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Original Article

Detailed exposure assessment of dietary furan for infants consuming commercially jarred complementary food based on data from the DONALD study

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Abstract

Furan is a possible human carcinogen regularly occurring in commercially jarred complementary foods. This paper will provide a detailed exposure assessment for babies consuming these foods considering different intake scenarios. The occurrence data on furan in complementary foods were based on our own headspace-gas chromatography/mass spectrometry (HS-GC/MS) analytical results ($n = 286$). The average furan content in meals and menus was between 20 and 30 μg kg^{-1}, which is in excellent agreement with results from other European countries. Using measured food consumption data from the Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) study, the average exposures for consumers of commercially jarred foods ranged between 182 and 688 ng kg^{-1} bw day^{-1}, with a worst case scenario for P95 consumers ranging between 351 and 1066 ng kg^{-1} bw day^{-1}. 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^{-1} bw day^{-1} for hepatocellular tumours in rats. The margin of exposures (MOEs) were below the threshold of 10 000, which is often used to define public health risks, in all scenarios, ranging between 7022 and 1861 for average consumers and between 3642 and 1200 for the P95 consumers. Mitigative measures to avoid furan in complementary foods should be of high priority for risk management.

Keywords: furan, baby food, infant nutrition, risk assessment, food contamination.

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Introduction

During the last few years, a considerable amount of evidence was gathered on the occurrence of furan (C_4H_4O), a substance classified as a possible human carcinogen (group 2B) by the International Agency for Research on Cancer (IARC 1995), in baby food (Heppner & Schlatter 2007). The furan formation in commercial ready-to-eat complementary foods can be explained by a heat-induced mechanism from various precursors during sterilization (Wenzl *et al*. 2007; Lachenmeier *et al*. 2009), similar to the process-related formation of acrylamide or benzene (Hilbig & Kersting 2006; Lachenmeier *et al*. 2008; Lachenmeier *et al*. 2010). With the exception of coffee products, commercial complementary foods were the food group with the highest furan concentrations in a recently conducted large monitoring in Europe including more than 2900 samples, from which 985 were baby foods [European Food Safety Authority

(EFSA) 2009]. It is interesting that 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. Such detailed consumption data are generally not available, with the exception of results from the Dortmund Nutritional and Anthropometrical Longitudinally Designed (DONALD) study (Kroke *et al*. 2004). Substances that were previously assessed in infant foods using DONALD data include pesticides (Kersting *et al*. 1998), acrylamide (Hilbig *et al*. 2004; Hilbig & Kersting 2006), polychlorinated dibenzodioxins and dibenzofurans (Lorán *et al*. 2010) as well as lead and nitrate from tap water (Hilbig *et al*. 2002). As the DONALD study includes detailed data down to the consumption of specific food items, it is also possible to assess exposure if the concentration of contaminants varies to a large degree or if the occurrence is predominant in single food items, as, e.g. in the case of benzene in carrot juice (Lachenmeier *et al*. 2010).

Data from the DONALD study were also used in the past for exposure assessments of furan in complementary foods (Heppner & Schlatter 2007; BfR 2009; EFSA 2009; Jestoi *et al*. 2009; Lachenmeier *et al*. 2009; Bakhiya & Appel 2010; Liu & Tsai 2010). However, all previous assessments used only comparably old summarized data from the period prior to 1996 (Kersting *et al*. 1998) and did not make use of the full data set. It is currently unknown if this approach might lead to overestimation or underestimation of exposures, especially considering that different complementary food groups have highly significant differences in their furan content (Lachenmeier *et al*. 2009). In this study, we will therefore conduct a more detailed exposure assessment on furan in commercial complementary foods based on occurrence data from a systematic literature review in addition to our own analytical data. This occurrence data will be combined with the current full DONALD data set to provide a detailed exposure estimate, which can be used for risk assessment using the margin of exposure approach based on a recent dose-response assessment by Carthew *et al*. (2010).

Materials and methods

Literature search

The literature search was conducted by researchers with qualifications in food science, chemistry, nutrition and toxicology, with special expertise in infant diet. Data on the occurrence of furan in complementary foods were obtained by a computer-assisted literature search using the key word ‘furan’ in combination with ‘food’ and ‘nutrition’, ‘baby’ or ‘infant’. Benchmark doses and toxicological dose descriptors were obtained by searching with the key word ‘furan’ and ‘margin of exposure’, ‘MOE’, ‘benchmark dose’, ‘BMD’, ‘BMDL’, ‘BMDL10’ or ‘T25’. Searches in English and German were carried out in July 2009, in the following databases: PubMed (U.S. National Library of Medicine, Bethesda, MD), Web of Science (Thomson Reuters, Philadelphia, PA), Scopus (Elsevier B.V., Amsterdam, The Netherlands) and Google Scholar (Google Inc., Mountain View, CA). Efforts were made to include all available studies; this was accomplished by a hand search of the reference lists of all articles for any relevant studies not included in the databases. The references, including abstracts, were imported into Reference Manager

Key messages

- Furan (C_4H_4O) is a substance classified as a possible human carcinogen.
- Commercially jarred complementary food may contain furan as heat-induced contaminant.
- Our evaluation shows that the exposure for children would be above thresholds.
- Mitigative measures to avoid furan in complementary foods should be developed.

