploch (1999) found that furan-treated rat hepatocytes show 95 % loss of ATP, due to irreversible uncoupling mitochondrial oxidative phosphorylation (Mugford *et al.* 1997). This depletes the energy stores, with activation of cytotoxic enzymes, including endonucleases that produce DNA double-strand breaks prior to cell death. The endonuclease inhibitor aurintricarboxylic acid reduced the formation of DNA double-strand breaks. These authors postulated that erroneous repair of the DNA double-strand breaks may lead to mutations that are involved in tumour development and supported an indirect mechanism for the formation of DNA double-strand breaks.

Taking into account all the presently available data on the mode of action of furan, the CONTAM Panel concluded that the weight of evidence indicates that furan-induced

carcinogenicity is probably attributable to a genotoxic mechanism. However, chronic toxicity with secondary cell proliferation may indirectly amplify the tumour response.

Conclusions

In summary the CONTAM Panel noted that for a reliable risk assessment on furan in food data in the following areas are needed:

- **Analytic:** Need to validate the performance of analytical methods through inter-laboratory trials to allow comparability of data between laboratories.
- **Exposure:** For a sound exposure assessment occurrence and formation data of furan in a wide variety of food and food products including prepared foods from home cooking and catering is needed.
- **Toxicology:** Furan is clearly carcinogenic in rats and mice, showing a dose-dependent increase in hepatocellular adenomas and carcinomas in both sexes and in rats also a dose-dependent increase in mononuclear leukaemia as well as a very high incidence of cholangiocarcinomas of the liver in both sexes. The CONTAM Panel concluded that the weight of evidence indicates that furan-induced carcinogenicity is probably attributable to a genotoxic mechanism. However, dose-response data at lower dose-levels combined with mechanistic studies and investigations of the role of species differences in metabolism in the generation of toxic metabolites are needed for clarification of the formation and significance of the cholangiocarcinomas in rats, which occur at a very high incidence at the lowest dose tested. To further improve the toxicity database of furan, studies on reproductive and developmental toxicity are also needed.

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Table 1. Furan in food. Data derived from the U.S. FDA Laboratory, the Swiss Federal Office of Public Health, the Kantonales Laboratorium Basel-Stadt Switzerland, the Confederation of the Food and Drink Industries of the EU, and the Chemische und Veterinäruntersuchungsamt Stuttgart Germany.

Food category	Minimum of positive samples (µg/kg)	Maximum of samples (µg/kg)	Number of samples (n<LOQ ²⁾)	Average consumption (GEMS Food) (g/day)	Range of intake ¹⁾ (µg/person)
Coffee ³	3	146	45 (4)	791 ⁷⁾	2.4 – 115.5
Baby food (including porridge, juices for babies and young children) ⁴⁾	1	112	273 (11)	234 ⁵⁾	0.2 – 26.2
Vegetables (canned or jarred)	3	61	35 (7)	372	1.1 – 22.7
Infant formula	2	13	19 (8)	870 ⁶⁾	1.7 – 11.3
Meat products	4	39	11 (6)	217	0.9 – 8.5
Cereals/products (only bread)	2	30	13 (8)	176	0.4 – 5.3
Beer	5	13	6 (0)	258 ⁷⁾	1.3 – 3.4
Fruit juices	1	6	18 (11)	69 ⁷⁾	0.1 – 0.4
Fish	5	7	6 (3)	47	0.2 – 0.3
Milk	< 0.5		1	336	< 0.2
Honey	3	10	5 (0)	1	0.003 – 0.01
Food non classified ⁸⁾	3	125	84 (11)	-	-

¹⁾ Calculated from the minimum and maximum of the positive samples
²⁾ Number of samples below the limit of quantification (LOQ)
³⁾ Both concentration and consumption figures are related to liquid coffee ready to drink. The consumption figure is for filter coffee.
⁴⁾ Out of 273 samples 33 Swiss samples were baby food in small glass jars containing mainly fruits with a range of furan levels from 1 (minimum) to 16 (maximum) µg/kg.
⁵⁾ Figure taken from DONALD study (Kersting *et al.* 1998).
⁶⁾ Figure in mL per day taken from SCF report (EC 2003).
⁷⁾ Figure taken from SCOOP report task 4.1 (EC 1996).
⁸⁾ Food non classified consist of soups, broths, sauces, tomato and chilli sauces, soy sauce.