Regulatory Toxicology and Pharmacology 65 (2013) 115–118

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

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

Commentary

# Menthol differs from other terpenic essential oil constituents

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ARTICLE INFO

*Article history:*
Received 8 November 2012
Available online 1 December 2012

*Keywords:*
Menthol
Eucalyptol
Cineol
Camphor
Thujone
Pharmacology
Pharmacokinetics
Safety

ABSTRACT

The European Medicines Agency concluded that there is a risk of suppositories containing terpenic derivatives, which are used to treat coughs and colds, inducing neurological disorders, especially convulsions, in infants and small children. Terpenic derivatives are found in essential oils obtained from plants and include camphor, eucalyptol (*syn.* 1,8-cineol), thujone, and menthol. Chemistry, pharmacodynamics and pharmacokinetics of these compounds are clearly different and explain the appearance of convulsions following camphor, thujone, and eucalyptus oil overdose/poisoning, whereas no convulsions have been reported in cases of menthol overdose/poisoning in accordance with the pharmacological properties of menthol. Thus, a general verdict on all terpenic derivatives without differentiation appears inappropriate.



## 1. Introduction

The European Medicines Agency has completed a review of the safety and effectiveness of suppositories containing terpenic derivatives, which are used to treat coughs and colds in children and adolescents. Terpenic derivatives are found in essential oils obtained from plants and include camphor, eucalyptol (*syn.* 1,8-cineol), thujone, and menthol. Based on the evaluation of the currently available data and the scientific discussion within the Agency's Committee for Medicinal Products for Human Use (CHMP), the CHMP concluded that there is a risk of these medicines inducing neurological disorders, especially convulsions, in infants and small children (EMA, 2012).

In obvious contrast, menthol (main constituent of peppermint oil) and eucalyptol (main constituent of eucalyptus oil) are used widely as fragrance ingredients in food (candies, chewing gum), but also in cosmetics, shampoos, soaps, household cleaners, and especially menthol as cigarette flavouring ingredient. For menthol, an acceptable daily intake (ADI) of up to 4 mg/kg body weight (bw) has been defined (JECFA, 2001). For eucalyptol, available data have been judged as inadequate to derive an ADI; a provisional tolerable daily intake (TDI) has been assigned at 0.2 mg/kg bw (EC, 2002). The European Scientific Committee on Food considered the available data inadequate to establish an ADI or TDI for thujone, whereas a previous assessment by the Council of Europe allocated a TDI for thujone as low as 0.01 mg/kg bw (EC, 2003). On the basis of recently completed long-term studies in mice and rats, an ADI of 0.11 mg/kg thujone was proposed (Lachenmeier and Uebelacker, 2010). The European Food Safety Authority concluded that a TDI for camphor cannot be derived from available toxicity data; however, the scientific panel suggested that maximum limits should be set to ensure that exposure to camphor does not exceed 2 mg/kg bw on a single day (AFC, 2008).

Apparently, terpenic essential oil constituents show biologic diversity, leading to a wide range of maximum acceptable/tolerable doses. In view of the extensive distribution of the above-named essential oil constituents in foods and medicinal products, a discussion of the diverse properties should provide help in the save use of these compounds.

## 2. Chemistry

Terpenes belong to structurally and functionally different classes. They represent combinations of several 5-carbon units called isoprene. The monoterpenes are formed from the coupling of two isoprene units. Monoterpens are the most representative molecules constituting 90% of the essential oil constituents and allow a great variety of structures. They consist of several functions, e.g. monocyclic alcohols (e.g. menthol), bicyclic ethers (e.g. eucalyptol), or bicyclic ketones (e.g. camphor, thujone) (Bakkali et al., 2008).

The functional groups determine not only the chemical properties of the terpenic essential oil constituents, but are essential for the pharmacological characteristics for receptor interactions and metabolism of the compounds (Table 1). Stereochemical aspects have been omitted for sake of simplicity.

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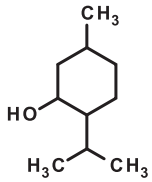
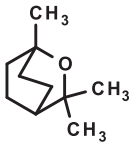
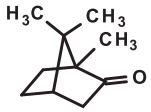
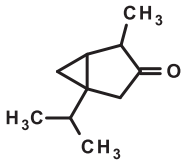
http://dx.doi.org/10.1016/j.yrtph.2012.11.009

**Table 1**
Formulae and biological data of four examples of essential oil constituents.

| Compound | Menthol | Eucalyptol (1,8-Cineol) | Camphor | Thujone |
|---|---|---|---|---|
| Structural formula |  |  |  |  |
| TRPM8 | Strong activation | Weak activation | Weak activation | |
| TRPA1 | Activation at μM, Inhibition at mM | | Inhibition | |
| TRPV3 | Weak activation | Weak activation | Strong activation | Weak activation |
| Experimental seizures | Anticonvulsant | Convulsant | Convulsant | Convulsant |
| Predominant metabolism | Glucuronidation | CYP-dependent hydroxylation | CYP-dependent hydroxylation | CYP-dependent hydroxylation |
| Seizures in humans | No | Yes | Yes | Yes |

For references see text.

