European Food Safety Authority

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# Camphor in flavourings and other food ingredients with flavouring properties

## Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission[1]

**(Question No EFSA-Q-2003-144)**

**Adopted on 22 May 2008**

**PANEL MEMBERS**

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**SUMMARY**

The European Food Safety Authority (EFSA) is asked to advise the Commission on substances used as flavouring substances or present in flavourings or present in other food ingredients with flavouring properties for which existing toxicological data indicate that restrictions of use or presence might be necessary to ensure safety of human health. In particular, EFSA is asked to advise the Commission on the implications for human health of the presence of *d*-camphor in the diet.

Dietary exposure to camphor arises from the consumption of foods flavoured by using either herbs (e.g. basil, coriander, marjoram, rosemary, sage), their essential oils or the chemically defined flavouring substance *d*-camphor. Camphor is easily absorbed in the gastrointestinal tract. The major metabolic pathway is the oxidation to 5- and 3-hydroxycamphor, followed by conjugation and excretion. Camphor did not show mutagenic activity in *Salmonella typhimurium* strains and did not induce chromosome aberrations *in vitro* with and without metabolic activation. There was no evidence of reproductive and developmental toxicity after oral administration to rats and rabbits.

[1] For citation purposes: Scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC) on a request from the Commission on Camphor in flavourings and other food ingredients with flavouring properties. *The EFSA Journal 729, 1-15.*

The available data on toxicity of camphor are limited and thus a TDI cannot be derived. However, based on the available toxicity data and the Panel´s conservative estimate of chronic exposure (15 mg/day equivalent to 250 µg/kg body weight (bw)/day) calculated using the maximum limits suggested by the Council of Europe, the Panel considered that there would be no safety concern regarding chronic toxicity.

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (Panel) considered that safety aspects of *d*-camphor in terms of acute toxicity needed to be addressed. The reported acute toxicity data on adults and children arise mostly from accidental ingestion of camphor-containing medications. The probable lethal oral bolus dose has been reported to be in the range of 50 to 500 mg/kg bw. No acute toxicity was reported after doses lower than 2 mg/kg bw and clinically insignificant signs of toxicity may be seen in sensitive individuals at doses of 5 mg/kg bw and higher, whereas clinically manifest toxicity in sensitive persons would require doses higher than 30 mg/kg bw.

Potential acute exposure related to the consumption of large amounts of certain foods on a single day was estimated by the Panel for several age groups. It was lowest in adults (from 0.14 to 0.34 mg/kg bw according to the food commodity) and highest in children under 6 (from 0.41 to 0.83 mg/kg bw according to the food commodity). The commodity leading to the highest potential acute exposure was fresh cheese in all age groups.

The acute exposure estimates for children and adults are about 60-120 times and 150-360 times, respectively, lower than the probable lowest lethal oral bolus dose of 50 mg/kg bw. The acute exposure estimates for children and adults are about 2-5 times and 6-14 times, respectively, lower than the dose of 2 mg/kg bw below which no acute effects have been reported in human case studies. Although these margins might appear to be low, the large number of cases describing the dose-response relationship suggests that the data sufficiently cover inter-individual variability in sensitivity. Therefore, the Panel concluded that it is unlikely that acute effects may occur in relation to consumption of foods providing less than 2 mg/kg bw in one large portion.

The acute exposure estimates considered by the Panel are based on observed high consumption in only one Member State and on maximum limits suggested by the Council of Europe. However, maximum permitted levels for *d*-camphor are not currently set in the EU legislation and there is uncertainty on its actual upper use levels in foods and beverages currently on the market and on the high consumption of food flavoured with *d*-camphor all over Europe. The Panel therefore suggests that maximum limits should be set to ensure that exposure to camphor does not exceed 2 mg/kg bw on a single day in any age group.

**KEYWORDS**

Flavourings; *d*-camphor; CAS no: 464-49-3; FL-no: 07.215.

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## BACKGROUND

### Previous scientific evaluations

The Panel of Experts of the Flavor and Extracts Manufacturers Association (FEMA) considered *d*-camphor as GRAS (Generally Recognized As Safe), based on the recognized detoxification pathways of the substance, its very low level of use and its presence as a natural component of traditional foods (FEMA, 1995).

