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Raspberry ketone in food supplements – High intake, few toxicity data – A cause for safety concern?

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ABSTRACT

Raspberry ketone (4-(4-hydroxyphenyl)-2-butanone) is marketed on the Internet as a food supplement. The recommended intake is between 100 and 1400 mg per day. The substance is naturally occurring in raspberries (up to 4.3 mg/kg) and is used as a flavouring substance. Toxicological studies on raspberry ketone are limited to acute and subchronic studies in rats. When the lowest recommended daily dose of raspberry ketone (100 mg) as a food supplement is consumed, it is 56 times the established threshold of toxicological concern (TTC) of 1800 μg/day for Class 1 substances. The margin of safety (MOS) based on a NOAEL of 280 mg/kg bw/day for lower weight gain in rats is 165 at 100 mg and 12 at 1400 mg. The recommended doses are a concern taking into account the TTC and MOS. Investigations of raspberry ketone in quantitative structure-activity relationship (QSAR) models indicated potential cardiotoxic effects and potential effects on reproduction/development. Taking into account the high intake via supplements, the compound's toxic potential should be clarified with further experimental studies. In UK the pure compound is regarded as novel food requiring authorisation prior to marketing but raspberry ketone is not withdrawn from Internet sites from this country.

1. Introduction

Raspberry ketone (4-(4-hydroxyphenyl)-2-butanone) is the key flavour of raspberries and has for a long time been widely used by the food industry as flavouring substance and for other purposes in perfumery and cosmetics. In the last few years, raspberry ketone has been sold as an ingredient in food supplements where it has been claimed to have a slimming effect. Raspberry ketone is not authorized for fortifications in food supplements in Denmark and is regarded as novel food in UK. However, food supplements containing raspberry ketone are marketed on Internet sites intended for UK or Danish consumers. Raspberry ketone is marketed as natural, which is often misinterpreted as inherently safe. Currently the recommended doses for raspberry ketone sold as food supplement on the Internet range from 100 to 1400 mg/day while the exposure from natural sources only account for a few mg per day. In this article we take a closer look at the safety of such doses of raspberry ketone by reviewing the available toxicity data and previous evaluations made by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA). In addition we present a tentative investigation of raspberry ketone with QSAR (quantitative structure–activity relationship) models to identify potential hazards based on its chemical structure.

2. Chemical identity

Raspberry ketone is an aromatic phenolic compound with the chemical name 4-(4-hydroxyphenyl)-2-butanone and CAS Registry Number 5471-51-2. Synonyms include: Frambinone; Oxaphenylon; 4-(*p*-Hydroxyphenyl)-2-butanone; Rheosmin and *p*-Hydroxybenzyl acetone (SciFinder, 2014). The molecular formula of raspberry ketone is $C_{10}H_{12}O_2$ and the molecular weight is 164.2 g/mol. Raspberry ketone is relatively insoluble in water and only moderately soluble in ethanol i.e. the water solubility of raspberry ketone is estimated to be 13.5 g/l (25 °C) and the log octanol-water

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partition coefficient (Kow) to be 1.48 using EPIWEB 4.1 WSKOW software (version 1.42). The chemical structure of raspberry ketone is shown in Fig. 1.

3. Occurrence and manufacturing

Raspberry ketone is the primary aroma compound of the fruit of raspberry (*Rubus idaeus* L.) where it is found in the highest concentration but is also found naturally in other berry fruits such as cranberry, boysenberry, blackberry, sea buckthorn and loganberry as well as in buckwheat honey according to the Volatile Compounds in Food (VCF) database (TNO, 2014). The content of raspberry ketone in raspberry ranges from 0.009 to 4.3 mg/kg (TNO, 2014).

Raspberry ketone is used as flavouring substance in a variety of processed foods such as soft drinks, puddings, yogurt, baked goods, sweets and ice cream (Beekwilder et al., 2007; Crispim et al., 2010; Gaunt et al., 1970).

Extraction of raspberry ketone from raspberries (or other fruits naturally containing raspberry ketone) is expensive due to seasonal limitations in addition to the limited concentrations of naturally occurring raspberry ketone. Instead raspberry ketone can be synthesised chemically via the condensation of *p*-hydroxybenzaldehyde with acetone or biosynthesised in genetically modified microorganisms such as bacteria or yeast (Beekwilder et al., 2007; Serra et al., 2005).

4. Dietary exposure

The dietary exposure of raspberry ketone from fruits and flavourings has been estimated to range between 1.8 and 3.8 mg/day for an adult (Crispim et al., 2010; EFSA, 2011; JECFA, 2001). This exposure is primarily due to the use of raspberry ketone as flavouring substance (Crispim et al., 2010).