V.12 (Thomson Reuters, Carlsbad, CA) and the relevant articles were manually identified and purchased in full text. We did not identify any article, which was available as abstract only or which we were not able to obtain in full text. No unpublished study was identified.

Survey of furan in baby foods

The survey of commercial ready-to-eat complementary foods included 282 products sampled and analysed between 2004 and 2010. As part of official food control in the German federal state of Baden-Württemberg, our institute covers the district of Karlsruhe in North Baden (Germany) with a population of approximately 2.7 million. The sampling has been done by local authorities directly at the food producers or at retail trade establishments including pharmacies and organic food stores. The samples have been randomly selected and collected by government food inspectors. Only products intended for use as foods specifically for infants and young children, in the sense of Commission Directive 2006/125/EC, were included in the survey (European Commission 2006).

Furan was analysed using a validated headspace-gas chromatography/mass spectrometry (HS-GC/MS) procedure with a deuterated internal standard and standard addition for quantification, previously described in detail (Lachenmeier *et al*. 2009).

Dietary intake assessment

The EFSA harmonized approach was used as basis for the dietary intake assessment (EFSA 2005). The EFSA recommends that risk assessments provide different exposure scenarios (e.g. for entire or specific groups of populations) along with their inherent uncertainties. Other than the mean and median, intakes from highly exposed individuals (due to high consumption or to average consumption of highly contaminated foods) should be considered as represented by the 90th, 95th, 97.5th and 99th percentiles.

Using our own data from the DONALD study, we provided two basic different scenarios: for consumers of commercially jarred complementary foods only ('consumer group') as well as for the whole data set ('total sample'). For each of these scenarios, we consider mean and median intakes as well as the percentiles. We think that this differentiation adequately considers the EFSA criteria to look at highly exposed individuals (consumer group) as well as for entire populations (total sample).

The DONALD study is an ongoing, longitudinal (open cohort) study that has been collecting detailed data on diet, growth, development and metabolism between infancy and adulthood since 1985 (Kroke *et al*. 2004). In short, the starting study sample included infants, children and adolescents recruited from cross-sectional studies conducted in schools and kindergartens ($n \approx 470$). Since 1989, infants have been recruited and followed up longitudinally at least until the age of 18 years.

The regular DONALD assessments include records of dietary intake, anthropometry, urine sampling and medical examination, once a year per study participant ≥2 years of age and every 3 months during the first year of life.

The DONALD study, which is exclusively observational and non-invasive, has been approved by the International Scientific Committee of the Research Institute of Child Nutrition and the Ethics Committee of the University of Bonn.

For the present evaluation, we analysed 3-day dietary records of subjects aged 3, 6, 9 and 12 months in the study period of 2000–2008. This selection resulted in 1155 records from 380 infants (197 boys, 183 girls). Per participant, one ($n = 40$; 11% of the total sample), two (58, 15%), three (129, 34%) or four (153, 40%) 3-day records were available and analysed. Parents weighed and recorded all foods and beverages consumed using electronic food scales (±1 g) on 3 consecutive days. Semi-quantitative recording (e.g. number of glasses) was allowed when weighing was not possible. The complete food collection details have been described elsewhere (Kroke *et al*. 2004).

Approach for risk assessment

Risk assessment was conducted according to the harmonized approach of the EFSA for the risk assessment of substances that are genotoxic and carcinogenic (EFSA 2005). The EFSA has developed and recommends an approach known as the margin of exposure (MOE). This approach uses the value of doses of substances that have been observed to cause low but measurably harmful responses in animals as a reference point, which is then compared with relevant substance-specific dietary intake estimates in humans, taking into account differences in consumption patterns.

To obtain the MOE, the benchmark dose lower confidence limit (BMDL10) for a benchmark response of 10% was suggested. In cases where the data are unsuitable for obtaining a BMDL10, the EFSA recommends the use of the T25 calculation, wherein the dose corresponding to a 25% incidence of tumours, after correction for spontaneous incidence, is represented.

Results and discussion

Occurrence of furan in baby foods

Sixteen references presenting data on the occurrence of furan in complementary foods were indentified (Becalski *et al*. 2005; Bianchi *et al*. 2006; Nyman *et al*. 2006; Vranová *et al*. 2007; Yoshida *et al*. 2007; Zoller *et al*. 2007; Morehouse *et al*. 2008; BfR 2009; EFSA 2009; Jestoi *et al*. 2009; Kim *et al*. 2009a; Lachenmeier *et al*. 2009; Van Lancker *et al*. 2009; Becalski *et al*. 2010; Liu & Tsai 2010; Wegener 2010). The results of this literature review are presented in Table 1. Our own analytical results are given in Table 2; these include data from products analysed in 2004–2007 (Lachenmeier *et al*. 2009) as well as new results from 2008–2010. We have categorized the data (if possible) into five broad groups: beverages (fruit juices, teas, tea-juice mixtures and others); fruits and vegetables (including vegetarian menus without meat); menus (combinations of vegetables, meat and potatoes/pasta/cereals); meat (exclusively or predominantly based on meat); porridge (combinations of cereals and milk); and infant formulas.