The Committee of Experts on Flavouring Substances of the Council of Europe (CEFS) included the substance, at a level of 25 mg/kg food, in the list of flavouring substances that may be added to foodstuffs without hazard to public health (Council of Europe, 1992). Later the CEFS set a tolerable daily intake (TDI) of 0.1 mg/kg bw based on a minimum lethal dose of 50 mg/kg bw, applying a safety factor of 500 (Council of Europe, 2001).

Recently, the Joint FAO/WHO Expert Committee of Food Additives (JECFA) evaluated *d*-camphor specifically as a chemically defined flavouring substance together with similar flavouring substances in a group of monocyclic and bicyclic secondary alcohols, ketones and related esters and concluded that it would not raise a safety concern at current estimated intakes as flavouring substance of 58 µg/day in Europe and 396 µg/day in the USA (WHO, 2006b).

### Current EU regulatory status

*d*-Camphor (FL no. 07.215; (1*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one) is listed in the Register of flavouring substances used in or on foodstuffs in the Member States adopted by Commission Decision (EC) No 1999/217/EC (EC, 1999), as last amended by Commission Decision (EC) No 2005/389/EC (EC, 2005).

## TERMS OF REFERENCE

EFSA is asked to advise the Commission on substances used as flavouring substances or present in flavourings or present in other food ingredients with flavouring properties for which existing toxicological data indicate that restrictions of use or presence might be necessary to ensure safety of human health.

In particular, EFSA is asked to advise the Commission on the implications for human health of the presence of *d*-camphor in the diet.

## ASSESSMENT

### Chemistry

*d*-Camphor (CAS number: 464-49-3)
Synonyms: (1*R*,4*R*)-(+)-Camphor; (1*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one; (+)-2-Bornanone; (*R*)-(+)-Camphor; D-(+)-Camphor.

*l*-Camphor (CAS number: 464-48-2)
Synonyms: Bicyclo[2.2.1]heptan-2-one, 1,7,7-trimethyl-, (1*S*)-; (1*S*,4*S*)-(-)- Camphor; (1*S*)-(-)-Camphor.

Camphor (CAS number: 76-22-2)
Synonyms: 1,7,7-Trimethylbicyclo[2.2.1]-2-heptanone; 1,7,7-Trimethylnorcamphor; 2-Bornanone; 2-Camphanone; DL-Camphor; *dl*-Camphor.

See Figure 1 for structure of camphor.

## EXPOSURE

*Occurrence*

Camphor is a constituent of a variety of foods; typical sources are herbs, such as basil, coriander, marjoram, rosemary and sage (Maarse and Visscher, 1989). Both enantiomers are naturally occurring. The essential oil from the so-called camphor tree (*Cinnamomum camphora*) contains up to 84% *d*-camphor. Essential oils from herbs are characterized by typical ratios of the enantiomers; for example, a 72-75% excess of the (1*S*,4*S*)-enantiomer (*l*-camphor) is characteristic of coriander oil (*Coriandrum sativum* L.) whereas an excess of the (1*R*,4*R*)-enantiomer (*d*-camphor) characterizes the essential oils of sage (>90% for *Salvia sclarea* L. and 50-70% for *Salvia officinalis* L.) and of basil (>94% for *Ocimum basilicum* L.) (Tateo *et al.*, 1999).

*Dietary Exposure*

Dietary exposure to camphor has been estimated by the CEFS (Council of Europe, 2001), taking into account the consumption of foods flavoured by using either herbs (basil, coriander, marjoram, rosemary, sage), their essential oils or the chemically defined flavouring substance *d*-camphor. The following use levels of *d*-camphor as chemically defined flavouring substance were provided by the European Flavour and Fragrance Association (EFFA) and the International Organization of the Flavor Industry (IOFI): 15 mg/kg in baked foods, 24 mg/kg in ice creams, 25 mg/kg in candies, 25 mg/kg in prepared dishes, 6 mg/kg in non-alcoholic beverages and 10 mg/kg in alcoholic beverages. Concentrations of camphor in foods prepared with basil, coriander, rosemary and sage or with the essential oils of these herbs were provided by the Association Nationale de l'Industrie Agro alimentaire francaise (ANIA). They varied from 1 mg/kg for non-alcoholic beverages prepared with sage essential oil to 50,000 mg/kg for condiments and sauces prepared with basil herb.