## 3. Pharmacodynamics

Essential oils have been largely employed for their properties already observed in nature, i.e. for their antibacterial, antifungal, and insecticidal activities, which are mainly based on their rather unspecific cytotoxic effects (Bakkali et al., 2008). Analgesic and anti-inflammatory effects have also been described (De Sousa, 2011; Miguel, 2010).

With the advent of molecular pharmacology, some specific properties of individual essential oil constituents have been detected. For instance, the cooling effect of menthol has been known for long (Eccles, 1994), but the molecular mechanism has been elaborated only recently. The cloning and characterization of the cold-menthol receptor, transient receptor potential melastatin subfamily channel 8 (TRPM8), was a major breakthrough in the study of thermosensation (Peier et al., 2002). In comparison to the full TRPM8 agonist icilin, menthol elicits 70% of the icilin response with high potency ($EC_{50} \sim 0.01$ mM). In contrast, eucalyptol elicits only 23% of the icilin response with low potency ($EC_{50}$ 7.7 mM) (Behrendt et al., 2004); these data do not suggest significant *in vivo* cooling effects of eucalyptol in agreement with clinical experience. Camphor at 2 mM showed only 20% of the menthol response at the TRPM8 (Vogt-Eisele et al., 2007).

During recent years, several other transient receptor potential (TRP) channels have been uncovered like the transient receptor potential ankyrin1 (TRPA1) and the transient receptor potential vanilloid 3 (TRPV3) channels. While TRPM8 senses cold by somatic primary afferent neurons, TRPA1 is the major contributor to cold sensing in vagal afferent fibres. Menthol at low micromolar concentration potently activates TRPA1 channels; however, menthol at high concentrations (e.g. 1 mM) also inhibits TRPA1 channels (Karashima et al., 2007). In contrast, camphor has been described only as antagonist of TRPA1, abrogating the responses to cold reversibly (Fajardo et al., 2008). TRPV3 is a thermosensitive ion channel activated by warmth and camphor (high efficiency but low potency with $EC_{50}$ of 6.0 mM) and has been hypothesized to be involved in skin sensitization. The relative TRPV3 activation efficiency of menthol, thujone, and eucalyptol were 65%, 50%, and 25%, respectively, in comparison to camphor (all compounds tested at 2 mM) (Vogt-Eisele et al., 2007).

In addition to interaction with peripheral TRP channels, effects on brain structures have been identified for some of the essential oil constituents. Menthol reduced the excitation of rat hippocampal neurons in culture and suppressed the epileptic activity induced by pentylenetetrazole and electrical kindling in mice. In this context, menthol not only enhanced currents induced by low concentrations of GABA but also directly activated $GABA_A$ receptors in hippocampal neurons. Furthermore, in the CA1 region of rat hippocampal slices, menthol enhanced tonic GABAergic inhibition, whereas phasic GABAergic inhibition was unaffected (Zhang et al., 2008). This investigation confirmed earlier results obtained with menthol, showing potentiation of the response of recombinant $GABA_A$ receptors expressed in *Xenopus* oocytes (Hall et al., 2004) and sharing general anaesthetic activity in *Xenopus* tadpoles and sites of action on the $GABA_A$ receptor with the intravenous anaesthetic propofol (Watt et al., 2008).

In contrast to the potential anticonvulsant activity of menthol, thujone suppressed GABA-induced peak currents in rat dorsal root ganglion neurons and produced convulsions in mice alleviated by diazepam and phenobarbital (Höld et al., 2000). The convulsant action of thujone and of the essential oil of sage has been confirmed in rats. The chemical analysis revealed camphor as the main constituent of the sage oil used (Millet et al., 1981). Similar to camphor essential oil, eucalyptol also produced electrocortical seizure activity in rat brain (Culic et al., 2009).

## 4. Pharmacokinetics

Systemic availability of essential oil constituents is an important determinant of potential systemic effects. Human plasma levels of intact menthol after oral administration were either not detectable or only in quantities less than 1% of the major metabolite, menthol glucuronide (Gelal et al., 1999; Hiki et al., 2011), suggesting a very efficient first-pass glucuronidation of menthol at the free hydroxyl group by e.g. UDP-glucuronosyltransferase 2B7 (Coffman et al., 1998). Thus, no significant systemic but only local effects can be expected after enteral absorption of commonly used doses of menthol.

Essential oil constituents with a more complex chemical structure like the cyclic ether eucalyptol or the bicyclic ketones camphor and thujone need to be metabolized by cytochrome-(CYP)-dependent Phase I metabolism before the resulting primary metabolites can be conjugated. Studies with human liver microsomes have characterized the hydroxylation of eucalyptol by CYP3A enzymes (Miyazawa et al., 2001); this process is apparently slow, since substantial plasma concentrations of eucalyptol have been measured in humans after inhalation, showing an elimination half-life of about 2 h (Jäger et al., 1996). CYP2A6 was identified as the major enzyme involved in hydroxylation of camphor by human liver microsomes (Gyoubu and Miyazawa, 2007). The most recent study with a comprehensive set of recombinant enzymes indicated that the principal CYP enzyme metabolizing thujone is CYP2A6, followed by CYP3A4 and, to a small extent, CYP2B6, leading to two