As we have previously described (Lachenmeier *et al*. 2009), the subgroups of baby foods contain significant differences in their furan contents. Most strikingly, the group of baby beverages has lower furan contents (median <10 μg kg^{-1}) than fruit and vegetable meals and other menus. According to our results and the study of Liu & Tsai (2010), infant formula also contains less furan than the jarred foods. However, in the EFSA report, higher concentrations – only slightly lower than in the jarred foods – were reported. The low number of infant formula samples analysed in all the studies allows no definite current conclusion regarding this group. The major focus of surveys was apparently the group of jarred complementary foods, as more than 1000 analytical values can be currently found in the literature regarding this category (Tables 1 and 2). The averages for fruit and vegetable meals and other menus consistently range from around 20 to 40 μg kg^{-1}. Our own results for the fruit and vegetable group (which is the most common group of complementary foods in Germany; see section on Exposure estimation using the DONALD data below) showed an average of 22 μg kg^{-1} and a median of 18 μg kg^{-1}. This is in excellent agreement, with the results of EFSA ($n = 985$), which reported an average of 24–25 μg kg^{-1} and a median of 18 μg kg^{-1} for all baby foods (no subgrouping available in the EFSA report). According to our results, menus contain slightly higher values (average 30 μg kg^{-1}, median 27 μg kg^{-1}), while meats and porridges contain lower concentrations than fruit/vegetables; however, this is based on comparably few analytical results.

Exposure estimation using the DONALD data

The intake of the different groups of complementary foods derived from the DONALD study is shown in Tables 3 and 4 for the consumer only, and for the total sample. The first and foremost question that arises in the exposure estimation of furan in complementary foods is the treatment of the different subgroups of complementary foods, as beverages and porridges in particular contain lower concentrations than other groups. In the past, this differentiation was not made (see introduction). Therefore, depending on the proportion of analysed beverages and porridges, the average furan content might be underestimated. The use of the summarized data from DONALD presents the problem that our table provides the total of 'baby foods (ready-to-eat or -drink)', meaning that bever-

Table 1. Literature review about the occurrence of furan in baby foods

Reference	Year	Products	Number of samples	Average (μg kg^{-1})	Median (μg kg^{-1})	Minimum (μg kg^{-1})	Maximum (μg kg^{-1})	P90	P95	P99
Swiss Federal Office of Public Health (Wegener 2010)	2004	Baby beverages	4	12	3	1	40	31	37	49
		Fruit and vegetable meals	76	19	7	1	80	34	40	53
		Menu	18	41	38	14	153	50	60	79
		Meals with meat	7	4	4	3	6	2	2	3
State Laboratory of the Canton Basel City (Wegener 2010)	2004	Fruit and vegetable meals	13	41	43	24	69	22	27	35
		Menu	7	19	20	12	25	7	8	11
Food and Drug Administration (Wegener 2010)	2004–2005	Baby beverages	11	3	3	2	8	3	4	5
		Fruit and vegetable meals	100	39	38	2	112	51	61	80
		Menu	32	31	29	1	87	35	42	55
		Meals with milk and cereals	3	1	0	0	4	–	–	–
Becalski *et al*. (2005)	2005	Fruit and vegetable meals	4	55	32	5	150	112	133	175
		Menu	5	43	26	6	100	64	76	100
Bianchi *et al*. (2006)	2006	Fruit and vegetable meals	6	52	33	3	141	94	111	146
Nyman *et al*. (2006)	2006	Fruit and vegetable meals	3	83	82	73.8	93.1	–	–	–
		Menu	2	27	27	15.9	39.7	–	–	–
Zoller *et al*. (2007)	2007	Baby beverages	4	12	3	1	40	31	37	49
		Fruit and vegetable meals	71	17	6	1	80	34	40	53
		Menu	18	41	38	14	153	50	60	79
		Meals with meat	7	4	4	3	6	2	2	3
Yoshida *et al*. (2007)	2007	Baby beverages	3	10	3	1.4	25	22	26	34
		Fruit and vegetable meals	4	17	19	2	29	20	24	32
		Menu	8	30	22	5	90	44	53	69
		Other products	11	4	1	0	36	17	21	27
Vranová *et al*. (2007)	2007	Fruit and vegetable meals	2	43	–	20.7	64.6	–	–	–
		Menu	2	22	–	16.4	28.5	–	–	–
Morehouse *et al*. (2008)	2008	Baby beverages	5	4	–	2.5	8.2	–	–	–
		Fruit and vegetable meals	62	40.2	43	4	80	48	57	75
		Menu	7	32.9	–	15.9	46.9	–	–	–
Van Lancker *et al*. (2009)	2009	Fruit and vegetable meals	3	116	100	75.1	172.7	–	–	–
		Menu	1	83.3	–	–	–	–	–	–
German Federal Institute for Risk Assessment [BfR (2009)]	2009	Fruit and vegetable meals	166	17	–	–	–	–	–	–
		Menu	94	24.8	–	–	–	–	53.3	–
		Meals with milk and cereals	12	25.0	–	–	–	–	–	–
EFSA (2009)	2009	Baby food	985	24–25	18	0–0.03	215	–	74	–
		Infant formula	35	18–19	15	0–2	56	–	47	–
Jestoi *et al*. (2009)	2009	Fruit and vegetable meals	14	23	18	4.7	73.4	31	37	48
		Menu	7	50	46	12.8	90.3	43	52	68
University Amsterdam/Nestlé (Wegener 2010)	2009	Baby beverages	21	10	6	2	33	16	19	25
Kim *et al*. (2009a)	2009	Baby beverages	17	5.5	–	1.2	21.0	–	–	–
		Fruit and vegetable meals	50	22.5	–	2.1	102.5	–	–	–
		Other products	29	3.8	–	1.0	20.7	–	–	–
Liu & Tsai (2010)	2010	Baby beverages	4	11	9	8.8	20.0	11	13	17
		Fruit and vegetable meals	3	28	14	11.2	58.5	44	52	68
		Menu	1	124.1	–	–	–	–	–	–
		Baby formulas	12	11	8	2.4	28.7	14	17	22
Becalski *et al*. (2010)	2010	Baby foods	17	96	66	8.5	331	215	257	316