Based on these data and on food consumption data collected on the French population by the Observatoire des Consommations alimentaires (OCA), the dietary exposure to camphor was estimated to be 1.5 mg/person/day (Council of Europe, 2001). Assuming an average body weight of 60 kg, this corresponds to an exposure of 25 µg/kg bw/day. It was estimated that about one third of the total dietary exposure to camphor originated from *d*-camphor added as a chemically defined flavouring substance.

The consumption levels for the various foods considered in this estimation varied from 1 g/day for candies to 75 g/day for prepared dishes. In the calculation it was assumed that 100% of all alcoholic and non-alcoholic beverages, ice creams and candies that were consumed contained the substance in question, but the daily levels of consumption considered were low (15 g, 11 g and 6 g for non-alcoholic beverages, alcoholic beverages and ice cream, respectively). In other foods included in the calculation camphor was assumed to be present in a certain percentage of the foods consumed, ranging from 0.1% of oils (consumption level considered: 2 g/day) to 80% of all prepared dishes (consumption level: 75g/day).
Limits for *d*-camphor, suggested by the Council of Europe were 10 mg/kg in beverages (including alcoholic drinks), 25 mg/kg in food in general, 100 mg/kg in candies, 140 mg/kg in fresh cheese, 150 mg/kg in sauces and condiments.

The JECFA estimated the dietary exposure to *d*-camphor only as a chemically defined flavouring substance on the basis of the annual production volumes of 406 kg *d*-camphor in Europe and 3007 kg in the USA to be 58 and 396 µg/person/day, respectively (WHO, 2006b). The limitations of dietary exposure estimates based on poundage data (Maximised Survey-Derived Intake, MSDI) have been emphasized previously by the Panel (EFSA, 2004a).

The Panel estimated the dietary exposure to *d*-camphor as a chemically defined flavouring substance through calculation of the Theoretical Added Maximum Daily Intake, i.e. using the approach previously applied for other flavouring substances, such as coumarin (EFSA, 2004b). However, the levels of camphor considered correspond to the limits suggested by the Council of Europe rather than to actual upper use levels. The calculation was performed considering the concomitant daily consumption of 324 g of beverages in general (containing 10 mg/kg camphor), 133.4 g of food in general (25 mg/kg camphor), 27 g of confectionery (100 mg/kg camphor), 20 g of sauces and condiments (150 mg/kg camphor) and 20 g of fresh cheese (140 mg/kg camphor). In the default TAMDI method fresh cheese is not considered as an exception; however, the Panel considered that a consumption level of 20 g/day was adequate for fresh cheese. A TAMDI of 15 mg camphor/day was calculated which, considering a body weight of 60 kg, would be equivalent to 250 µg camphor/kg bw/day.
The Panel noted that camphor is also present in foods and beverages which have been prepared with herbs or essential oils of herbs.

Potential acute exposure to camphor was estimated based on the French individual consumption data from an INCA (Individuelle et Nationale sur les Consummations Alimentaires) survey based on 7 day records (Volatier *et al.,* 2000). Large single day amounts of commodities consumed during the survey period were assessed in the adult population (15 years and over), in children under 6 years and in children from 6 to 14 years. The values for large single day amounts correspond to the 97.5 percentile among eaters only that are generally used to assess acute exposure to pesticides (WHO, 2006a). Potential acute exposure was estimated based on the limits suggested for *d*-camphor by the Council of Europe Committee of Experts on Flavouring Substances (Council of Europe, 2001). For each food

category to which camphor may be added, the corresponding INCA food category was identified (Table 1).

