Proposed harmonised classification and labelling of Melaleuca aternifolia, ext. and Melaleuca alternifolia, essential oil; tea tree oil (TTO) as reproductive toxic category 1B

SMEunited and its member COSMED consider that the reproductive toxicity category 1B (H360F) classification based on RAC's opinion adopted on 30 November 2023 is not justified. We base our arguments on the following elements of the CLP Regulation:

1. Effects not observed in humans

The CLP regulation states:

3.7.2.3.1. Classification as a reproductive toxicant is made on the basis of an assessment of the ***total weight of evidence,*** *see section 1.1.1. This means that all available information that bears on the determination of reproductive toxicity is considered together,* ***such as epidemiological studies and case reports in humans*** *and specific reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs.*

In the RAC opinion we can read "*Dossier Submitter (DS) noted the effects on fertility, testes, epididymides and sperm observed in two species (rats and dogs) in four acceptable studies at dose levels inducing slight or moderate general systemic toxicity****. DS also expressed some doubt on human relevance, taking into account that such effects were not reported in humans exposed to components of TTO at relatively high doses with food. DS proposed Repro cat. 2; H361f.***"

On this point RAC concludes:

- *The DS and stakeholders expressed some doubt on human relevance, taking into account that such effects were not reported in humans exposed to components of TTO at relatively high doses with food.* ***However, DS and RAC note that no human data on TTO are available.***
- *Regarding the comments that there is history of safe use of monocyclic terpenes in diet and other products,* ***no relevant data to address this (e.g., epidemiology studies in humans exposed to the substance) were provided to RAC to support this comment.*** *RAC notes the findings in animal studies described above.*

While for TTO no epidemiological studies are available on humans, there is nevertheless robust vigilance data on humans available:

1.1. Nutrivigilance

The ANSES report (Ref 1, 2021) on the use of essential oils of Melaleuca in food supplements discusses some oral uses of TTO in dietary supplements and food. These uses include exposures of up to 178 mg/day in adults (with exclusion of pregnant and breastfeeding women) over potentially long periods. Indeed, dietary supplements are not taken only once, but are typically recommended as a cure, over a period ranging from 1 to 3 months.

To compile adverse effects associated with the consumption of Melaleuca essential oils, ANSES has analyzed the following assessments:

- The French ANSES' nutrivigilance system was requested during 2009 and 2019 to analyze reports of adverse effects potentially associated with the consumption of dietary supplements containing Melaleuca essential oils.
- To obtain more data, ANSES requested information from other health agencies of the European Union (Switzerland, Croatia, Ireland, Austria, Hungary, Greece, Finland, Czech Republic, Lithuania, Spain, Belgium, Sweden, Italy) in 2017 related to the consumption of dietary supplements containing essential oils. (Page 43, ANSES report 2021)
- In addition, Canadian data from Canada vigilance between 1 January 1965 and 31 March 2018 were analysed for adverse effects on TTO (Page 43, ANSES report 2021)
- In the United States data from the FDA-Medwatch database was analysed for TTO. (Page 43, ANSES report 2021)
- Finaly, ANSES used cases reported in the literature in humans after oral exposure of TTO (Page 44, ANSES report 2021)

All these assessments have the following in common: **Despite oral use of TTO in large doses over long periods of time, none of the described effects had an impact on fertility.**

1.2. Pharmacovigilance

In the Assessment report on Melaleuca alternifolia from the European Medicines Agency (Ref 2, 2014 and Ref 3, 2023) TTO shows a consistent and long-standing

use for at least 30 years, is for its undiluted form and for the following preparations and indications:

- Liquid preparation containing 0.5% to 10% of essential oil to be applied to the affected area 1-3 times daily for treatment of small superficial wounds and insect bites or 1-2 drops (0.033-0.066 ml) of the undiluted essential oil applied to the affected area using a cotton bud 1-3 times daily.
- Oily liquid or semi-solid preparation, containing 10% of essential oil, to be applied to the affected area 1-3 times daily or 0.7-1 ml of essential oil stirred in 100 ml of lukewarm water to be applied as an impregnated dressing to the affected areas of the skin for treatment of small boils (furuncles and mild acne). The undiluted essential oil is to be applied to the boil using a cotton bud 2-3 times daily.
- Oily liquid or semi-solid preparation, containing 10% of essential oil, to be applied to the affected area 1-3 times daily for the relief of itching and irritation in cases of mild athlete´s foot. The undiluted essential oil is to be applied to the affected area using a cotton bud 2-3 times daily until the condition is cleared up.
- 0.17–0.33 ml of TTO to be mixed in 100 ml of water for rinse or gargle several times daily for symptomatic treatment of minor inflammation of oral mucosa. This volume corresponds to approx. 150-300 mg of the essential oil daily.

According to EMA's report, this type of products also have a known safety profile with a long history of usage in traditional medicinal. **Pharmacovigilance and individual case reports did not detect any effect on fertility in humans.** Note that TTO is used on damaged skin, which increases its systemic exposure.

1.3. Conclusion on human data:

Both nutrivigilance and pharmacovigilance data obtained over many years, at significant exposure levels (up to 178 mg/day from food, up to 300 mg/day for oromucosal use and on application on damaged skin) for significant periods of time did not show any effects on human fertility.