Table 2. Occurrence of furan in commercial infant foods analysed between 2004 and 2010*

Sample matrix	Numbers of samples in the range (μg kg^{-1})								Furan concentrations (μg kg^{-1})		
	<2	2–5	5–10	10–20	20–30	30–40	40–50	>50	Mean ± standard deviation (SD)	Median	95th percentile
Beverages	4	7	3	–	2	3	1	1	15.1 ± 19.3	4.4	37.7
Fruit/vegetables	18	31	14	17	21	21	11	16	21.5 ± 20.2	18.0	39.7
Menus	–	–	3	19	21	10	8	8	30.4 ± 16.4	27.0	32.1
Meats	–	5	2	–	–	–	–	2	21.6 ± 35.9	4.0	70.3
Porridges	5	5	3	2	–	1	–	–	6.1 ± 9.6	2.5	18.8
Infant formula	18	–	–	–	–	–	–	–	0.3 ± 0.3	0.6	0.6

*A subset of these results analysed between 2004 and 2007 was previously published (Lachenmeier *et al.* 2009).

Table 3. Intake of jarred commercial complementary food (g day^{-1}) in the consumer group

Age	Mean	Standard deviation (SD)	Median	10th percentile	90th percentile	95th percentile
Beverages (boys/girls)						
3 months	–/27.9	–/–	–/27.9	–/27.9	–/27.9	–/27.9
6 months	68.9/57.9	108.7/60.4	32.4/44.4	3.4/10.1	149.3/113.7	224.0/236.7
9 months	58.4/59.6	55.0/61.7	32.2/40.2	13.0/10.0	137.0/133.3	190.2/225.3
12 months	112.4/103.2	138.0/147.3	60.0/73.1	12.1/19.7	246.8/171.3	357.3/203.3
Fruits/vegetables (boys/girls)						
3 months	33.3/100.3	–/–	33.3/100.3	33.3/100.3	33.3/100.3	33.3/100.3
6 months	119.3/81.5	88.9/54.2	112.7/73.7	21.2/20.3	206.7/144.9	293.3/200.7
9 months	163.9/141.0	98.9/90.2	145.7/123.1	60.6/41.9	314.7/264.2	380.4/308.4
12 months	142.5/112.1	110.1/92.3	116.6/90.7	27.7/32.3	287.7/210.7	375.7/255.3
Menus (boys/girls)						
3 months	–/–	–/–	–/–	–/–	–/–	–/–
6 months	114.1/112.6	61.0/54.2	117.8/120.0	48.7/39.3	190.0/183.7	190.3/190.0
9 months	137.6/129.7	59.6/56.8	146.0/133.7	56.7/58.5	212.3/210.4	220.0/220.0
12 months	136.2/119.6	67.8/64.2	141.3/114.6	53.0/43.3	220.8/219.7	234.7/225.7
Meats (boys/girls)						
3 months	–/–	–/–	–/–	–/–	–/–	–/–
6 months	31.5/27.7	13.0/16.9	35.1/26.7	8.8/8.8	44.8/58.3	44.8/58.3
9 months	31.3/19.0	20.9/10.4	30.1/17.6	5.3/6.8	63.3/34.8	74.6/41.7
12 months	24.0/35.9	13.6/22.6	20.7/38.9	11.6/9.7	42.0/69.1	55.2/80.0
Porridges (boys/girls)						
3 months	–/–	–/–	–/–	–/–	–/–	–/–
6 months	118.6/56.4	73.2/47.8	126.7/61.0	41.7/6.0	187.3/127.3	187.3/127.3
9 months	62.2/58.2	50.7/32.6	61.5/55.0	10.3/29.9	172.5/126.7	172.5/126.7
12 months	80.0/98.8	62.8/59.5	63.7/71.0	25.8/33.7	182.2/173.3	229.7/173.3

ages were included in this value (Kersting *et al.* 1998). The use of this value without adjustment for beverages might therefore lead to an overestimation of furan exposure. The first effect (underestimation by inclusion of beverages) appears not as relevant if we, e.g. compare our values (without beverages) with the values of EFSA (all baby foods), which are nevertheless in good agreement (see discussion above). The second effect could be larger, especially in the 12-month group, as considerable amounts of baby beverages are consumed. Therefore, we have estimated the exposures for all groups separately in Tables 5 and 6, again separated into the consumer group and total sample. The average of all jarred