Table 1. Potential acute exposure to *d*-camphor related to the consumption of large single day amounts of food or beverage containing the flavouring substance at the limits suggested by Council of Europe

| Food category | Corresponding INCA category | Large daily amount for children under 6 | Large daily amount for children from 6 to 14 | Large daily amount for adults (over 15) | Limit suggested by Council of Europe | Potential acute exposure for children under 6 | Potential acute exposure for children from 6 to 14 | Potential acute exposure for adults over 15 |
|---|---|---|---|---|---|---|---|---|
| | | (g / kg bw/day) | (g / kg bw /day) | (g / kg bw /day) | (mg / kg) | (mg / kg bw /day) | (mg / kg bw/day) | (mg / kg bw/day) |
| beverages | soft drinks | 42.7 | 27.9 | 14.0 | 10 | 0.43 | 0.28 | 0.14 |
| food in general | all food* | 19.2 | 13.3 | 8.2 | 25 | 0.48 | 0.33 | 0.20 |
| candies | candies | 5.9 | 3.6 | 1.6 | 100 | 0.59 | 0.36 | 0.16 |
| fresh cheese | cheese | 5.9 | 4.2 | 2.4 | 140 | 0.83 | 0.59 | 0.34 |
| sauces and condiments | sauces and condiments | 2.7 | 2.4 | 1.2 | 150 | 0.41 | 0.36 | 0.18 |

* excluding soft drinks, cheese, sauce and condiments, water

Potential acute exposure related to the consumption of one of these large single day amounts was lowest in adults (from 0.14 to 0.34 mg/kg bw according to the food commodity) and highest in children under 6 (from 0.41 to 0.83 mg/kg bw according to the food commodity). The commodity leading to the highest potential acute exposure was fresh cheese in the three age groups.

## HAZARD IDENTIFICATION/CHARACTERISATION

### *Absorption, distribution, metabolism and excretion*

Camphor is easily absorbed in the gastrointestinal tract. In rabbits, orally administered *d*- and *l*-camphor were shown to be oxidized to 5-*endo*-hydroxycamphor and 3-*endo*-hydroxycamphor, the former predominating in each case. A reduction to borneol was also observed to some extent (Robertson and Hussain, 1969). In dogs the major hydroxylation products of *d*- and *l*-camphor detected in urine after extraction and hydrolysis were 5-*endo*- and 5-*exo*hydroxycamphor, and probably the *endo*-stereoisomer of 3-hydroxycamphor (Leibman and Ortiz, 1973) (Figure 1). *In vitro* studies with liver preparations from rats and rabbits demonstrated these reactions to occur in liver microsomes. A small amount of 2,5-bornanedione was also formed in liver microsomes. The 5-keto group of 2,5-bornanedione was reduced in liver cytosol, and there was interconversion between the *endo*- and the *exo*-isomers of 5-hydroxycamphor in the presence of both microsomes and cytosol, but this interconversion could not account for the production of both 5-hydroxy isomers from camphor in liver microsomes. The 2-keto group of *d*-camphor underwent no detectable reduction in rat liver preparations; *l*-camphor was reduced to a small extent. However, rabbit liver cytosol mediated a vigorous stereospecific *endo*-reduction of *d*-camphor to borneol; a small amount (1%) of isoborneol was also formed (Leibman and Ortiz, 1973).
In humans admitted to hospital in a state of acute intoxication after ingestion of 6-10 g camphor, camphor hydroxylated in the positions 3, 5 and 8(or 9) were identified as major metabolites in the urine. 5- and 8-(or 9-)hydroxycamphor were subsequently oxidised to the

corresponding ketones and carboxylic acids, the latter being conjugated with glucuronic acid (Köppel *et al.*, 1982).

In a recent study, it was shown that the incubation of human liver microsomes with *l*-camphor in the presence of an NADPH-generating system resulted in the formation of 5-*exo*-hydroxycamphor as the only oxidation product (Gyoubu and Miyazawa, 2007). Recombinant human P450 enzymes expressed in baculovirus-infected insect cells were tested for their activities to catalyze the oxidation of *l*-camphor. Among the eleven enzymes tested, only CYP2A6 was found to hydroxylate *l*-camphor to 5-*exo*-hydroxycamphor. The oxidation of *l*-camphor was inhibited by (+)-menthofuran and anti-CYP2A6 antibody. The important role of CYP2A6 in this reaction was supported by the good correlation between contents of CYP2A6 and rates of formation of 5-*exo*-hydroxycamphor in liver microsomes from 9 human samples. These data suggest that there may be species-related differences in the metabolism of camphor to 3-hydroxycamphor, 5-*exo*-hydroxycamphor and 5-*endo*-hydroxycamphor.

