EFSA STATEMENT

EFSA statement on the presence of 4-methylbenzophenone found in breakfast cereals

(Question No EFSA-Q-2009-410)

Issued on 4 March 2009

SUMMARY

On 2 February 2009, the German authorities have notified through the Rapid Alert System for Food and Feed the migration of 4-methylbenzophenone from packaging into certain cereal products, in a concentration of 798 micrograms/kg. The Belgian Authorities have also provided data later in February, reporting concentrations of 4-methylbenzophenone in cereals up to 3729 µg/kg.

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission has asked the European Food Safety Authority to evaluate if the substance 4-methylbenzophenone would be covered by the TDI on benzophenone and hydroxybenzophenone and evaluate the risk of the presence of 4-methylbenzophenone found in cereals by 3 March 2009. In addition the Commission has asked EFSA to re-asses the TDI on benzophenone and hydroxybenzophenone in view of the new toxicological studies available, by end of May 2009. Concerning the first request on 4-methylbenzophenone, EFSA has informed the Commission that due to such a short timeline, it is only able to publish an EFSA statement on the issue rather than a CEF Panel opinion. Concerning the second request on the TDI on benzophenone and hydroxybenzophenone, the CEF Panel is expected to adopt an opinion by the end of May 2009.

4-Methylbenzophenone is used as a photo-initiator of UV-cured printing inks and lacquers applied on the surface of the packages, mainly cardboard boxes. 4-Methylbenzophenone may be used in combination with or as replacement of benzophenone. Given their volatility, both substances may migrate into the package and contaminate even solid foodstuffs.

In the literature, there is very little information useful for the toxicological assessment of 4-methylbenzophenone itself. Much more information is available on benzophenone, which has a very similar structure.

There is insufficient direct evidence available on the genotoxicity of 4-methylbenzophenone. However, based on structural considerations and experimental results on the structurally related benzophenone, it can be concluded that 4-methylbenzophenone does not raise concern for genotoxicity.

4-Methylbenzophenone is expected to be metabolised by the same metabolic pathways as benzophenone, with the addition of oxidation of the 4-methyl group to the corresponding alcohol and further oxidation to the carboxylic acid with its glycine and glucuronide conjugates.

Like benzophenone, 4-methylbenzophenone is expected to be a non genotoxic carcinogen.

Due to the lack of toxicity data for 4-methylbenzophenone and to the specific metabolic pathway, it is currently not scientifically sound to include 4-methylbenzophenone into the group-TDI for benzophenone and hydroxybenzophenone. Therefore at present a TDI cannot be derived for 4-methylbenzophenone.

For the purpose of addressing this urgent request for advice to risk managers, the Margin of Exposure (MoE) approach is proposed. An uncertainty factor of two is considered appropriate for read-across from benzophenone.

Benzophenone has been studied in subchronic (90-day) and chronic studies. In the latter, liver tumours were observed at a LOAEL of 15 mg/kg b.w. per day. In a two-generation study with benzophenone, livers of parental animals showed adverse effects, which could be related to the carcinogenicity in the chronic assay. From this study a LOAEL of 6 mg/kg b.w. per day could be derived.

This LOAEL is used as a basis for calculation of the MoE for 4-methylbenzophenone. A factor of 100 for inter- and intraspecies differences in sensitivity, a factor of 3 for use of a LOAEL (instead of a NOAEL) and a factor of 2 for read-across from benzophenone to 4-methylbenzophenone are applied. Hence the estimated MoE should be greater than 600. The MoE is calculated by dividing the LOAEL (6 mg/kg b.w. per day) by the estimated exposure in each case.

Based on analytical results from 17 samples of breakfast cereals as provided by the Belgian Authorities (AFSCA, 2009), exposure estimates to 4-methylbenzophenone were derived for children and adults according to a conservative and to a highly conservative scenario. Both scenarios are based on the highest consumption of breakfast cereals as registered in Ireland: 2.45 g/kg b.w. per day for children and 0.96 g/kg b.w. per day for adults (Table 2). The conservative scenario assumes average concentration of 4-methylbenzophenone as calculated from the results on the 17 samples from the Belgian market whilst the highly conservative scenario assumes the maximum concentration found in these samples.

For children the conservative scenario leads to a dietary exposure via breakfast cereals of 2 µg 4-methylbenzophenone /kg b.w. per day. The highly conservative scenario for children leads to a dietary exposure via breakfast cereals of 13.2 µg 4-methylbenzophenone/kg b.w. per day.

For adults the conservative and the highly conservative scenarios lead to dietary exposures via breakfast cereals of 0.79 and 5.2 µg of 4-methylbenzophenone /kg b.w. per day, respectively.
In the absence of adequate data, a rough estimate of hypothetical dietary exposure to 4-methylbenzophenone from other sources was calculated, based on the consumption of food that may contain benzophenone as a proxy, given that these two substances are used for a similar purpose. For that purpose a survey on benzophenone (FSA, 2006) was used assuming the 4-methylbenzophenone was used instead.

