Food and Chemical Toxicology 48 (2010) S69–S74

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Application of the margin of exposure (MoE) approach to substances in food that are genotoxic and carcinogenic
Example: Furan (CAS No. 110-00-9)

Philip Carthew [a,*], Michael DiNovi [b], R. Woodrow Setzer [c]

[a] Unilever Research, UK
[b] US Food and Drug Administration, USA
[c] US Environmental Protection Agency, USA

ARTICLE INFO

Article history:
Received 8 June 2009
Accepted 12 October 2009

Keywords:
Furan
Margin of exposure
MoE

ABSTRACT

Furan is commonly found in foods such as coffee, canned and jarred foods, including baby food containing meat, and various vegetables. It is thought to be formed by the thermal decomposition of carbohydrates. Furan is carcinogenic in rodents, although the detailed mechanism of action has not been completely established, for all the tumour types induced. Dose–response modelling of the data for hepatocellular tumours gives a BMDL10 of 1.23 mg/kg/day, and MOEs of between 750 and 4300 for exposures of infants and adults.

1. Toxicological data

1.1. Genotoxicity

Furan induced gene mutations, (NTP, 1993) chromosome aberrations and sister chromatid exchanges (SCEs) in cultured mammalian cells (Stich et al., 1981; NTP, 1993) and chromosomal aberrations in mice bone marrow cells (NTP, 1993). Cis-2-butene-1,4-dial has been identified as a key reactive and cytotoxic metabolite of furan (Chen et al., 1995). Cis-2-butene-1,4-dial induced gene mutations in bacterial cells, DNA single-strand breaks and DNA cross-links in cultured mammalian cells. Cis-2-butene-1,4-dial can react with deoxyribonucleotides *in vitro* to form unstable DNA adducts (Byrns et al., 2002). The European Food Safety Authority (EFSA) Contaminants Panel concluded in 2004 that taking into account all the presently available data on the mode of action of furan, the weight of evidence indicates that furan-induced carcinogenicity is probably attributable to a genotoxic mechanism (EFSA, 2004).

A review of the available genotoxicity data on furan in 2005 resulted in the UK Committee on Mutagenicity (UK COM) concluding that furan should be regarded as an *in vitro* mutagen, but there was insufficient evidence to reach a conclusion on its genotoxicity *in vivo* on the available *in vivo* mutagenicity data (UK COM, 2005). The key *in vivo* bone marrow chromosomal aberration assay was undertaken as part of the National Toxicology Program (NTP) programme on furan; however the data from this study could not be interpreted with certainty because of the confounding effects of toxicity at the dose level used.

1.2. Carcinogenesis

Furan is carcinogenic to rats and mice, showing a dose-dependent increase in hepatocellular adenomas and carcinomas in both sexes. In rats, a dose-dependent increase in mononuclear leukaemia was seen in both sexes. A very high incidence of cholangiocarcinoma of the liver was present in both sexes, even at the lowest dose tested.

Although the EFSA Contaminants Panel considers that the presently available data on the mode of action of furan, indicates that furan-induced carcinogenicity is probably attributable to a genotoxic mechanism, it was considered that chronic toxicity with secondary cell proliferation may promote the liver tumour response. Furan is undoubtedly a multi-site carcinogen in both sexes of rats and mice.

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

* Corresponding author. Address: ILSI Europe, Avenue E. Mounier 83, B6 1200 Brussels, Belgium. Tel.: +32 2 771 00 14; fax: +32 2 762 00 44.
E-mail address: publications@ilsieurope.be

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doi:10.1016/j.fct.2009.10.017

1.3. Mode of action

The mode of action (MOA) of carcinogenicity may differ in rats and mice. This will have a significant effect in choosing the dataset for evaluation in the MOE.

As stated previously the UK COM did not think the evidence for *in vivo* mutagenicity was sufficient to demonstrate that it was an *in vivo* mutagen, however EFSA considered that it should be regarded as such, presumably using the precautionary principle.