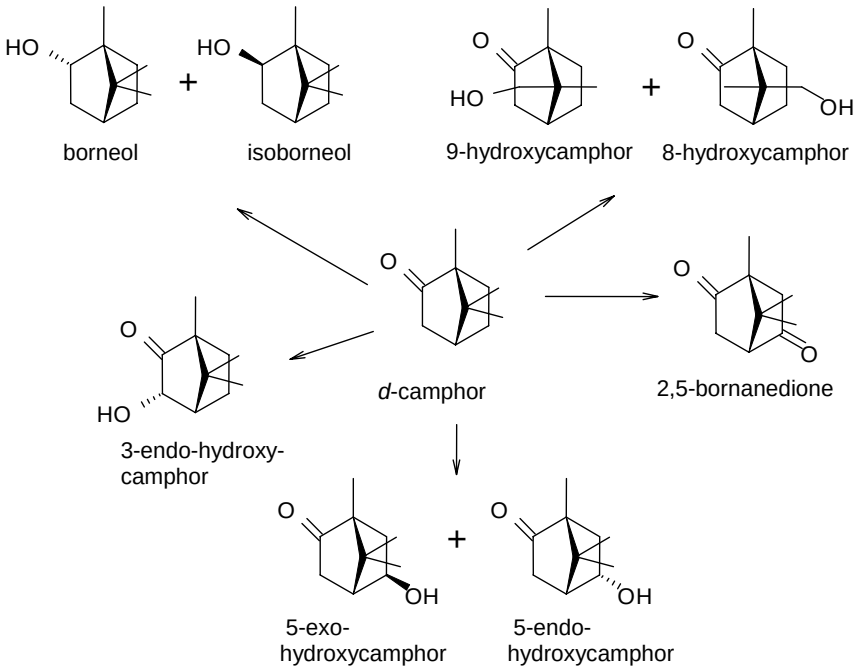


Figure 1: Structures of *d*-camphor metabolites

*Acute toxicity*

The oral LD50 of camphor exceeded 5 g/kg bw in rats and was found to be 1.31 g/kg bw in mice (Opdyke, 1978).

*Subacute/subchronic toxicity*

Groups of 8 female Swiss albino mice received 0, 50, 150 and 300 mg camphor/kg bw daily by gavage in olive oil for 20 days. Effects on body weight, liver phase I and II enzymes and levels of reduced glutathione in liver, lung, stomach, kidney and spleen were studied. Increases of hepatic cytochrome P450 and cytochrome b5 levels, aryl hydroxylase activity, glutathione-S-transferase activity and levels of reduced glutathione in the liver were only observed at the highest dose (Banerjee *et al.,* 1995).
In an 8-week toxicity study with groups of 5 white rats, a daily dose of 250 mg/kg bw *Salvia* oil (sage oil) was well tolerated when given by oral administration. When the dose was increased to 500 mg/kg bw/day, some convulsing was observed. Upon increase to 1000 mg/kg bw/day, most animals died and all animals died when the level was increased to 1250 mg/kg bw/day (Skramlik, 1959). The levels of camphor in 25 different commercial sources of sage leaves varied from 7 to 50% (Lawrence, 1998). Based on these values, the observed No Observed Adverse Effect Level (NOAEL) of 250 mg sage oil/kg bw/day would correspond to camphor intakes of 18 and 125 mg/kg bw/day, respectively.

*Chronic toxicity/carcinogenicity*

No oral studies on chronic toxicity or carcinogenicity are available.
No skin carcinomas developed after 4.5-6 months of twice-weekly skin-painting of mice with a mixture of cyclic terpenes including camphor. The carcinoma incidence from benzo(a)pyrene (BaP) was decreased by the combined or alternate painting of BaP and the terpene mixture (Benko *et al.,* 1963).