This resulted in hypothetical dietary exposures of 1 µg 4-methylbenzophenone/kg b.w. per day for adults and 2 µg 4-methylbenzophenone/kg b.w. per day for children.

The hypothetical overall exposure from all potentially contaminated foods has been estimated by combining exposure from all potentially contaminated foods (breakfast cereals + other foods). The conservative scenario leads to an overall exposure of 1.79 µg 4-methylbenzophenone/kg b.w. per day for adults and 4 µg 4-methylbenzophenone/kg b.w. per day for children

The highly conservative scenario leads to a hypothetical overall estimated exposure from all potentially contaminated foods of 6.2 µg 4-methylbenzophenone/kg b.w. per day for adults and 15.2 µg 4-methylbenzophenone/kg b.w. per day for children.

Based on the LOAEL of benzophenone of 6 mg/kg b.w. per day and the hypothetical overall exposure from all foods, Margins of Exposure could be estimated as follows:

For adults: 3351 and 968 for conservative and highly conservative scenarios respectively.

For children: 1500 and 395 for conservative and highly conservative scenarios respectively.

Thus for adults, the estimated exposure is unlikely to lead to a health concern, since the estimated MoE is higher than 600. For children, the estimated exposure based on a conservative scenario (high consumption of breakfast cereals, average concentration of 4-methylbenzophenone) is also unlikely to pose a health concern. However, for children, based on the highly conservative scenario (high consumption of breakfast cereals, highest concentration of 4-methylbenzophenone), the estimated MoE is below 600. Therefore a health concern cannot be excluded in this case.

Based on the limited exposure data available and applying knowledge on the toxicity of a similar substance, benzophenone, EFSA concludes that short term consumption of contaminated breakfast cereals should not pose a risk to most people. However, if the use of 4-methylbenzophenone is to be continued, more data on occurrence of the substance in foods should be provided as well as appropriate toxicity data corresponding to the level of exposure for a full risk assessment.

Key words: benzophenone, 4-methylbenzophenone, photoiniators, printing inks, cereals.

ACKNOWLEDGEMENTS

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Catherine Simoneau also provided references on analytical work in the context of the collaboration agreement between JRC and EFSA.

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BACKGROUND AS PROVIDED BY THE COMMISSION

A recent notification from the German authorities under Art 50 of the Regulation (EC) No178/2002 on the *Rapid Alert System for Food and Feed* (RASFF) has reported the migration of 4-methylbenzophenone from packaging into certain cereal products in a quantity of 798 micrograms/kg. According to the German authorities the contamination derives from the transfer of 4-methylbenzophenone from the printed surface of the cardboard box where it is used as photo-initiator in the UV hardened lacquer.

Inks are not covered by a specific European legislation on food contact materials. However, the use of printing inks has to comply with the general rules of Regulation (EC) No 1935/2004 and with good manufacturing practice as laid down in Commission Regulation (EC) No 2023/2006.

The Belgian authorities reported later that during storage the migration can be as high as 3729 µg/kg. Based on this migration value, the Belgian authorities have provided to the Commission a draft risk assessment which is sent to EFSA with this request.

On behalf of the printing ink producers and of the cardboard box manufacturers, the European Printing Ink Association (EuPIA) has provided risk assessments performed on their request. These are also sent to EFSA with this request.

The above two mentioned risk assessments apply a read across approach using toxicological data available for benzophenone and hydroxybenzophenone. The Scientific Committee on Food has established in 1991 and 1992 for the related substances hydroxybenzophenone and benzophenone a tolerable daily intake (TDI) of 0.01 mg/k bodyweight (b.w.) (SCF 1991; SCF, 1992). From the provided risk assessments it becomes evident that new toxicological data are available on benzophenone since the establishment of the TDI which may influence the TDI.

TERMS OF REFERENCE AS PROVIDED BY THE COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission (Letter from the Commission on 18.02.2009 received on 19.02.2009) asks the European Food Safety Authority to evaluate if the substance 4-methylbenzophenone would be covered by the TDI on benzophenone and hydroxybenzophenone and evaluate the risk of the presence in of 4-methylbenzophenone found in cereals by 3 March 2009. In addition the Commission asked EFSA to re-assess the TDI on benzophenone and hydroxybenzophenone in view of the new toxicological studies available, by end of May 2009.

PROPOSED ACTION TO THE TERMS OF REFERENCE

In relation to the Commission request to evaluate if the substance 4-methylbenzophenone would be covered by the TDI on benzophenone and hydroxybenzophenone, as established by the Scientific Committee on Food, and to evaluate the risk of the presence of 4-methylbenzophenone found in cereals, due to such a short timeline, EFSA was only able to publish a statement on this issue rather than a scientific opinion of the CEF Panel.

In addition to this statement, it is expected that the CEF Panel will adopt an opinion by the end of May 2009 concerning the request to re-assess the group TDI on benzophenone and hydroxybenzophenone in view of the new toxicological studies available (Letter of the Executive Director of EFSA to the Commission on 20.02.2009).