As indicated in paragraph 3.7.2.3.1 of the CLP, the weight of evidence, taking into account data in humans, would therefore direct towards a Reproductive toxicity category 2 rather than 1B.

2. Toxicokinetics

The CLP regulation states:

3.7.2.3.2. ***Toxicokinetic studies in animals and humans****, site of action and mechanism or mode of action study results* ***may provide relevant information which reduces or increases concerns about the hazard to human health****. If it is conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans* ***or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans, then a substance which produces an adverse effect on reproduction in experimental animals should not be classified****.*

In the CLH report the Dossier submitter states "*However, data is available for bicyclic monoterpenes (a-Terpineol, a constituent of Tea Tree Oil and very similar to its main component Terpinen-4-ol*) where reproductive studies were conducted both via gavage and via diet administration. It was demonstrated that after dietary administration of a-Terpineol sperm damage did not occur.* ***Pharmacokinetic analysis confirmed that oral gavage at high doses clearly resulted in much higher systemic exposure*** *than expected,* ***leading to biologically non-relevant effects that should not be considered for classification purposes***".

** EFSA consider that a group NOAEL of 250 mg/kg bw can be used for terpineol, a-terpineol, terpineol acetate and 4-terpinenol (Ref 4 2012).*

The RIFM fragrance ingredient safety assessment of terpineol. They compared the concentration of terpineol between diet and gavage administration. The plasma concentration was 10-times higher with gavage administration (Ref 5, 2017):

Table 3
Radioactivity levels.

	Gavage	Dietary	Gavage	Dietary	Gavage	Dietary
	75 mg/kg/day		250 mg/kg/day		750 mg/kg/day	
Tmax (h)	1.5	24	1	24	1	24
Cmax (µg eq/g)	25.3	2.57	84.5	9.35	246	27.2
Factor	10		9		9	

In relation to gavage administration, the RAC states "*Concerning the comment relating to the applicability of studies dosed by gavage, RAC considers such studies as relevant for hazard classification (as also noted in the STOT RE section), as this is consistent with the OECD TG under which these studies were conducted*."

The RAC opinion on this aspect is conclusive. Nevertheless, paragraph 3.7.2.3.2 of the CLP regulation indicates that "when the toxicokinetic differences are so

marked that it is certain that the hazardous property will not be expressed in humans then a substance which produces an adverse effect on reproduction in experimental animals should not be classified".

Therefore, even if RAC correctly concluded that gavage is relevant for reprotoxic classification, this has limitations. This may be the case when the form of exposure has a huge impact on toxicokinetics and this form of exposure is not expected under conditions of human use (humans will never be exposed by gavage). There is no toxicokinetic study in humans of a-Terpineol or terpinene-4-ol through diet, but based on the effect observed in rats, we concluded that human effects are comparable.

Given the strong difference in absorption between gavage and diet, paragraph 3.7.2.3.2 of the CLP should apply. Based on that, TTO should be classified as reproductive toxic category 2.

3. Doubt on Relevance of the Mechanism to Human

Already in the CLH dossier the submitter and other stakeholders raise doubts about the relevance of the effects observed on male fertility in the rat studies for humans. While these doubts are based on several factors, a very important one is a proposed mechanism of toxicity that may occur in rats but not in humans.

The RAC opinion states "*Therefore, it is not possible to either exclude another MoA nor conclusively demonstrate the human non-relevance*[2]." The CLP guidance document states "*However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate*." Since the RAC does not propose any other potential MoA, it is just a hypothetical concern. Furthermore, conclusive evidence of non-relevance is scientifically not required, and category 2 should be applied just like proposed by the DS.

4. Overall Conclusion

Based on 1) the absence of effects observed in humans exposed to high dosages through food supplements and pharmaceuticals for many years, 2) the huge toxicokinetic difference between gavage and diet administration and 3) the justified doubts about the relevance of the effects seen on rats, we are of the opinion that the **classification of TTO as reproductive toxic category 1B (H360F) is not justified, while category 2 (H361F) would be adequate**.

References

1: AVIS de l'Anses relatif l'utilisation d'huiles essentielles de Melaleuca dans la composition des compléments alimentaires

2: Assessment report on Melaleuca alternifolia (Maiden and Betch) Cheel, M. linariifolia Smith, M. dissitiflora F. Mueller and/or other species of Melaleuca, aetheroleum. Melaleucae alternifoliae aetheroleum - AR (europa.eu)

3: Addendum to Assessment report on Melaleuca alternifolia (Maiden and Betche) Cheel; Melaleuca linariifolia Smith; Melaleuca dissitiflora F. Mueller and/or other species of Melaleuca, aetheroleum. Melaleuca aetheroleum - Addendum (europa.eu)

4: Scientific Opinion on the safety and efficacy of aliphatic, alicyclic and aromatic saturated and unsaturated tertiary alcohols and esters with esters containing tertiary alcohols ethers (chemical group 6) when used as flavourings for all animal species (wiley.com)

5: RIFM fragrance ingredient safety assessment, terpineol, CAS Registry Number 8000-41-7 (elsevier.com)