In rats, the liver tumours do occur at very high incidence and low dose, which is characteristic of a genotoxic MOA, however the mouse tumours have been regarded by most authors as being the result of a cytotoxicity driven proliferation in the liver. Recently, Moser et al. (2009) have tried to clarify this by correlating the dose response for bromodeoxyuridine (BrdU) labelling index in hepatocytes of short-term (3 weeks) furan treated animals to the threshold for tumours. This has not supported the hypothesis that the mode of action is driven entirely by cytotoxicity and regenerative hyperplasia, as the increase in BrdU labelling index was not significantly increased below 8 mg/kg-bw, although cytotoxicity was increased at an exposure level of 1 mg/kg-bw and above, both for the 3 week and 2 year studies. Tumour occurred at exposures of 4 mg/kg-bw and above.

More recently, Durling et al. (2007) used a flow cytometer-based micronucleus assay in mice and the cytokinesis-block micronucleus assay in human lymphocytes to investigate the genotoxic potential of furan. Three *in vivo* experiments were performed: intraperitoneal or subcutaneous injection of furan in male Balb/C mice (0–300 and 0–275 mg/kg body weight, respectively) and intraperitoneal injection of male CBA mice (0 and 225 mg/kg body weight). No increased level of micronucleated erythrocytes was detected in any of the *in vivo* experiments. In the *in vitro* studies, human lymphocytes from two donors were treated with furan in concentrations from 0 to 100 mM, either with or without metabolic activation (liver homogenate from rat). There was no significant increase in the frequency of micronucleated cells in the *in vitro* human lymphocyte studies. The authors concluded that as neither the *in vivo* nor the *in vitro* studies demonstrated any significant increase in the micronucleus formation with furan their results indicate that the carcinogenicity of furan is mediated caused by a non-genotoxic mode of action.

Until some more definitive work with transgenic rats is carried out, to examine whether the potential mutagenic action of furan is expressed in the target tissues for tumour induction, the question of whether the MOA is reliant on genotoxicity as a key event remains unresolved. There is also the uncertainty as to whether the rat or the mouse is the more appropriate model for the possible carcinogenic effects in man.

1.4. Epidemiological data

None identified.

1.5. Dose–response relationships

Rat studies

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 for 2 years with interim kills of 10 rats per group after 9 and 15 months (NTP, 1993). Mean body weights of male rats that received 8 mg/kg furan 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 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 Table 1).

Table 1
Summary of dose response for tumours in furan 2-year rat bioassay.

Rat	Dose mg/kg/day			
	0	2	4	8
Male				
2-Year survival	33/50	28/50	26/50	16/50
Cholangiocarcinoma	0/50	43/50	48/50	49/50
Hepatocellular adenoma or carcinoma	1/50	5/50	22/50	35/50
Mononuclear cell leukaemia	8/50	11/50	17/50	25/50
Female				
2-Year survival	34/50	32/50	28/50	19/50
Cholangiocarcinoma	0/50	49/50	50/50	48/50
Hepatocellular adenoma or carcinoma	0/50	2/50	4/50	8/50
Mononuclear cell leukaemia	8/50	9/50	17/50	21/50

A separate stop-exposure study, of up to 2-years was conducted in which 50 male rats were administered 30 mg/kg furan in corn oil by gavage 5 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 two males at the 15-month interim evaluation.

Mouse studies

In the 2-year mice study, animals of each sex ($n = 50$) received doses of furan of 8 or 15 mg/kg-bw 5 days per week for 2 years (NTP, 1993). Mean body weights of male and female mice that received 15 mg/kg furan 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 Table 2).

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/kg-bw furan, but not in mice dosed with 0.5, 1.0, or 2.0 mg/kg-bw furan (Goldsworthy et al., 2001).

1.6. Data quality, uncertainties and limitations

An important consideration in the modelling of the dose response for the rat and mouse studies with furan is the uncertainty in estimating the BMDL, given that the rat data shows such high incidences of liver tumours, even at the lowest dose, the uncertainty in the BMDL will be considerable. Having said that the BMDL

Table 2
Summary of dose response for tumours in furan 2-year mouse bioassay.