Table 4. Intake of jarred commercial complementary food (g day^{-1}) in the total sample

Age	Mean	Standard deviation (SD)	Median	10th percentile	90th percentile	95th percentile
Beverages (boys/girls)						
3 months	–/0.3	–/2.8	–/–	–/–	–/–	–/–
6 months	11.4/10.4	50.4/33.7	–/–	–/–	26.0/40.1	56.7/75.4
9 months	19.6/18.0	42.0/43.5	–/–	–/–	65.3/54.4	112.8/108.0
12 months	31.8/28.3	88.8/89.4	–/–	–/–	100.0/78.1	190.3/116.7
Fruits /vegetabless (boys/girls)						
3 months	0.4/1.0	3.5/10.2	–/–	–/–	–/–	–/–
6 months	68.8/51.6	89.6/58.4	29.8/34.1	–/–	184.2/132.8	240.3/161.8
9 months	142.3/119.7	107.6/97.3	129.3/102.5	–/–	279.2/251.3	364.6/304.8
12 months	103.8/84.2	113.4/93.5	63.3/60.3	–/–	253.6/193.9	361.6/232.6
Menus (boys/girls)						
3 months	–/–	–/–	–/–	–/–	–/–	–/–
6 months	44.3/47.3	67.4/65.8	–/–	–/–	162.4/171.8	188.3/180.6
9 months	84.0/79.4	81.8/77.4	67.0/63.3	–/–	205.7/196.7	215.3/213.0
12 months	85.0/66.5	85.1/76.4	73.3/43.3	–/–	211.0/190.0	227.0/220.0
Meats (boys/girls)						
3 months	–/–	–/–	–/–	–/–	–/–	–/–
6 months	1.1/1.7	6.2/7.7	–/–	–/–	–/–	–/10.3
9 months	3.6/1.7	12.1/6.3	–/–	–/–	10.0/–	31.0/16.7
12 months	1.8/2.3	7.3/10.5	–/–	–/–	–/–	16.7/12.5
Porridges (boys/girls)						
3 months	–/–	–/–	–/–	–/–	–/–	–/–
6 months	2.1/1.9	17.6/12.8	–/–	–/–	–/–	–/–
9 months	3.0/2.7	16.9/13.9	–/–	–/–	–/–	–/–
12 months	4.6/3.2	23.6/20.1	–/–	–/–	–/–	30.7/–

commercial foods (including beverages) was not calculated by a simple summation of the different groups, but rather by calculation of the individual exposure of any child in the DONALD study, averaging this data over all children. The difference between both calculation methods was negligible (data not shown), but we think that the individual calculation adds a further degree of accuracy and validity to our estimation.

Compared with our previous exposure estimation (Lachenmeier *et al.* 2009), based on occurrence data from 2004 to 2007 and using only averages and the old DONALD data (Kersting *et al.* 1998), no large differences to the current more detailed evaluation can be seen for the average values in the age groups 6, 9 and 12 months; e.g. we previously estimated an exposure of 0.5 μg kg^{-1} bw day^{-1} for the age group of 9 months and now have calculated it to be 645 ng kg^{-1} bw day^{-1}. Only for the age group of 3 months in the total sample did we previously overestimate the exposure (0.5 μg kg^{-1} bw day^{-1}), while the detailed DONALD data shows the consumption of jarred baby foods in this group is rather low (<10 ng kg^{-1} bw day^{-1}), but the exposure is however higher and relevant in the consumer group (182 ng kg^{-1} bw day^{-1}). However, it must be noted that only three children in this age group belonged to the consumer group (190 children in the total group). In the other age groups, most children belonged to the consumer group (6 months: 226/320, 9 months: 299/319, 12 months: 286/326). This high ratio of consumers explains the only very slight differences in the exposure calculations between both groups. The highest exposure occurs in the 9-month group, and may reach over 1 μg kg^{-1} bw day^{-1} for a P90 intake of food with average contamination level. Afterwards, the exposure again decreases, due to the fact that both bodyweight and the use of non-jarred foods increase.