EVALUATION

1. Introduction

This statement is based on literature searches, on data provided on analysis of 4-methylbenzophenone in food samples by the Belgian Federal Agency for the Safety of the Food Chain and by industry, on two surveys by the UK Food Standards Agency on occurrence in foods of a similar substance, benzophenone (FSA, 2000 and 2006) and documents provided by the Commission.

In the area of printing inks, 4-methylbenzophenone and benzophenone are used as photoinitiators for inks and lacquers that are cured with ultraviolet light. Benzophenone is widely used because is relatively cheap and effective. UV-cured inks and lacquers are used without solvent; they contain typically 5–10% photoinitiator (Anderson and Castle, 2003).

4-Methylbenzophenone may be used instead of benzophenone and, less frequently, in combination with benzophenone as provided by the European Printing Ink Association (EuPIA communication to EFSA by e-mail).

Photoiniators are not completely used up or removed during or after the printing process, nor are bound irreversibly into the print film layer.

Due to their volatility, 4-methylbenzophenone and benzophenone may migrate through packaging to the food if no functional barrier, such as aluminium foil, is present. Internal plastic bags, used a barrier to moisture, do not always act as a functional barrier (Song *et al.*, 2003, Choi *et al*, 2002, Feigenbaum *et al.*, 2005, Pastorelli *et al.*, 2008). Specific migration studies have shown that benzophenone can migrate from paper and board into dry foods (Triantafallou *et al.*, 2007, Jickells *et al.*, 2005, Anderson and Castle, 2003, Johns *et al.*, 2000) or into powders simulating dry foods (Nerin and Assensio, 2002).

4-Methylbenzophenone is also used as a constituent of synthetic perfumes and as sunscreen agent to reduce skin damage to UV solar radiation (EuPIA, 2009)

2. Legislation

Printing inks are not covered by specific European legislation on food contact materials. However the use of printing inks has to comply with the general rules of Regulation (EC) No 1935/2004 and with good manufacturing practice (GMP) as laid down in Commission Regulation (EC) No 2023/2006.

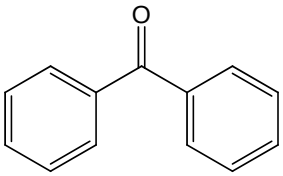
In relation to components of packaging such as inks, Regulation (EC) No 1935/2004 states that under normal or foreseeable conditions of use they should not transfer their constituents to food in quantities which could endanger human health.

There is a specific migration limit (SML) for benzophenone of 0.6 mg/kg (Directive 2002/72/EC) for its use as an additive in plastics following an opinion of the Scientific Committee on Food in 1992 which established a group TDI for benzophenone and 4-hydroxybenzophenone of 0.01 mg/kg b.w. (SCF, 1992). The evaluation of the SCF was based on a metabolism study and on a 90-day oral rat study.

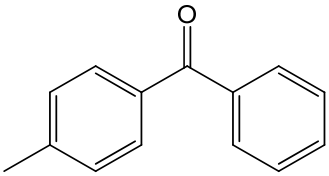
3. Chemistry

4-Methylbenzophenone (CAS No.134-84-9) and benzophenone (Cas. No. 119-61-9) are aromatic ketones with a molecular weight of 196 g/mol and 182 g/mol respectively. 4-Methylbenzophenone differs from benzophenone only by a methyl group. Given their conjugated structure, with a carbonyl group bridging two phenyl rings, they are strong absorbers of UV light. Consequently, they find use in sun screen creams and as photoinitiators for polymerisation reactions.

Both substances are sparingly soluble in water (32 to 43 mg/L) and freely soluble in organic solvents such as ethanol, benzene and propylene glycol. They are both lipophilic with similar octanol/water partition coefficients (LogPo/w 3.2-3.7). Both substances are semi volatile with a discernable vapour pressure even at room temperature (vapour pressure 1.1 - 1.2 Pa at 25°C).



Benzophenone



4-Methylbenzophenone

4. Toxicity

The currently available data on 4-methylbenzophenone are insufficient to enable the assessment of this substance with respect to its human toxicological effects. Therefore the toxicological studies conducted on a similar compound, benzophenone, were used by EFSA for the purpose of giving advice to the Commission in a very short timeframe on the risk of 4-methylbenzophenone found in breakfast cereals.

4.1. Acute oral toxicity of 4-methylbenzophenone and benzophenone

The oral toxicity of both compounds is low as the rat LD50 is >10 g/kg b.w. and the mouse LD50 is 2.9 g/kg b.w. for benzophenone (EC, 2000) and >2 g/kg for 4-methylbenzophenone. (Haselbach, 2009, tox review for industry, study not available to EFSA).