In a pulmonary tumor response test *d*-camphor injected intraperitoneally into strain A/He mice (groups of 15 males and females) three times a week for 8 weeks in total doses of 3.6 and 18 g/kg bw induced no increase in primary lung tumours and was not considered by the authors to be carcinogenic for lung (Stoner *et al.,* 1973).

*Genotoxicity*

Camphor did not show mutagenic activity in *Salmonella typhimurium* strains TA 1535, TA 1538, TA 98 and TA 100 with and without S9 activation (Anderson and Styles, 1978). No mutagenic effect was found with *d*,*l*-camphor in strains TA 97a, TA 98, TA 100 and TA 102 with and without metabolic activation (Gomes-Carneiro *et al.,* 1998).
*d*-Camphor did not induce chromosome aberrations in CHO cells with and without rat liver S9 activation (NTP, 1992a).
A peripheral blood micronucleus test with *d*,*l*-camphor, administered by skin painting over 90 days to male and female B6C3F1 mice, was also negative (NTP, 1999).

*Reproductive and developmental toxicity*

For developmental toxicity evaluation, female Sprague-Dawley rats were dosed by gavage with either *d*-camphor (100, 400 and 800 mg/kg bw) or vehicle (corn oil) on the 6th to 15th day of gestation. Signs of maternal toxicity included an increase in relative and absolute liver weights, decreased food consumption on days 6-9, decreased weight gain at 800 mg/kg bw, and increased water consumption at all dose levels. No adverse effects on fetal growth, viability, or morphological development were reported (NTP, 1992b).

In a similar study, *d*-camphor was administered in corn oil by gavage to pregnant rabbits in doses of 0, 50, 200 and 400 mg/kg bw/day on day 6-19 of gestation. Maternal weight gain tended to decrease with increasing dose. No effect on fetal growth, viability or morphological development was observed (NTP, 1992c).

The developmental toxicity of *d*-camphor was investigated in Sprague-Dawley rats and Himalayan rabbits (Leuschner, 1997). *d*-Camphor elicited no evidence of teratogenicity when administered orally to pregnant rats during the period of organogenesis, at doses of 216, 464 and 1000 mg/kg bw/day, or to pregnant rabbits at doses of 147, 316 and 681 mg/kg bw/day. In rat dams, a dose-dependent reduction in food intake and increased salivation were noted from 464 mg/kg bw/day upwards. The high dose of 1000 mg/kg bw/day resulted in fairly pronounced signs of toxicity, such as clonic convulsions, pilo-erection, reduced motility and reduced body weight gain. In rabbit dams, the high dose level of 681 mg/kg bw/day resulted in reduced body weight gain and food consumption. No increased incidences in variations, retardations or malformations were observed at any of the treated dose levels.

*Human data*

In humans signs of camphor intoxication include central nervous stimulation, oral and gastric irritation, nausea and vomiting, excitement, hallucinations, delirium, muscular excitability, tremors, convulsions and urinary retention (Opdyke, 1978). Locally it can produce irritation of skin, eyes and mucous membranes of the respiratory tract.

Intoxications from camphor have been frequently reported in literature, mostly involving the accidental ingestion of camphorated oil (20% camphor in cottonseed oil). For example, Benz (1919) reported cases of 20 children aged 1 to 4 years who became ill after ingestion of 1 to 1.5 tablespoons of camphorated oil equivalent to about 3 to 4.5 g camphor. Most of them had seizures, but recovered. According to Smith and Margolis (1954), as little as 1 g camphor ingested in 1 teaspoonful of camphorated oil was fatal in a 19-month-old child. On the basis of these and similar data, a probable lethal dose was estimated to be in the range of 50 to 500 mg/kg bw (Gleason *et al.,* 1969; Phelan, 1976).