This confirms the opinion of the German Federal Institute for Risk Assessment (BfR) (BfR 2009; Bakhiya & Appel 2010), which assumed the highest

Table 5. Exposure with furan for the consumer group (data from Table 2)

Intake	Exposure scenarios for different furan concentrations in the foods (ng kg^{-1} bw day^{-1})				
	Mean	Standard deviation (SD)	Median	P90	P95
Furan concentration	Mean/P95	Mean/P95	Mean/P95	Mean/P95	Mean/P95
Beverages*					
3 months	71/177	–/–	71/177	71/177	71/177
6 months	119/297	124/309	91/227	233/582	486/1212
9 months	107/266	110/275	72/179	238/595	403/1006
12 months	168/420	240/599	119/297	279/697	331/827
Fruits/vegetables*					
3 months	363/669	–/–	363/669	363/669	363/669
6 months	238/439	158/292	215/397	423/780	585/1080
9 months	359/662	229/423	313/578	672/1240	784/1447
12 months	260/479	214/395	210/388	488/901	592/1092
Menus*					
3 months	–/–	–/–	–/–	–/–	–/–
6 months	464/491	223/236	494/524	757/801	783/829
9 months	466/493	204/216	480/509	756/800	790/837
12 months	391/415	210/223	375/397	719/762	739/782
Meats*					
3 months	–/–	–/–	–/–	–/–	–/–
6 months	81/264	49/161	78/255	171/556	171/556
9 months	48/158	27/87	45/146	89/289	106/347
12 months	83/272	53/171	90/295	161/524	186/606
Porridges*					
3 months	–/–	–/–	–/–	–/–	–/–
6 months	47/144	40/122	51/155	106/324	106/324
9 months	42/129	24/72	40/122	92/281	92/281
12 months	65/200	39/120	47/144	114/351	114/351
Average, all jarred baby foods[†]					
3 months	182/351	181/320	87/173	391/721	391/721
6 months	521/795	326/514	495/713	893/1360	1072/1633
9 months	688/1066	412/627	677/971	1246/1917	1411/2141
12 months	576/896	418/683	486/763	1148/1854	1349/2137

*The values were calculated with the furan concentrations from Table 4 with the following assumptions: average bodyweights for females (3 months 5.9 kg; 6 months 7.4 kg; 9 months 8.5 kg; 12 months 9.3 kg). [†]Calculation by averaging over the individual exposure of each Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) subject (average for males and females).

furan exposure for a 9-month-old baby. The BfR calculated exposures as between 0.8 and 1.6 μg kg^{-1} bw day^{-1} for average consumers (average and P95 furan content, respectively), while the EFSA assumed a mean exposure of 1.01 μg kg^{-1} bw day^{-1}and a P95 exposure of 1.26 μg kg^{-1} bw day^{-1} for this age group. Based on a mean Finnish consumption figure (172 g day^{-1}) and their own analytical data, Jestoi *et al.* (2009) assumed furan exposures between 0.1 and 2.1 μg kg^{-1} bw day^{-1} for Finland. For Taiwan, the furan intake from infant formulas was assumed in the range of <0.05–0.56 μg kg^{-1} bw day^{-1}, while the intake from baby foods was estimated as equal to Europe, in the range of <0.11–3.42 μg kg^{-1} bw day^{-1} (median: 0.47 μg kg^{-1} bw day^{-1}) (Liu & Tsai 2010). All of these exposure estimations are in considerable agreement with our data. The only exception is the study of Kim *et al.* (2009a) from Korea, which reported a considerably lower exposure (17.4–84.9 ng kg^{-1} bw day^{-1}) based on the two food groups ‘powdered milk’ and ‘baby soup’, for which a comparably low intake of 13.5 and 3.0 g day^{-1} was assumed. The difference

Table 6. Exposure with furan in the total sample (data from Table 3)

Intake	Exposure scenarios for different furan concentrations in the foods [ng kg^{-1} bw day^{-1}]				
	Mean	Standard deviation (SD)	Median	P90	P95
Furan concentration	Mean / P95	Mean / P95	Mean / P95	Mean / P95	Mean / P95
Beverages*					
3 months	1/2	7/18	–/–	–/–	–/–
6 months	21/53	69/173	–/–	82/205	155/386
9 months	32/80	78/194	–/–	97/243	193/482
12 months	46/115	146/364	–/–	127/318	190/475
Fruits/vegetables*					
3 months	4/7	37/68	–/–	–/–	–/–
6 months	151/278	170/314	99/184	387/715	472/871
9 months	304/562	247/457	261/481	639/1179	775/1430
12 months	195/360	217/400	140/258	449/829	539/995
Menus*					
3 months	–/–	–/–	–/–	–/–	–/–
6 months	195/206	271/287	–/–	708/750	744/788
9 months	285/302	278/294	227/241	706/748	765/810
12 months	218/231	250/265	142/150	622/659	720/763
Meats*					
3 months	–/–	–/–	–/–	–/–	–/–
6 months	5/16	23/73	–/–	–/–	30/98
9 months	4/14	16/52	–/–	–/–	43/139
12 months	5/17	24/80	–/–	–/–	29/95
Porridges*					
3 months	–/–	–/–	–/–	–/–	–/–
6 months	2/5	11/33	–/–	–/–	–/–
9 months	2/6	10/31	–/–	–/–	–/–
12 months	2/6	13/41	–/–	–/–	–/–
Average, all jarred baby foods†					
3 months	3/6	29/55	–/–	–/–	–/–
6 months	368/562	363/564	317/519	848/1228	1004/1537
9 months	645/1000	432/660	623/893	1234/1895	1403/2106
12 months	506/786	435/704	418/634	1104/1766	1314/2004

*The values were calculated with the furan concentrations from Table 4 with the following assumptions: average bodyweights for females (3 months 5.9 kg; 6 months 7.4 kg; 9 months 8.5 kg; 12 months 9.3 kg). †Calculation by averaging over the individual exposure of each Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) subject (average for males and females).