Mouse	Dose mg/kg/day		
	0	8	15
Male			
2-Year survival	33/50	17/50	16/50
Hepatocellular adenoma or carcinoma	26/50	44/50	50/50
Adrenal medulla benign pheochromocytoma	1/49	6/50	10/50
Female			
2-Year survival	29/50	25/50	2/50
Hepatocellular adenoma or carcinoma	7/50	34/50	50/50
Adrenal medulla benign pheochromocytoma	2/50	1/50	6/50

(or T25) will certainly be lower for the rat data than the mouse. While the mouse data can probably be modelled to give a less uncertain estimate of the BMDL, it is by no means certain that this data is appropriate for a genotoxic carcinogen, since there are significant questions remaining about the MOA in mice. The object of the current exercise with deriving the MOE is to select data that is derived from animal data where the MOA for tumour development is at least partly considered genotoxic in nature. Deriving an MOE using both sets of data will certainly be interesting and will highlight the dependency of the result on an understanding of the MOA, and especially the relevance of it to human exposure.

It may also encourage the prioritisation of some MOA studies with furan to resolve whether it is an *in vivo* mutagen and therefore a site-specific genotoxic carcinogen.

2. Human dietary exposure analysis

2.1. Sub-populations of interest

Infants may have an increased susceptibility to furan carcinogenesis, considering the liver is a tumour site in animals and the rate of cell proliferation in the developing liver may increase the subsequent risk of liver cancer (EPA, Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens, 2005).

2.2. Concentration in food

The United States Food and Drug Administration (US FDA) has published on its website its findings, derived over the 2004–2006 time period, on the occurrence of furan in various foods (US FDA, 2007a). Furan has been detected in a large number of food types at levels ranging from below the level of detection (LOD) to approximately 175 μg/kg. Canned soups, pastas, and sauces (gravies) made with meat typically show the highest levels. Due to the volatility of furan, however, heating of these products in open containers may result in a much lower exposure to the food as consumed. Brewed coffees are also uniformly high, with levels up to approximately 100 μg/kg. Jarred baby foods consistently showed furan levels of 10–100 μg/kg, with mixtures of meat and vegetables having the highest levels. Fresh fruits and vegetables show little or no furan. Irradiation of cut, fresh fruits and vegetables produces low levels of furan, typically less than 5 μg/kg (US FDA, 2007a). Data published by the Swiss Federal Office of Public Health were consistent with the published US FDA data (Reinhard et al., 2004). Coffee powders had very high levels of furan, however, ranging from 2650 to over 5000 μg/kg. The coffee beverages prepared from these powders had furan levels ranging from 3 to 25 μg/kg. A recent publication from the Swiss Federal Office of Public Health (Zoeller et al., 2007) confirms these findings. An addition report on levels of furan in foods has been published by EFSA (EFSA, 2009). This analysis confirms and extends the data published by FDA. Levels of furan in most foods were similar to that reported in the FDA analysis. Significantly, roasted coffee, which can be prepared and consumed in a different manner to that in the US, showed higher levels of furan in the European analysis, up to 5 mg/kg in beans, with an average of approximately 1 mg/kg in ground coffee. Instant coffee showed lower levels, approximately 600 μg/kg. Data on levels in brewed coffee were not included. In infant formula, the mean level was 8 μg/kg; in jarred food the mean was 25 μg/kg.

2.3. Dietary exposure

National estimates

The US FDA has prepared an estimate of dietary exposure to furan (US FDA, 2007b). Mean dietary exposure was reported to be 0.26 μg/kg-bw/day with a 90th percentile of 0.61 μg/kg-bw/day.

Table 3
Overall Summary of BMDs and BMDLs for tumour types induced by Furan.