According to a review of 182 cases involving ingestion or inhalation of camphor, 101 patients who had ingested less than 2 mg/kg bw remained asymptomatic. Of the 81 patients who had ingested more than 2 mg/kg bw, 90% remained asymptomatic (mean dose 61 mg/kg bw; range 2-330 mg/kg bw; median 32 mg/kg bw), 4% developed minor symptoms (mean dose 15 mg/kg bw; range 5-27 mg/kg bw; median 13 mg/kg bw) and 6% major symptoms (mean dose 152 mg/kg bw; range 59-475 mg/kg bw; median 80 mg/kg bw). No deaths were reported (Geller *et al.,* 1984). In a literature review of 64 cases, the same authors found 6 death reports. They calculated a mean fatal dose of 199 mg/kg bw (range 64-570, median 113). This study demonstrates a large variation in sensitivity of humans to the acute toxicity of camphor. At acute doses below 2 mg/kg bw no effects are to be expected, whereas mild (and clinically insignificant) symptoms may occur in sensitive people after an acute dose of 5 mg/kg bw or higher. The authors conclude that clinically significant camphor toxicity is not manifest below 30 mg/kg bw, and is uncommon below 50 mg/kg bw.

The American Academy of Pediatrics concluded that although adults recovered from ingestions of as much of 42 g camphor, the ingestion of 2 g generally produces dangerous effects. In children, ingestions of 0.7 to 1.0 g of camphor have proven fatal (AAP, 1994).

In 1983 the FDA regulated that over-the-counter products may not exhibit concentrations of camphor which exceed 11% (FDA, 1983). As a result of this ruling and improvements in the medical management of patients poisoned with camphor, fatal poisoning cases are now rare. However, cases of severe toxicity and convulsions are still reported to occur (Manoguerra *et al.,* 2006). According to a recently published case report, a 10-year old boy presented at the emergency room with symptoms of lethargy, nausea, vomiting and rigors. Approximately 24 hours previously, he had chewed three over-the-counter cold remedy transdermal patches containing 4.7% (95.4 mg/patch) camphor and 2.6% menthol as active ingredients (Ragucci *et al.,* 2007). On the basis of an assumed body weight of 30 kg, this would correspond to an intake of camphor of approximately 10 mg/kg bw.

## CONCLUSION

The available data on toxicity of camphor are limited and thus a TDI cannot be derived. However, based on the available toxicity data and the Panel´s conservative estimate of chronic exposure (15 mg/day equivalent to 250 µg/kg bw/day) calculated using the maximum limits suggested by the Council of Europe, the Panel considered that there would be no safety concern regarding chronic toxicity.

The Panel considered that safety aspects of *d*-camphor in terms of acute toxicity needed to be addressed. The reported acute toxicity data on adults and children arise mostly from accidental ingestion of camphor-containing medications. The probable lethal oral bolus dose has been reported to be in the range of 50 to 500 mg/kg bw. No acute toxicity was reported after doses lower than 2 mg/kg bw and clinically insignificant signs of toxicity may be seen in sensitive individuals at doses of 5 mg/kg bw and higher, whereas clinically manifest toxicity in sensitive persons would require doses higher than 30 mg/kg bw.

Potential acute exposure related to large amounts of certain foods consumed on a single day was estimated by the Panel for several age groups. It was lowest in adults (from 0.14 to 0.34 mg/kg bw according to the food commodity) and highest in children under 6 (from 0.41 to 0.83 mg/kg bw according to the food commodity). The commodity leading to the highest potential acute exposure was fresh cheese in all age groups.

The acute exposure estimates for children and adults are about 60-120 times and 150-360 times, respectively, lower than the probable lowest lethal oral bolus dose of 50 mg/kg bw. The acute exposure estimates for children and adults are about 2-5 times and 6-14 times, respectively, lower than the dose of 2 mg/kg bw below which no acute effects have been reported in human case studies.

Although these margins might appear to be low, the large number of cases describing the dose-response relationship suggests that the data sufficiently cover inter-individual variability in sensitivity. Therefore, the Panel concluded that it is unlikely that acute effects may occur in relation to consumption of foods providing less than 2 mg/kg bw in one large portion.

The acute exposure estimates considered by the Panel are based on observed high consumption in only one Member State and on maximum limits suggested by the Council of Europe. However, maximum permitted levels for *d*-camphor are not currently set in the EU legislation and there is uncertainty on its actual upper use levels in foods and beverages currently on the market and on the high consumption of food flavoured with *d*-camphor all over Europe.

The Panel therefore suggests that maximum limits should be set to ensure that exposure to camphor does not exceed 2 mg/kg bw on a single day in any age group.

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