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. In contrast, higher exposures were assumed for Canada (1.12 μg kg^{-1} bw day^{-1} on average for 1–4 years) than in Europe due to the considerably higher furan concentrations found in infant foods in that country (Becalski *et al.* 2010). This evaluation was, however, based on a comparably small sample (17 products from only two different producers).

All in all, based on our detailed exposure estimation and its correspondence to the data from other European countries, we judged the data adequate for the purposes of quantitative risk assessment.

Risk assessment of furan in baby foods

During our literature research, the recent paper of Carthew *et al.*, with detailed dose-response modelling data for furan, was identified (Carthew *et al.* 2010). The BMDL10 for hepatocellular tumours was 1.28 mg kg^{-1}

Table 7. Margin of exposure (MOE) for furan in the different exposure scenarios (MOE = BMDL10/exposure). Calculated with BMDL10 of 1.28 mg kg bw^{-1}day^{-1} from Carthew *et al.* 2010

Intake of complementary food	MOE for different exposure scenarios based on the average consumption of jarred commercial complementary foods (Tables 5 and 6)			
	Mean	Median	P90	P95
Furan concentration	Mean/P95	Mean/P95	Mean/P95	Mean/P95
Consumer group				
3 months	7022/3642	14 756/7388	3276/1775	3276/1775
6 months	2458/1609	2586/1795	1434/941	1194/784
9 months	1861/1200	1891/1319	1027/668	907/598
12 months	2221/1429	2632/1679	1115/690	949/599
Total sample				
3 months	444 716/230 681	–/–	–/–	–/–
6 months	3480/2278	4040/2466	1510/1043	1275/833
9 months	1986/1280	2054/1434	1037/675	912/608
12 months	2531/1629	3061/2020	1159/725	974/639

BMDL, benchmark dose lower confidence limit.

bw day^{-1}, and the T25 was 1.6 mg kg^{-1} bw day^{-1}. An earlier evaluation reported a T25 of 1.4 mg kg^{-1} bw day^{-1} (Sanner *et al.* 2001), which we previously used for our preliminary risk assessment (Lachenmeier *et al.* 2009). For this evaluation, we decided to apply the BMDL10 of 1.28 mg kg^{-1} bw day^{-1}, which is the preferred point of departure if both values are available (Benford *et al.* 2010). The MOE values based on this BMDL10 are shown in Table 7. With the exception of the 3-month-old children, all MOEs were below 10 000 in the total sample, reaching values below 1000 in the worst-case scenarios (P90 and P95). This evaluation has therefore fully confirmed our previous preliminary assessment, in which the MOEs were also below 10 000, a finding which signifies a potential public health concern for this contaminant (EFSA 2005). Other recent MOE studies similarly and consistently reported MOEs below 10 000, e.g. Carthew *et al.* (2010) based on FDA and EFSA data (MOE range 1000–4300) and Liu & Tsai (2010), using data from Taiwan (MOE range 352–8750).

As an alternative to the MOE approach, the US EPA (2003) oral reference dose (RfD) is worth mentioning. Notably, the exposures at P90 intake for the age groups 9 and 12 months may exceed the RfD of 1 μg kg^{-1} bw day^{-1} (noncarcinogenic effects). The RfD is based on the assumption that thresholds exist and was estimated based on a no observed adverse effect level from a 13-week study in mice and rats with application of an uncertainty factor of 1000. If an additional safety factor of 10 for exposures to children between 0 and 2 years of age as suggested by Barton *et al.* (2005) would be applied, even the mean intake scenarios would exceed the RfD. While we prefer the MOE over the RfD approach for furan as a possible genotoxic carcinogen, it nevertheless further strengthens the potential public health concern.

In comparison with our previous assessment (Lachenmeier *et al.* 2009), the current study has improved quality because of its use of more detailed exposure and intake calculations, the confirmation of our furan ranges by other studies from Europe and worldwide as well as the use of BMDL10 instead of T25. We agree with Carthew *et al.* (2010) that the variability of furan levels within a food type is small, so additional measurements will not affect exposure greatly. In infant foods, at least for the jarred complimentary foods, the available analytical data appear to allow for a valid MOE calculation. Only for formulas, more analyses appear to be needed to improve the estimation for the age group below 3 months.

Limitations of the risk assessment

Several authors, even in the most 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 & Tsai 2010). If this would really result in a considerable evaporation of furan, and parents would adhere to this practice, this would basically invalidate all exposure assessments in the literature (including ours), which are typically based on analytical values of closed, untreated jars.