	BMD10	BMDL10	BMD05	BMDL05	BMD01	BMDL01
Cholcarc@2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Cholcarc@1	0.0512	0.000723	0.0170	0.000049	0.000788	0.00001
Hepaadencarc@3	1.888	0.681	0.9810	0.3413	0.2033	0.0646
Hepaadencarc@1	1.840	1.277	1.282	0.729	0.5514	0.2323
Monoleuk@1	2.329	1.149	1.314	0.4236	0.3366	0.0536
Monoleuk@2	2.700	1.261	1.483	0.4325	0.3682	0.0252
Hepaadencarc@4	3.792	1.947	2.484	1.139	0.6953	0.2776
Hepaadencarc@2	5.449	3.899	2.954	1.611	0.6979	1.01
Adrepheo@3	9.110	5.053	4.961	1.001	1.142	0.0000
Adrepheo@4		11.28		5.493		1.076

Data sets codes: F344 rats male 1, F344 rats female 2, B6C3F1 mice, male 3, B6C3F1 mice, female 4.
Tumour type codes:
Adrepheo – adrenal gland pheochromocytomas
Cholcarc – cholangiocarcinoma
Hepaadencarc – liver adenoma or carcinoma (combined)
Monoleuk – mononuclear cell leukaemia.

Table 4
Furan male rat hepatocellular adenoma or carcinoma combined.

Model	*P* value	ll	AIC	BMD10	BMDL10	BMD05	BMDL05	BMD01	BMDL01
Log-probit	0.291	−86.56	179.1	1.922	1.340	1.456	0.9183	0.865	0.4518
Log-logistic	0.236	−86.71	179.4	1.846	1.234	1.306	0.766	0.607	0.264
Weibull	0.112	−87.29	180.6	1.641	1.000	1.040	0.530	0.370	0.126
Multistage	0.078	−87.58	181.2	1.565	0.872	0.894	0.426	0.212	0.083
Gamma	0.152	−87.04	180.01	1.775	1.078	1.212	0.603	0.533	0.163
Logistic	0.027	−89.70	183.4	2.185	1.806	1.320	1.038	0.329	0.239
Probit	0.046	−89.07	182.1	2.063	1.711	1.238	0.973	0.310	0.223
Average model	0.139			1.840	1.277	1.282	0.729	0.551	0.232

Brewed coffee was the largest contributor to the total population mean. Dietary exposure from baby foods (for 0–1 year olds) was 0.41 μg/kg-bw/day at the mean, and 0.99 μg/kg-bw/day at the 90th percentile. Dietary exposure from the consumption of infant formula as sole source of nutrition was estimated to be 0.9 μg/kg-bw/day. Dietary exposure derived using the European data showed a higher dietary exposure for furan. The most conservative estimate was 0.78 μg/kg-bw/day at the mean, with 95th percentile exposure at 1.75 μg/kg-bw/day. Considering potential reductions in furan from preparation of coffee reduces these figures to 0.53–0.66 μg/kg-bw/day at the median and 1.19–1.47 μg/kg-bw/day at the 95th percentile. Infant exposures were estimated to range from 0.3 μg/kg-bw/day to 1.0 μg/kg-bw/day. The European report concludes that the estimate of dietary exposure to furan will likely be reduced by analysis of addition food data.

International estimates

Because furan is produced in many complex processed food product mixtures, and is not commonly found in raw agricultural commodities, the use of the GEMS/Food database to prepare international estimates of dietary exposure is not indicated.

2.4. Dietary exposure assessment (values to be used in the MOE calculation)

The large number of analysed food types and the availability of good food consumption data from the US FDA analyses support 0.3 μg/kg-bw/day as the low end of the exposure range and 1 μg/kg-bw/day as the higher end of the range of dietary exposures to furan over a lifetime in the USA, and for Europe, recent estimates