4.2. Genetic Toxicity of 4-methylbenzophenone and benzophenone

No experimental data on the genotoxic properties of 4-methylbenzophenone are available. Only a negative Ames test is quoted without further details in a toxicological review (Haselbach, 2009, tox review for industry, study not available to EFSA). However, no significant genotoxicity is foreseen for this substance. The *in silico* structure-activity evaluation of 4-methylbenzophenone by the Toxtree v1.51 software developed by the European Commission Joint Research Centre (http://ecb.jrc.ec.europa.eu/qsar/qsar-tools/index.php?c=TOXTREE) does not highlight any structural alert for genotoxicity. Supportive evidence on the lack of genotoxicity of 4-methylbenzophenone can also be obtained from reading-across from the structurally related benzophenone, for which an adequate evidence of absence of genotoxicity is available.

Benzophenone has been extensively tested in the framework of an NTP research programme (NTP, 2006), giving negative results in mutagenicity tests *in vitro* in bacteria and in mammalian cells, and in mouse erythropoietic cells *in vivo*.

There is insufficient direct evidence available on the genotoxicity of 4-methylbenzophenone. However, based on structural considerations and experimental results on the structurally related benzophenone, it can be concluded that 4-methylbenzophenone does not raise concern for genotoxicity.

4.3. Metabolism of 4-methylbenzophenone and benzophenone

No metabolism studies on 4-methylbenzophenone could be found in the literature.

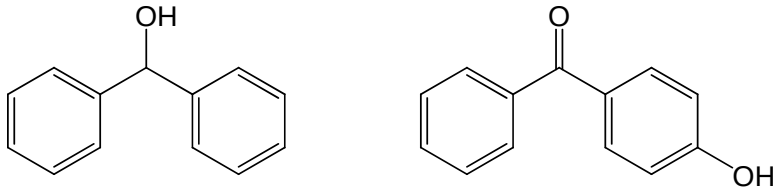
In vitro, benzophenone is metabolised to benzhydrol (reduction of ketone group), 4-hydroxybenzophenone (aromatic hydroxylation) (Figure 1) and to the sulphate conjugate (Nakagawa,Y *et al*, 2000). Studies *in vivo* in rats show that, as in the *in vitro* reports, benzophenone mainly gives benzhydrol and 4-hydroxybenzophenone (Figure 1) (Jeon *et al.*, 2008) probably with the sulphate and glucuronide conjugates.

Since the structures are so similar, it is likely that 4-methylbenzophenone would give the 4-methylbenzhydrol. It can also be expected to undergo aromatic hydroxylation in the 4'- position to form 4'-hydroxy-4-methylbenzophenone (Figure 2) and subsequently its sulphate and glucuronide conjugates. It is likely that the 4-methyl group could undergo oxidation to the alcohol (-CH_2OH) and then the carboxylic acid (-COOH) (Figure 2) with further metabolism to the glycine and/or glucuronide conjugates (BAG, 2009). This metabolic pathway is specific to 4-methylbenzophenone as benzophenone lacks the 4-methyl group.

Given that these metabolites can be conjugated, 4-methylbenzophenone is expected to be easily metabolised and excreted in man.

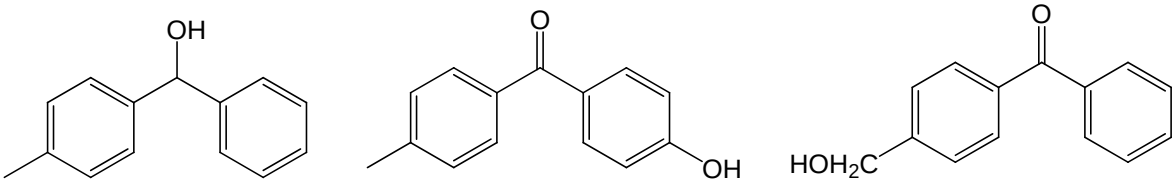
In conclusion 4-methylbenzophenone is expected to be metabolised by the same metabolic pathways as benzophenone, with the addition of a specific pathway: oxidation of the 4-methyl group to the corresponding alcohol and further oxidation to the carboxylic acid.

Figure 1: Primary metabolites of benzophenone (according to Nakagawa *et al.*, 2000 and Jeon *et al.*, 2008)



Benzhydrol 4-Hydroxybenzophenone

Figure 2: Likely primary metabolites of 4-methylbenzophenone



4-Methylbenzhydrol 4-Methyl-4'-hydroxybenzophenone 4-Hydroxymethylbenzophenone

4.4. Repeated-dose studies on benzophenone

In 14-week studies with benzophenone, rats were treated with daily doses up to 850 mg/kg b.w. for males and up to 1000 mg/kg b.w. for females; doses up to 3300 mg/kg b.w. were given to male mice and up to 4200 mg/kg b.w. to female mice (NTP, 2000). In both species, the liver was identified as a primary target organ of benzophenone. In rats, the kidney was also identified as an additional target organ based on increases in kidney weights and microscopic changes. In more recent 2-year studies (NTP 2006) rats were treated with doses up to 60/65 mg/kg b.w. (males/females) and mice were treated with 160/150 mg/kg b.w. (males/females). In these studies some evidence was reported for carcinogenic activity of benzophenone in male rats based on increased incidences of renal tubule adenoma and in mice based on increased incidences of hepatocellular neoplasms and increased incidences of histocytic sarcoma in males and females, respectively. No NOAELs could be derived from these studies. The LOAEL for the rat study was 15 mg/kg b.w. per day, the LOAEL from the mouse study was 35 mg/kg b.w. per day.