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). Other researchers found that furan persists during the normal heating practices that precede consumption (Hasnip *et al*. 2006). This was confirmed by several studies (Crews & Castle 2007; Roberts *et al*. 2008; Lachenmeier *et al*. 2009; Van Lancker *et al*. 2009; Kim *et al*. 2009b), which indicated only minor losses (generally below 30%) or even an increase of furan content during heating. Furan appears to be well dissolved within the matrix of infant food, and opening the jars exposes only a relatively small surface area (Lachenmeier *et al*. 2009). Van Lancker *et al*. (2009) have shown that the retention of furan in baby foods may also depend on fat content, as the highest retention was found in baby foods with added oils. The literature therefore consistently shows that a considerable evaporation of furan does not occur during normal warming of baby jars, and – in contrast to the initial assumptions – furan is retained to a relatively high degree. For this reason, the use of our analytical data of the closed untreated jars appears to be useful for an initial exposure estimate. Regarding the magnitude of our MOE values, the interpretation would not change even if we were to assume a 30% evaporation during food preparation; the values would still be below the threshold of 10 000.

A further limitation of our study includes the fundamental appropriateness of the MOE approach to evaluating furan. Generally, the MOE approach is currently preferred in assessing genotoxic carcinogens, and several authors used it in the past for evaluating furan (Lachenmeier *et al*. 2009; Benford *et al*. 2010; Carthew *et al*. 2010; Liu & Tsai 2010). Only Bakhiya & Appel (2010) suggested it as inappropriate to elucidate the risk associated with furan exposure with certainty. They specifically pointed out the lack of data in the relevant low-dose range, especially in rats as the more sensitive species below 2 mg kg^{-1} bw day^{-1}, a range in which only data from mice are available (Moser *et al*. 2009). A further limitation in the MOE approach concerns the choice of tumour type for modelling (Carthew *et al*. 2010). Furan caused cholangiocarcinomas in rats at considerably lower dose levels than hepatocellular adenomas and carcinomas; however, the data for cholangiocarcinomas were inappropriate for dose-response modelling due to considerably broad confidence limits leading to very low BMDL10 values (0.000723 mg kg^{-1} bw day^{-1}) (Carthew *et al*. 2010). While the use of such a value for cholangiocarcinomas is very likely to overestimate the cancer risk, the use of our point of departure (hepatocellular tumours) may similarly underestimate the risk if the mechanism for causing cholangiocarcinomas at low doses would be relevant for humans. Furthermore, the relevance of a genotoxic mechanism at low doses needs to be elucidated, as the mice study pointed to a threshold for the induction of hepatic tumours, which is mechanistically plausible as the genotoxicity of *cis*-butene-1,4-dial, the active metabolite of furan, is thought to play only a minor role in the lower relevant dose range, similar to other reactive aldehydes (Bakhiya & Appel 2010). The recent industry-funded studies of Hickling *et al*. (2010a,b) using a single very high dose level (30 mg kg^{-1} bw) supported the hypothesis that the cholangiocarcinomas may be due to oxidative stress, a non-genotoxic mechanism.

Fundamental toxicological studies are therefore necessary to elucidate the mode of action as well as the relevance to humans (Carthew *et al*. 2010). Jestoi *et al*. (2009) also remarked that while a rising cancer trend among children in various organs was evident, this was not the case for hepatic tumours (Kaatsch *et al*. 2006), the probable target site of furan. In our opinion, this constitutes no clear evidence for the absence of a health risk of furan, as it is extremely difficult to design adequate studies capable of credibly demonstrating risks of low or medium levels

(Lachenmeier 2009). The probability that additional epidemiological data will become available in the near future on compounds assigned to IARC group 2B was described to be rather remote (Tomatis 2006).

While we basically agree with Bakhiya & Appel (2010) and Jestoi *et al*. (2009) that it would be preferable to have additional data from either animal experiments or even epidemiology, we still think in line with the other authors (Benford *et al*. 2010; Carthew *et al*. 2010; Liu & Tsai 2010), that it would not be prudent for public health protection – especially for children – to ignore the available data and wait for the slim chance that additional data will become available.

Concluding remarks

One of the advantages of the MOE is the comparability between different agents and exposures for risk management prioritization. As the approach is relatively new, no systematic data are currently available for contaminants in baby foods. For acrylamide, for example, based on a median (maximum) intake ranging from 0.19–0.45 (0.91–2.04) μg kg^{-1} bw day^{-1} (Hilbig & Kersting 2006) and a BMDL10 of 0.16 mg kg^{-1} bw day^{-1} (Bolger *et al*. 2010), the MOE would be in the range of 842–355 (175–78). This shows that the MOE of furan is in the same order of magnitude as that of acrylamide (or even lower if the BMDL10 for cholangiocarcinomas had been used), which would therefore justify similar mitigative measures as conducted in the past for acrylamide. In contrast, the MOE of benzene in carrot juices for infants has been consistently above 100 000 (Lachenmeier *et al*. 2010), so we would suggest this agent as least significant for mitigative measures. Interestingly, all three substances (i.e. furan, acrylamide and benzene) are formed as heat-induced contaminants in commercial infant foods, so improving sterilization conditions might simultaneously avoid all three.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions

DWL conceived of the study and drafted the manuscript; EM conducted the literature review and summarized the analytical data; HR supervised sampling and coordinated the analyses; TK developed the original HS-GC/MS methodology and supervised the measurements; MK and UA provided the data from the DONALD study and conducted the intake and exposure calculations; EM, TK, HR, MK and UA revised the manuscript; all authors read and approved the final manuscript; DWL has primary responsibility for final content.

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