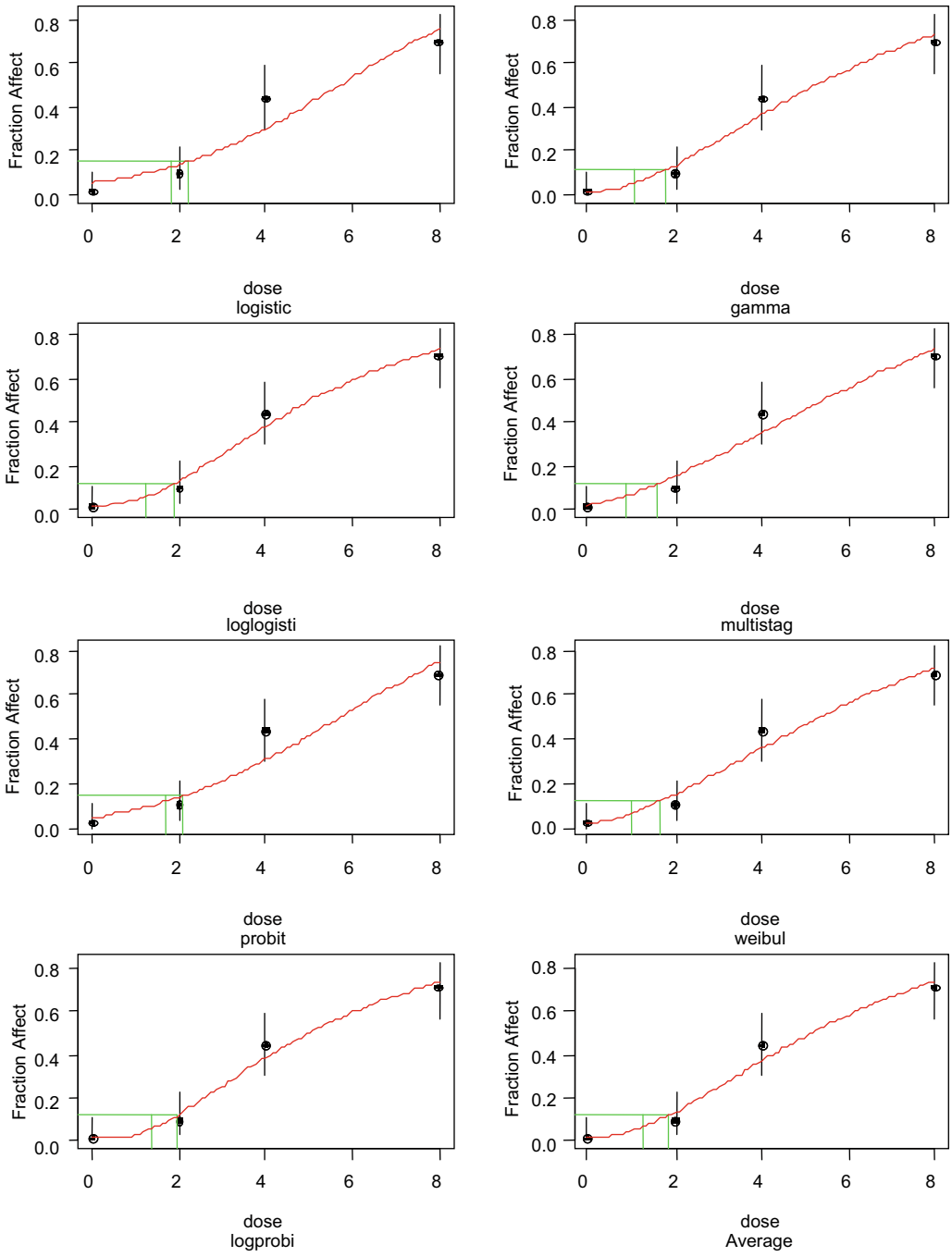

Fig. 1. Benchmark dose modelling for hepatocellular adenoma or carcinoma combined, in male rats exposed to furan, using the various individual models.

support the use of 0.8 μg/kg-bw/day as the low end of the exposure range and 1.75 μg/kg-bw/day as the higher end of the range.

2.5. Data quality, uncertainties and limitations

Conclusions on variability and uncertainty

The variability of furan levels within a food type is small so additional measurements will not affect exposure greatly.

The number of food types tested is currently limited (Reinhard et al., 2004; Zoeller et al., 2007; US FDA, 2007a,b; EFSA, 2009) and further measurements in additional food types will refine the overall exposure estimates and reduce uncertainty in exposure.