The reproductive toxicity of benzophenone was examined in a two-generation study in rats (Hoshino *et al*, 2005). Dose-dependent histopathological findings in adult animals were observed in liver, where there was an increase in liver weight and centrilobular hypertrophy, and in kidney. Based on these findings a LOAEL of 6 mg/kg b.w. per day was derived. Reproductive toxicity was not observed in this study, effects on the offspring were observed at the highest dose only.
Additionally, an estrogenic potency of benzophenone has been reported in ovariectomized rats at a higher dose (400 mg/kg b.w. per day) (Nakagawa and Tayama, 2002).

4.5. Evaluation of toxicity of 4-methylbenzophenone

There is insufficient direct evidence available on the genotoxicity of 4-methylbenzophenone. However, based on structural considerations and experimental results on the structurally related benzophenone, it can be concluded that 4-methylbenzophenone does not raise concern for genotoxicity. Consequently, a margin of exposure (MoE) approach for the risk assessment can be followed.

4-Methylbenzophenone is expected to be metabolised by the same metabolic pathways as benzophenone, with the addition of oxidation of the 4-methyl group to the corresponding alcohol and further oxidation to the carboxylic acid with its glycine and glucuronide conjugates (BAG, 2009).

Like benzophenone, 4-methylbenzophenone is expected to be a non genotoxic carcinogen.

Due to the lack of toxicity data for 4-methylbenzophenone and to the specific metabolic pathway, it is currently not scientifically sound to include 4-methylbenzophenone into the group-TDI for benzophenone and hydroxybenzophenone. Therefore at present a TDI cannot be derived for 4-methylbenzophenone.

For the purpose of addressing this urgent request for advice to risk managers, the Margin of Exposure (MoE) approach is proposed. An uncertainty factor of two is considered appropriate for read-across from benzophenone.

Benzophenone has been studied in subchronic (90-day) and chronic studies. In the latter, liver tumours were observed at a LOAEL of 15 mg/kg b.w. per day. In a two-generation study with benzophenone (Hoshino *et al.*, 2005), livers of parental animals showed adverse effects, which could be related to the carcinogenicity in the chronic assay. From this study a LOAEL of 6 mg/kg b.w. per day could be derived.

This LOAEL is used as a basis for the calculation of the MoE for 4-methylbenzophenone. A factor of 100 for inter- and intraspecies differences in sensitivity, a factor of 3 for use of a LOAEL (instead of a NOAEL) and a factor of 2 for read-across from benzophenone to 4-methylbenzophenone are applied. Hence the MoE should be greater than 600.
The estimated MoE is calculated by dividing the LOAEL (6 mg/kg b.w. per day) by the estimated exposure in each case.

5. Occurrence

5.1 RASFF notification of 4-methylbenzophenone found in food in Germany

On 2 February 2009, German authorities reported through RASFF that 4-methylbenzophenone had been detected at a concentration of 798 µg/kg in chocolate crunch muesli (breakfast cereal) produced in Belgium and packaged in a polyethylene bag inside a printed carton board outer package (EC, 2009). Results from other sources reported to EFSA are outlined below.

5.2 Food manufacturer results on the presence of 4-methylbenzophenone

Through the Scientific Committee of the Belgian Federal Agency for the Safety of the Food Chain (CS AFSCA) EFSA received data from urgent further analyses performed by the food manufacturer on ten different samples of cereals. The results showed the presence of 4-methylbenzophenone in seven samples at concentrations from 384 up to 3,729 µg/kg, giving a mean concentration of 1,059-1,068 µg/kg when applying the lower or upper bounds[1] (CS AFSCA, 2009). Since these results were not from random market sampling, they were not used for the exposure assessment.

5.3 Official testing of products on the Belgian market for the presence of 4-methylbenzophenone

Following the first set of data, AFSCA (AFSCA, 2009) provided EFSA with a second set of analytical results covering the presence of 4-methylbenzophenone in 32 food samples of

[1] To calculate the lower bound and the upper bound of average concentration values, zero and the actual limit of quantification (LOQ) are entered for values below LOQ, respectively.

which 17 were breakfast cereals. 4-Methylbenzophenone was extracted from the food matrix with acetonitrile and the extracts were analysed with HPLC-MS or GC-MS with a quantification limit of 50 µg/kg food (LOQ). Both methods were suitable for the determination of the substance in food.
The results showed the presence of 4-methylbenzophenone in eight of the 17 samples of breakfast cereals. The average concentration of 4-methylbenzophenone reported for the 17 samples of breakfast cereals was 795-819 µg/kg with the range indicating lower and upper bounds, respectively, and a maximum of 5,400 µg/kg food.
Of the few samples tested, it is of interest to note that the presence of 4-methylbenzophenone was also detected in two samples of croquettes and one sample of biscuits indicating that the finding of 4-methylbenzophenone is not limited to breakfast cereals (AFSCA, 2009).
The concentrations of 4-methylbenzophenone as reported in February 2009 by AFSCA in Belgium are compiled in Table 1.