The daily doses of raspberry ketone recommended by food supplement suppliers range from 100 to 1400 mg/day i.e. between 26 and 368 times higher than the highest estimated exposure from diet.

Since the intake of raspberry ketone from the diet is so limited compared to the intake from food supplements containing raspberry ketone, this additional exposure is negligible for food supplement users.

5. Metabolism of raspberry ketone

The metabolism of raspberry ketone has been investigated in rats (n = 13), guinea pigs (n = 5) and rabbits (n = 2) (Sporstøl and Scheline, 1982). Raspberry ketone was rapidly absorbed from the gastrointestinal tract after administration of a single dosage of 1 mmol/kg (164 mg/kg bw) by oral gavage. The majority of ingested raspberry ketone was excreted in urine within the first 24 h as its phase II conjugated metabolites (glucuronide and/or sulphate conjugates). The amounts of phase II conjugates excreted in urine were 59 ± 3 (rats), 70 ± 8 (guinea pigs) and 38 ± 2% (rabbits) of the dose. Not considering the phase II conjugates, a total of 14 metabolites were identified in urine. Except for the reduction product, 4-(4-hydroxyphenyl)butan-2-ol, excreted in 10 ± 1 (rats), 15 ± 3 (guinea pigs) and 31 ± 1% (rabbits) of the dose, the excretion of the remaining metabolites were less than 10% of the dose. The total urinary recovery was close to 90% for all three species. Only trace amounts were excreted in faeces where raspberry ketone was the only detectable metabolite (Sporstøl and Scheline, 1982). To the best of our knowledge no toxicological information on 4-(4-hydroxyphenyl)butan-2-ol has been published.

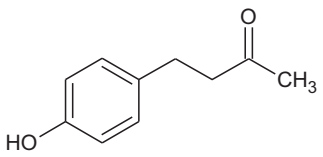

Fig. 1. Raspberry ketone.

6. Toxicological data on raspberry ketone

6.1. Toxicological studies

A review of the literature covering the bibliographic databases SciFinder (encompassing the databases ChemAbs and PubMed) and Scopus was performed to search for toxicological data on raspberry ketone. SciFinder was searched for the CAS registry number for raspberry ketone (5471-51-2) excluding patents, without any other restrictions. This yielded a total of 397 references. Scopus was searched for "raspberry ketone" without any restrictions and yielded a total of 126 references. In addition, grey literature was searched for on Google, www.INCHEM.org and the homepage of EFSA (http://www.efsa.europa.eu/). Only one study on the toxicity of raspberry ketone in laboratory animals was identified in the literature search (Gaunt et al., 1970). This study in addition to a few other unpublished studies have previously been described in evaluations of raspberry ketone as flavouring substance by EFSA and JECFA. A short description is presented here.

An oral LD_{50} (lethal dose, 50%) value of 1320 mg/kg bw for raspberry ketone has been reported in both male and female rats (Gaunt et al., 1970; unpublished study by Merkel 2003 cited from JECFA, 2011).

Lower weight gain in male rats has been observed in two separate 90-day studies (Gaunt et al., 1970; unpublished study by Hoffman 2004 cited from JECFA, 2011). JECFA (2001) established a No Observed Effect Level (NOEL) for raspberry ketone of 280 mg/kg bw/day on the basis of a statistically significant lower weight gain in male rats in a 90-day feeding study, while EFSA (2011) allocated a No Observed Adverse Effect Level (NOAEL) of 100 mg/kg bw/day based on lower relative weights of liver and kidneys from the same study (Gaunt et al., 1970). When JECFA used raspberry ketone as a supporting substance (chemically related substance that is used to fill in potential data gaps for the substance under evaluation) when evaluating 1-(4-hydroxy-3-methoxyphenyl)-decan-3-one, a NOAEL for raspberry ketone of 70 mg/kg bw/day was established based on a 90-day dietary toxicity study in rats (unpublished study by Hoffman 2004 cited from JECFA, 2011). The NOAEL was based on dose-related statistically significant higher liver weights in the two highest dose groups (275 and 700 mg/kg bw/day). Additionally, higher serum enzyme activity levels (alanine aminotransferase and aspartate aminotransferase) were observed in these dose groups. The raspberry ketone stemmed from a commercial dietary supplement preparation and the intake level was calculated based on 12% of raspberry ketone in the dietary supplement. No information on what constituted the remaining 88% of the test material was provided, which raise doubt regarding whether the observed effects could have been caused by the remaining unspecified 88% of the test material. This factor could be the explanation for the higher liver weights observed in this study compared to the lower relative liver weights found by Gaunt et al. (1970) after dosing with the pure compound (purity 96%). No genotoxicity studies with raspberry ketone were identified in the literature search. Raspberry ketone does not contain structural alerts for genotoxicity (Benigni and Bossa, 2006).