3. Modelling

3.1. Furan summary of BMD and BMDL values (Table 3)

For male F344 rats the model average *P* value was 0.68 for the BMD_{10}s for cholangiocarcinoma. The model average $BMDL_{10}$ for cholangiocarcinoma in male rats was 0.0012, while the other models produced a range from 0–0.367. For liver adenomas and carcinomas (combined) the logprobit, loglogistic, gamma and Weibull models all gave *P* values of >0.1, with a model average *P* of 0.14 (for all models) and a model average $BMDL_{10}$ of 1.28 mg/kg/day. For male rat mononuclear cell leukaemia all of the models gave *P* values >0.1 with a model average of the $BMDL_{10}$ of 1.1 mg/kg/day.

For male B6C3F1 mice, the *P* values for liver adenoma and carcinoma (combined) were all above 0.1, however the $BMDL_{10}$s ranged from 0.42 to 1.85 mg/kg/day, with a model average of 0.7 mg/kg/day. The male mouse adrenal gland pheochromocytomas had a higher $BMDL_{10}$ average of 5 mg/kg/day.

For female rats, there was difficulty fitting any of the models to the tumour data and a model average BMDL could not be derived. The *P* values for liver adenoma and carcinoma (combined) derived for female rats were all above 0.1, with a model average of 0.842, however the $BMDL_{10}$s were all in the range of 4.8–6.5 mg/kg/day, with a model average of 3.8 mg/kg/day.

For mononuclear cell leukaemia in female rats, the *P* values were similar and all above 0.1, giving $BMDL_{10}$s in the range 1.4–2.3 with a model average of 1.2 mg/kg/day.

There was a wide range of *P* values for B6C3F1 female mouse liver adenoma and carcinoma (combined), between 0.14 and 0.99. The model average *P* was below 0.1 (0.086) and the model average $BMDL_{10}$ was 2 mg/kg/day. This was not considered suitable for use in deriving an MOE.

Using the tumour type from the sex and species with the lowest $BMDL_{10}$, would mean selecting the male rat cholangiocarcinoma $BMDL_{10}$ (0.0012 mg/kg/day) as the value to use in deriving the MOE. However, the cholangiocarcinomas induced by furan in the rat are most likely derived by a mechanism involving oxidative stress and indirect DNA damage rather than a direct acting genotoxic carcinogen which is the scope of the present exercise (Hickling et al., 2009a,b). This is based on the pathogenesis of the tumours in rats involving cholangiofibrosis and mucin secreting and intestinal metaplastic glands, which are thought to indicate a non-genotoxic mode of action.

A similar case of a non-genotoxic mechanism has been proposed for the hepatocellular tumour in furan treated mice, where the proposed MOA is thought to involve prolonged cytotoxicity, causing regenerative hyperplasia leading to tumour formation. Interestingly, an analysis of the threshold for liver cytotoxicity and cell proliferation compared to the threshold for tumour development does not show that increased hepatocellular proliferation occurs at the threshold for tumour development (Moser et al., 2009).

The leukaemia found in both male and female rats are a tumour type that occurs naturally in the F344 rat and are unlikely to be induced by a genotoxic mode of action.

Table 5
Summary of the range of MOEs for adult exposure (>2 years) to furan using the $BMDL_{10}$s for male rat liver adenomas and carcinomas.

1. Points of departure derived for MOE calculation Tumours	BMD_{01}[a]	$BMDL_{01}$[a]	BMD_{05}[a]	$BMDL_{05}$[a]	BMD_{10}[a]	$BMDL_{10}$[a]	T25[b]
Male rat liver adenoma and carcinoma[c]	0.551	0.232	1.282	0.729	1.84	1.277	1.6

2. Calculated MOEs for hepatocellular adenoma and carcinoma (combined) for child and adult exposure (>2 years)	MOE for $BMDL_{01}$	MOE for $BMDL_{05}$	MOE for $BMDL_{10}$	MOE for T25
US exposure estimate[d] (μg/kg-bw/day)				
Average (50%)[d] 0.3 μg/kg-bw/day	800	2400	4300	5300
High level (90%)[d] 0.6 μg/kg-bw/day	400	1200	2100	2650
European exposure estimate[e] (μg/kg-bw/day)				
Average (50%)[e] 0.8 μg/kg-bw/day	300	900	1600	2000
High level (95%)[e] 1.75 μg/kg-bw/day	150	400	750	900