Table 1: Average and maximum concentration of 4-methylbenzophenone in 32 food samples analysed in Belgium (AFSCA, 2009) (LOQ=50 µg/kg food)

Food products	Number of samples	Number of samples with measurable results	Average upper bound (µg /kg)	Maximum (µg /kg)
Breakfast cereals	17	8	819	5,400
Croquettes	4	2	123	200
Warm ready meals	4	-	<LOQ	<LOQ
Biscuits	3	1	107	220
Coffee	2	-	<LOQ	<LOQ
Ice Cream	1	-	<LOQ	<LOQ
Milk based Drinks	1	-	<LOQ	<LOQ

6. Assessment of dietary exposure to 4-methylbenzophenone

6.1 Consumption of breakfast cereals

The contaminated cereals were produced in Belgium and notified by Germany. However, the contaminated breakfast cereals may be available in other Member States as well. The highest consumption levels per kg body weight are expected to occur in children. Therefore, since adequate data on children consumption of breakfast cereals are available for Ireland, the Netherlands (Ocké et al., 2008) and Italy (Leclercq at al., 2009), these values are used here (Table 2). Among these studies, the highest level of consumption of breakfast cereals was registered in Ireland in children aged from 5 to 12 years: 0.94 and 2.45 g/kg b.w. per day at the mean and 95th percentile levels, respectively (IUNA, 2005). Lower consumption levels were recorded in Italy in children aged from 3 to 9.9 years: 0.15 and 0.99 g/kg b.w. per day at the mean and 95th percentile levels, respectively and in the Netherlands in children aged from 2 to 3 years: 0.36 g/kg b.w. per day at the mean level.

Table 2: Mean and high levels of consumption of breakfast cereals by children in three EU countries

Country	Food category	Age class (years)	Number of subjects	Average body weight (kg)	% consumers	Consumption			
						Mean		95th percentile	
						g per day	g/kg b.w. per day	g per day	g/kg b.w. per day
Ireland	"Ready to eat" breakfast cereals	5-12	594	33	93	31	0.94	81	2.45
The Netherlands	Breakfast cereals	2-3	639	15.4	25.5	5.5	0.36	-	-
Italy	Breakfast cereals	3-9.9	193	26.2	25.9	3.8	0.15	22.5	0.99

The Irish 95th percentile consumption for breakfast cereals for children (2.45 g/kg b.w. per day) was considered by EFSA in order to perform a conservative assessment of dietary exposure to 4-methylbenzophenone.
For comparative reasons the Irish 95th percentile adult consumption of breakfast cereals of 72 g or 0.96 g/kg b.w. per day (assuming an observed average body weight of 75 kg) was also used (Galvin *et al*., 2003).

6.2 Potential dietary exposure to 4-methylbenzophenone from breakfast cereals

In order to assess potential dietary exposure to 4-methylbenzophenone from breakfast cereals, the mean (819 µg/kg) and maximum (5,400 µg/kg) concentrations found in the 17 samples of breakfast cereals officially reported by AFSCA (AFSCA, 2009) were used in combination with the estimated high consumption level of breakfast cereals in children (2.45 g /kg b.w. per day) and in adults (0.96 g/kg b.w. per day).

Table 3: Potential dietary exposure of adults and children to 4-methylbenzophenone in breakfast cereals due to migration from packaging.

Target population (standard body weight)		Adults	Children
Observed high level of consumption of breakfast cereals (g/kg b.w./day)		0.96	2.45
Conservative scenario: Average concentration of 4-methylbenzophenone in 17 samples of breakfast cereal (819 µg/kg)	Dietary exposure (µg/kg b.w. per day)	0.79	2.0
	Estimated MoE	7,595	3,000
Highly conservative scenario: Maximum concentration of 4-methylbenzophenone in 17 samples of breakfast cereal (5,400 µg/kg)	Dietary exposure (µg/kg b.w. per day)	5.2	13.2
	Estimated MoE	1,154	455

For children a conservative dietary exposure scenario is that of a child weighing 33 kg (observed average body weight in the age range for which the highest consumption of breakfast cereals has been registered in Ireland) and consuming 2.45 g breakfast cereals/kg b.w. per day (Table 2) containing 4-methylbenzophenone at the average concentration (819 µg/kg) reported by the Belgian Authorities in the 17 samples tested (AFSCA, 2009). Dietary exposure to 4-methylbenzophenone under this scenario is 2 µg/kg b.w. per day. A highly conservative scenario for children, based on the highest concentration value of 5,400 µg/kg breakfast cereals, indicates a total dietary exposure of 13.2 µg 4-methylbenzophenone/kg b.w. per day.

For adults the conservative and the highly conservative scenarios lead to dietary exposures of 0.79 and 5.2 µg of 4-methylbenzophenone /kg b.w. per day, respectively.
The two exposure scenarios were based on results from testing of only 17 food samples and a considerable uncertainty is attached to the figures. Further, they do not include potential contribution from foods other than breakfast cereals. A sensitivity analysis was performed to attempt to estimate exposure to 4-methylbenzophenone in relation to total food intake.

6.3 Sensitivity analysis based on available data on benzophenone

Although the presence of 4-methylbenzophenone was also detected in a few food samples other than breakfast cereals, the sparse data make it impossible to directly calculate their contribution to overall exposure. On the other hand comprehensive surveys of dietary exposure to benzophenone in foods have been conducted by FSA (2006). In the absence of more adequate data, a rough estimate of potential dietary exposure to 4-methylbenzophenone from other sources was calculated based on the consumption of food that may contain benzophenone as a proxy, given that these two substances are used for a similar purpose.
In calculating potential dietary exposure to benzophenone, the FSA (2006) estimated an overall consumption of food that may contain benzophenone to be equal to 449 g/day or 5.9 g/kg b.w. per day for a 76.5 kg person at the 97.5th percentile consumption level. EFSA used this figure to extrapolate the equivalent consumption by children by comparing energy intake. On average food intake of children (at 9.5 years of age and 30 kg b.w.) would be 84% of the adult food consumption, given 8 MJ of energy per day for the child vs. 9.5 MJ for an adult (Commission for the European Community, 1993). A high consumption level of 377 g/day can therefore be estimated or 12.6 g/kg b.w. per day for such a child. Hypothetical exposure to 4-methylbenzophenone in foods other than breakfast cereals was calculated by using this estimated food intake, less breakfast cereal consumption from Table 3, and the mean concentration of 200 µg/kg for its proxy benzophenone observed in the survey conducted by FSA in 2006 (Table 4).

Table 4: Hypothetical dietary exposure of adults and children to 4-methylbenzophenone based on average concentration of benzophenone in foods other than breakfast cereals

Target population	Adults	Children
Estimated high level of consumption of foods other than breakfast cereals potentially contaminated* (g/kg b.w. per day)	4.9	10.15
Hypothetical dietary exposure estimate to 4-methylbenzophenone (µg/kg b.w. per day) based on average concentration of benzophenone (200 µg/kg)*	1.0	2.0

(*) this was calculated from the FSA survey on benzophenone (FSA, 2006), assuming that benzophenone was replaced by 4-methylbenzophenone .

The estimated hypothetical exposure from 4-methylbenzophenone in foods other than breakfast cereals can potentially double overall exposure when added to the conservative scenario from Table 3. The impact is less for the highly conservative scenario from Table 3. An overview of the calculations is given in Table 5.

Table 5: Hypothetical overall dietary contributions from 4-methylbenzophenone in different scenarios for all potentially contaminated foods.

	Dietary exposure (µg/kg b.w. per day)	
	Adults	**Children**
Contribution from breakfast cereals in the conservative scenario (1)	0.79	2.0
Contribution from foods other than breakfast cereals (µg/kg b.w. per day) (2)	1.0	2.0
Calculated overall dietary exposure	1.79	4.0
Estimated MoE	**3,351**	**1,500**
Contribution from breakfast cereals in the highly conservative scenario (3)	5.2	13.2
Contribution from other foods (µg/kg b.w. per day) (2)	1.0	2.0
Calculated overall dietary exposure	6.2	15.2
Estimated MoE	**968**	**395**

(1) Based on average concentration of 4-methylbenzophenone in 17 samples of breakfast cereal (819 µg/kg)
(2) Hypothetical dietary exposure estimate to 4-methylbenzophenone based on average concentration of benzophenone (200 µg/kg) (FSA, 2006)
(3) Based on maximum concentration of 4-methylbenzophenone in 17 samples of breakfast cereal (5,400 µg/kg)

Calculation of the MoE for the combined estimated exposure from all potentially contaminated foods lead to estimated MoE above the reference value of 600 in all scenarios but in the highly conservative scenario for children. In this case the estimated MoE is 395 However it should be acknowledged that inputs to the calculations are associated with high uncertainty.

The hypothetical exposure estimate should be refined in the future when more data are made available on the presence of 4-methylbenzophenone especially in foods other than breakfast cereals.

6.4 Other possible sources of exposure

The use of 4-methylbenzophenone in cosmetics may contribute to the overall human exposure: it is used as a constituent of synthetic perfumes and as sunscreen agent to reduce skin damage to UV solar radiation (EuPIA, 2009). Exposure from such sources may also be significant but it could not be included in the exposure assessment.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

There is insufficient direct evidence available on the genotoxicity of 4-methylbenzophenone. However, based on structural considerations and experimental results on the structurally related benzophenone, it can be concluded that 4-methylbenzophenone does not raise concern for genotoxicity.