3. Calculated MOEs for hepatocellular adenoma and carcinoma (combined) for infant exposure (0–1 year)	MOE for $BMDL_{01}$	MOE for $BMDL_{05}$	MOE for $BMDL_{10}$	MOE for T25
US exposure estimate[f] (μg/kg-bw/day)				
Average (50%)[f] 0.4 μg/kg-bw/day	600	1800	3000	4000
High level (90%)[f] 1 μg/kg-bw/day	230	700	1000	1600
European exposure estimate[g] (μg/kg-bw/day)				
Average (low)[g] 0.3 μg/kg-bw/day	800	2400	4300	5300
High level (high)[g] 1 μg/kg-bw/day	230	700	1000	1600

[a] Model average doses in mg/kg-bw/day.
[b] Derived from dose of 2.9 mg/kg/day.
[c] Observed dose ranges and source 2–8 mg/kg-bw/day (NTP, 1993).
[d] Available at: <http://www.fda.gov/OHRMS/DOCKETS/ac/04/slides/2004-4045s2.htm>.
[e] Available at: <http://www.efsa.europa.eu/cs/BlobServer/Report/datex_report_furan_en.pdf?ssbinary=true>.
[f] Available at: <http://www.fda.gov/OHRMS/DOCKETS/ac/04/slides/2004-4045s2.htm>.
[g] Available at: <http://www.efsa.europa.eu/cs/BlobServer/Report/datex_report_furan_en.pdf?ssbinary=true>.

The most likely tumour type to be induced by a possible genotoxic mechanism would be the hepatocellular adenomas and carcinomas in the rat. The lowest BMDL for this tumour type was therefore selected for deriving the MOEs in Table 3.

This was the male rat hepatocellular adenoma and carcinoma with a model average $BMDL_{10}$ of 1.28 mg/kg/day (Table 4).

The corresponding figures for these models for hepatocellular adenoma or carcinoma in male rats combined are plotted in Fig. 1.

3.2. T25 calculation

The T25 (Dybing et al., 2008) for furan was derived from the male rat hepatocellular adenoma and carcinoma data, using the mid dose value of the tumour incidence (22/50, 44%) in the 4 mg/kg/day group. The control incidence was 1/50 (2%). The T25 is derived as increased risk in male rats $(44-2)/100-2)/100 = 42.9\%$. T25 = 25/42.9 × 4 mg/kg/day = 2.3 mg/kg/day.

Exposure correction for dosing 5 days week for 2 years. Corrected dose = 5/7 dose from T25.

$$\text{Corrected T25} = 5/7 \times 2.3 = 1.6\,\text{mg/kg/day}.$$

3.3. MOE calculations

See Table 5.

3.4. Modelling limitations

The major modelling limitation concerns the appropriate choice of species and tumour type. Clearly, if the cholangiocarcinoma data was modelled, the MOE would have been even lower than that obtained with the hepatic adenoma and carcinomas combined. The $BMDL_{10}$s for rat and mouse hepatic adenomas and carcinomas did not differ greatly, so the BMDLs were not heavily model dependant for these tumours for either species.

4. Learning points

The choice of the tumour to be modelled significantly affects the BMDL and therefore the derived MOE. There was little difference to the derived MOE from using the mouse rather than the rat liver tumour data.

The MOEs derived clearly indicate that it is now a priority to understand the mode of action for the development of the liver tumours in the rat after exposure to furan and whether this is relevant to man. The MOE values derived from the mouse data are also a cause for concern, unless the mode of action in the mouse is accepted as being dependent on a thresholded mechanism, based on the rate limiting step of cytotoxicity and compensatory liver regeneration, rather than a genotoxic mechanism in the liver.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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