4-Methylbenzophenone is expected to be metabolised by the same metabolic pathways as benzophenone, with the addition of oxidation of the 4-methyl group to the corresponding alcohol and further oxidation to the carboxylic acid with its glycine and glucuronide conjugates.

Like benzophenone, 4-methylbenzophenone is expected to be a non genotoxic carcinogen.

Due to the lack of toxicity data for 4-methylbenzophenone and to the specific metabolic pathway, it is currently not scientifically sound to include 4-methylbenzophenone into the group-TDI for benzophenone and hydroxybenzophenone. Therefore at present a TDI cannot be derived for 4-methylbenzophenone.

For the purpose of addressing this urgent request for advice to risk managers, the Margin of Exposure (MoE) approach is proposed. An uncertainty factor of two is considered appropriate for read-across from benzophenone.

Benzophenone has been studied in subchronic (90-day) and chronic studies. In the latter, liver tumours were observed at a LOAEL of 15 mg/kg b.w. per day. In a two-generation study with benzophenone, livers of parental animals showed adverse effects, which could be related to the carcinogenicity in the chronic assay. From this study a LOAEL of 6 mg/kg b.w. per day could be derived.

This LOAEL is used as a basis for calculation of the MoE for 4-methylbenzophenone. A factor of 100 for inter- and intraspecies differences in sensitivity, a factor of 3 for use of a LOAEL (instead of a NOAEL) and a factor of 2 for read-across from benzophenone to 4-methylbenzophenone are applied. Hence the estimated MoE should be greater than 600. The MoE is calculated by dividing the LOAEL (6 mg/kg b.w. per day) by the estimated exposure in each case.

Based on analytical results from 17 samples of breakfast cereals as provided by the Belgian Authorities (AFSCA, 2009), exposure estimates to 4-methylbenzophenone were derived for children and adults according to a conservative and to a highly conservative scenario. Both scenarios are based on the highest consumption of breakfast cereals as registered in Ireland: 2.45 g/kg b.w. per day for children and 0.96 g/kg b.w. per day for adults (Table 2). The conservative scenario assumes average concentration of 4-methylbenzophenone as calculated from the results on the 17 samples from the Belgian market whilst the highly conservative scenario assumes the maximum concentration found in these samples.

For children the conservative scenario leads to a dietary exposure via breakfast cereals of 2 µg 4-methylbenzophenone /kg b.w. per day. The highly conservative scenario for children leads to a dietary exposure via breakfast cereals of 13.2 µg 4-methylbenzophenone/kg b.w. per day.

For adults the conservative and the highly conservative scenarios lead to dietary exposures via breakfast cereals of 0.79 and 5.2 µg of 4-methylbenzophenone /kg b.w. per day, respectively.
In the absence of adequate data, a rough estimate of hypothetical dietary exposure to 4-methylbenzophenone from other sources was calculated, based on the consumption of food that may contain benzophenone as a proxy, given that these two substances are used for a similar purpose. For that purpose a survey on benzophenone (FSA, 2006) was used assuming the 4-methylbenzophenone was used instead.

This resulted in hypothetical dietary exposures of 1 µg 4-methylbenzophenone/kg b.w. per day for adults and 2 µg 4-methylbenzophenone/kg b.w. per day for children.
The hypothetical overall exposure from all potentially contaminated foods has been estimated by combining exposure from all potentially contaminated foods (breakfast cereals + other foods). The conservative scenario leads to an overall exposure of 1.79 µg 4-methylbenzophenone/kg b.w. per day for adults and 4 µg 4-methylbenzophenone/kg b.w. per day for children

The highly conservative scenario leads to a hypothetical overall estimated exposure from all potentially contaminated foods of 6.2 µg 4-methylbenzophenone/kg b.w. per day for adults and 15.2 µg 4-methylbenzophenone/kg b.w. per day for children.

Based on the LOAEL of benzophenone of 6 mg/kg b.w. per day and the hypothetical overall exposure from all foods, Margins of Exposure could be estimated as follows:

For adults: 3351 and 968 for conservative and highly conservative scenarios respectively.

For children: 1500 and 395 for conservative and highly conservative scenarios respectively.

Thus for adults, the estimated exposure is unlikely to lead to a health concern, since the estimated MoE is higher than 600. For children, the estimated exposure based on a conservative scenario (high consumption of breakfast cereals, average concentration of 4-methylbenzophenone) is also unlikely to pose a health concern. However, for children, based on the highly conservative scenario (high consumption of breakfast cereals, highest concentration of 4-methylbenzophenone), the estimated MoE is below 600. Therefore a health concern cannot be excluded in this case.

Based on the limited exposure data available and applying knowledge on the toxicity of a similar substance, benzophenone, EFSA concludes that short term consumption of contaminated breakfast cereals should not pose a risk to most people.

RECOMMENDATIONS

If the use of 4-methylbenzophenone is to be continued, more data on occurrence of the substance in foods should be provided as well as appropriate toxicity data corresponding to the level of exposure for a full risk assessment.

DATA PROVIDED TO EFSA

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